R E V I E W

Future prospects in the treatment of erectile dysfunction: focus on avanafil

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Abstract: The treatment of erectile dysfunction (ED) has been revolutionized in the last 15 years with the introduction of type 5 phosphodiesterase (PDE5) inhibitors. Their efficacy, safety, and ease of administration have made them first-line treatment for ED. This article reviews the current therapies available for ED, and the new PDE5 inhibitors that are being investigated. Furthermore, it examines all the current ED treatment options that are in different phases of development (including oral and topical pharmacotherapy, gene therapy, and tissue engineering). A special emphasis is on avanafil, a new PDE5 inhibitor that has been studied extensively in Phase I and II clinical trials and has undergone several Phase III trials. Avanafil is a promising medication for ED due to its favorable pharmacokinetics, safety, and efficacy.

Keywords: PDE5, sexual performance, pharmacokinetics

Introduction

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] It is frequently associated with emotional distress and reduced self-esteem. This emotional distress can have a significant impact on the patient's social or marital life, emphasizing the importance of treating this condition adequately.[2] The Massachusetts male aging study, conducted from 1987 to 1989 in areas around Boston, was a cross-sectional survey of 1290 men aged 40–70 years that looked at the prevalence of ED. Participants self-reported ED, and the condition was classified into mild, moderate, and severe. It was found that the prevalence of ED increased with age, as prevalence was 40% at 40 years of age and 70% at 70 years of age.[3] Penile erection is caused through vascular pressure changes within the corpora cavernosa. The nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway is the key physiological mediator of erection. During psychogenic, reflexogenic, or nocturnal tumescense, NO is released to cause relaxation of the smooth muscle cells of the trabeculae and arterioles of the corpora cavernosa, thus increasing penile blood flow and resulting in erection. Type 5 phosphodiesterase (PDE5) is the main hydrolyzing enzyme of cGMP, thus causing detumescense. PDE5 inhibitors act through competing with cGMP for the enzyme, making cGMP more available and prolonging erection.[4] ED can be the result of organic or psychogenic causes, and often both. Organic causes can be classified based on the cause (diabetic, traumatic), or the neurovascular mechanism of the erectile process (failure of initiation [neurogenic], failure of filling [arterial], and failure of storage [venous]).[4,5] Since ED can be an early indicator of cardiovascular disease, all patients should undergo a complete medical,

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sexual, and psychosocial history, focused physical examination, and laboratory tests. Certain optional and specialized tests of proven value in select situations can be performed and are left to the clinical judgment of the physician.[1]

The ideal treatment of ED should be: easy to administer, noninvasive, not painful, and highly efficacious, with minimal side effects.[6] Due to the earlier limited understanding of the basic physiological and biochemical mechanisms involved in erection, early treatment of ED consisted of several psychological and hormonal strategies and the use of penile implants and vacuum devices. However, the later deeper understanding of the erection mechanism has allowed the introduction of intracorporeal injections and the later oral PDE5 inhibitors. The oral PDE5 inhibitors have revolutionized the treatment of ED and have become first-line treatment due to their effectiveness and good safety profile. As we continue to understand the erectile mechanism even further, the need for better treatment options for ED has risen. This is mainly due to the shortcomings of the current oral PDE5 inhibitors, which include their occasional ineffectiveness, their limited spontaneity, and their inability to correct the underlying cause of ED. Therefore, researchers are constantly exploring newer and more effective therapies for ED.

In this review, current available therapies for ED are presented. Several advanced and early ED therapy research efforts that are currently being investigated at different stages of development are described, with a special focus on avanafil and its future role in ED treatment.

The authors of this review searched for English language, original articles published in MEDLINE, focusing on erectile dysfunction, between 1991 and 2011. The search terms used were "erectile dysfunction," "new treatment," "avanafil," and "PDE5 inhibitors." The relevant articles were selected, and their reference lists were searched for further articles.

Current ED therapies
Type 5 phosphodiesterase inhibitors

The American Urological Association (AUA) has recommended the use of three PDE5 inhibitors so far (sildenafil, tadalafil, and vardenafil) as first-line therapy for ED[7] (Table 1).

