

Frequently asked questions about tadalafil for treating men with erectile dysfunction

Keywords

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Part I – Optimizing Tadalafil Therapy

Introduction

Erectile dysfunction (ED) is a topic of considerable importance to men's health. In men with cardiovascular disease and diabetes mellitus especially, ED is increasingly being recognized as a comorbid condition. ED is a treatable condition, but some treatment options—sex therapy, implants, vacuum devices, intracavernosal injections, and herbal medications and creams—could be time consuming, painful, awkward, or of questionable efficacy. The advent of oral phosphodiesterase 5 (PDE5) inhibitors has revolutionized the treatment of men with ED. Clinicians now have the option of prescribing one of three PDE5 inhibitors – sildenafil citrate (Viagra[®]), tadalafil (Cialis[®]), or vardenafil HCl (Levitra[®]).

As with any therapy for any disorder, treatment success may be influenced greatly by such diverse factors as dosing instructions, timing of desired effect following dosing, food and medication interactions, and knowledge of adverse events. For the clinician, an awareness of pharmacodynamic and pharmacokinetic properties of a medication can facilitate patient education, and appropriate follow-up provided by an informed clinician can detect obstacles to successful treatment. This report is designed to provide primary care clinicians with answers to frequently asked questions about tadalafil.

The report is provided in two parts. The first is frequently asked questions about optimizing tadalafil therapy in treating men with ED. The second reviews frequently asked questions about how the safety and tolerability of tadalafil have been established. The intent is to apply recent scientific research to “the bedside” or clinic in a practical fashion. The review is framed in a question and answer style so that busy clinicians can quickly and easily find the questions for which they have the most interest.

The information presented is based on data from the scientific literature, product labeling, and the clinical insights of the authors. Because men's health is a global issue, this report is written from a global perspective, but information regarding prescribing is based on the United States Package Insert (“label”). Physicians in other countries should note that label language and doses might vary in different countries and regions. This is a normal consequence of different regulatory agencies viewing a dataset pertaining to a particular pharmacological agent in different ways.

I. Tadalafil and Erectile Dysfunction Basics

Q: How is ED diagnosed?

ED is defined as the inability to achieve an erection that is adequate for intercourse [1].

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ED is generally a patient-driven diagnosis, determined by taking a careful medical history. There are no specific laboratory tests that clinically diagnose the presence or absence of ED.

Q: What is the physiological mechanism of an erection?

An erection is a neuro-vascular event in which the degree of erection depends upon the balance between arterial inflow and venous outflow (Figure 1) [2]. Psychological or physical sexual stimulation initiates the release of nitric oxide—the “first messenger”—from neurons and endothelial cells in the penis. Nitric oxide leads to increased generation of cyclic guanosine monophosphate (cGMP). The cGMP, which is an intracellular second messenger, in turn activates protein kinase G. Protein kinase G decreases calcium in the cytosol, which ultimately leads to the relaxation of the smooth muscle of the corpus cavernosum. Arterial inflow increases and the venules are compressed, impeding the outflow of blood, which causes an erection by increased blood trapping.

Q: How should men with ED be evaluated prior to therapy?

Except in rare circumstances, the initial evaluation of men does not impact what will be

offered for treatment. Rather, screening aims to identify comorbid cardiovascular disease, diabetes, hyperlipidemia, hypertension, hypogonadism, and depression, all of which merit intervention in their own right.

Because most men with ED have a disproportionate burden of comorbidities, it is considered appropriate to measure lipids and glucose after an overnight fast, and to record blood pressure to screen for treatable conditions. Since ED may be medication-induced, screening for concomitant administration of possible causative medicines (eg., thiazide diuretics, beta blockers, serotonin-selective reuptake inhibitors (SSRIs), alpha-reductase inhibitors, and aldosterone antagonists) is important [3–8].

Hypogonadism is an uncommon cause of ED (causative in less than 5% of ED cases). Testosterone testing is of utility in men with low libido. In such men initial screening with a morning total testosterone is reasonable, to be followed with a repeat morning total testosterone and free testosterone if the initial screen is below normal or in the low normal range. The practice of measuring testosterone in men with intact libido has been reported to not be cost-effective [9].

Q: What is phosphodiesterase 5 (PDE5)?

