

Tadalafil Once-Daily: Patient and Partner Perspective in the Management of Erectile Dysfunction

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Abstract: Phosphodiesterase type 5 (PDE5) inhibitors are arguably the gold standard for treatment of erectile dysfunction in men. While all three PDE5 inhibitors approved for use in the U.S. are effective in treating ED, they possess different characteristics. Tadalafil differs from both sildenafil and vardenafil in its long half-life, which makes it ideal for daily dosing. This regimen has been shown to be effective over placebo, and studies suggest that it may be preferable by both partners over on-demand dosing. Side effects are typically mild in nature and infrequently lead to discontinuation of the drug. Once-daily dosing has also shown to be effective in ‘difficult-to-treat’ groups, such as diabetics and non-responders to on-demand therapy. The implementation of once-daily therapy represents a significant advancement in the understanding of male erectile dysfunction.

Keywords: erectile dysfunction, phosphodiesterase type 5 inhibitors, male

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Introduction

Erectile dysfunction (ED) has been defined by the National Institutes of Health Panel on Impotence as the persistent and/or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual intercourse.¹ As study design, definition of ED, and age of cohorts vary in the literature, the prevalence of ED ranges from 10% to 52%, with an incidence in Western countries between 25 and 30 new cases per 1000 inhabitants per year.² Results of one large epidemiologic study suggest that between 5% and 20% of men may have moderate or severe ED, which may translate into nearly 200 million men globally (2006 estimates).^{3,4} After age adjustment is performed, a higher probability of impotence correlated directly with concomitant heart disease, hypertension, diabetes, and associated medications, while cigarette smoking was associated with a greater probability of complete impotence in men with heart disease and hypertension.³ ED can be distressing because of its negative effect on self-esteem, quality of life (QoL), and interpersonal relationships. Men with ED may have a diminished self-image and self-esteem, anxiety and fears of rejection, and even depression.^{5,6} The female partner may also suffer from female sexual dysfunction secondary to her partner's ED.⁷

While primary treatment for in all men with ED should focus on minimizing the impact of risk factors and comorbidities such as hypertension, hypercholesterolemia, obesity, and diabetes mellitus, complementary therapy is often warranted. Options such as vacuum erection devices, intracavernosal injection therapy, and multi-component penile prostheses are viable options; however, oral therapy with phosphodiesterase type 5 (PDE5) inhibitors is considered by most to be the first-line treatment option in the 21st century.⁸ Currently, sildenafil, vardenafil, and tadalafil have been approved by the U.S. FDA, while other PDE5 inhibitors (eg, udenafil, mirodenafil, avanafil, lodenafil, SLx-2101, and UK-369, 003) are either not available in the U.S. or are in development. While efficacy has been demonstrated after administration of all three on-demand drugs,⁹ tadalafil has a significantly longer half-life, which makes it possible to take the drug several hours before intercourse. Tadalafil is also the only PDE5 inhibitor that is currently available in a once-daily preparation, which may even further separate

medication use from sexual activity and improve adherence to medication.¹⁰ The objective of this manuscript is to review to available data regarding the efficacy of once-daily tadalafil in the treatment of ED, with a focus on patient and partner satisfaction.

Mechanism of Action of PDE5 Inhibitors

In humans, the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway is the key mechanism responsible for penile erection.¹¹ NO is produced from oxygen and L-arginine under the control of nitric oxide synthase (NOS). Sexual arousal results in NO release from nerves and endothelial cells directly into the corpora cavernosa, and it is thought that immediate relaxation of cavernosal tissue is induced by neurogenic NO, whereas endothelial NO is involved in maintenance of relaxation.¹² NO subsequently binds to soluble guanylyl cyclase (sGC) in the cytoplasm of smooth muscle cells and causes a conformational change in this enzyme, producing cGMP from guanosine triphosphate. Cyclic GMP, in turn, activates cGMP-dependent protein kinase G (PKG), which phosphorylates several proteins.¹³ The end result is depletion of intracellular calcium levels which leads to a dissociation of calmodulin from myosin light chain (MLC) kinase and its inactivation. Myosin is subsequently detached from actin via dephosphorylation by MLC phosphatase. This cascade results in arterial smooth muscle relaxation, arterial dilatation, venous constriction, and, ultimately, erection of the corpora cavernosa.¹⁴ PDE5 inhibits erections by degrading intracellular cGMP, while PDE5 inhibitors lower the activity of PDE5 by competing with cGMP and inhibiting its hydrolysis. The level of cGMP subsequently increases, perpetuating the NO/cGMP pathway and improving erectile capability.