Sildenafil (Viagra®, Pfizer Inc, New York, NY) is rapidly absorbed from the gut to reach the peak plasma concentration within 1 hour.[8,9] Its half-life ($t_{1/2}$) is 3–5 hours, with duration of action up to 12 hours.[10] The time to peak concentration (T_{max}) is reduced with high fatty meal consumption. It demonstrates some cross-reactivity to PDE6 receptors, which are present in the retinal photoreceptors, resulting in color vision abnormalities in some patients.[11,12] Vardenafil (Levitra®, Bayer, Leverkusen, Germany) is rapidly absorbed and its peak plasma concentration is obtained within an hour, with a median of 0.7 hours.[13,14] The $t_{1/2}$ is 4–5 hours. The T_{max} is not affected with moderate fat intake but is slightly reduced with a high fat diet.[15] Vardenafil demonstrates higher selectivity to PDE5 than the other two PDE5 inhibitors.[13,16] Tadalafil (Cialis®, Eli Lilly, Indianapolis, IN) is also rapidly absorbed to reach a peak plasma concentration within 2 hours.[16,17] Its $t_{1/2}$ is, however, 17 hours, which allows a unique duration of action up to 36 hours. Its T_{max} is not affected with fat intake.[18] Tadalafil has some cross-reactivity with PDE11, which is present in the testes and prostate, but there is no known clinical effect associated with this cross-reactivity. It does cause back pain and myalgia in 6% of patients however.[19] All the available PDE5 inhibitors are associated with headache, flushing, dyspepsia, nasal congestion, and dizziness.[20] They are all contraindicated with nitrates as they might precipitate severe hypotension.[21] They can be used with α-blockers with caution, as the patient should be on α-blocker for some time before introducing PDE5 inhibitor, and they should be spaced for at least 4 hours.[22] PDE5 inhibitors are not recommended for retinitis pigmentosa and have to be used with caution in diseases with a risk of priapism (eg, leukemia and multiple myeloma). There is currently no epidemiological evidence that nonarteritic anterior ischemic optic neuropathy is associated with the use of PDE5 inhibitors; however, the patient should inform the health professional about a history of loss of vision as this warrants ophthalmologic evaluation.[23–25]

Local therapy

Currently, intracavernosal injection (ICI) of vasoactive substances is considered second-line therapy for ED when oral pharmacotherapy fails or is inappropriate. Intracavernosal

Table 1 Comparison of avanafil pharmacokinetics to other available PDE5 inhibitors

Parameters	Sildenafil	Vardenafil	Tadalafil	Avanafil
Available doses, mg	25, 50, 100	5, 10, 20	5, 10, 20	20, 50, 100
T_{max}, hours	1 (0.5–2.0)	0.7 (0.25–3.00)	2 (0.5–6.0)	0.593 (0.686–0.555)
$t_{1/2}$, hours	3–5	4–5	17.5	1.19 (1.07–1.23)
Other possible receptor affinity	PDE6	PDE6	PDE11	PDE6

alprostadil (prostaglandin E1) has an efficacy rate of 87%,[26] while another intracavernosal bimix therapy (phentolamine plus papaverine) has an efficacy rate of 60%,[27] whereas a trimix therapy (phentolamine, papaverine, and alprostadil) has an increased efficacy rate to 92%.[28] ICI can be associated with penile fibrosis, penile pain, hematoma, and priapism.[29]

Intraurethral alprostadil (MUSE™, Vivus, Menlo Park, CA) represents another second-line pharmacotherapy for ED. It is less efficacious than intracavernosal alprostadil injection with 60% or less efficacy rate; however, most patients accept it as an easier method of ED treatment. The most common side effects associated with this treatment are urogenital pain and minor urethral bleeding.[30]

Mechanical devices

The vacuum erection device (VED) is a cylindrical pump that is placed over the penis. Air is pumped out of the device causing blood to flow into the penis. Once erection is achieved, an occlusive ring is placed at the base of the penis to maintain erection. It has an efficacy of 80%–95%, with long-term efficacy at 60%. It is contraindicated in bleeding disorders or in patients on anticoagulation. There have been several side effects associated with VED use, the commonest being penile pain. Other side effects include: pain on ejaculation, retarded ejaculation, petechiae on the penis, skin necrosis, and Peyronie's disease.[31]

Penile prosthesis represents a third-line of treatment when other types of less invasive treatments fail. Efficacy is not an issue, as erection is always achieved, and patient satisfaction reaches more than 80%.[32] There are two types of penile implants: inflatable and non-inflatable (malleable). The inflatable type is more desired by patients; however, it requires more manual dexterity. The 5-year survival of the three-piece inflatable type is 90%–95%.[33] The main complications for penile implants are mechanical failure, infection, and erosion.[32]

Future treatment of ED
Pharmacotherapy

Udenafil is a newer PDE5 inhibitor that has a similar affinity to PDE5 as sildenafil. In a multicenter, double-blind, placebo-controlled, fixed-dose, parallel-group Phase III trial done in Korea, udenafil was found to be an effective and well tolerated therapy for ED.[34] Udenafil is currently available in several countries, such as Korea and Russia, under the trade name Zydena® (Dong-A PharmTech Co, Seoul, South Korea).