Phosphodiesterase 5 (PDE5) is an enzyme that terminates the activity of cGMP by converting it to an inactive form [10,11]. In the penis, the inactivation of cGMP by PDE5 blocks the cascade of events supporting erection, resulting in detumescence.

Q: What is tadalafil and how does it work?

Tadalafil is currently approved in at least 90 countries as an oral treatment for erectile dysfunction (ED). It is marketed throughout the world as Cialis[®] (pronounced “See-AL-is”). In Saudi Arabia, tadalafil is marketed as both Cialis[®] and Snafi[®].

Tadalafil is an inhibitor of PDE5. After entering smooth muscle cells in arteries within the corpus cavernosum of the penis, tadalafil competitively inhibits PDE5, and prevents the inactivation of the intracellular messenger cGMP. Consequently, by inhibiting PDE5 in the corpus cavernosum, tadalafil prolongs the action of cGMP, facilitating the erectile response to sexual stimulation.

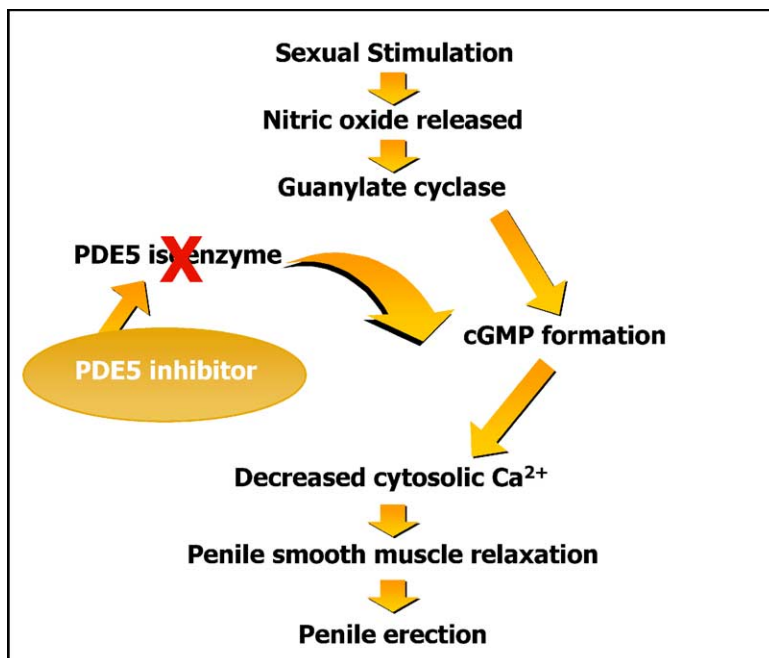


Figure 1

Q: Are there other PDE enzymes? Does tadalafil inhibit other PDEs?

The term *phosphodiesterase* refers to a “super-family” of enzymes consisting in humans of 11 families (isozymes or isoenzymes). Classification of the PDEs is based on their structure and whether they regulate the substrate cAMP, cGMP, or both. The PDEs are variously distributed throughout the body.

Different drugs have different selectivity for inhibiting the various PDE families. For example, a number of older compounds such as theophylline and papaverine inhibit many or all of the PDE isozymes including PDE5 [12–14]. In contrast, the three PDE5 inhibitors are more selective for inhibiting PDE5 relative to the other PDE isoenzymes. None of the PDE5 inhibitors has any significant effect against PDEs 1–4 and 7–10, but sildenafil citrate and vardenafil HCl do have some activity against PDE6 and tadalafil has some activity against PDE 11 [15].

Q: What is the clinical significance of inhibiting PDE6 and PDE11?

PDE6 is located in the retina, and is an essential component of visual transduction. Inhibition of PDE6 can result in transient vision changes such as blue halos and increased sensitivity to light [16]. Tadalafil has no significant effect on PDE6. Sildenafil and vardenafil inhibit PDE6 at concentrations within the therapeutic range.

The localization of PDE11 has not been fully characterized. PDE11 protein and/or messenger RNA have been reported in a number of human tissues, including prostate, pituitary, skeletal muscle, and testes [17,18]. However, the function of PDE11 is unknown. No clinical consequences of PDE11 inhibition have been identified, including no adverse effects on spermatogenesis or serum reproductive hormones [19]. Neither sildenafil nor vardenafil inhibit PDE11 at therapeutic concentrations. Tadalafil inhibits PDE11 at high plasma concentrations within the therapeutic range [20,21].

