



Tadalafil: a long-acting PDE5 inhibitor for the management of erectile dysfunction

Allen D. Seftel, MD

Associate Professor of Urology
and Reproductive Biology,
Case Western Reserve
University School of
Medicine, Cleveland,
OH, USA
Tel.: +1 216 844 5504
Fax: +1 216 844 1900
ads6@po.cwru.edu

Erectile dysfunction is a significant medical condition affecting the total health of patients and their partners. Phosphodiesterase type 5 inhibitors treat erectile dysfunction by selectively inhibiting the nitric oxide–cyclic guanosine monophosphate pathway. Tadalafil is a unique phosphodiesterase type 5 inhibitor that has a long period of responsiveness – up to 36 h. Additionally, the absorption of tadalafil is not affected by a high-fat meal. These characteristics may give couples freedom in timing their sexual activity. Tadalafil is safe and effective for improving erectile function in both general and special populations. The most common treatment-emergent adverse events are generally mild or moderate in severity and include headache, flushing or dyspepsia. Tadalafil may cause mild vasodilation; it should not be given concomitantly with organic nitrates or α -blockers, except for tamsulosin (0.4 mg once daily).

Erectile dysfunction (ED), expected to affect some 322 million men worldwide by 2025 [1], is defined as the inability to achieve or sustain an erection sufficient to complete satisfactory sexual intercourse [2]. ED is a significant medical condition affecting the total health of patients and their partners and may also be a marker for endothelial dysfunction and comorbid cardiovascular disease, diabetes or depression [3]. In addition, ED is undertreated – in a study of men over 45 years of age, only 10% of subjects with sexual dysfunction reported seeking or receiving treatment [4].

Treatment options for ED are varied and historically, have ranged from counseling and lifestyle modification to vacuum constriction devices, intraurethral suppositories, surgical implants and intracavernosal injectable preparations such as alprostadil, papaverine and phentolamine [5]. The development of the phosphodiesterase (PDE) type 5 inhibitors has brought a new era in ED treatment by giving men the added option and convenience of oral medication. The PDE5 inhibitors have been shown to be safe and well tolerated in most patient populations [6–8].

Overview of the market

PDE5 inhibitors have been used globally since 1998 [9], however, each of the PDE5 inhibitors – sildenafil [9]; vardenafil [10] and most recently, tadalafil [11] – have distinctive characteristics based on molecular structure, enzyme inhibition profile and pharmacokinetic properties [12]. Tadalafil, for example, has a long period of responsiveness

[12,13] while sildenafil and vardenafil are associated with a shorter period of responsiveness; as a consequence, couples have a more limited window of opportunity for sexual intercourse.

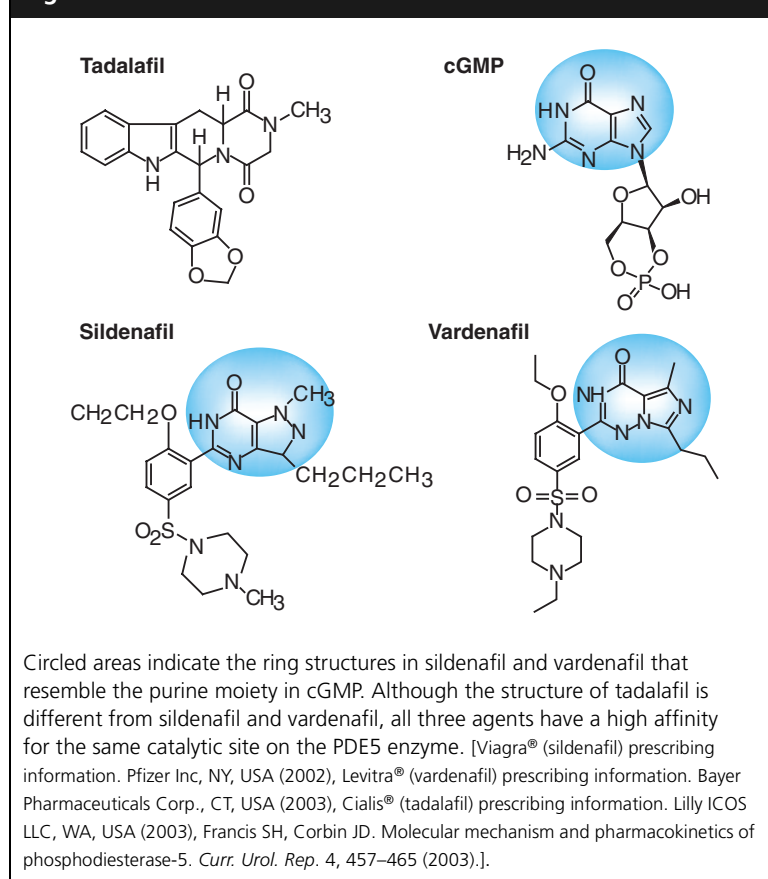
Tadalafil is also unique in that the rate and extent of its absorption are unaffected by consumption of high-fat food. Interactions with sildenafil and vardenafil and high-fat food may result in reductions and/or delays in drug absorption [12].

Other PDE5 inhibitors currently in development include FR229934 and TA-1790, available in oral and transurethral forms. FR229934 is currently in the preclinical trial stages of development [14]. TA-1790 is a highly selective, potent, orally active PDE5 inhibitor, believed to work faster than sildenafil to produce a maximum increase in penile rigidity [101]. Thus far, preclinical data indicates that TA-1790, when combined with nitrates, causes a minimal drop in blood pressure. A transurethral form is also being developed for men who cannot tolerate the oral form [14]. Intranasal PT-141, a melanocortin receptor agonist, has shown early promise as an effective and well-tolerated drug for managing ED. In a recent study, the erectile response induced by PT-141 at a dose greater than 7 mg was statistically better than that achieved by placebo. Erectile response increased in a dose-dependent manner between 7 and 20 mg. Time-to-onset of first erection averaged 30 mins after dosing. The drug was well tolerated; most common adverse effects were flushing and nausea and there were no changes in vital signs or electrocardiogram parameters [15].

