Phosphodiesterase-5 (PDE_5) Inhibitors In the Management of Erectile Dysfunction

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INTRODUCTION

Erectile dysfunction (ED) is the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] According to data from the Massachusetts Male Aging Study, up to 52% of men between the ages of 40 and 70 are affected by ED.[2] Based on findings from the 2001–2002 National Health and Nutrition Examination Survey (NHANES), it is estimated that 18.4% of men in the U.S. who are 20 years of age and older have ED.

Although ED is not an inevitable consequence of aging, there is a positive correlation with age. The prevalence of 5.1% in 20- to 39-year-old men increases to 70.2% in men 70 years of age and older. Because the etiology of ED often involves a combination of vascular, neurological, endocrinological, and psychological factors, the condition is not limited to elderly men. Other risk factors such as cardiovascular disease, hypertension, diabetes, hypercholesterolemia, and smoking have been strongly associated with an increased prevalence of ED.[3]

Historically, a limited understanding of the physiological mechanism of erections restricted the treatment of ED to vacuum-constriction devices, prosthetic implants, intracavernosal injections, and intraurethral suppositories.[4] Since its advent, the class of agents known as type-5 phosphodiesterase (PDE_5) inhibitors has revolutionized the management of ED. PDE_5 inhibitors have become the first-line therapy for ED, as recommended by the American Urological Association (AUA) and the European Association of Urology (EAU).[4,5]

The four oral PDE_5 inhibitors commercially available in the U.S. are sildenafil (Viagra, Pfizer), vardenafil (Levitra and Staxyn, Bayer/GlaxoSmithKline), tadalafil (Cialis, Eli Lilly), and a more recently approved drug, avanafil (Stendra, Vivus). The expansion of this class has allowed for greater flexibility in prescribing based on individual response.

CLASSIFICATION AND HISTORY

Sildenafil, vardenafil, tadalafil, and avanafil are classified as PDE_5 inhibitors and are indicated for the treatment of men with ED. Sildenafil, the first PDE_5 inhibitor, was introduced in 1998. More than 20 million men were treated with sildenafil in its first 6 years on the market.[5] In 2003, vardenafil was approved, offering patients an alternative option. Tadalafil followed several months later and was also approved in 2003. Nicknamed the "weekend pill," tadalafil's 36-hour effectiveness offered patients more spontaneity.

In 2010, a 10-mg oral disintegrating tablet (ODT) formulation of vardenafil (Staxyn) was introduced; this ODT discreet formulation is considered more convenient to administer.

Several years after the introduction of tadalfil on the market, researchers toyed with the idea of a chronic, low-dose formulation to further enhance spontaneity. In 2008, Eli Lilly obtained FDA approval for the once-daily administration of tadalafil. In October 2011, tadalafil (Cialis) was also approved to treat benign prostatic hyperplasia (BPH) with or without ED. Avanafil (Stendra) was approved in April 2012, offering an onset of action as early as 15 minutes after administration and further expanding treatment options for men with ED.

Sildenafil and tadalafil are also used to treat pulmonary arterial hypertension (PAH) under the trade names Revatio (sildenafil 20-mg tablets and 10-mg/12.5-mL single-use vial injections) and Adcirca (tadalafil 20-mg tablets).

Although alternative roles exist for these agents, PDE_5 inhibitors for the treatment of ED are the focus of this review.

PHARMACOLOGY

During sexual arousal, nitric oxide (NO) is released from nerve terminals and endothelial cells in the corpus cavernosum. NO activates guanylate cyclase to convert guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), triggering a cGMP-dependent cascade of events. The accumulation of cGMP leads to smooth-muscle relaxation in the corpus cavernosum and increased blood flow to the penis.

PDE_5 is an enzyme found primarily in the smooth muscle of the corpus cavernosum that selectively cleaves and degrades cGMP to 5′-GMP. PDE_5 inhibitors are similar in structure to cGMP; they competitively bind to PDE_5 and inhibit cGMP hydrolysis, thus enhancing the effects of NO. This increase in cGMP in the smooth muscle cells is responsible for prolonging an erection.