SLX-2101 is another PDE5 inhibitor that is being studied. It has shown a strong potency both ex vivo and in vivo. It has a long duration, reaching 36–48 hours, with a safety and tolerability that makes it a candidate for once-daily use.[35] Its M1 metabolite increases its duration of action even further leading to further benefit for ED patients.

Mirodenafil is a PDE5 inhibitor that has been available in Korea since 2007 as M-vix® (SK Chemicals, Seoul, South Korea). A multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study was conducted in Korea and showed the drug to be effective and well tolerated in ED due to several etiologies.[36]

Avanafil is a highly selective PDE5 inhibitor, as discussed later in this review. Several other PDE5 inhibitors have been studied in preclinical trials. FR226807, a nitrobenzamide derivative, inhibits PDE5 isolated from human platelets.[37] It has, however, the disadvantage of being metabolized to several potential toxic metabolites such as nitroso and hydroxylamine derivatives. T-1032 (an isoquinoline derivative) is a novel, potent, and specific PDE5 inhibitor that has been found to increase cGMP levels in rat vascular smooth muscle cells in a dose-dependent manner.[38] KF31327 is more potent than sildenafil as a PDE5 inhibitor, through binding to cGMP noncompetitively.[39] UK369003 is a PDE5 inhibitor that has been more studied for its effect on lower urinary symptoms than on ED. JNJ-10280205 and JNJ-10287069 are new novel, potent, and selective PDE5 inhibitors that display superior selectivity against PDE1-4 and -6 when compared with sildenafil. In anesthetized dogs, they both exhibit similar efficacy as sildenafil in enhancing erectile function, with no significant effect on cardiovascular parameters. Both compounds are suitable candidates for clinical trials in men with ED.[40] NCX 911 has a similar efficacy to sildenafil in causing corporal smooth muscle relaxation; however, since it generates NO it might have a promising role in the future in ED conditions with low NO.[41]

Bremelanotide, a cyclic, heptapeptide melanocortin analog, is an active metabolite of melanotan-II.[42] It is erectogenic in men by an action believed to occur at central MC3-R and MC4-R.[43] Bremelanotide has been studied in Phase II clinical trials examining its efficacy and safety in variable doses from 0.3 to 10 mg. It was found to be effective at doses greater than 1 mg.[44] In a randomized, double-blind, placebo-controlled study, it was shown to be effective in individuals who have not responded to sildenafil, who cannot tolerate the side effects of PDE5 inhibitors, and in whom sildenafil is contraindicated.[45]

The use of topical treatment for ED has always been an interesting one, as it avoids the systemic effects of the treatment. Absorption through the skin and the thick tunica albuginea is an issue of ongoing research. So far, alprostadil has shown some promise as an effective topical agent. In a double-blind, placebo-controlled study, topical gel of 1% alprostadil (Topiglan®, MacroChem Co, Lexington, MA) applied to the glans penis was found to be effective and safe for the treatment of ED, with the main side effect being urogenital pain.[46]

Aviptadil is an injectable formulation of vasoactive intestinal polypeptide in combination with the adrenergic drug phentolamine, which is injected intracavernosally, thus limiting the systemic absorption of the medication. It has been approved in several countries including Denmark and New Zealand and uses autoinjector. This combination was compared with intracavernosal alprostadil in a randomized, open-label, crossover study. Although alprostadil was more effective than the combination, more patients preferred to take the combination because alprostadil was associated with more pain.[47]

Apomorphine is a nonselective dopaminergic agonist that works centrally and has been known for a long time to have erectogenic properties. Initially, the drug was in a sublingual form and was approved in many countries before it was removed from all markets due to its poor efficacy and low patient preference when compared with sildenafil.[48] VR004 is a novel new inhaled formulation of apomorphine that was examined in two consecutive, randomized, multicenter trials and demonstrated rapid onset of action and reproducible efficacy and safety profiles, making it a possible future first-line therapy for ED.[49] ABT-724 is a selective dopaminergic D4 agonist that has been shown in rat models to induce erections. It might have a role in the future as a replacement of apomorphine since it bypasses the D2 receptor, therefore possibly avoiding the nausea that can be associated with apomorphine.[50]