Pharmacokinetics of Tadalafil

Results of in vitro studies indicate that 94% of tadalafil in plasma is protein bound within the therapeutic concentration range.¹⁵ Tadalafil is predominantly cleared via hepatic cytochrome P450 3A (CYP3A) to a catechol that undergoes methylation and is extensively conjugated to form the major circulating metabolite, a methylcatechol glucuronide.^{15,16} A minor amount of the unconjugated metabolite is also detected in plasma.



Tadalafil is eliminated primarily as metabolites in the feces (61%) and urine (36%).¹⁵ These metabolites do not appear to be pharmacologically active at therapeutic dose levels owing to negligible affinity for PDE5 *in vitro*.¹⁵ Therapeutic concentrations of tadalafil likewise do not appear to affect significant changes in the clearance of drugs that undergo CYP3A metabolism.^{15,17} Conversely, medications that inhibit CYP, such as erythromycin, ketoconazole, and protease inhibitors, may slow the excretion of tadalafil.

The concentration required to inhibit PDE5 activity by 50% (IC_{50}) is a surrogate value for a drug's potency. Tadalafil has an IC_{50} for PDE5 equal to 1.8 nmol/L, which is considered of intermediate potency and may indicate that a lower dose may be required than other medications in this class to achieve the desired effects.^{18,19} The biochemical selectivity of PDE5 inhibitors is expressed in terms of their IC_{50} potency to inhibit PDE5 as opposed to other PDEs. Tadalafil is approximately 700 times more selective for PDE5 than PDE6 found in the retina.^{20,21} As tadalafil has minimal affinity for PDE6 as compared with sildenafil and vardenafil, the incidence of vision-related side effects is much lower.^{22,23} Tadalafil's relatively higher affinity for PDE11 found in skeletal muscle may be related to the higher incidence of myalgia and back pain in men on tadalafil therapy; however, the functional sequelae of this relationship are not completely understood.^{18–20,24}

The maximum plasma concentration (C_{max}) for tadalafil is 378 ng/ml while the time required for attaining C_{max} (T_{max}) is 2 hours.^{18,19} The time required for elimination of half the inhibitor from the plasma ($T_{1/2}$) is 17.5 hours for tadalafil.^{18,19,25} The long $T_{1/2}$ may be attributed to the low volume of distribution (62.6 L), slow hepatic clearance, and approximately 80% bioavailability.^{15,21} Subsequently, the extended

$T_{1/2}$ provides a longer therapeutic effect than either sildenafil or vardenafil.^{17,18} Food has minimal effects on the rate of tadalafil absorption and the drug appears to have a slightly lower bioavailability when taken in the evening.¹⁵ A comparison of the pharmacodynamics and pharmacokinetics of the FDA-approved PDE5 inhibitors is summarized in Table 1.

Rationale for Once-Daily Dosing

As previously mentioned, on-demand PDE5 administration has been considered the treatment of choice for ED for many years. This method is safe and overall efficacy of on-demand dosing may be effective in approximately 60% to 70% of men with ED.^{9,26} However, several facts suggest that these regimens may be suboptimal for some men. First, men with certain comorbidities, such as severe neurovascular disease, diabetes mellitus, and those undergoing radical prostatectomy for prostate cancer, may respond poorly to standard, on-demand therapy.²⁷ Even after accounting for confounding factors such as incorrect drug usage and inadequate patient education, an estimated 30% to 35% of these men still fail to respond, suggesting that this population may benefit from higher or flexible dosing.^{27,28} Second, it has been observed that even among those men who respond to on-demand therapy with PDE5 inhibitors, 35% to 47% voluntarily discontinue therapy beyond a year.^{29,30} Common reasons cited by responders to PDE5 inhibitors are lack of spontaneity and “naturalness” with on-demand regimens.³⁰