PDE_5 inhibitors lack a direct effect on corpus cavernosum smooth-muscle relaxation. Therefore, after administration, adequate sexual stimulation is necessary for an erection to occur.[6,7]

Pharmacokinetics

PDE_5 inhibitors have been studied to determine their pharmacokinetic characteristics in absorption, distribution, metabolism, and excretion. A summary of the pharmacokinetic activity of these agents is presented in Table 1.

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Absorption

As a class, although PDE_5 inhibitors can reach maximum observed plasma concentrations (C_{max}) in as little as 30 minutes, the median times to maximum concentration (T_{max}) are 60 minutes for sildenafil and vardenafil and 2 hours for tadalafil. For avanafil, a median T_{max} of 30 to 45 minutes is reported, possibly translating to a quicker onset of action; however, the actual clinical significance has not been determined.

The exact values for vardenafil ODT (Staxyn) have not been reported, but this drug provides a higher systemic exposure compared with the film-coated formulation (Levitra). For this reason, these two formulations are not equivalent milligram for milligram and therefore are not interchangeable. In addition, despite the perception that an ODT formulation would take effect more quickly, both the film-coated tablets and the ODT formulation have similar onsets of action.

A comparison of agents in the PDE_5 drug class is presented in Table 2.[8–12]

Except for tadalafil, the rate and extent of absorption of PDE_5 inhibitors are diminished when they are ingested with high-fat meals. Despite the similar rate and extent of change observed with vardenafil and avanafil, only sildenafil has been found to have clinical significance, according to its manufacturer. Absorption is affected significantly with a mean reduction in C_{max} of 29% and a mean delay in T_{max} of 60 minutes. Patients are advised to avoid taking sildenafil after a high-fat meal to avoid a possible diminished potency and delay in the onset of effect.[8]

Unique to vardenafil ODT is the effect of water on the drug's absorption. When vardenafil was taken with water, the T_{max} was shortened by 60 minutes and the area-under-the curve (AUC) concentration was decreased by 29%. To maintain appropriate onset and maximum potency, patients should not take vardenafil ODT with liquids.[12]

Distribution

High volumes of distribution (V_d) for sildenafil (105 L), vardenafil (208 L), and tadalafil (63 L) suggest extensive tissue binding; data are unavailable for avanafil. All PDE_5 inhibitors are highly protein-bound (94%–99%), contributing to the observed high volume of distribution.[8–12] Therefore, disease states that alter protein levels, such as malnutrition and liver disease (e.g., cirrhosis), can be expected to cause variations in the distribution of PDE_5 inhibitors.

Metabolism

Each PDE_5 inhibitor undergoes metabolism predominantly through the hepatic isoenzyme cytochrome P450 (CYP) 3A4 pathway. Minor pathways include CYP2C9 for sildenafil, CYP3A5 and CYP2C for vardenafil, and CYP2C for avanafil. Because the metabolism of these agents relies primarily on CYP3A4, moderate-to-strong inhibitors, such as erythromycin (Ery-Tab, E-Mycin, Abbott; Eryc, Warner Chilcott), ketocon-

Table 1 Phosphodiesterase-5 (PDE_5) Inhibitors: Pharmacokinetic Summary

	Sildenafil (Viagra)	Vardenafil (Levitra)	Vardenafil ODT (Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Bioavailability	41% (mean) 25%–63% (range)	15% (mean)	—	—	—
T_{max}	1 hour (median) 0.5–2 hours (range)	1 hour (median) 0.5–2 hours (range)	1.5 hours (median) 0.75–2.5 hours (range)	2 hours (median) 0.5–6 hours (range)	0.5–0.75 hours (range)
V_d	105 L	208 L	208 L	63 L	—
Protein binding	96%	95%	95%	94%	99%
Metabolism	Major: CYP3A4 Minor: CYP2C9	Major: CYP3A4 Minor: CYP3A5, CYP2C	Major: CYP3A4 Minor: CYP3A5, CYP2C	CYP3A4	Major: CYP3A4 Minor: CYP2C
Active metabolite (% effect)	Yes (20%) *N*-desmethylation	Yes (7%) Desmethylation	Yes (7%) Desmethylation	No	Yes (4%) Methylation, glucuronidation
Half-life	4 hours	4–5 hours	4–6 hours	17.5 hours	5 hours
Elimination	80% feces 13% urine	91%–95% feces 2%–6% urine	91%–95% feces 2%–6% urine	61% feces 36% urine	62% feces 21% urine
Ingestion with high-fat meals	↓ C_{max} 29% ↑ T_{max} by 1 hour Avoid	↓ C_{max} 18%–50% May use (per manufacturer)	↓ C_{max} 35% May use (per manufacturer)	Not affected	↓ C_{max} 24-39% ↑ T_{max} by 1.12–1.25 hours May use (per manufacturer)
Additional PDE inhibition	PDE_1, PDE_6	PDE_1, PDE_6	PDE_1, PDE_6	PDE_{11}	—

