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Therapy of ED

PDE-5 Inhibitors

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The development of phosphodiesterase inhibitors, which are selective for the type 5 isoenzyme, has revolutionized the initial evaluation and treatment of men with erectile dysfunction. These agents can be taken orally and are effective in 60–70% of patients with erectile dysfunction, and they have low incidences of side effects when taken as recommended. The major contraindications are concomitant use with nitrates or the alpha-blockers terazosin and doxazosin. The major difference in the three approved inhibitors is that tadalafil has a considerably longer serum half-life, which provides a longer window of opportunity and potentially side effects.

Key Words: Erectile dysfunction; type 5 phosphodiesterase inhibitors; PDE-5 inhibitors; sildenafil; vardenafil; tadalafil.

Pharmacology of Erection

Erectile function results from a complex interaction of hemodynamic, neurologic, and hormonal factors. In fact, erection may be considered a neurovascular reflex (Fig. 1). The primary hemodynamic events of penile tumescence/detumescence are regulated by cavernosal smooth muscle relaxation/contraction, respectively. Tumescence (erection) is mediated by (1) the parasympathetic nervous system's release of acetylcholine, and (2) the nonadrenergic, noncholinergic cavernous nerve release of nitric oxide (NO) with subsequent activation of cyclic guanosine monophospate (cGMP). This NO/cGMP mechanism appears to play a major role in modulating erectile function. So much so, that organic or psychogenic factors causing pathway alterations can impair the relaxation of smooth muscle or even increase its contraction, thereby causing ED *(1)*.

A pivotal event in tumescence is the active clearance of calcium from the cavernosal smooth muscle cells. These smooth muscle cells are in a tonic state of contraction that, upon relaxation (reduction of intracellular calcium), allows for dilation of sinusoids and helicine arteries, and eventually, compression of emissary veins. Smooth muscle contraction is the result of an alpha-adrenergic neural activation. It relies on the interaction between thin and thick muscle filaments. This interaction (which results in force generation) can occur only after the phosphorylation of a 20 kDa light-chain of myosin by a Ca^{2+}/calmodulin-dependent myosin light chain kinase *(2)*. In the absence of calcium thin and thick muscle filaments are held apart, allowing for relaxation. In the normal corpora smooth muscle, relaxation results in tumescence *(2)*.

Energy is required to remove intracellular calcium and promote tumescence. The corporal smooth muscle cells have two different energy generators used to pump calcium to the extracellular space via calcium channels, or, to sequester calcium in the cell's endoplasmic reticulum. These two energy sources are cAMP and cGMP. By inhibiting degradation, these two energy sources can be potentiated. This is accomplished by blocking phosphodiesterases which act to convert active cAMP/cGMP into inactive 5'AMP/5'GMP, respectively. Sildenafil, tadalafil, and vardenafil block phosphodiesterase type 5 (PDE-5), which specifically inhibits cGMP breakdown (Fig. 2).

PDE-5 inhibitors potentiate cGMP activity only after cGMP is produced. Sexual stimulation is necessary to enable PDE-5 inhibitors to be effective. Sexual stimulation triggers the nonadrenergic–noncholingeric release of NO, which increases cGMP levels. PDE-5 inhibitors potentiate this rise in cGMP.

Sildenafil's success caused an explosive growth in the development of agents affecting penile erection. Not only are new agents being developed that act at different locations (either centrally or peripherally), but also, additional PDE-5 inhibitors have been developed in attempts to improve efficacy, safety, and pharmacologic profile. The pharmacokinetic properties of the different PDE-5 inhibitors are shown in Table 1 *(3)*.

Sildenafil

Sildenafil (Viagra®, Pfizer) is an orally active, potent, and selective inhibitor of cGMP PDE-5 *(4)*. Although five PDE isoenzymes have been identified in penile tissues (PDE