The excitatory amino acid glutamate was found to be a major regulator of erectile function in the central nervous system (CNS) through its hippocampal receptors. These receptors are divided into NMDA (N-methyl D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and ACPD (1-amino-1,3-dicarboxycyclopentane) receptors. It was shown that by injecting glutamate into each of these receptors in rat models, NMDA was associated with the highest increase in intracavernous pressue (ICP), more than AMPA receptors. ACPD receptors had no statistically significant increase in ICP. This might suggest that NMDA is a future target in ED treatment.[51]

Serotonin exerts a general inhibitory effect on male sexual function, although it can produce an excitatory or inhibitory effect on the erectile function, depending on the action at different sites and different serotonin receptors.[52] Trazodone, a selective serotonin agonist, has been reported to have a stimulatory effect on erection.[53] The 5-HT2C receptor was found to be the main serotonin mediator for erection.[54] RSD 992, an agonist at 5-HT2C receptors, induces erections and facilitates male copulative behavior, suggesting an important role for the 5-HT2C receptor in the control of erectile mechanisms.[52] YM348 is a novel, potent and orally active 5-HT2C receptor agonist that has been found to induce penile erections and hypolocomotion in rats.[55]

BAY41-2272 was synthesized and shown to stimulate soluble guanylate cyclase in a NO-independent manner, without an effect on cGMP breakdown, thus providing an opportunity to treat ED when endogenous NO production is impaired as in diabetics. In comparison to YC-1, another NO-independent soluble cGMP activator, it has been shown to have distinctly higher potency and no phosphodiesterase inhibitory activity.[56,57]

Rho-kinase is known to inhibit myosin light chain (MLC) phosphatase, thus phosphorylating MLC and causing increased level of activated myosin, thereby causing muscle contraction.[58] Rho-kinase antagonism was found to stimulate penile erection in rat models.[59] Topical application of Y-27632 (rho-kinase inhibitor) was studied in rats and it was found to induce erection. High doses of the drug cause a reduction of the systemic blood pressure, but when used topically with appropriate doses it might have potential in the future of ED treatment.[60]

Hexarelin analogue peptides stimulate erectile function centrally by acting on the paraventricular nucleus at the hypothalamus and activating oxytocinergic neurotransmission, in a manner similar to apomorphine.[61] Hexarelin analogue peptides can also stimulate erection when given systematically, although to a lesser degree than when injected directly into the paraventricular nucleus.[62,63] Human studies are still lacking.

Oxytocin stimulates erection when injected into the lateral cerebral ventricle, the paraventricular nucleus, the hippocampus, or intrathecally in rats. It stimulates erection through induction of NO,[64] and its effects are androgen dependent.[52] Currently, research is only limited to animals.[65]

Gene therapy

Gene therapy represents a very attractive future direction. The defective gene in the corporal tissue can be restored or the mutant gene can be antagonized. The penis is an easier organ

to inject the gene therapeutic material directly into without having to inject it through the systemic circulation. The tunica albuginea has a slow turnover rate, making the effect of gene therapy last longer. There will be many categories of patients in which gene therapy will be useful, including diabetic, aging, and in hypercholesterolemia. hMaxi-K is the first gene transfer to go through Phase I clinical trial for ED. The results are encouraging as they show a good safety profile. However, efficacy rate cannot be properly evaluated from a Phase I trial with no control group.[66] Further clinical trials will need to be done.

Regenerative medicine

Tissue engineering is being studied for its use in reconstructing the penis or treating ED. Kim et al have developed a technique using a sural autologous nerve graft to preserve the continuity of the cavernous nerves during radical prostatectomy, with good results.[67] Kershen et al presented evidence that human corporal smooth muscle cells used along with biodegradable polymer scaffolds can be used as corporal smooth muscle tissue both in vivo and in vitro.[68] Falke et al showed that human corporal smooth muscle cells and endothelial cells embedded in a mesh acellular collagen matrix are able to form well vascularized corporal tissue in vivo.[69] Pilatz et al have described cell isolation protocols and characterized their culture compositions, excluding mainly fibroblasts, in order to develop pure smooth muscle cells, endothelial cells, and fibroblastic cells that are derived from the penis.[70] Regenerative therapy remains mostly at the basic science level and still needs further research and development.