C_{max} = peak concentration; CYP = cytochrome P450; ODT = oral dissolving tablet; T_{max} = time to peak concentration.
Data from prescribing information for sildenafil;[8] vardenafil;[9] tadalafil;[10] avanafil;[11] and vardenafil ODT.[12]

PDE_5 Inhibitors for Erectile Dysfunction

Table 2 Phosphodiesterase-5 (PDE_5) Inhibitors: Product Comparison

	Sildenafil (Viagra)	Vardenafil (Levitra)	Vardenafil ODT (Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Manufacturer	Pfizer	Bayer/ GlaxoSmithKline	Bayer/ GlaxoSmithKline	Eli Lilly	Vivus
Year of approval	1998	2003	2010	2003	2012
Usual dosage	25–100 mg/day	5–20 mg/day	10 mg/day	5–20 mg/day (as needed); 2.5–5 mg/day once daily	50–200 mg/day
Administration time	1 hour before sexual activity	1 hour before sexual activity	1 hour before sexual activity	At least 0.5 hours before sexual activity	0.5 hours before sexual activity
Time frame of efficacy	0.5-4 hours post dose	—	—	Up to 36 hours post dose	As early as 0.25 hours post dose
Dosage adjustments	**Renal** CrCl < 30 mL/minute: starting dose 25 mg **Hepatic** Hepatic impairment: starting dose 25 mg **Drug Interactions** • Potent CYP3A4 inhibitors: starting dose 25 mg • Ritonavir: maximum 25 mg/48 hours **Other** >65 years old: starting dose 25 mg	**Renal** Do not use in patients receiving hemodialysis **Hepatic** • Moderate impairment: starting dose 5 mg; maximum 10 mg • Severe impairment: do not use **Drug Interactions** • Moderate CYP3A4 inhibitors: maximum 5 mg/ 24 hours • Potent CYP3A4 inhibitors: maximum 2.5 mg/24 hours • Ritonavir: maximum 2.5 mg / 72 hours **Other** ≥65 years of age: starting dose 5 mg	**Renal** Do not use in patients receiving hemodialysis **Hepatic** Moderate/severe impairment: do not use **Drug Interactions** Moderate/potent CYP3A4 inhibitors: do not use	***As-needed use:*** **Renal** • CrCl 30–50 mL/minute: starting dose 5 mg/day; maximum 10 mg/48 hours • CrCl < 30 mL/minute or if patient is receiving hemodialysis: maximum 5 mg/72 hours **Hepatic** • Mild/moderate impairment: maximum 10 mg/day • Severe impairment: do not use **Drug Interactions** Potent CYP3A4 inhibitors: maximum 10 mg/72 hours ***Once-daily use:*** **Renal** CrCl <30 mL/minute or if on hemodialysis: do not use **Hepatic** • Mild/moderate impairment: use with caution • Severe impairment: do not use **Drug Interactions** Potent CYP3A4 inhibitors: maximum 2.5 mg/day	**Renal** Do not use if CrCl < 30 mL/minute or in patients receiving hemodialysis **Hepatic** Severe impairment: do not use **Drug Interactions** • Moderate CYP3A4 inhibitors: maximum 50 mg/day • Potent CYP3A4 inhibitors: do not use
Common adverse reactions	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, back pain, myalgia	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis
Time required from last dose to administration of a nitrate (e.g., nitroglycerin)	24 hours	24 hours	24 hours	48 hours	12 hours
AWP unit cost	$22.49 (100 mg)	$21.46 (20 mg)	$13.98 (10 mg)	$24.48 (20 mg)	—

AWP = average wholesale price; CrCl = creatinine clearance; CYP = cytochrome P450.

azole (Nizoral, PriCara/ Janssen), itraconazole (Sporanox, Janssen), and ritonavir (Norvir, Abbott) and inducers, such as rifampin, phenytoin (Dilantin, Pfizer) of this isoenzyme can be expected to affect the blood concentrations of PDE_5 inhibitors.