Q: What is the pharmacokinetic profile of tadalafil?

Pharmacokinetics (PK) simply stated is “what the body does to the drug” (ie, how the drug is absorbed, eliminated and metabolized). Phar-

macodynamics or PD is “what the drug does to the body.”

Absorption: After single oral-dose administration of tadalafil, the maximum observed plasma concentration (C_{max}) is achieved between 30 minutes and 6 hours (median time of 2 hours), although an erectogenic effect is not predicated on the need to reach C_{max}. The time to reach C_{max} is referred to as T_{max}. Neither the rate nor the extent of absorption of tadalafil is influenced by food. Thus tadalafil may be taken with or without food.

Metabolism: Tadalafil is predominantly metabolized by CYP3A4 to a methyl catechol glucuronide metabolite. In vitro data suggest that metabolites are not expected to be pharmacologically active following a dose of tadalafil.

Elimination: The mean elimination half-life (also sometimes referred to as “terminal half-life”) for tadalafil is 17.5 hours in healthy subjects. The half-life is the time it takes for the plasma concentration of drug in the body to be reduced by 50%. Tadalafil is excreted predominately as inactive metabolites, mainly in the feces and to a lesser extent, urine.

Q: Does tadalafil have an erectogenic effect in the absence of sexual stimulation?

No. Sexual stimulation (tactile, visual, etc.) is required to release nitric oxide to initiate its activation of cGMP. Tadalafil does not augment nitric oxide release and only works by inhibiting phosphodiesterase 5.

Q: How does tadalafil differ from the other two PDE5 inhibitors sildenafil and vardenafil?

Tadalafil differs from these two other PDE5 inhibitors in several ways. First, the tadalafil molecule belongs to a distinct chemical class and is structurally different from the other PDE5 inhibitors. Second, tadalafil has a plasma half-life of 17.5 hrs, resulting in an ability to improve erectile function for up to 36 hours [22–24]. The plasma half-life of sildenafil citrate is about 4 hours and the plasma half-life of vardenafil HCl is about 4.5 hours [25,26]. The duration of action of sildenafil citrate has been shown in one study to be up to 4 hours [27]. The duration of action of vardenafil HCl has not been determined. Third, the rate and

extent of absorption of tadalafil are not affected by food [21]. In contrast, the extent of absorption of vardenafil HCl is affected by a high-fat meal, and both the extent and rate of absorption of sildenafil citrate is affected by a high-fat meal [25,26]. Fourth, there are differences in the selectivity for inhibiting other isoenzymes of phosphodiesterase [20]. Sildenafil citrate and vardenafil HCl can inhibit PDE6 and tadalafil can inhibit PDE11. Fifth, the adverse event profiles (“side effects”) of the three PDE5 inhibitors are slightly different. The 4 most commonly reported adverse events for sildenafil and vardenafil include headache, flushing, dyspepsia, and nasal congestion [25,26]. The 4 most commonly reported adverse events for tadalafil include headache, dyspepsia, back pain, and myalgia [21]. Finally, instructions on the co-administration of alpha-blockers varies with the three drugs. A precaution is given for the combined use of sildenafil citrate and alpha-blockers; sildenafil citrate doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker. Combined use of vardenafil HCl and alpha-blockers is contraindicated. Combined use of tadalafil and alpha-blockers, except for tamsulosin 0.4 mg (Flomax[®]) once daily, is contraindicated. There are no restrictions in the timing of co-administration of tadalafil and tamsulosin 0.4 mg.

II. Tadalafil Efficacy

Q: How is efficacy for ED treatments measured? What are the IIEF, SEP, and GAQ?