Owing to the long $T_{1/2}$ and the theoretical separation of medicine intake from the act of intercourse, some studies have suggested that on-demand tadalafil may be preferable to sildenafil and vardenafil.¹⁰ Martin-Morales et al demonstrated in an observational study of over 8000 European men that those taking

Table 1. Pharmacodynamics and pharmacokinetics of PDE5 inhibitors.^{18,19}

Drug	Maker	FDA Approval	IC_{50} for PDE5 (nmol/L)	PDE selectivity (activity)	T_{max} (h)	C_{max} (ng/ml)	$T_{1/2}$ (h)
Sildenafil	Pfizer Inc.	1998	3.7	Low vs. PDE6; v. low vs. PDE1	0.8	450	3–5
Tadalafil	Lilly-ICOS	2003	1.8	Low vs. PDE11	2.0	378	17.5
Vardenafil	GSK / Bayer	2003	0.091	Low vs. PDE6; very low vs. PDE 1	0.7–0.9	20.9	4–5

Abbreviations: FDA, U.S. Food and Drug Administration; IC_{50} , half maximal inhibitory concentration; T_{max} , time to peak plasma concentration; C_{max} , peak plasma concentration; $T_{1/2}$, plasma half-life.



tadalafil showed higher levels of satisfaction than men taking sildenafil and vardenafil owing to improvement in the “Time Concerns” domain.⁹ In another subanalysis of the EDOS study, the authors determined that the continuation rates were 89% in the tadalafil cohort of treatment-naïve men, vs. 63% to 64% in the sildenafil and vardenafil cohorts.³¹ The variables most strongly associated with increased risk of switching were prescription of sildenafil or vardenafil (vs. tadalafil) at baseline (OR 4.43 and 4.14, respectively; $P < 0.0001$). Of patients who switched from tadalafil to another treatment, nearly 25% had switched back to tadalafil by the end of the study. In contrast, of patients who switched from sildenafil or vardenafil, <10% from each cohort switched back to their original treatment by study end. These results should be interpreted with caution due to the observational nature of the EDOS study.

The long $T_{1/2}$ and subsequent 36-hour period of responsiveness likewise provide a favorable pharmacokinetic profile for once-daily dosing.³² Steady-state plasma concentrations are attained within five days of 5 mg once-daily dosing, and the exposure is approximately 1.6 times greater than after a single dose.^{15,32} The concept of daily dosing has been introduced to provide a treatment alternative to on-demand PDE5 inhibition by more closely approximating “natural” sexual function.³³ McMahon performed an open-label flexible dose evaluation in 100 men who failed to completely respond to on-demand tadalafil 20 mg.³³ These men were treated with a 4-week course of on-demand tadalafil 20 mg, followed by a 4-week washout period, followed by a 12-week course of once-daily tadalafil 10 mg or 20 mg. The author noted that in men who previously did not respond to on-demand tadalafil, daily dosing with tadalafil led to improvement in all efficacy outcome variables when compared with baseline and after four weeks of on-demand therapy. In a follow-up open-label cross-over study, McMahon confirmed greater improvement in all outcome variables for once-daily tadalafil and daily dosing was preferred by 72% of men compared with 28% preferring on-demand therapy.³⁴

Clinical Efficacy of Once-Daily Tadalafil

Prior to a discussion of clinical outcomes, it is important to summarize the commonly-employed outcome measures found in the literature. The measures of

success most often consist of the erectile function domain of the International Index of Erectile Function (IIEF-EF), Sexual Encounter Profile (SEP), and a Global Assessment Question (GAQ). The IIEF is the most widely-used validated quantitative scale for ED treatment assessment. The questionnaire consists of 15 items covering five domains of male sexual function (sexual desire, erectile function, intercourse satisfaction, orgasmic function, and overall satisfaction).³⁵ Six items of the IIEF pertain directly to erectile function (IIEF-EF; range 5–50), with scores ≤ 10 indicating severe ED.^{35,36} The SEP diary consists of five questions completed by the subject after each intercourse attempt (SEP1–5), while the partner diary consists of three questions (pSEP1–3).³⁷ The SEP diaries are scored in such a way that if the answer to a SEP question is “no,” all subsequent SEP questions are scored as “no” for that intercourse attempt.