Of the four agents available in the U.S., only tadalafil has metabolites that are not pharmacologically active. Sildenafil produces an active metabolite that retains approximately 50% of the potency of the parent drug, contributing to approximately 20% of its total pharmacological activity.[8] Vardenafil and avanafil produce active metabolites that contribute to the total pharmacological activity of each of these agents (7% and 4%, respectively).[9,11]

The precise clinical impact of these active metabolites, particularly in patients with impaired ability to metabolize or eliminate these agents, has not been determined.

Elimination

PDE_5 inhibitors are eliminated predominantly as metabolites in the feces and, to a lesser extent, in the urine. Sildenafil, vardenafil, and avanafil share similar mean terminal half-lives of 4 to 5 hours. In contrast, tadalafil has an extended half-life of approximately 17.5 hours, allowing its use as a once-daily agent.[8–12]

Renal Impairment

In patients with mild-to-moderate renal impairment or with a creatinine clearance (CrCl) above 30 to 80 mL/minute, the pharmacokinetic properties of sildenafil remain unaltered. However, in patients with severe renal impairment (CrCl, 30 mL/minutes or less), the AUC concentration and the C_{max} are doubled. As a precaution, it is recommended that sildenafil be initiated at 25 mg per dose in men with severe renal impairment.[8]

When vardenafil was studied in patients with moderate and severe renal impairment (CrCl, 50 mL/minute or less), the AUC concentration was increased by 20% to 30% compared with patients with a CrCl exceeding 80 mL/minute, resulting in no need for dosage adjustments. Because pharmacokinetic parameters for vardenafil have not been assessed in patients undergoing dialysis, this drug is not recommended in this population. These renal dosing recommendations also apply to vardenafil ODT.[9,12]

When avanafil was administered to patients with mild-to-moderate renal impairment (a CrCl of 30–90 mL/minute or more), the AUC concentration and the C_{max} increased slightly, resulting in no need for dosage adjustments. However, because avanafil has not been studied in patients with severe renal impairment or in patients on dialysis, it is not recommended for these patient populations.[11]

When tadalafil was given to patients with mild-to-moderate renal impairment (a CrCl of 30–80 mL/minute or more), the AUC concentration doubled, resulting in changes to the dosing recommendations. Therefore, in patients with moderate renal insufficiency (CrCl, 30–50 mL/minute) who used tadalafil as needed, a starting dose of 5 mg no more than once daily is recommended, with a maximum of no more than 10 mg in 48 hours.

Patients who have severe renal impairment (CrCl, below 30 mL/minute) or men who are receiving dialysis should not take more than 5 mg of tadalafil within 72 hours. The once-daily use of tadalafil is not recommended for men with severe renal insufficiency.[10]

Hepatic Impairment

Patients with mild-to-moderate hepatic impairment (Child–Pugh class A and B) who received sildenafil experienced increased AUC concentrations (85%) and C_{max} (47%). A starting dose of sildenafil 25 mg is recommended for these patients.[8]

In men with moderate hepatic impairment who received vardenafil, the AUC concentration and the C_{max} were increased by 160% and 130%, respectively. Therefore, the recommended starting dose of vardenafil in patients with moderate hepatic impairment is 5 mg with a maximum dose of 10 mg per dose.[9] Vardenafil ODT is not recommended for use in men with moderate hepatic impairment.[12]

When tadalafil is used as needed in patients with mild-to-moderate hepatic impairment, doses exceeding 10 mg are not recommended. Once-daily tadalafil has not been well studied in patients with mild-to-moderate hepatic impairment and should be used with caution.[10]

In patients with moderate hepatic impairment, avanafil's AUC concentration was increased by 11% and the C_{max} was decreased by 51%. No dosage adjustments are recommended for avanafil in patients with mild-to-moderate hepatic impairment.[11]

As a result of insufficient data, none of the four agents are recommended for men with severe hepatic impairment (Child–Pugh class C).