The efficacy of tadalafil has been established in clinical studies by demonstrating a significant improvement in erectile function at the end of the study (“endpoint”) compared to the start of the study (“baseline”) compared to treatment with placebo. Tadalafil trials typically have used a co-primary endpoint of change in International Index of Erectile Function (IIEF) Erectile Function Domain score, measured at the end of the trial, and percent of “yes” responses to Sexual Encounter Profile (SEP) diary questions 2 and 3, recorded after each sexual encounter during the study:

IIEF: The International Index of Erectile Function (IIEF) [28] is a 15 question measurement of erectile function that has been cross-

culturally validated. The IIEF is typically administered prior to treatment to determine baseline erectile function and severity, and at endpoint, to determine the effect of treatment. The IIEF is a recall instrument that asks the man to think back over a period of time (typically 4 weeks), then answer each of the 15 questions. Because each question is assessed on a 0–5 or 1–5 scale, the IIEF score is expressed as a score. The 15 questions are divided into five domains (Erectile Function, Orgasmic Function, Sexual Desire, Intercourse Satisfaction, and Overall Satisfaction). Six questions comprise the Erectile Function (EF) Domain with a score for this domain ranging from 1 to 30. The EF domain is used to determine the severity of ED [29]. A score ≥ 26 is categorized as “no erectile dysfunction.”

SEP: The Sexual Encounter Profile (SEP) diary is composed of 5 questions. SEP Question 2 (“penetration”) is “Were you able to insert your penis into your partner’s vagina?” and SEP Question 3 (“maintenance”) is “Did your erection last long enough for you to have successful intercourse?” SEP3 is typically synonymous with “successful completion” or “successful intercourse.” Men complete the 5 questions in the SEP diary after each intercourse attempt. Because each question has a “yes” or “no” response, the SEP “score” is expressed as a percentage of “yes” responses.

Numerous other efficacy endpoints are also used and are designated for study purposes as secondary study endpoints. One common example is the GAQ, or Global Assessment Question. The GAQ is a question asked typically only at the end of the trial. The GAQ asks, “Has the treatment you have been taking during this study improved your erections?” Because the GAQ is only asked once at the end of the study, the GAQ is expressed as the overall percentage of “yes” responses. Considering that a yes response to the GAQ does not necessarily indicate an erection adequate for intercourse, the authors believe that the SEP3 responses are the most clinically relevant indicators of successful treatment of ED.

Q: How efficacious is tadalafil in the treatment of ED?

A meta-analysis of data from 2102 patients obtained in 11 placebo-controlled clinical trials [23] showed that for men taking tadalafil

20 mg, the mean per-patient rate of successful intercourse (SEP3) was 68% compared to 31% for placebo ($p < 0.001$). At the end of the 12-weeks, 71% (tadalafil 10 mg) and 84% (tadalafil 20 mg) of men responded via the GAQ that tadalafil had improved their erections compared to 33% taking placebo ($p < 0.001$).

Q: How quickly does tadalafil work after administration?

In a study using stopwatch methodology, tadalafil 20 mg facilitated an erectile response 16 minutes post-dose ($p = 0.012$ versus placebo) and tadalafil 10 mg facilitated an erectile response within 30 minutes post-dose ($p = 0.042$ versus placebo) [30]. These results are similar to those found for vardenafil HCl (16 minutes) and sildenafil citrate (14 minutes) [31,32]. However, it is important to note that the majority of men do not respond at these early time points. In all three studies, about one-third of men respond at these early time points. Most men will require more time to achieve an erection sufficient for vaginal penetration and intercourse.

Q: Tadalafil has a Tmax of 2 hours. Does this mean it takes 2 hours for tadalafil to work in men with ED?

No. Tmax is the time to peak plasma concentration and is a *pharmacokinetic* property of the drug. In contrast, time to onset of action is a *pharmacodynamic* measurement assessed clinically (i.e., the elapsed time between taking a pill and achieving the desired clinical effect – in this case, an erection). Because Tmax predicts the time to maximum plasma concentration, clinicians sometimes mistakenly equate it with the time to onset of efficacy. However, maximum plasma concentrations are typically not required for efficacy. Consequently, the time required to reach efficacious plasma levels is usually shorter than the time required to achieve peak plasma levels.

Q: How will I know how long it will take tadalafil to work in an individual patient?

Research data are typically reported as means and ranges for the group studied—an average of the results in many individual patients. Consequently, all research requires translation to an

individual patient in a given practice locale [33]. The only way to know how an individual patient will respond is to have him give the medication a trial and test his time to onset of an erection sufficient for penetration and successful completion of intercourse.