Keywords: absorption, adverse events, erectile dysfunction, half-life, long duration of effectiveness, PDE5 inhibitors, pharmacokinetics, sildenafil, tadalafil, vardenafil



Figure 1. PDE5 inhibitors versus cGMP.



Local therapies are available and, in certain circumstances, are being used for the treatment of ED. Currently on the market, MUSE® is a noninjectable, local transurethral delivery system that can deliver a microsuppository of alprostadil directly to the urethra. Alprostadil is a vasodilator that, when given intraurethraly, increases blood flow to the penis and supports erection. According to the manufacturer, onset of action is within 5 to 10 mins and the period of responsiveness is 30 to 60 mins [14,16].

Some investigators are exploring the possibility of gene therapy, which could potentially restore physiologic erectile function, eliminating the need for 'on-demand' medications. Avenues being explored include the use of gene therapy with nitric oxide (NO) synthase, calcitonin-related peptide, brain-derived neurotrophic factor and vascular endothelial growth factor [17].

Introduction to the compound

Tadalafil is the latest PDE5 inhibitor to be introduced to the global market. Unlike sildenafil and vardenafil, which have a short terminal half-life (4–5 h for sildenafil) [18], the

period of responsiveness of tadalafil lasts for up to 36 h [9,13]. This may provide couples with greater flexibility in timing their sexual activity. Tadalafil also differs from other PDE5 inhibitors in that its absorption is not affected by high-fat food consumption [19]. Sildenafil or vardenafil may have diminished efficacy or delayed onset of action when taken with a meal [20,21]. Therefore, the unique pharmacodynamic advantages of tadalafil translate into important clinical benefits.

Chemistry

Tadalafil's empirical formula is $C_{22}H_{19}N_3O_4$ and its chemical designation is Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6*R*,12*aR*)-. Tadalafil is structurally distinct from sildenafil and vardenafil, which may account for the unique pharmacokinetic profile of the drug (Figure 1) [11].

Pharmacodynamics

Mechanism of action

Penile erection can be initiated through three major pathways, two of which cause formation of cyclic guanosine monophosphate (cyclic-3', 5' GMP), and the third of which causes the formation of cyclic adenosine monophosphate (cAMP). All three of these pathways are triggered by penile or sexual stimulation [22–24].

The two cGMP pathways are the primary and the secondary. In the primary cGMP pathway, visual or tactile sexual stimulation causes the release of acetylcholine (ACh) from the parasympathetic nervous system, which in turn innervates the nonadrenergic–noncholinergic (NANC) nerves. NO is released by NANC neurons resulting in the activation of the enzyme guanylate cyclase, which in turn catalyzes the conversion of guanosine 5'-triphosphate (GTP) to the neurotransmitter cGMP. cGMP then activates specific protein kinases that, through phosphorylation, ultimately cause potassium channels to open and calcium channels to close. Intracellular calcium levels drop, smooth muscle relaxes and the penis becomes erect [22–24].

In the secondary cGMP pathway, NO can also be released from the vascular endothelial cells. NO activates the enzyme guanylate cyclase, which catalyzes the conversion of GTP to cGMP. Accumulation of cGMP then triggers a cascade of intracellular biochemical events that ultimately leads to a decrease in intracellular calcium and relaxation of the penile smooth muscle. During

this smooth muscle relaxation, the penile arteries dilate, resulting in blood flow into the corpus cavernosa. The penile veins become compressed, trapping blood in the penis and producing an erection [22–24].

In the cAMP pathway, the enzyme adenylate cyclase catalyzes the formation of cAMP. Adenylate cyclase is stimulated in three of the following ways:

- Vasoactive intestinal peptide, which is widely distributed in the autonomic nerves
- Prostaglandins (PG)E₁ and E₂, which are synthesized by the smooth muscle
- Neural or circulating catecholamines – specifically, in this pathway, norepinephrine and epinephrine

PGE₁ and PGE₂ promote erection by a direct muscle relaxant effect and reduce adrenergic tone by inhibiting the release of noradrenaline. In addition, the cAMP-dependent protein kinase can induce smooth muscle relaxation by opening potassium channels and hyperpolarizing the cell. Hyperpolarization closes voltage-dependent calcium channels, reducing the entry of calcium from the extracellular compartment, thus reducing concentrations of intracellular free calcium, leading to relaxation of the cavernosal smooth muscle and erection [22,23]. In men with ED, the PDE5 isoenzymes appear to degrade cGMP before accumulation of intracellular concentrations sufficient to produce an erection [22–24].

Tadalafil improves erectile function by inhibiting PDE5 isoenzyme, thereby blocking cGMP degradation. As a result, the PDE5 inhibitors act synergistically with NO to markedly increase the levels of cGMP [12,25], which in the presence of sexual stimulation, lead to an erection. In the absence of sexual stimulation, NO is not released locally and the PDE5 inhibitors do not affect the penis [24]. Thus, sexual stimulation is needed to initiate the erectile mechanism for the PDE5 inhibitors to take effect [26].