Pharmacodynamics

Mammalian phosphodiesterases (PDEs) comprise 11 gene families, which are distributed in different areas of the body. Each PDE family contributes to various physiological functions.[13] Because the smooth muscle of the corpus cavernosum expresses type-5 PDEs predominantly, the specificity and selectivity of PDE_5 inhibition play a crucial role in prolonging erections and in limiting adverse effects from nonspecific PDE inhibition.

All of the currently available PDE_5 inhibitors are highly selective for the type-5 gene family. Sildenafil and vardenafil, however, are less selective against PDE_6, which is expressed in the retina.[13,14] Patients have reported vision-related adverse effects consistent with PDE_6 inhibition, such as dose-related impairment in color discrimination (blue/green) or cyanopsia (objects appearing blue).[8–10] By contrast, although tadalafil is selective against PDE_6, it also expresses selectivity against PDE_{11}, which is concentrated in the prostate, testes, and skeletal muscles.[13,14] Inhibition of the type-11 PDE isoenzyme has been associated with pain and myalgia.[15]

DRUG–DRUG INTERACTIONS

CYP3A4 Isoenzymes

Because of their extensive CYP3A4 metabolism, PDE_5 inhibitors carry a risk of interacting with potent CYP3A4 inhibitors and inducers. The concomitant use of potent CYP3A4 inhibitors increases plasma concentrations of sildenafil. When sildenafil 100 mg was administered with erythromycin (e.g., Ery-Tab, E-Mycin, Eryc) and saquinavir (Invirase, Hoffman-LaRoche) (both are considered relatively potent CYP3A4 inhibitors), the AUC concentration was increased by 182% and 210%, respec-

tively. More notably, when sildenafil 100 mg was administered with ritonavir (Norvir), a highly potent CYP3A4 inhibitor, the AUC concentration was increased by 11-fold (1,000%). Therefore, a starting dose of 25 mg is recommended in patients initiating sildenafil therapy with the concomitant use of moderate-to-strong CYP3A4 inhibitors such as ketoconazole (Nizoral), itraconazole (Sporanox), erythromycin, and saquinavir. Doses of sildenafil should not exceed 25 mg in 48 hours when it is taken with ritonavir.[8]

The use of potent CYP3A4 inhibitors with vardenafil has also been studied. A dramatic 49-fold increase in the AUC concentration resulted when vardenafil 5 mg was taken with ritonavir 600 mg twice daily. Coadministration with erythromycin, ketoconazole, and indinavir (Crixivan, Merck) may also lead to an increase in the AUC concentration of vardenafil by four-fold to 16-fold. Consequently, a maximum dose of vardenafil 5 mg per 24 hours is recommended when it is used concomitantly with moderate CYP3A4 inhibitors (e.g., erythromycin, ketoconazole 200 mg, and itraconazole 200 mg).

With potent CYP3A4 inhibitors such as indinavir, saquinavir, atazanavir (Reyataz, Bristol-Myers Squibb), ketoconazole 400 mg, itraconazole 400 mg, and clarithromycin (Biaxin, Abbott), doses of vardenafil 2.5 mg per 24 hours should not be exceeded, except for ritonavir, the dose of which should not exceed 2.5 mg every 72 hours.[9]

The concomitant use of moderate or potent CYP3A4 inhibitors with vardenafil ODT is not recommended.[12]

When given with ketoconazole 400 mg daily, a single dose of tadalafil 20 mg increased the AUC concentration of tadalafil by 312%. When ritonavir 500 to 600 mg twice daily or 200 mg twice daily was taken with a single dose of tadalafil 20 mg, tadalafil's AUC concentration increased by 32% and 124%, respectively. Nonetheless, when tadalafil is prescribed as needed, a maximum dose of 10 mg in a 72-hour period should not be exceeded when used concomitantly with any potent CYP3A4 inhibitor. Similarly, for daily use of tadalafil, a maximum dose of 2.5 mg/day is recommended in patients taking potent CYP3A4 inhibitors.[10]