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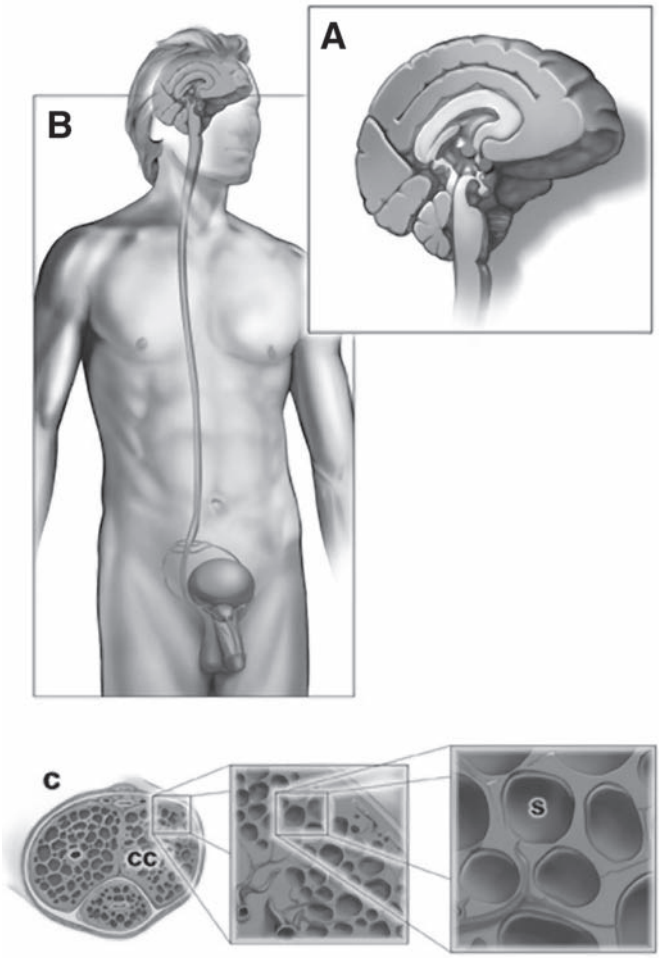

Fig. 1. Penile erection. (**A**) CNS. Cortical processes (visual, osmic, auditory, and memory) affect hypothalamic centers that activate parasympathomimetic pathways leading to penile tumescence. (**B**) Spinal cord. The spinal cord transmits CNS-mediated stimuli, and it also receives sensory input from the penis that can elicit spinal cord reflexes that cause tumescence and augment CNS stimulated erections. (**C**) Corpora cavernosa. Vascular smooth muscle in the corpora cavernosa and in the arterioles supplying the corpora relaxes in response to neural stimulation and to nitric oxide (NO). This leads to increased arterial inflow, engorgement of the lacunae in the cavernosa with blood, and compression of the veins that drain the corpora, which in conjunction with the inelastic tunica albuginea that surrounds the cavernosa, causes penile rigidity.

2, 3, 4, 5, and 11), the predominant isoform is PDE-5. Currently, 11 PDEs have been identified. After oral administration, sildenafil is absorbed rapidly with a bioavailability of 40%. The time to peak plasma concentration (t_{max}) while fasting is 30–120 min with a median time of 60 min. After a high-fat meal, the time to peak plasma concentration is prolonged (by an additional 60 min), and the peak plasma concentration is reduced by 29%. The terminal half-life of sildenafil is 3–5 h *(4,5)*. Clinically, responses to the medication may be observed for upwards of two to three half-lives (8–12 h).

Metabolism and Dosing

Sildenafil is metabolized by hepatic microsomal cytochrome P450 isoenzymes 3A4 (major route) and 2C9 (minor route) *(4,5)*. Potent P450 3A4 inhibitors, such as cimetidine, erythromycin, and ketaconazole, can retard metabolism. Sildenafil levels can be increased two- to eightfold in patients taking one or more of these drugs. Interestingly, even with higher serum drug concentrations, side effect profiles were no different than that of the general study population. Patients taking ritonavir, a protease inhibitor sharing two metabolic pathways with sildenafil, should not be given sildenafil at doses greater than 25 mg or at a frequency of greater than 48 h. Since an active metabolite of sildenafil is excreted in the feces (80%) and urine (13%) *(5)*, downward dose adjustments (starting with 25 mg) are recommended for patients who are over 65 yr of age, have hepatic impairment, or have severe renal insufficiency. The recommended dose of sildenafil ranges from 25 to 100 mg. Because of increased plasma concentrations and efficacy (and possible side effects), a 25 mg starting dose is recommended for patients over 65 yr of age, those with liver failure or severe renal insufficiency, and individuals who are concomitantly taking drugs that inhibit cytochrome P450 isoenzyme 3A4 (see above). In the American flexible-dose study, 75% of patients ultimately chose the 100 mg dose, 23% the 50 mg dose, and 2% the 25 mg dose *(6)*.