Q: What is the duration of action for tadalafil?

Tadalafil 10 and 20 mg have been shown to improve erectile function for up to 36 hours after dosing in most men [21-24].

Q: Does a man with ED need to “time” his dosing of tadalafil prior to anticipating sexual intercourse?

For other oral PDE5 inhibitors, patients must plan to have sexual intercourse soon after taking their medication, typically within 4 hours. In contrast, tadalafil has been shown to be efficacious up to 36 hours after dosing. Therefore, patients are not required to engage in sexual intercourse soon after taking tadalafil. In a recent study of men from the US and Puerto Rico, patients treated with tadalafil 20 mg were receptive to the 36-hour duration, and the majority (55.2%) of intercourse attempts occurred between 4 and 36 hours after dosing [34]. Intercourse success during the interval 4–36 hours was 71% for patients treated with tadalafil compared to 18% for patients receiving placebo [34]. For example, in France, tadalafil has been dubbed “le weekend” drug based on the strategy of taking the drug Friday afternoon or evening in advance of anticipated sexual relations during the weekend.

Q: How does the efficacy of tadalafil compare to sildenafil citrate and vardenafil HCl?

No blinded, head-to-head efficacy comparisons of the three PDE5 inhibitors have been published in peer-reviewed journal articles. However, because their mechanism of action is similar, there is no reason to assume there will be any significant differences in ED efficacy for the first several hours following dosing of all three PDE5 inhibitors [35]. The efficacy results from sildenafil citrate, tadalafil, and vardenafil HCl trials seem to be generally similar when the same statistical analysis methods are used. Clinicians should

note that ED therapy trials may vary regarding the population of men studied, severity of ED, presence of comorbid illnesses, first time therapy with a PDE5 inhibitor (“PDE5 inhibitor naïve”), and previous success or failure with another PDE5 inhibitor, or other ED therapy. Comparison of study data from separate studies enrolling different populations is inherently speculative and can lead to erroneous conclusions. Nevertheless, all three PDE5 inhibitors have been extensively studied across broad populations of men with ED of varied etiology and functional severity, and have been shown to improve erectile function in the majority of such men.

Q: Which sub-populations of men with ED are typically more difficult to treat with PDE5 inhibitors?

Depending on the severity of the underlying etiology and other factors, the efficacy of PDE5 inhibitor therapy may be diminished. In general, ED that is associated with severe nerve injury or severe vascular/endothelial injury (advanced generalized atherosclerosis and diabetes) will be more difficult to treat with PDE5 inhibitor therapy.

Two of the most common difficult to treat causes of ED are diabetes mellitus and post-radical prostatectomy. Diabetes mellitus can produce ED through multiple pathophysiological mechanisms including autonomic neuropathy, accelerated atherosclerosis, and endothelial dysfunction. Radical prostatectomy may result in permanent nerve damage. Even nerve-sparing techniques, which attempt through meticulous anatomical dissection to avoid direct injury to the pelvic nerves, may result in neurapraxia.

Q: Is tadalafil efficacious in treating ED associated with diabetes mellitus?

Yes. The risk of ED is 4-fold higher in men with diabetes and approximately 50% of men with diabetes mellitus have ED [36]. Although the causes of ED in diabetes mellitus are multifactorial, at least two major mechanisms are involved – endothelial dysfunction of the penile microvasculature and neuropathy of the nerve fibers that innervate the penis. The efficacy of tadalafil has been evaluated in 637 men with Type 1 and Type 2 diabetes ($HbA_{1C} \leq 13\%$) [37]. Treatment with tadalafil significantly improved

erectile function in men with diabetes regardless of baseline HbA_{1C} levels or type of diabetes therapy (insulin, oral agents, or diet alone). The mean proportion of successful intercourse attempts in these patients with diabetes was 53% (tadalafil 20 mg) and 49% (tadalafil 10 mg) compared to 22% of patients receiving placebo ($p < 0.001$).

Q: Is tadalafil efficacious in treating ED following nerve-sparing radical prostatectomy?