Selectivity

Tadalafil is a highly selective inhibitor of the enzyme PDE5, which is most concentrated in the corpus cavernosum of the penis and is somewhat less distributed in vascular smooth muscle cells [12,25]. Tadalafil is far more selective for PDE5 than for PDE isoenzymes which are widely distributed in heart, brain tissue, blood vessels, liver, and other organs; which mediate numerous processes [8,12]. The high selectivity of tadalafil for PDE5 over other PDE isoenzymes may have a clinical impact

on its low incidence of adverse events. For example, tadalafil, with its low selectivity for PDE6 (distributed in the retinal cells), may cause fewer visual effects compared with sildenafil [12]. In tadalafil clinical trials, changes in color vision were reported in less than 0.1% of subjects [11]. In clinical trials of men with diabetes and retinopathy, tadalafil was associated with few adverse visual effects [6,27,28].

Tadalafil is 14-fold more selective for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle. Sildenafil and vardenafil are relatively poor inhibitors of PDE11 compared with tadalafil. However, neither the physiological role nor the clinical relevance of PDE11 inhibitors are yet known in humans [29].

Tadalafil has no clinically significant effect on sperm morphology, spermatogenesis or levels of testosterone, luteinizing hormone or follicle-stimulating hormone [30].

Pharmacokinetics

Absorption

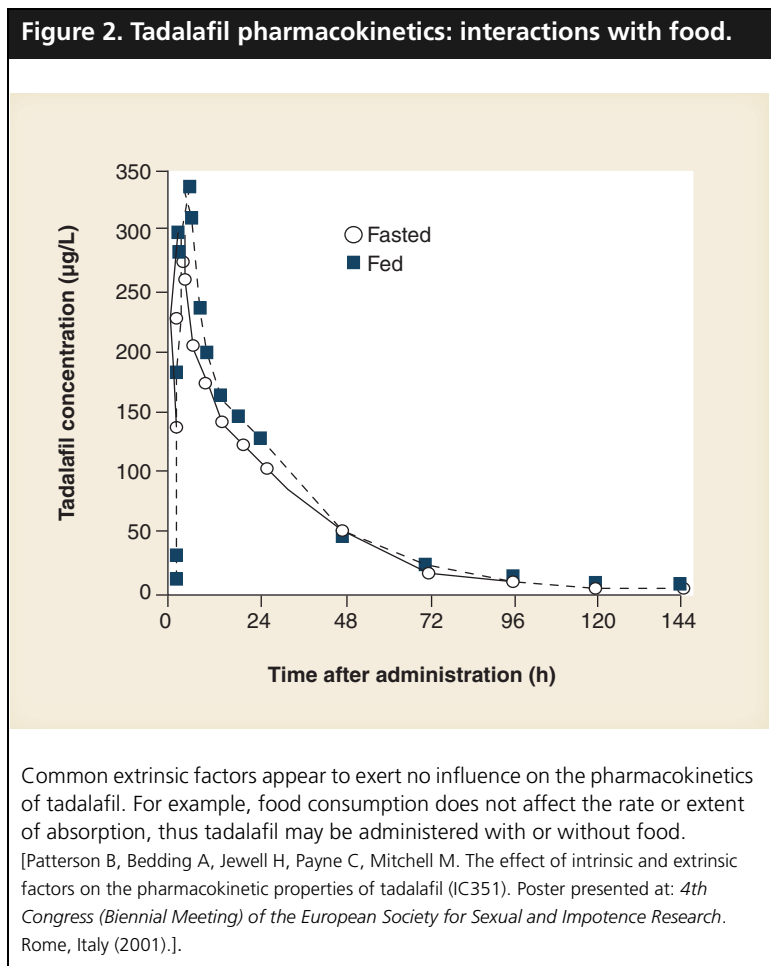
Tadalafil is absorbed rapidly [31]. Mean peak plasma levels have been observed between 30 mins and 6 h (median of 2 h) following a single oral dose [11,31].

The rate and extent of tadalafil absorption is unaffected by food consumption (Figure 2) [11,19]. As a result, tadalafil can be taken without regard to meals. Patients and their partners need not be concerned that a recent meal may decrease the effectiveness of the drug, as may be the case with sildenafil and vardenafil.

Duration of effectiveness

The half-life of tadalafil is 17.5 h, and its period of responsiveness is up to 36 h [11,13]. Several studies have examined whether this unique pharmacokinetic profile translates clinically into rapid onset and long period of responsiveness [8,13,32,33]. Time-to-onset was assessed in one study that found that tadalafil enabled the onset of an erection sufficient for the completion of intercourse as early as 16 mins after administration of a 20 mg dose ($p = 0.025$ as compared with placebo). In a study to assess the period of responsiveness of tadalafil, a 10 mg dose demonstrated a statistically significant difference at 24 h compared with placebo ($p < 0.001$) [32].

Among men ($n = 348$) randomized to a 20 mg dose of tadalafil, incidence of successful intercourse attempted at approximately 36 h (34 to 38 h) was 59%, versus 28% for the placebo group ($p < 0.001$) (Table 1) [13]. In an integrated analysis of 11 double-blind, placebo-controlled



studies including 2102 men with ED, 50% of subjects taking tadalafil attempted sexual intercourse at least once during the 12 to 24 h following dosing and 33% did so between 24 and 36 h after dosing, which provides evidence that men took full advantage of the pharmacokinetic profile of tadalafil [34]. Furthermore, completion of successful intercourse attempts made at both time periods (12–24 and 24–36 h) after dosing was significantly higher for patients in the tadalafil group (10–20 mg) compared with

Table 1. Successful intercourse attempts maintained with tadalafil up to 36 hours.