Efficacy

The New Drug Application to the FDA for sildenafil was based on 4526 patients: 576 in phase I studies, 3,003 in phase II–III studies, and 769 in long-term extension studies (with 550+ patients treated longer than 1 yr). The mean patient age was 55 yr, and the range was 18–87. Fifty-two percent of patients were diagnosed with an organic etiology, 18% with psychogenic, and the remaining 25.7% with mixed etiology. Co-morbid conditions were common: 24% had hypertension, 16% had diabetes mellitus, 14% had cardiovascular disease, 14% had hyperlipidemia, 6% were individuals with spinal cord injury, 5% had depression, and 4% had a radical prostatectomy *(6–10)*.

Sildenafil clinical trials employed four different efficacy measures (some of which have been subsequently modified for efficient clinical use). These include: (a) The International Index of Erectile Function (IIEF): a 15-item questionnaire addressing relevant domains of sexual function. These questions address: erectile function, orgasm, desire, satisfaction with intercourse, and overall sexual satisfaction. This questionnaire has been validated in 20 different languages and is both sensitive and specific for detecting treatment-related changes. (b) A global assessment question (GAQ). This requires a simple "yes" or "no" response to: "Did the treatment improve your erections?" *(6–10)*. (c) A diary of erectile activity whereby the patient recorded information on the date and dose taken, the presence of sexual stimulation, and whether successful sexual intercourse took