Yes. Erectile dysfunction following bilateral nerve sparing retropubic radical prostatectomy results from smooth muscle degeneration secondary to neurapraxia and hypoxia [38]. Even with nerve-sparing surgical techniques, nerve injury may result from the unintentional surgical severing of nerve tissue, nerve stretching during prostate retraction, thermal or ischemic injury to nerves, or local inflammatory effects. [39] Tadalafil 20 mg has been shown to improve erectile function in men following bilateral nerve-sparing radical retropubic prostatectomy (BNSRRP) [40]. The mean percentage of successful intercourse attempts (SEP3) was 41% for men taking tadalafil compared to 19% on placebo ($p < 0.001$). The improvements in IIEF, SEP, and GAQ scores were higher overall for a subgroup of men with evidence of tumescence ability after prostatectomy (i.e., less severe ED). This study evaluated men who had ED 12–48 months post-surgery. PDE5 inhibitor therapy administered on a daily basis within 30 days of radical prostatectomy is being studied to determine if this facilitates the earlier return of erectile function [41].

Q: Does tadalafil work in older men with ED?

Yes. In an analysis of 11 integrated studies where 23% of men were over age 65 [23], the mean change in IIEF EF Domain scores from baseline to endpoint for men ≤ 65 taking tadalafil 20 mg was 8.8. For men > 65 , the mean change from baseline was 8.0. For men taking tadalafil 10 mg, the mean change from baseline to endpoint was 6.6 (≤ 65 y) and 6.3 (> 65 y) ($p < 0.001$ for all comparisons of tadalafil to placebo). The mean changes from baseline to endpoint for the two age groups were not significantly different ($p = 0.74$). Thus, the response to tadalafil was not influenced by age.

III. Maximizing Tadalafil Therapy

Q: How frequently can tadalafil be taken?

Tadalafil can be taken up to once a day prior to sexual activity.

Q: Is the half-life of tadalafil long in comparison to other commonly prescribed pharmaceutical agents?

The half-life of tadalafil is 17.5 hours. For comparison, the half-lives of other commonly used drugs in primary practice include 14 hours for atorvastatin (Lipitor[®]), about 15 hours for tamsulosin (Flomax[®]), 15 hours for naproxen sodium (Anaprox[®]), about 22 hours for doxazosin (Cardura[®]), 24 to 26 hours for sertraline (Zoloft[®]), and 5 weeks for dutasteride (Avodart[®]).

Q: What is the recommended starting dose for tadalafil?

In approximately 60% (56/90) of countries including the USA, the recommended starting dose for most men is 10 mg. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. In approximately 40% (34/90) of countries, the recommended starting dose is 20 mg. Please refer to the package insert pertaining to your locale to determine the recommended starting dose.

Q: Why do dosing instructions vary from country to country?

Variations in label language among countries are common for most drugs, including tadalafil, and are in general due to differences in interpretation of data regarding medications by the different regulatory agencies. The label language (prescribing instructions) for tadalafil in a given country is based on the core data regarding the drug and the interpretation of local regulatory authorities.

Q: When should I adjust the dose of tadalafil?

No dosing adjustment are needed for the following parameters: age, body mass index (BMI), smoking, or concurrent diabetes mellitus.

Dosing needs to be adjusted for the following:

Renal insufficiency: (USA Label) No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency, a starting dose of 5 mg not more than once daily is recommended, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. For patients with severe (creatinine clearance <30 mL/min) renal insufficiency on hemodialysis, the maximum recommended dose is 5 mg.

Hepatic impairment: For patients with mild or moderate degrees of hepatic impairment (Child-Pugh Class A or B), the dose of tadalafil should not exceed 10 mg once daily. In patients with severe hepatic impairment (Child-Pugh Class C), the use of tadalafil has not been studied.

CYP3A inhibitors: Because CYP3A4 inhibitors reduce the metabolism of tadalafil, concurrent use with these agents may increase tadalafil plasma levels and lengthen the amount of time that tadalafil levels are detectable. For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of tadalafil is 10 mg, and the drug should not be taken more frequently than once every 72 hours. Other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure, although the specific interactions of these compounds with tadalafil have not been studied.

Because tadalafil neither inhibits nor induces the major CYP450 isoforms to a clinically significant degree, tadalafil is not anticipated to affect the metabolism of other agents metabolized by the CYP4503A4 pathway [21].

Q: Can tadalafil be taken with alcohol (ethanol)?