The efficacy of tadalafil on-demand has been documented in several randomized controlled trials (RCTs). In over 2100 men, tadalafil was significantly better than placebo in IIEF-EF, SEP3, and GAQ at the 12-week endpoint.³⁸ Likewise, Eardley et al reported similar outcomes in a Western European population, while Guo et al confirmed these findings in Southeast Asian Men.^{39,40} The efficacy of once-daily tadalafil has likewise been firmly established in several RCTs (Table 2). Additionally, in a report on open label extensions from two prior studies,^{41,42} Porst et al found that the IIEF-EF domain improved significantly from baseline to the end of the 1-year and 2-year extensions.⁴⁸ At the conclusion of the 2-year open-label extension, 95.7% and 92.1% of the patients reported positive responses to GAQ1 (improved erections) and GAQ2 (improved ability to engage in sexual activity), respectively.

The onset of efficacy of once-daily tadalafil has also been recently evaluated.⁴⁷ During a 14-day double-blind period, men treated with once-daily tadalafil 5 mg and 2.5 mg experienced efficacy onset as early as day 2 and day 3 of therapy, respectively. During a 4-week open label period, all men received tadalafil 5 mg daily and achieved a significant increase in the percent of successful attempts even if they had not responded to tadalafil during the double-blind period.

Recently, Ricardi et al compared the efficacy and safety of on-demand 20-mg tadalafil with once-daily tadalafil 5-mg in patients with ED following

**Table 2.** Outcomes of RCTs of once-daily tadalafil in the treatment of ED.

First Author	N (Enrolled/Completed)	Study Length	Drug Dosage	Outcomes
Porst ⁴¹	293/234	12w	Placebo 5 mg 10 mg	Significant change for both doses in: mean Δ IIEF-EF, SEP2, SEP3, % improved erections, and % with no ED
Rajfer ⁴²	287/238	24w	Placebo 2.5 mg 5 mg	Significant change for both doses in: mean Δ IIEF-EF, mean Δ (+)SEP2 & (+)SEP3, intercourse satisfaction, sexual confidence, overall satisfaction with sexual life
Hatzichristou ⁴³	298/254 (Diabetics)	12w	Placebo 2.5 mg 5 mg	Significant change for both doses in: mean Δ IIEF-EF, mean Δ (+)SEP2 & (+)SEP3, mean success rates for vaginal penetration, completion of intercourse, and overall treatment satisfaction
Rubio-Aurioles ⁴⁴	342/307	12w	Placebo 5 mg	Significant change in: mean Δ IIEF-EF, mean Δ (+)SEP2 & SEP3, SQoL (patient and partner)
McVary ⁴⁵	281/251	12w	Placebo 5 mg	Significant change in: mean Δ IIEF-EF, mean Δ IPSS at 6w and 12w
Seftel ⁴⁶	342/307	12w	Placebo 5 mg	Significant change in: mean Δ IIEF-EF, mean Δ (+)SEP4, SEP5, & pSEP3; satisfaction; IIEF domains of intercourse satisfaction & overall satisfaction
Seftel ⁴⁷	372/337	14d	Placebo 2.5 mg 5 mg	Significantly more men in 5 mg group had successful intercourse by day#2 vs. placebo; Significantly more men in 2.5 mg group had successful intercourse by day#3 vs. placebo

Abbreviations: Δ , change; IIEF-EF, EF domain of the International Index of Erectile Function; SEP, Sexual Encounter Profile; SQoL, Sexual Quality of Life domain of the Sexual Life Quality Questionnaire (subject and partner).