	Placebo (n=173) [§]	Tadalafil 20 mg (n=175) [§]	
Duration	Successes	Successes	p value
22–26 h	29%	53%	< 0.001
34–38 h	28%	59%	< 0.001

[§]n = 348; based on SEP Q3 (Did your erection last long enough to have successful intercourse?) responses.

patients in the placebo group ($p < 0.001$), as assessed by the Sexual Encounter Profile Question 3 (SEP Q3) [34, Appendix B].

Distribution

At therapeutic concentrations, 94% of tadalafil is bound to plasma proteins, and after oral administration, tadalafil is distributed into tissues (an approximate mean apparent distribution volume of 63 L) [11,19].

Elimination

The mean terminal half-life of tadalafil is 17.5 h, which significantly exceeds the half-lives of sildenafil (3.7 h) and vardenafil (4–5 h) [10,13]. Tadalafil is metabolized via cytochrome P450 (CYP)3A4; however, it neither inhibits nor induces clearance of other CYP3A4 substrates [35]. No active metabolites of tadalafil have been identified at therapeutic concentrations. Excretion is primarily through feces (61%) and urine (36%) [11].

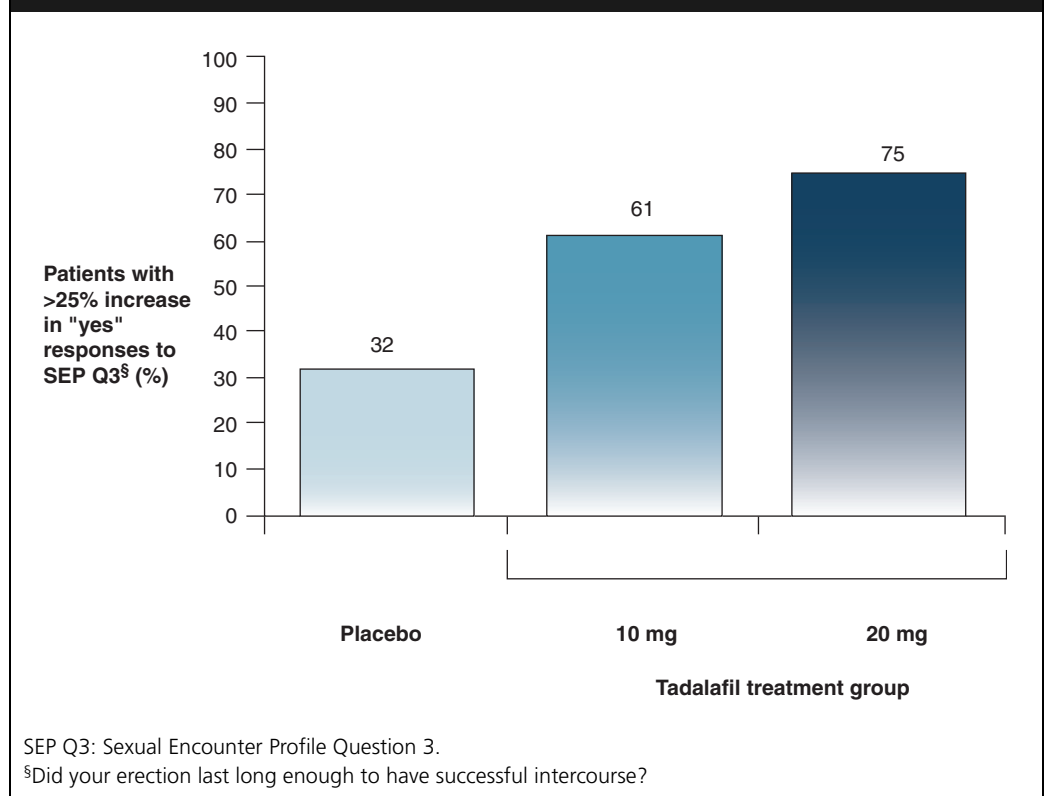
Dosing

The recommended starting dose of tadalafil is 10 mg, taken before anticipated intercourse. The dose can be decreased to 5 mg or increased to 20 mg, based on individual efficacy and tolerability; no adjustment is needed based on age alone. The maximum recommended dosing frequency is once per day for most patients [11,31]. The same dosing recommendations apply for men with diabetes or mild renal insufficiency [11]. Dosage restriction is recommended for men with renal insufficiency, either moderate (5 mg not more than once daily) or severe (5 mg not more than once in 48 h). Dosage restrictions are also recommended for men with mild-to-moderate hepatic impairment (maximum of 10 mg) [11]; tadalafil is not recommended for men with severe hepatic impairment [11]. No dosing adjustment is warranted when tadalafil is combined with CYP3A4 inducers [11]. However, since drugs that inhibit CYP3A4 can increase tadalafil exposure, men taking a potent CYP3A4 inhibitor (e.g., ritonavir, ketoconazole, itraconazole) should take no more than 10 mg of tadalafil once every 72 h [11].

Efficacy – Phase III studies

General population

A variety of scoring systems are used to assess the severity of ED: the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF); the SEP Diaries; and the Global Assessment Questions (GAQ) [5, Appendix C].

Figure 3. Tadalafil – 12-week efficacy evaluation.

Ample evidence from studies using these scoring systems supports the efficacy and tolerability of tadalafil in a range of dosages and in a broad population of men with ED [36].

One integrated analysis involved five trials and 1112 men with ED, some of whom had hypertension (30%) or diabetes (21%) [37]. According to the EF domain of the IIEF, a significant improvement in erectile response occurred at all tadalafil doses (2.5 mg, $p < 0.05$, to 20 mg, $p < 0.001$) compared with placebo. GAQ scores demonstrated that most men reported that tadalafil (10 or 20 mg) had significantly improved their erections compared with men who received placebo ($p < 0.001$). Intercourse attempts were twice as successful in subjects taking 20 mg of tadalafil than in men taking placebo (75 vs 32%, $p < 0.001$) (Figure 3). By study end point, 59% of men taking 20 mg and 40% of men taking 10 mg of tadalafil attained normal erectile function (compared with 11% receiving placebo; $p < 0.001$), as defined by the IIEF [37].