Avanafil

As mentioned earlier, there is a need for different medications for ED because the current PDE5 inhibitors do not work for every patient. Therefore, newer PDE5 inhibitors have been developed. One of these new drugs, avanafil, is currently undergoing Phase III clinical trials. Avanafil, an oral medication for the treatment of ED, has been designed to be a fast-acting and highly selective PDE5 inhibitor.

Avanafil (4-[(3-chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide;(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-pyrimidinylmethyl)carbamoyl]pyrimidine) is a pyrimidine derivative that exists as a single enantiomer with S stereochemistry and has a molecular weight of 483.95 Da. In its pure form it looks as a white crystalline powder that is minimally

soluble in water and moderately soluble in organic solvent. It is more soluble in acidic buffer and less soluble in neutral and alkaline buffers.[71]

The enzymatic inhibition of different PDE isoenzymes for avanafil was examined and compared with that of sildenafil. Both avanafil and sildenafil inhibit PDE5 isolated from canine lung in a dose-dependent manner; however, the inhibition of PDE6 and PDE1 was less than PDE5 in avanafil compared to with sildenafil.[71] Using electroretinogram (ERG) as a method to determine the degree of inhibition of PDE6 in the retina in anesthetized dogs, sildenafil caused a dose-dependent time delay to peak of ERG positive wave, indicating decreased activation of retinal cone cells secondary to increased inhibition of PDE6; whereas avanafil showed that it is unlikely to affect retinal function at pharmacologically appropriate doses. The results were replicated in the awake male and female dogs, further confirming the low likelihood of avanafil affecting retinal function.[71]

In anesthetized dogs, both sildenafil and avanafil potentiated nitroglycerine (NTG)-induced hypotension, but to a lesser degree in avanafil than in sildenafil. Both drugs also potentiated sodium nitroprusside (SNP)-induced inhibition of platelet aggregation but to a lesser extent in avanafil than in sildenafil. In-vitro analysis of human platelet-rich plasma from healthy male volunteers demonstrated that avanafil potentiated the SNP-induced inhibition of platelet aggregation at a concentration of 10 μM; however, sildenafil had the same effect at concentrations of only 0.1 nM and 1 μM.[71]

Studies in rats showed that there is no change in behavior or physical activity at oral doses of 30 mg/kg and 180 mg/kg of avanafil when observed for 24 hours. When they were given up to 1000 mg/kg there was no change in bodyweight. Two hours after 1000 mg/kg administration, one of six rats demonstrated reduction in spontaneous physical activity, which resolved at 4 hours after administration. Extensive CNS studies in rats did not show a change in sleeping time, spontaneous locomotor activity, acetic acid-induced writhing, or rectal temperature at oral doses of 100 or 300 mg/kg.[71]

Further tests on conscious dogs showed no change in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) at avanafil doses up to 10 mg/kg, but at 30 mg/kg two of four dogs demonstrated a drop of SBP, DBP, and MBP at 1 and 3 hours post-administration, which was accompanied by an 80% increase in HR. There was no change in respiratory rate or ECG parameters. Both avanafil and sildenafil caused vasodilatory action in rat aorta, but less pronounced with avanafil at 10 μM. In the gastrointestinal tract, avanafil

showed a mild inhibition of spontaneous jejunal movement in rabbits and agonist-induced contraction of guinea pig ileum. No effect was seen on gastric emptying or small intestinal transit time in mice, and no effect on gastric juice secretions in rats. In addition, no effect was seen for avanafil on urine output, urinary electrolyte excretion, hematocrit, prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, or euglobulin clot lysis time in male rats.[71]

Two studies have looked into the pharmacokinetics of avanafil, with one studying the effect of 200 mg once daily and the other studying the dosing at 12 hour intervals for 7 days, and they demonstrated rapid absorption rate with T_{max} of 0.555–0.686 hours, and a $t_{1/2}$ of 1.07–1.23 hours, without significant accumulation of the drug, whether in once- or twice-daily dosing. The pharmacokinetics parameters were similar after 14 days of daily administration and after single dose[72,73] (see Table 1). Avanafil is metabolized through the liver cytochrome P450 to 11 metabolites that are less active against PDE5 than the parent compound, with the main route of excretion through the bile for both the oral and the intravenous forms. Thirty-four percent is reabsorbed through the enterohepatic circulation, and it takes 96 hours to eliminate nearly all the drug and its metabolites, with the feces through the bile being the major route of elimination ($>$92%).[71] A double-blind, randomized, placebo-controlled, parallel-group, dose-escalation study was conducted at the Asan Medical Center (Seoul, Korea). Subjects were randomly allocated to receive 50, 100, or 200 mg tablets of avanafil or placebo once daily for 7 days. Avanafil was generally well tolerated and had linear pharmacokinetic properties at daily doses of 50–200 mg over 7 days in these healthy Korean male volunteers.[74]