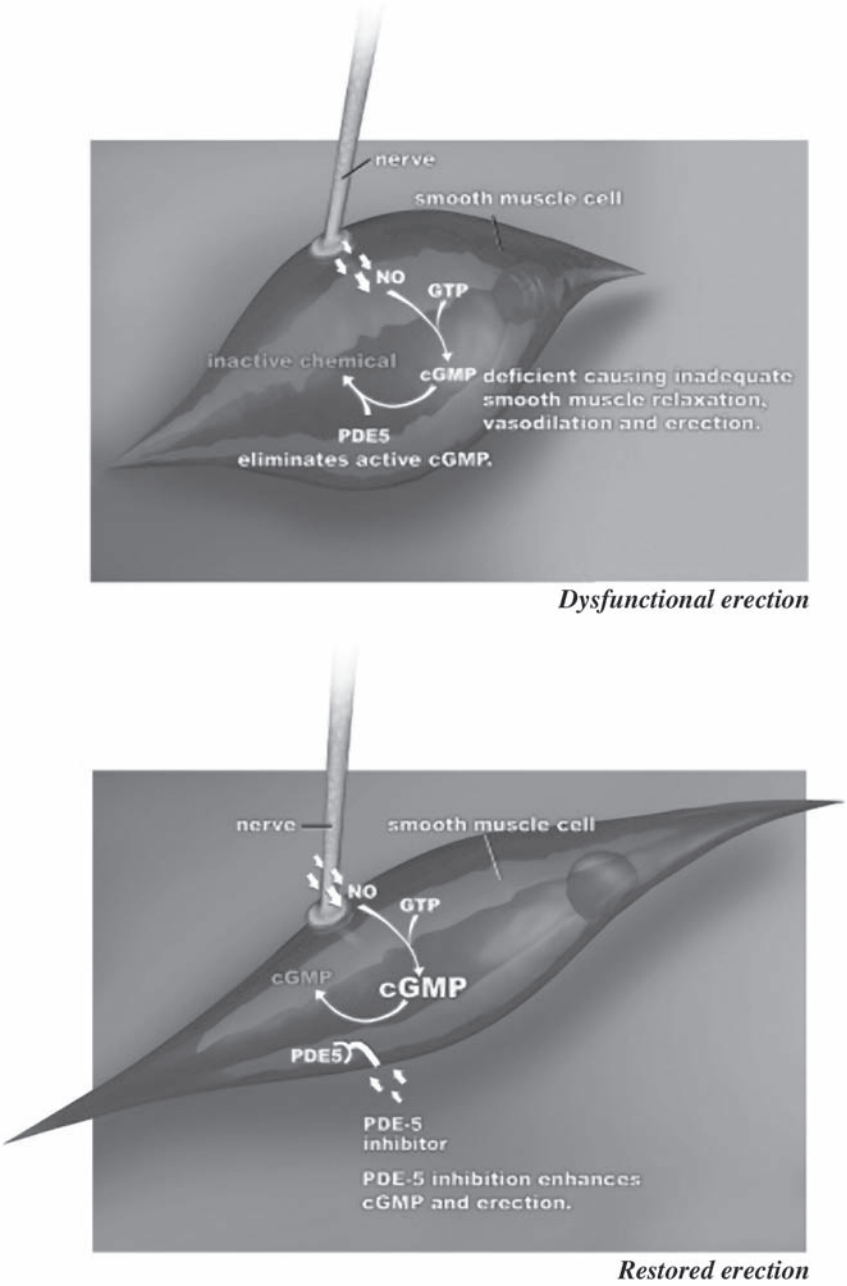

Fig. 2. Mechanism for phosphodiesterase type 5 (PDE-5) inhibition improving penile erections. The cavernosal nerve releases nitric oxide (NO), which stimulates production of cGMP, and cGMP causes smooth muscle relaxation. If stimulation fails to adequately increase cGMP, smooth muscle relaxation may not be adequate for normal erections. Inhibiting PDE-5, the enzyme responsible for degrading cGMP, can increase cGMP levels and improve erections in many men with erectile dysfunction.

place. The 24-wk, fixed-dose, American trial included a four-point scale to measure penile rigidity. Grade three was "an erection hard enough for penetration but not completely hard," and grade four was a "fully rigid erection." (d) The last survey, which was optional, assessed the partner's perception of the patient's ability to achieve, and then maintain, an erection.

IIEF results were compiled from over 3000 patients from 21 American and European, randomized, double-blinded, placebo-controlled, phase III trials lasting up to 6 mo. To address the NIH definition of ED *(9)*, primary endpoints for measuring efficacy were based on the results of only two questions on the IIEF questionnaire: question 3—the ability to achieve an erection, and question 4—the ability to maintain an erection *(11)*. In all 21 studies, sildenafil produced a significantly improved erection when compared to placebo (Fig. 3). Significant improvements were reported for both question 3 (attain erection) and 4 (maintain erec-

Table 1
Pharmacokinetic Parameters of Selective PDE-5 Inhibitors[a]

Parameter	Sildenafil	Tadalafil	Vardenafil
In vitro IC_{50} (n*M*)	3.5	6.7	0.1
C_{max} (ng/mL)	560	378	209
T_{max} (h)	0.8	2.0	0.7
$t_{1/2}$ (h)	3.7	17.5	3.9
AUC (ng × h/mL)	1685	8066	74.5
Metabolism	Hepatic	Hepatic	Hepatic
Protein binding (%)	96	—	94
Bioavailability (%)	40	—	—

[a]In vitro IC_{50}: concentration of the drug that inhibits a given response (PDE-5) by 50%; C_{max}: maximum total plasma concentration; T_{max}: time to C_{max}; $t_{1/2}$: half-life; AUC: area under the plasma concentration-time curve.

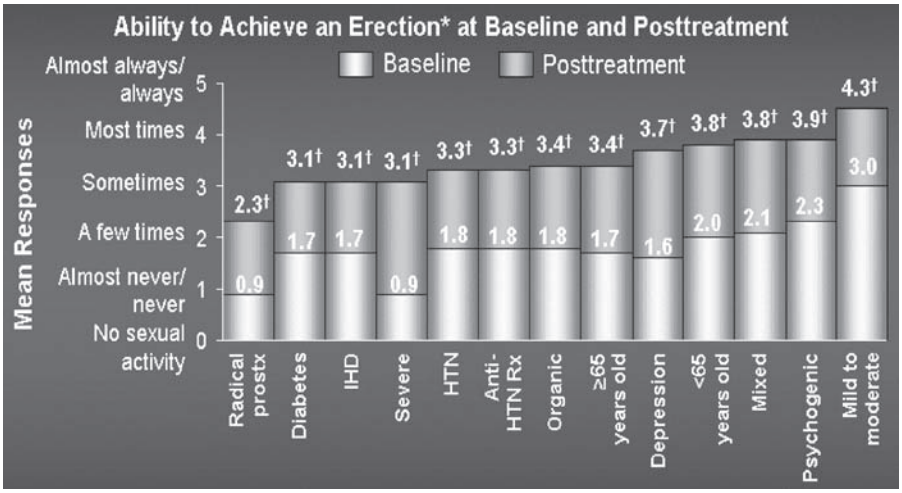

Fig. 3. Sildenafil citrate is effective across a wide spectrum of patients regardless of age, etiology, or concomitant conditions. *International Index of Erectile Function, Question 3; $^{+}p < 0.0001$. Note: patients in one group may be included in other groups. Data on file, Pfizer, Inc., New York, NY. Based on a retrospective analysis of the intent-to-treat population from 11 double-blind, placebo-controlled, flexible-dose, clinical trials at wk 12.