A subsequent analysis of 11 randomized, double-blind, 12-week efficacy trials involving more than 2000 men indicated that tadalafil is effective, regardless of the baseline severity of ED [38]. In this study, normal EF, as defined by the IIEF, was achieved by 73% of men with mild ED and 40%

with severe ED who took 20 mg of tadalafil ($p < 0.001$) compared with 29 and 3%, respectively, for the placebo groups. In another analysis including five randomized, double-blind studies, men with severe ED ($n = 279$) experienced a 46 and 68% success rate with 10 or 20 mg of tadalafil, respectively, versus 20% for placebo ($p < 0.001$) through their first four doses of tadalafil. For men with mild-to-moderate ED ($n = 531$), early success averaged 84 (10 mg) or 92% (20 mg) versus 61% for placebo ($p < 0.001$) [39]. These results indicate that tadalafil provides effective treatment for ED, regardless of ED severity, at baseline.

Factors such as age and ethnicity do not appear to influence the response to tadalafil. Systemic exposure to tadalafil in men (aged 65 years) appears to be slightly higher, probably related to delayed clearance, but this effect is not clinically significant. Thus, no dosage adjustment is necessary in men age 65 years and older [19]. In studies involving ethnically diverse men (white, Hispanic, black, Asian or other), efficacy of tadalafil was not altered among the various groups treated [11,40].

Special populations

Men with diabetes

Tadalafil is effective in men with ED and diabetes. In one study, tadalafil significantly

improved the EF domain scores (IIEF), with a change of 7.3 from baseline in the 20 mg tadalafil group ($p < 0.001$), 6.4 in the 10 mg tadalafil group ($p < 0.001$) and 0.1 in the placebo group [27]. End point scores for successful intercourse attempts (SEP Q3) were also improved ($p < 0.001$) (Figure 4) [Appendix B]. By the end of 12 weeks, positive responses to GAQ were higher for tadalafil, with 64% of men in the 20 mg group and 56% of men in the 10 mg group reporting improved erections, compared with 25% of men in the placebo group ($p < 0.001$). These benefits occurred regardless of diabetes type (I or II) or level of glycemic control [27].

Men postprostatectomy

ED develops in a wide range (10–100%) of men who undergo radical retropubic prostatectomy (RRP) [41] and tadalafil has been shown to significantly improve EF in this group of patients [42]. In patients who developed ED after bilateral nerve sparing RRP, 20 mg of tadalafil increased their IIEF EF domain scores by a clinically relevant five points at end point, compared with a one-point increase for placebo-treated patients [42]. By the end of 12 weeks of treatment, the

percentage of successful intercourse attempts as reported by SEP Q3 averaged 41% in men taking 20 mg of tadalafil, compared with 19% for those on placebo [42].

Safety of tadalafil in the general population

Adverse event profile

Clinical trials comparing tadalafil and placebo ($n = 1112$) indicate that tadalafil is safe and generally well tolerated in men with ED. In an integrated analysis, the most common treatment-emergent adverse events reported at all tadalafil doses included headache (14%), dyspepsia (10%) and flushing (4%), which were mostly mild or moderate in severity and tended to decrease in frequency in most patients with continued treatment (Table 2) [37].

In all tadalafil groups (2.5 mg to up to 20 mg), 6% of men ($n = 804$) reported back pain [37]. A similar profile of adverse events was observed in men with comorbid diabetes [29]. In general, back pain was reported as mild or moderate in severity and resolved without medical treatment. Overall, only 0.5% of all tadalafil-treated subjects discontinued treatment as a consequence of back pain or myalgia [11].

Figure 4. Efficacy evaluation in men with DM.