radiotherapy for prostate cancer.⁴⁹ Men were randomized and treated for 12 weeks, with changes in the IIEF domain scores and SEP2 and SEP3 positive response rates representing the main outcome measures. Forty-four patients were evaluable for efficacy. A significant improvement in all IIEF domains was observed in both arms ($P = 0.0001$) with mean erectile function domain scores values of 25 and 27.1 for the 20-mg and 5-mg tadalafil, respectively ($P = 0.19$). SEP2 and 3 positive response rates increased from 0% in both arms at baseline to 81% and 70% in the 20-mg arm and 90% and 73% in the 5-mg arm, respectively, at the end of treatment ($P = 0.27$). End of treatment global efficacy question positive answers were 86% in the 20-mg arm and 95% in the 5-mg arm ($P = 0.27$). Higher treatment compliance was shown in the once-daily arm (100%) as compared with the on-demand arm (86%). There was a nonstatistically significant trend toward fewer side effects in favor of the 5-mg daily dose arm.

Safety of Tadalafil Administration

The majority (54%–80%) of side effects from the administration of once-daily tadalafil have been mild in nature.^{20,33,41} Typical symptoms include headache,

flushing, indigestion, nasal congestion, and back and/or girdle pain.¹⁸ Washington and Shindel compiled a summary of side effects from several RCTs and 1-year and 2-year extension studies.²⁰ The rates of headache (1%–13.6%), dyspepsia (0.9%–11.4%), back pain (0.9%–11%), and myalgia (0%–8%) varied with dosage. A dose-dependent relationship has not been confirmed in every study.^{20,33,50} Tadalafil has not been shown to prolong the QT interval.⁵¹ Tadalafil also had no adverse effects on spermatogenesis, as assessed by sperm concentration, sperm count per ejaculate, percent sperm motility, normal morphology or serum reproductive hormones.⁵² In general, there appears to be a very low rate of clinically significant hypotension with tadalafil, with or without alpha-adrenergic blockers used for the treatment of BPH/LUTS.⁵³ This effect appeared to be consistent with both on-demand and daily-dosing schedules.⁵⁴

Post-marketing experience compiled in the package insert summarized the following serious adverse events associated with tadalafil. It must be noted that a causal relationship has not been clearly established. Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported post-marketing in



temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis have been reported, as have central nervous system conditions, such as migraine, seizures, and transient global amnesia. Ophthalmologic sequelae have included visual field defects, retinal vein occlusion, and retinal artery occlusion. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE5Is, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It was not possible to determine whether these events were related directly to the use of PDE5Is, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Cases of sudden decrease or loss of hearing have been reported post-marketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. It was not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. If changes in hearing occur, patients should stop their tadalafil and seek immediate medical attention. Finally, tadalafil has been associated with prolonged erections or priapism (painful erections lasting more than six hours). Patients should be instructed to seek immediate medical help if they experience an erection lasting more than four hours.

As with most medications, drug-drug interactions are possible with the administration of tadalafil. In clinical pharmacology studies, tadalafil was shown to increase heart rate and potentiate the hypotensive effect of nitrates. Administration of tadalafil to patients who are using any form of organic nitrate (eg, nitroglycerin and isosorbide dinitrate) is contraindicated. In a patient who has taken tadalafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Caution is advised when PDE5 inhibitors are co-administered with alpha blockers. PDE5 inhibitors and alpha-adrenergic blockers are both vasodilators with blood-pressure-lowering effects. Individuals who take alpha-blockers should be on a stable dose of the alpha-blocker before tadalafil is started, and, in such situations, tadalafil should be started at the lowest dose. If the patient is already taking tadalafil, the alpha-blocker should be started at the lowest dose. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. Alcohol is also a mild vasodilator, and substantial consumption of alcohol (eg, 5 units or greater) in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

The potential for other drugs to affect tadalafil levels has also been evaluated. Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil. An increase in gastric pH resulting from administration of nizatidine (an



H2-blocker) had no significant effect on pharmacokinetics of tadalafil. Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure. Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure and decrease the breakdown and elimination of tadalafil from the body. If these drugs are being used at the same time as tadalafil, the dose of tadalafil should be reduced in order to avoid side effects from high levels of tadalafil.