In a Phase II double-blind, randomized, crossover, at-home trial, avanafil was found to have comparable efficacy to sildenafil, as 80% of the subjects on each product developed erections sufficient for vaginal penetration.[75] In another Phase II double-blind, crossover clinical trial, avanafil interaction with NTG was studied and compared with sildenafil. Avanafil when taken with NTG caused smaller changes in SBP and HR, a shorter duration of interaction, and fewer subjects with clinically significant hypotension than seen with sildenafil. This suggests that avanafil may be the preferred PDE5 inhibitor of choice in patients that may potentially need to take NTG.[76] In a multicenter, double-blind, randomized, parallel-design Phase II study, avanafil was found to produce dose-related significant erections sufficient for completion of sexual activity, with a good safety profile in patients with mild to moderate ED. These effects were seen

when avanafil was taken 30 minutes before sexual intercourse regardless of food intake.[77]

In a randomized, double-blind, placebo-controlled, Phase III efficacy and safety study that evaluated three doses of avanafil (50, 100, and 200 mg) in 646 men with a history of ED, the participants had dose-dependent increases of 45%–64%, 46%–74%, and 48%–77% success rates for vaginal penetration ($P < 0.001$ versus placebo). The rate of successful completion of sexual intercourse increased to 41% from 13% in the 50 mg avanafil group and to 57% from 14% and 12% in the 100 and 200 mg groups, respectively ($P < 0.001$ versus placebo). Of males who tried to have intercourse within 15 minutes of dosing, 66%–72% had successful intercourse compared with 29% in the placebo group ($P < 0.001$).[78]

The data from a 16-week, randomized, double-blind, placebo-controlled Phase III study evaluating two doses of avanafil (100 and 200 mg) in 390 men with both diabetes and ED, showed that men with both diabetes and ED had similar positive results as men with only ED while taking avanafil, and that more than 60% of subjects on the 200 mg dose of avanafil had erections sufficient for vaginal penetration. The erections sufficient for penetration increased from 32% to 54% with the 100 mg dose, and from 42% to 63% with the 200 mg dose, versus an increase of just 36% to 42% in the placebo group ($P < 0.001$). Rates of successful intercourse are increased from 8% to 34% and from 8% to 40% in the 100 and 200 mg groups, respectively, while the placebo group showed an increase of only 10%–20% ($P < 0.001$).[79] There are two other Phase III clinical trials ongoing right now with results still to be published.

The most commonly observed side effects for avanafil in Phase I and II clinical trials were headaches, flushing, nausea, back pain, fatigue, and muscle cramps, with postural hypotension and vasovagal responses at higher doses. In Phase III trial, the most commonly reported side effects are headache, flushing, nasal congestion, nasopharyngitis, sinusitis, and dyspepsia. There were no reports of blue vision, hearing loss, or priapism.[78,79]

Conclusion

The current three available PDE5 inhibitors (sildenafil, vardenafil, and tadalafil) are considered a first-line treatment for ED and a great advancement in its management. They are preferred by both physicians and patients due to their rapid onset of action, safety profile, and ease of administration. However, there are subsets of patients that do not respond to these PDE5 inhibitors or in whom they are contraindicated.

Therefore, there is an ongoing need to develop better and safer alternatives.

Avanafil has gone through the three phases of clinical trials, and is still undergoing further Phase III trials. It demonstrates a favorable and unique pharmacokinetic profile with rapid onset of action and short $t_{1/2}$ without accumulation of the drug. It has proven to be a safe and effective medication in the treatment of ED. Further research is still lacking to compare avanafil head to head with other PDE5 inhibitors, and to determine the patient groups in which the drug would be most effective, and the patient preference.

As mentioned earlier, there are many future research topics under different stages of development. They range from new forms of PDE5 inhibitors other than avanafil such as (SLX 2101 and mirodenafil), to other forms of pharmacotherapy such as apomorphine and bremelanotide. Topical therapy with alprostadil is also under investigation, while gene therapy and tissue engineering represent an interesting new frontier in ED management.

Disclosure

The authors report no conflicts of interest in this work.

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