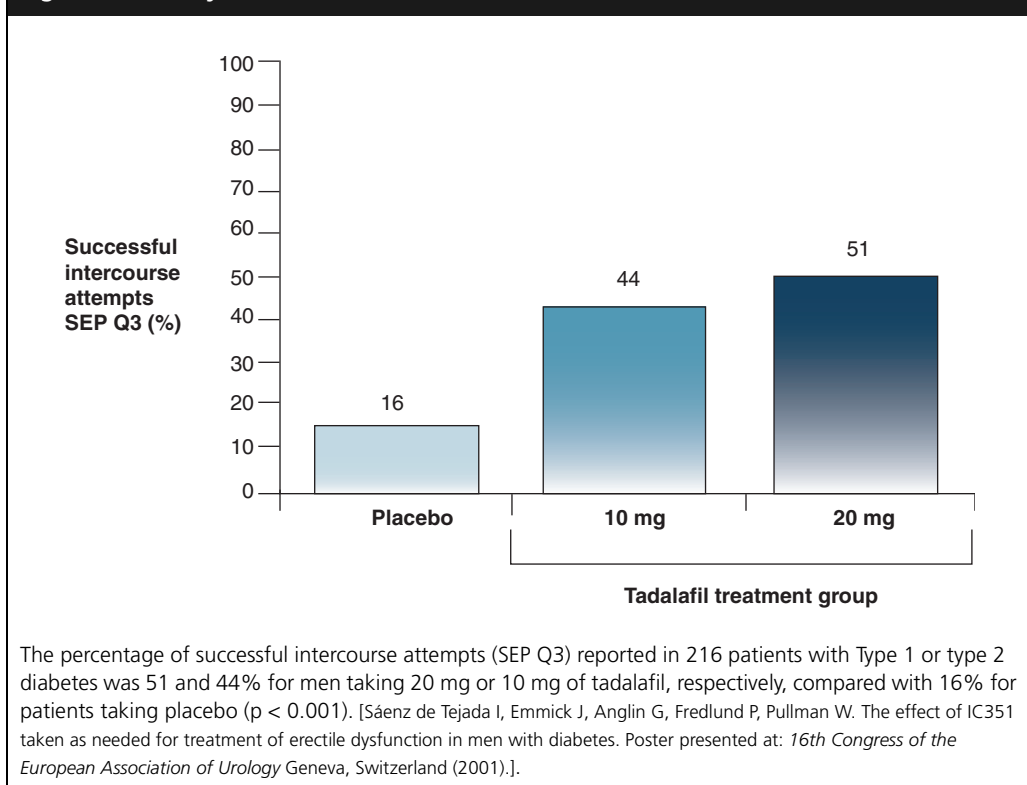


Table 2. Tadalafil tolerability.[§]

Adverse events	Patients reporting event (%)	
	Placebo (n=308)	Tadalafil (n=804) (10 mg)
Headache	6	14
Dyspepsia	2	10
Back pain	5	6
Myalgia	2	5
Nasal congestion	4	5
Flushing	2	4

Data taken from [Brock GB, McMahon CG, Chen KK et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J. Urol.* 168(4 Pt 1), 1332–1336 (2002).

[§]Phase III/III adverse events greater than or equal to 2%.

Long-term safety

Tadalafil was assessed for long-term safety and tolerability in 1173 patients enrolled in a 24-month, open-label study [43]. Treatment-emergent adverse events experienced by men taking 10 or 20 mg tadalafil over a period of 18 to 24 months, generally reflected the adverse events observed in the short-term studies. Headache (15%), dyspepsia (11%) and nasopharyngitis (11%) were most commonly reported. Back pain, rhinitis, and flu syndrome averaged 8, 4, and 3%, respectively. Most reported adverse events were mild or moderate in severity. Tolerability was good in a broad range of men taking tadalafil for up to 2 years; a few men (3.1%) in this study discontinued treatment because of tadalafil-related adverse events [43].

Safety in men with cardiovascular disease

Since PDE5 inhibitors relax vascular smooth muscle, mild vasodilation can occur that may affect patients with comorbid cardiovascular conditions, such as hypertension or coronary artery disease (CAD). In addition, the potential for interactions between PDE5 inhibitors and cardiovascular drugs, especially nitrates, should be considered [44–48].

Incidence of adverse cardiovascular events

Tadalafil does not increase the risk of cardiovascular-related adverse events, including flushing, dizziness, hypertension and syncope, compared with placebo [48]. The rate of myocardial infarction among patients taking tadalafil in Phase II and III and open-label studies was 0.39 per 100 patient-years in tadalafil-treated patients compared with

1.1 per 100 patient-years in the placebo group. Moreover, the incidence of myocardial infarction among patients treated with tadalafil was no lower than that reported by a group of similar age-standardized men (0.6 per 100 patient-years) [49]. Nonetheless, the potential cardiac risk of sexual activity in patients with cardiovascular disease should be considered [11].

Effects on other cardiovascular parameters

Tadalafil has little effect on systemic arterial pressure, as evidenced by data from over 5700 men in clinical trials worldwide [11]. In one study of 80 healthy men, single doses of tadalafil (10 or 20 mg) had only modest effects on standing systolic or diastolic blood pressure (Figure 5) [49]. Tadalafil also had no significant effect on heart rate in this group [49].

The potential effects of tadalafil on cardiac electrophysiology have been examined at 100 mg doses, up to five times the highest recommended dose. Tadalafil had no clinically relevant effect on the QT interval [49].

Additionally, exercise tolerance is not affected by tadalafil. In one study, tadalafil did not reduce exercise time or time to ischemia in a group of men with ED and stable CAD who had demonstrated ischemia during a screening exercise test [50].

Cardiovascular drug interactions

Interaction with nitrates

All of the PDE5 inhibitors potentiate the hypotensive effect of nitrates [9–11]. Therefore, administering tadalafil to patients who regularly or intermittently use any form of organic nitrates is contraindicated [11,44,45,47].