Yes. Alcohol can be consumed with tadalafil. PDE5 inhibitors, including tadalafil, and alcohol are both mild systemic vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. The substantial consumption of alcohol (e.g., 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. A unit of alcohol is roughly

equivalent to a half pint of beer, 25 mL measure of “hard alcohol” (eg., vodka, whisky, or gin), or 125 mL of wine. In a clinical study when 0.7 g/kg alcohol (equivalent to 6 ounces of 80-proof vodka in an 80 kg male) was imbibed within 10 minutes concomitantly with tadalafil, more subjects had clinically significant decreases in blood pressure than in subjects receiving alcohol alone. When tadalafil 20 mg was administered concurrently with alcohol at a lower dose of 0.6 g/kg (equivalent to approximately 4 ounces of 80-proof vodka imbibed within 10 minutes), hypotension was not observed and dizziness occurred with a similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Clinicians should discuss with their patients the following precautions before prescribing tadalafil for the treatment of erectile dysfunction: There is the potential for PDE5 inhibitors to augment the blood pressure lowering effect of excessive alcohol consumption. Additionally, excessive alcohol consumption may impair sexual performance and the ability to achieve an erection.

Q: Does food affect the absorption of tadalafil?

Neither the extent nor the rate of absorption of tadalafil are affected by food, including a high-fat meal [42,43]. A “high-fat” meal can be defined as any meal that contains at least 59 g of fat, which roughly equates to a large cheeseburger sandwich and large french fries.

Q: How should patients with ED associated with diabetes mellitus be counseled?

Since diabetes is a common risk factor for ED, all patients presenting with ED should be screened for elevations in fasting glucose. In a recent study, Lewis noted that 12% of patients presenting with ED had pre-existing underlying diabetes [44]. ED associated with diabetes is often severe and typically presents at a younger age than ED in the general population. For example, Nicolosi found that the incidence of ED in men with diabetes age 45 to 49 was similar to the incidence of ED in nondiabetic men over 70 [45].

Since ED often presents at a younger age in men with diabetes, the impact of ED on qual-

ity of life is likely greater in these men. Despite the impact, men with diabetes and ED are reluctant to proactively discuss erectile function with healthcare professionals. On the other hand, practitioners also seem to be reluctant to broach the subject with their patients. Nicolosi found that only 14.4% of men with diabetes were asked about sexual health during a routine medical visit [45]. Therefore, annual health maintenance screening in men with diabetes should include questions about erectile function, along with efforts to improve glycemic and lipid control, normalize blood pressure, and screen for microvascular complications. Early detection of ED—prior to diabetes-associated endothelial cell and nerve function damage—allows for a more robust response to PDE5 inhibition and is rewarding to the patient, partner, and physician alike.

Q: How should patients with ED post-radical prostatectomy be counseled?

Clinicians should consider counseling patients with post-radical prostatectomy (nerve sparing) ED that recovery from the neurapraxia may be gradual and delayed, and noninvasive erectogenic treatment should not be abandoned until adequate recovery time has passed. In general patients should be advised that a number of baseline parameters will significantly influence the final postoperative outcome in terms of recovery of erectile function. They include: patient age at time of surgery (patients younger than 60 years do better); potency status (patients preoperatively having rigid erections sufficient to complete a satisfactory sexual intercourse do better); use of PDE5 inhibitor (patients who regularly use a PDE5 inhibitor to achieve good erections prior to surgery usually report worse results postoperatively); and systemic comorbidities (patients without vascular comorbidities do better) [39,46,47]. Surgical expertise remains of fundamental importance, in that the extent of neurovascular bundle preservation is an independent predictor of erectile function recovery [48]. Based on our (F.M.) clinical experience, in a patient with the above mentioned baseline conditions and treated with a bilateral nerve sparing radical prostatectomy, a PDE5 inhibi-

tor may be expected to enhance the erectile response and help generate erections sufficient to engage in sexual activity within 6–18 months after surgery.

Part 2 - Safety and Tolerability

Introduction

This report is the second of two parts designed to provide primary care clinicians with answers to frequently asked questions about tadalafil. The first answered frequently asked questions about optimizing the efficacy of tadalafil in treating men with ED. The second part answers frequently asked questions about how the safety and tolerability of tadalafil have been established.