The use of both ketoconazole 400 mg daily and ritonavir 600 mg twice daily has been shown to increase avanafil's AUC concentration by 13-fold. As recommended by the manufacturer, the avanafil dose should not exceed 50 mg/day in patients who are also taking moderate CYP3A4 inhibitors. Avanafil should not be used in patients taking potent CYP3A4 inhibitors.[11]

Not all interactions with moderate and potent CYP3A4 inhibitors have been studied with each PDE$_5$ inhibitor; however, dosage adjustments and avoiding concomitant use altogether in some cases should be considered.

Alpha Blockers

Coadministration of PDE$_5$ inhibitors with alpha-adrenergic blocking agents can result in additive vasodilatory effects, causing potentially significant reductions in blood pressure (BP).[16] PDE$_5$ inhibitor therapy for ED should be initiated only if the patient's BP is already stable with alpha blockers and at the lowest recommended dose.

Vardenafil ODT (Staxyn) is not recommended for patients who are taking alpha blockers, particularly new users of this combination. Alternatively, low-dose, film-coated vardenafil tablets (Levitra) can be used. Patients taking PDE$_5$ inhibitors and alpha blockers concomitantly should be monitored closely.[8–12]

Nitrates

Nitrates such as nitroglycerin increase the production of cGMP. PDE$_5$ inhibitors decrease cGMP degradation. The concomitant use of these agents can cause a significant increase in cGMP accumulation, resulting in a synergistic reduction in BP. Therefore, the use of PDE$_5$ inhibitors with any form of organic nitrates is contraindicated. In emergency situations, if patients have taken a PDE$_5$ inhibitor and experience chest pain requiring treatment, a non-nitrate containing agent (e.g., a calcium-channel blocker or a beta blocker) can be used as an alternative when appropriate.[17]

A minimum of 24 hours should elapse after the last dose of sildenafil or vardenafil is taken before a nitrate can be used.[8,9] A period of at least 12 hours for avanafil and 48 hours for tadalafil should elapse before the patient takes a nitrate.[10,11,18] In such an event, nitrates should be administered only under close monitoring.

CLINICAL EFFICACY

Results from clinical trials of PDE$_5$ inhibitors have shown consistent improvement in erectile functioning compared with placebo. Studies commonly use questionnaires based on diaries and event logs to evaluate efficacy and functional improvements.

One of the most extensively used measurements is the mean score derived from the International Index of Erectile Function–Erectile Function domain (IIEF–EF). Scores range from 0 to 30 based on 15 questions. Separate evaluation of responses to Question 3 (successful penile penetration) and Question 4 (maintenance of erection after penetration) are often used to further determine the efficacy of PDE$_5$ inhibitors.

The Sexual Encounter Profile (SEP) is a diary that has also been used to document a patient's sexual experiences. In particular, responses to Question 2 (SEP2, erection sufficient for penetration) and Question 3 (SEP3, erection sufficient for successful intercourse) are used to measure efficacy outcomes.

The Global Assessment Question (GAQ) asks the patient whether the treatment has improved erectile function and is reported as the percentage of patients responding "yes."

In a published systematic review and meta-analysis of randomized controlled trials by Tsertsvadze et al., the efficacy of oral PDE$_5$ inhibitors was found to be consistent in the treatment of ED.[19] In 16 trials that evaluated sildenafil in men with various comorbidities, the mean per-patient percentage of successful sexual intercourse was 69% with treatment (range, 52%–85%) compared with 35.5% for placebo (range, 19%–68%). Data pooled from four trials reported a 34.4% improvement from baseline in successful intercourse attempts.

In 13 trials evaluating vardenafil in men with various comorbidities using SEP3, the mean per-patient percentage of successful sexual intercourse attempts was 68% for vardenafil (range, 50%–88%) versus 35% for placebo (range, 20%–49%). Data pooled from two trials reported a 33.2% improvement from baseline in successful intercourse attempts.

Fifteen trials that assessed the use of tadalafil in men with various comorbidities were conducted to determine the mean per-patient percentage of successful intercourse attempts

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