HIV Protease inhibitors such as ritonavir, an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure by 32% with a 30% reduction in C_{max} , relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single-dose exposure by 124% with no change in C_{max} , relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure.

Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure. Rifampin (600 mg daily) reduced tadalafil 10-mg single-dose exposure by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of tadalafil for once daily use.

The potential for tadalafil to affect other drugs has been studied. Tadalafil did not potentiate the increase in bleeding time caused by aspirin. Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 isoforms. Studies have shown that

tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. Tadalafil had no significant effect on the pharmacokinetics of theophylline (CYP1A2). When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed. Tadalafil had no significant effect on AUC to warfarin (CYP2C9), nor did tadalafil affect changes in prothrombin time induced by warfarin. Tadalafil had no significant effect on the steady-state pharmacokinetics of midazolam, lovastatin, or digoxin.

Partner Perspective

While significant research has been devoted to the experience of ED among men with ED, far less has been written about the perceptions and sexual experiences of the female partners of those men. In an attempt to address some of the gaps in the understanding of the partner's experience, Fisher et al administered questionnaires assessing the frequency of sexual activity and the nature of the sexual experience to 293 female partners of men on PDE5 therapy.⁵⁵ Surveys were administered both before and after the development of their partner's ED, as well as in relation to their partner's use of PDE5 inhibitors. Women reported engaging in sexual activity significantly less frequently after their partner developed ED as compared with before ($P < 0.001$). Moreover, significantly fewer women experienced sexual desire, arousal, or orgasm "almost always" or "most times," and significantly fewer women reported satisfaction with their sexual relationship after their partner developed ED, compared with before ($P < 0.001$). Decreases in female sexual satisfaction and frequency of orgasm were significantly related to the male partner's self-reported severity of ED ($P < 0.01$). The proportion of women who experienced sexual desire, arousal, and orgasm "almost always" or "most times" was significantly higher in the group whose partners were currently using a PDE5 inhibitor ($P < 0.05$). Clearly, ED has significant adverse effects on the female partner's sexual experience and women with partners who were currently using PDE5 inhibitors had a more satisfying sexual experience than those whose partners did not use a PDE5 inhibitor.



Further evidence has shown that the partner plays a key supportive role in the treatment of a man's ED and in successful long-term ED therapy.⁵⁶ Dean et al suggested that including the partner in consultations may highlight discordant attitudes and communication problems between couple members which may indicate treatment acceptance or rejection, or realistic or unrealistic treatment expectations. The authors also suggested that physicians should consider encouraging the patient to bring the partner into the office and, often more realistically, seeking information about, and providing information to, the partner, via the patient.

Several studies have examined the partner's experience after the man has been on tadalafil therapy. Conaglen and Conaglen performed a partner preference study on 100 couples comparing on-demand sildenafil and tadalafil.⁵⁷ A total of 79.2% of the women preferred their partner's use of tadalafil, while 15.6% preferred sildenafil. Women preferring tadalafil reported feeling more relaxed, experiencing less pressure, and enjoying a more natural or spontaneous sexual experience as reasons for their choice. Recently, there have been studies citing similar findings in men taking once-daily tadalafil. In a multicenter, parallel RCT, Rubio-Aurioles et al showed that the sexual QoL of men and their female partners, as measured by the SQoL domain, was significantly improved with once-daily tadalafil 5 mg ($P < 0.001$) compared with placebo.⁴⁴ Specifically, men on tadalafil and their partners reported greater frequency of sex, duration of sex, ease of penile insertion, ease of achieving orgasm, ease of initiating sex, pleasure of anticipation, carefree feelings during sex, pleasure with orgasm, overall pleasure, and perception of partner's overall pleasure.