tion), where increases of 100% and 130% were recorded, respectively *(6–10)*. In flexible-dose studies, 69% (94/134) of patients taking sildenafil reported erections sufficient for vaginal penetration on "most to all" occasions, compared with 23% (32/138) taking placebo. In addition, 62% (85/132) of sildenafil users were able to maintain their erections after penetration on "most to all" occasions, in comparison with 15% (21/138) of the placebo group. Overall, 59% (81/137) of patients treated with sildenafil reported that they were able to achieve and maintain their erections on most to all occasions compared to 15% (21/138) of placebo-treated patients *(12)*. Similar results were observed in a single center study *(13)*.

On subset analysis, these results were consistent regardless of age, race, baseline severity, or etiology of dysfunction. Furthermore, sildenafil was found to be effective for those patients with each of the following ED risk factors: coronary artery disease, hypertension, peripheral vascular disease, diabetes mellitus, coronary artery bypass grafting, radical prostatectomy, transurethral resection of the prostate, and spinal cord injury (Fig. 3). This held true even for patients currently being medicated for those conditions. In addition, effective treatment was also seen in depressed patients, as well as those taking antidepressants and antipsychotic medication *(5)*.

Overall erectile improvement with sildenafil, as evaluated by the GAQ, was 74% (101/136) compared to 16% (23/118) in the placebo group ($p < 0.0001$) *(2,14)*. Once again, improved erections were seen in all patient groups regardless of etiology. The greatest success (80% of patients) was reported in the psychogenic group. Improvement was noted in nearly 70% of men with organic and 75% of mixed ED *(2,5,7,14)*. Dose escalation increased the number of patients with improved erections. Compared to 24% of patients tak-

ing placebo, 63%, 74%, and 82% of patients taking 25, 50, and 100 mg of sildenafil respectively, reported improvement in erections (n = 1797) *(5)*.

An analysis of patient diaries, which used a 4-point grading scale for penile rigidity, also demonstrated a dose response. Seventy-five percent of patients receiving 25 mg, 80% receiving 50 mg, and 85% of patients receiving 100 mg of sildenafil reported a grade 3 or 4 erection in comparison to 50% of patients receiving placebo *(8)*. In these two groups of treated patients, 80% of those responding at a grade 3 and 94% of those reaching grade 4, also reported successful sexual intercourse. Long-term open-label follow-up studies of 1, 2, 3, and 4 yr, demonstrate that more than 95% of patients continued to have improved erections, and also improved ability to engage in sexual activity *(2,14)*.

Nonresponders

Studies have shown that careful patient re-education with supplemental written information and possible video instruction can turn many nonresponding patients into "responders." Many of the individuals reporting initial failure had tried the drug only one time, had only used 25 or 50 mg doses, and had lacked concomitant sexual stimulation *(12,15)*. It is important for patient education to include: (1) reminders that absorption is best on an empty stomach (at least a low-fat diet), (2) tobacco cessation will improve responses, and (3) they should avoid the sedative effects of alcohol. In a prospective study of 622 patients referred to an urologist, 38% (98/622) reverted to "responders" after higher doses (100 mg) and re-education *(12)*. A separate study reported a 54% (41/76) salvage rate. Patients with hypogonadism and ED, who have a poor response to sildenafil, may benefit from testosterone replacement improving their response to sildenafil *(16)*.