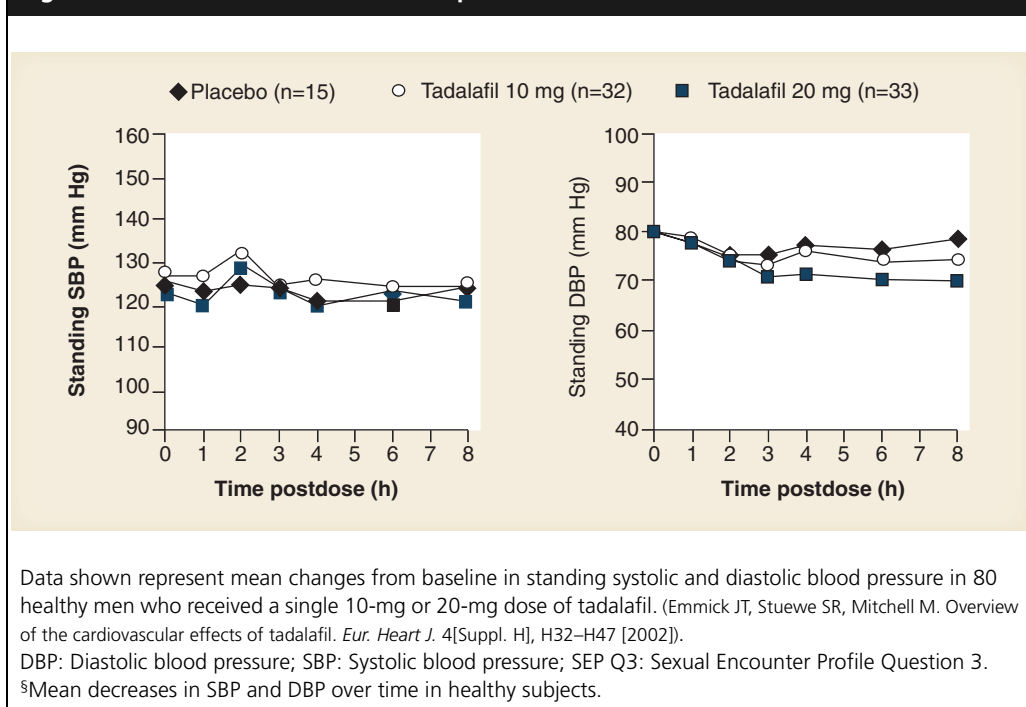
Results of a recent placebo-controlled study indicate that tadalafil (20 mg) enhances the hypotensive effects of sublingual nitroglycerin for up to 24 h after dosing [47]. The magnitude of this effect subsides with time and is not clinically significant after 48 h [47].

In emergency situations, current recommendations suggest waiting for at least 48 h after administering tadalafil before administering nitrates. Even then, nitrates should be administered only under close medical supervision and with hemodynamic monitoring (Table 3) [11,47].

Interactions with α -blockers & other antihypertensives

PDE5 inhibitors can augment the hypotensive effect of α -blockers, such as doxazosin. A study of the potential for a hemodynamic interaction between tadalafil (20 mg) and doxazosin (8 mg),

Figure 5. Tadalafil – effects on blood pressure.[§]



an α -blocker indicated for the treatment of both bilateral prostatic hypertrophy and hypertension, was undertaken in healthy subjects. The blood-pressure-lowering effect of doxazosin was significantly augmented with concomitant tadalafil administration. Therefore, the use of doxazosin and tadalafil is contraindicated [11]. The interaction between tadalafil and tamsulosin was examined in a study of healthy men who received 0.4 mg of tamsulosin daily for 7 days and 20 mg of tadalafil or placebo 2 h after the tamsulosin dose. Tadalafil produced mean maximal decreases in standing systolic and diastolic blood pressure that were 2.3 mmHg (95% confidence interval [CI], 4–9) and 2.2 mmHg (95% CI, 6–6) greater than placebo, respectively [51]. Based on this evidence, tadalafil is contraindicated for patients taking any α -blocker other than tamsulosin (0.4 mg once daily) [11].

In randomized, placebo-controlled studies in men receiving one or more antihypertensive agent(s), tadalafil demonstrated either little or no additive effect on blood pressure [49]. No further decreases in blood pressure were reported with concomitant administration of tadalafil and calcium channel blockers or thiazide diuretics. Only minimal changes in blood pressure were reported when tadalafil was administered with β -blockers and a small additive effect was observed when tadalafil was combined with angiotensin-converting enzyme inhibitors or

angiotensin-receptor blockers [11,52]. Moreover, data from Phase III clinical trials with tadalafil in men with ED showed that the rates of treatment-emergent cardiovascular adverse events were comparable between patients who received concomitant antihypertensive therapy and those who did not, except in hypertensive episodes, which would be expected to occur periodically despite treatment [49].

Recent data demonstrate that tadalafil is safe and does not increase the incidence of cardiovascular events or hypotensive symptoms, compared with placebo, in patients receiving two or more concomitant antihypertensive agents. Any additional blood pressure reduction caused by tadalafil is generally mild and causes no orthostatic symptoms [49,52].

Conclusion

Tadalafil is a highly selective inhibitor of the cGMP-specific PDE5 isoenzyme found in the penile vascular smooth muscle and it is a safe and effective oral treatment for ED. Clinical studies have shown favorable safety and efficacy profiles of tadalafil for the general ED population, as well as in men with ED and diabetes, hypertension or heart disease. Tadalafil, with its long duration of effectiveness and absence of food interactions, may be the optimal choice for men with ED and their partners who prefer a more flexible approach when resuming sexual activity.

Table 3. Emergency administration of nitrates following PDE5 inhibitor use.

Drug	Time interval for nitrate administration during a medical emergency. ⁵
Sildenafil	Has not been definitively determined After 24 h, may be considered based upon the pharmacokinetic profile.
Tadalafil	At least 48 h should elapse after the last dose before nitrate therapy is considered.
Vardenafil	Has not been definitively determined, but clinical data show that additional blood pressure and heart rate changes were not detected when the drug was dosed 24 h before nitrate administration.

⁵*Under close medical supervision and patient monitoring. Although these are the recommendations, all PDE5 inhibitors are contraindicated with any form of nitrates. [Kloner RA, Watkins VS, Costigan TM, Bedding A, Mitchell MI, Emmick JT. Cardiovascular profile of tadalafil, a new PDE5 inhibitor. J. Urol. 167(Suppl. 4), 176–177 (2002) (Abstract 707); Viagra® (sildenafil) prescribing information. Pfizer Inc, NY, USA (2002); Levitra® (vardenafil) prescribing information. Bayer Pharmaceuticals Corp., CT, USA. (2003); Cialis® (tadalafil) prescribing information. Lilly ICOS LLC, WA, USA (2003).]*

Tadalafil is not associated with an increased incidence of serious cardiovascular adverse events. However, the potential for clinically significant vasodilation precludes concomitant administration of tadalafil with any form of organic nitrates or α -blockers, other than 0.4 mg once-daily tamsulosin [11].