Althof et al pooled data from four double-blind, placebo-controlled, 12-week trials that included 746 couples.⁵⁸ Patients were randomized to placebo or tadalafil 10 mg or 20 mg. Tadalafil significantly improved the responses for the patient and partner-evaluated SEP questions 1–3 ($P < 0.001$, both doses vs. placebo). Partners tended to report greater overall satisfaction than patients at baseline and post-baseline. The mean percentage of agreement by couple was approximately 98% for erection achievement and penetration and 85% for overall satisfaction. For successful intercourse attempts, patients and partners treated

with tadalafil reported more overall satisfaction than those treated with placebo ($P < 0.05$, tadalafil vs. placebo comparisons). Additionally, Althof et al recently pooled data from two multicenter,^{41,44} 12-week RCTs comparing once-daily tadalafil 5 mg to placebo.³⁷ Subjects and partners in the tadalafil-treated group reported significantly greater improvements in the man's ability to achieve some erection, vaginal penetration, and overall sexual satisfaction compared with the placebo-treated group ($P < 0.001$). As in the previous study, there was high concordance among couples in their responses to the man's treatment for ED. For all intercourse attempts, the mean per-couple percentage of agreement for those in the tadalafil and placebo groups, respectively, was high for erection achievement, vaginal penetration, and overall satisfaction. Finally, in a follow up to the data set reported by Rubio-Aurioles et al,⁴⁴ Seftel et al reported that the partners of tadalafil-treated men were more likely to answer affirmatively to pSEP3 relative to the partners of placebo-treated men (70% vs. 30%).⁴⁶ The authors also found that improvements in the IIEF-EF domain of men on once-daily tadalafil correlated positively with their partner's satisfaction with ED treatment.

Place in Therapy

While both on-demand and once-daily treatment with tadalafil is effective in restoring erectile function, it is not completely clear where to position once-daily dosing in the treatment algorithm. The current data does not distinctly identify a population of patients that would be more likely to benefit from once-daily dosing; however, as previously stated, certain populations of men may be strongly considered. Studies by McMahon and Hatzimouratidis et al have both demonstrated significant improvement in erectile function in men who have previously not responded to on-demand tadalafil.^{33,59} Other difficult-to-treat populations, such as men with diabetes, have also responded well to once-daily tadalafil.⁴³ While once-daily tadalafil has not yet been tested in men who have undergone radical prostatectomy, the use of PDE5 inhibitors is an emerging practice in the setting of penile rehabilitation.⁶⁰ Additionally, men with difficulty adhering to on-demand medication regimens may particularly benefit from once-daily therapy.



Conclusions

Treatment of male ED with PDE5 inhibitors is arguably the current standard of care. This mode of therapy offers a safe and effective way to treat a chronic condition that significantly impacts the quality of life of the man and their partner. While all three of the PDE5 inhibitors currently available in the U.S. are effective in the on-demand treatment of ED, only tadalafil is available for once-daily dosing. Tadalafil differs from sildenafil and vardenafil in its long half-life, which makes it ideal for daily dosing and the ability to effectively separate the ingestion of medicine from the sex act. To date, multiple studies have shown a preference for tadalafil by both man and partner, specifically for its ability to assist in restoring spontaneity and a “normal” sex life. Several rigorous RCTs have demonstrated the superiority of once-daily tadalafil to placebo. Additional studies have documented success in diabetic men and non-responders to on-demand tadalafil therapy. Although once-daily dosing does not necessarily represent the optimum regimen for every man with ED, it does add an additional and viable option to our armamentarium in restoring the couple’s sexual health.

The availability of multiple therapeutic options for a couple’s sexual health amplifies the need for extensive counseling and the inclusion of both partners in the decision-making process. This statement is underscored by the addition of “Viagra Divorce” to our lexicon. This term applies to the disconnect between aging men who take Viagra to restore their erectile capacity and their partners who may lack the desire for sexual intimacy. The goal of sexual intercourse may lead men to partners outside the bonds of marriage and ultimately divorce. While little has been written on this topic in academic journals, the term has penetrated mainstream media and will undoubtedly be cited frequently as the market for PDE5 inhibitors grows.

Conflict of Interest

Neither of the authors have any disclosures to report regarding a relationship with the makers of tadalafil or any other PDE5 inhibitor.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of

conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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