Adverse Effects

The most common adverse events in sildenafil clinical trials have included vasodilator effects such as headaches, flushing, and nasal congestion from hyperemic nasal mucosa. In addition, dyspepsia has been observed. A dog model has demonstrated that PDE-5 may have a role in maintaining gastroesophageal sphincter integrity. Blocking PDE-5 can allow for reflux, and result in dyspepsia. A recent review by Morales of more than 3700 patients in 18 of 21 clinical trials, examined adverse experiences from sildenafil in a total exposure of 1631 man-years *(17)*. Adverse events experienced by the 2199 patients in 10 separate long-term studies were headache (10%), flushing (9%), dyspepsia (6%), and respiratory tract infection (6%). Abnormal vision was reported by 2% of the patients. A total of 574 adverse events occurred in 734 sildenafil-treated patients. Most events were transient in nature and described as mild (62%) or moderate (31%) *(17)*. Overall, discontinuation rates due to adverse events were comparable in the sildenafil (2.5%) and placebo (2.3%) treatment groups. Headaches (1.1%), flushing (0.4%), and nausea (0.4%) were the most common causes leading to discontinuation. The nausea side effect presumably arises from dyspepsia. Lastly, only 1 of the 2722 patients treated with (up to) 100 mg of sildenafil discontinued treatment because of abnormal vision *(18)*.

An expected event resulting from PDE-5 inhibition is the potentiation of the hypotensive (vasodilator) effects of nitrates, because small amounts of PDE-5 are also found in the smooth muscle cells of the systemic circulation. Sildenafil is contraindicated in patients taking organic nitrates or other NO donors. This includes patients taking nitrates on an intermittent basis, or even recreationally (amyl nitrate, "poppers") *(19)*. All routes for nitrate administration are included: sublingual, transnasal, transdermal, and orally.

An update on product labeling by the US Food and Drug Administration (FDA) has cautioned against the use of sildenafil in patient populations that have generally been excluded in clinical trials. This includes patients who have sustained a myocardial infarction, stroke, or life-threatening arrhythmia within the past 6 mo; patients with resting hypotension (<90/50 mm Hg) or hypertension (>170/110 mm Hg); patients with cardiac failure or coronary artery disease causing unstable angina; and patients with retinitis pigmentosa *(2,5)*. In addition, caution is recommended in administering sildenafil to men receiving alpha-blockers such as doxazosin. Such a co-administration might cause transient symptomatic hypotension. Therefore, a minimum interval of 4 h is recommended between sildenafil and alpha-blockers *(2)*. Cardiovascular events, such as myocardial ischemia/infarction, are related more to the physical exertion of sexual activity rather than a direct effect of sildenafil.

Tadalafil

Tadalafil (Cialis™, Lilly ICOS, Indianapolis, IN) is a new PDE-5 inhibitor, which has proven in in vitro trials to have a very high selectivity for PDE-5 enzyme *(2)*. Compared to sildenafil, tadalafil has a longer half-life of 17.5 h *(20)*. The various trials demonstrated the effectiveness of tadalafil in ED patients with a broad spectrum of diseases, including diabetes.

Efficacy

An integrated analysis of the efficacy of tadalafil was conducted for five randomized, double blind, placebo-controlled phase 3 trials enrolling 1112 men *(26)*. The mean age was 59 yr (range 22 to 82). Men with mild to severe ED of various etiologies were randomized to placebo or tadalafil, taken as desired without food or alcohol restrictions, at fixed daily doses of 2.5, 5, 10, or 20 mg. The three co-primary outcome measures were changes from baseline in the erectile function domain of the IIEF and the proportion of "yes" responses to questions 2 and 3 of a diary and the Sexual Encounter Profile (SEP). Additional efficacy measures included a Global Assessment Question (GAQ).

Compared with placebo, tadalafil significantly enhanced all efficacy outcomes. Patients receiving tadalafil 20 mg had a significant mean improvement of 7.9 in IIEF erectile function domain score from baseline (p <0.001 vs placebo), 75% of intercourse attempts (SEP question 3, a secondary efficacy outcome) were successfully completed (p <0.001 vs placebo) and 81% reported improved erections at end point compared with 35% in the control group (p <0.001). Tadalafil was consistently efficacious in all disease severities and etiologies, as well as in all ages.

The therapeutic effects of tadalafil were investigated 24 and 36 h after dosing in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 348 men (mean age 57 yr) with ED *(25)*. Patients were stratified by baseline severity of ED using the Erectile Function domain score of the IIEF and then randomly allocated within the severity group to receive tadalafil 20 mg (n = 175) or placebo (n = 173). Subsequently, participants were randomly assigned to two 4-wk treatment intervals, during which they were requested to attempt sexual intercourse approx 24 or 36 h after tadalafil or placebo dosing. The primary outcome measure was the proportion of successful sexual intercourse attempts (completed to ejaculation) according to patient self-report using the SEP diary. Of the 348 patients, 327 (94%) completed the trial (163 of 175 in the tadalafil group and 164 of 173 in the placebo group). Thirty-six hours after tadalafil dosing, 59.2% of intercourse attempts were successful vs 28.3% in the placebo group (p < 0.001). The proportion of successful intercourse attempts at approx 24 h after treatment was also significantly greater with tadalafil (52.9%) than with placebo (29.1%; p < 0.001).