Expert opinion

While all of the PDE5 inhibitors represent a safe and effective treatment option for men with ED, tadalafil offers two important advantages over sildenafil and vardenafil: tadalafil has a prolonged period of responsiveness and its absorption is unaffected by high-fat food. These differences translated into preferences for tadalafil as shown in a double-blind, crossover study with 219 patients randomized to either 20 mg of tadalafil or 50 mg of sildenafil citrate. Each group followed specific dosing instructions according to each drug's profile [53]. Results from this study showed that 73% of patients preferred tadalafil over sildenafil citrate. Furthermore, in the assessment of dosing instruction preference, 67% of patients selected tadalafil and its dosing instructions [53]. These results agree with a previous comparative trial with 150 patients successively receiving sildenafil, tadalafil and vardenafil (15% naive patients; 85% long-term sildenafil users). Results showed that 13% of patients preferred sildenafil, 45% preferred tadalafil and 30% preferred vardenafil. Although 12% of the patients had no preference, these men were considered nonresponders to all PDE5 inhibitors

[54]. Another study of 226 patients examined a preference for sildenafil or tadalafil. In this study, 21% preferred sildenafil (8% naive patients; 92% long-term sildenafil users) and 66% preferred tadalafil (18% naive patients; 82% long-term sildenafil users). Again, most of the 13% who had no preference had not responded to either drug [54].

Oral PDE5 inhibitors may not be the end point in ED therapy. The diverse enzymatic interactions inherent in the NO–cGMP pathway open the door to the development of novel pharmacotherapies. Areas attracting investigation include regulation of PDE5 expression in the corpus cavernosum; the interaction of NO and cyclic nucleotide stimulatory systems; changes in the action of transcription factors affecting PDE5 gene expression and alternative molecular targets of the NO–cGMP pathway, such as guanylyl cyclases.

Combination therapy is another intriguing area for investigation. For example, one study found that adding a PDE5 inhibitor improved sexual satisfaction in men who used a penile prosthesis [55]. Combining psychosocial counseling with oral therapy addresses both the psychogenic and organic components of sexual function and can be very effective [56]. The combination of sildenafil and intraurethral/intracavernosal PGE₁ (alprostadil) is an effective option for men who do not respond well to either agent alone [57,58] and can also produce greater sexual satisfaction, even in men who do respond to monotherapy [59]. More investigation needs to be carried out, but early evidence holds promise for combination therapy.

Outlook

With therapeutic advances, we are likely to see changes in the field of ED treatment with potential changes in drug administration schedules. New drugs may be developed that have even greater selectivity for potential targets along the NO–cGMP pathway.

It is also likely that the use of PDE5 inhibitors may expand to include new indications. PDE5 inhibition with sildenafil, for example, acutely improves endothelium-dependent, flow-mediated vasodilation in patients with congestive heart failure. It also increases coronary artery flow reserve with minimal incidence of adverse events and without significant impact on such cardiovascular variables as heart rate and blood pressure [47,60].

Interest is also emerging regarding the use of PDE5 inhibitors as treatment for pulmonary hypertension. Sildenafil reduces both pulmonary

Highlights

- Tadalafil has unique pharmacokinetics that account for its long period of responsiveness of up to 36 h. In addition, absorption of the drug is unaffected by high-fat food.
- The long period of responsiveness of tadalafil is an important consideration for those patients seeking greater flexibility and a treatment that fits their sexual lifestyle.
- Tadalafil significantly improves erectile function, regardless of the severity of erectile dysfunction (ED). It is also just as effective in special patient populations (men with diabetes or heart disease) as it is in the general male population.
- The most common adverse events reported with tadalafil include headache, dyspepsia and flushing, which are generally mild or moderate in severity and tend to resolve after a few hours.
- Tadalafil has a good safety profile with minimal hemodynamic effects and can be used successfully in a broad population of patients, including men with cardiovascular disease.

vascular resistance and pulmonary artery pressure in patients with pulmonary vascular disease and produces further improvement after iloprost inhalation. In patients with severe pulmonary hypertension, sildenafil produces pulmonary vasodilation and improves cardiac index better than inhaled nitrates [60].

An added benefit of PDE5 inhibitors for men with ED is relief of lower urinary tract symptoms.

Treatment with sildenafil, for example, improves these symptoms. In a study of 112 men presenting with ED, a third had moderate (26%) to severe (6%) lower urinary tract symptoms, and these scores improved with treatment [61].

Conflict of interest

Allen D. Seftel is a medical consultant and a member of the Lilly ICOS speakers bureau.

Appendix A. Measurement Instruments.

Question no.	Questions
1.	How often were you able to get an erection during sexual activity?
2.	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3.	When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
4.	During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
5.	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
15.	How do you rate your confidence that you could get and keep an erection?

International Index of Erectile Function. Erectile Function Domain questions 1 to 5 and 15: Over the past 4 weeks...

Appendix B. Sexual Encounter Profile (SEP).

Question no.	Questions
1.	Were you able to achieve at least some erection?
2.	Were you able to insert your penis into your partner's vagina?
3.	Did your erection last long enough to have successful intercourse?
4.	Were you satisfied with the hardness of your erection?
5.	Were you satisfied with the overall sexual experience?

Appendix C. Global Assessment Questions (GAQ).

Question no.	Questions
1.	Has the treatment taken during the study improved your erections?
2.	If "yes," has the treatment improved your ability to engage in sexual activity?

Administered at end of treatment period during efficacy studies.

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