Adverse Effects

Major differences compared to sildenafil are a higher PDE-5 selectivity, especially in terms of PDE-6, resulting in minimizing the visual side effects, and the longer half-life, leading to a longer window of opportunity and potential side-effects *(22–26)*. The trials showed a favorable adverse effect profile *(22–26)*. Tadalafil was well tolerated with most adverse events reported as only mild to moderate in intensity. The incidences of four treatment-emergent adverse events were significantly greater in the tadalafil group than in the placebo group (all p < 0.05): headache, flushing, dyspepsia, and myalgia. As with other PDE-5 inhibitors, tadalafil is contraindicated in men taking nitrates *(27)*.

Vardenafil

Vardenafil (Levitra®, Bayer Corp., West Haven, CT) is another new PDE-5 inhibitor that has high potency in vitro [50% inhibitory concentration (IC_{50}), 0.1 n*M*] and selectivity for PDE-5 compared with other isoenzymes *(28–30)*.

Efficacy

Pharmacokinetic data in humans were obtained in two randomized, double-blind, placebo-controlled threefold crossover studies with a single oral dose of 10, 20, or 40 mg of vardenafil in men with mild to moderate ED *(31,32)*. RigiScan data showed a significant difference in rigidity at the base of the penis between placebo and vardenafil at all doses, but there was no significant difference between 20 and 40 mg of vardenafil. The duration of rigidity greater than 60% at the base and the tip of the penis increased from 25 min to more than 60 min with 40 mg of vardenafil.

At-home, oral administration of vardenafil was carried out in Europe, the US, and South Africa in randomized, double-blind, placebo-controlled studies of 601 men with ED. Efficacy was assessed using the IIEF, the Fugl–Meyer Quality of Life Questionnaire, as well as a GAQ. Compared to placebo, vardenafil showed significant improvement in the questionnaires as well as in the GAQ *(34)*.

The durability of key efficacy response parameters of vardenafil was evaluated in a pivotal trial conducted in a broad population of men with erectile dysfunction (ED) in North America. In this randomized, double-blind, placebo-controlled, multicenter, fixed-dose, parallel-group, 6-mo comparison study, men >18 yr of age with ED for >6 mo received 5 mg, 10 mg, and 20 mg doses of vardenafil as needed for up to 26 wk *(33–35)*. The primary efficacy variables were the IIEF, EF domain scores, the SEP mean per-patient success rates for penetration (SEP question 2), and maintenance of erections (SEP question 3). All three doses of vardenafil were superior to placebo across all primary efficacy variables and all study time points, regardless of etiology or severity. Improvement in all primary efficacy variables was observed in all vardenafil groups versus placebo. These improvements occurred early and were either sustained or increased through wk 26. Vardenafil in 10 and 20 mg doses was significantly superior to placebo at all time points for all efficacy variables (p < 0.01), and all doses were superior to placebo at endpoint (p < 0.001). Vardenafil also was found to have significant efficacy in men with ED and diabetes *(35)*.

Adverse Effects

Vardenafil was well tolerated, with headache (8–18%), vasodilation (6–13%), rhinitis (1–8%), and dyspepsia (2–6%) listed as the most common adverse events *(34)*. Most treatment-emergent adverse events were mild or moderate in intensity, and incidence generally decreased over time *(34)*. Similar to other PDE-5 inhibitors, vardenafil is contra indicated in men taking nitrates.

Summary

PDE-5 inhibitors have revolutionized the treatment of erectile dysfunction. Not only are they highly effective oral agents with significant efficacy in approximately 70% of men with a wide range of ED risk factors, they are also well tolerated. Concomitant use of nitrates is a contra-indication for the PDE-5 inhibitors. With newer, more selective

PDE-5 inhibitors, ED treatment options will continue to grow, have longer efficacy, and fewer adverse events.

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