Q: How many men have taken tadalafil?

Tadalafil has been studied in over 100 clinical pharmacology studies and clinical trials involving over 12,000 patients. More than 10,000 additional patients are currently involved in on-going studies. Almost 3 million men are estimated to have taken tadalafil since it was first approved in 2002 in the European Union. Tadalafil is now approved in 90 countries with submission approvals pending in the remaining countries where the drug will ultimately be commercially available.

Q: How has the safety of tadalafil been assessed?

Regulatory agencies around the world have approved up to once-daily dosing of tadalafil at doses of up to 20 mg. The safety of a drug is determined by the monitoring of adverse events reported in humans that take a drug during clinical trials or in a real-world setting. The evidence of the safety of tadalafil is based on data from over 12,000 patients in over 100 studies, including men who have taken tadalafil 10 mg or 20 mg daily for up to 6 months, and global safety monitoring from use in nearly 3 million men. The safety of tadalafil is continually monitored worldwide to add to this core safety database.

In a long-term (18 to 24 months) study of tadalafil taken as needed, 493 men completed 24 months of treatment, and a further 234 completed 18 months of treatment. The total

tadalafil exposure was 1676.0 patient-years. The rate of discontinuations due to adverse events for this 18 to 24 month duration study was 6.3% and the rate of discontinuation for any individual adverse event was <1%.

No consistent pattern of serious adverse events assessed as causally associated with tadalafil administration was observed in this study. None of the four deaths that occurred during the study was assessed as tadalafil related. There were no clinically significant laboratory abnormalities, electrocardiographic findings, or changes in vital signs in mean baseline-to-endpoint analysis attributable to tadalafil. Tadalafil administration was not causally associated with hepatotoxicity, neutropenia, thrombocytopenia, or renal dysfunction. As a result, tadalafil at doses of 5, 10, or 20 mg taken as needed up to once daily for 18 to 24 months was considered to be safe and well tolerated. [Cardiac safety will be discussed below].

The safety profile of any medication, including tadalafil, is established by a combination of clinical pharmacology trials exploring drug interactions, placebo controlled efficacy and safety trials, long-term, open-label safety studies, and finally post-marketing surveillance. To date, studies have shown that even with long-term use, inhibition of PDE5 can be used to treat ED safely and effectively [49,50,55–57].

Q: What are the common side effects of tadalafil?

The side effects that occurred in at least 3% of patients during short-term (12 weeks) studies of tadalafil include headache, dyspepsia, back pain, nasopharyngitis, myalgia, flushing, and nasal congestion [22,23]. A similar profile of adverse events was seen in a long-term study (18 to 24 months) of tadalafil [50]. In most patients, these events are mild or moderate in severity, and they are not persistent. Over the course of the clinical trials, the incidence of new-onset adverse events declined from the initial visits to the last patient visits for the tadalafil-treated subjects [22].

Q: Does tadalafil cause back pain?

Back pain and/or myalgia (the two may overlap) are seen with all PDE5 inhibitors, but

are reported more frequently with tadalafil. Generally, about 5% of men taking tadalafil will experience back pain, which may occur 12 to 24 hours after dose administration, and typically resolves within 48 hours [21,22]. For the men who are troubled by this symptom, an over the counter analgesic such as acetaminophen can be taken for relief. Only about 0.5% of men taking tadalafil (less than 1 in 100) found the back pain sufficiently problematic that drug discontinuation occurred. Most importantly, prospective evaluation of patients experiencing back pain or myalgia did not reveal any evidence of an inflammation, rhabdomyolysis, or renal abnormality.

Q: Since tadalafil has a long duration of efficacy, does that mean the side effects will last a long time?

Side effects with tadalafil usually go away after a few hours. Specifically, patients who get back pain and muscle aches usually get it 12 to 24 hours after taking tadalafil. Back pain and muscle aches usually go away by themselves within 48 hours.

Q: Does tadalafil affect semen or reproductive hormones?

Tadalafil 20 mg given daily for 6 months to men 45 years or older had no adverse effects on spermatogenesis—as assessed by sperm concentration, sperm count per ejaculate, sperm motility, and normal morphology—or serum reproductive hormones (testosterone, follicle stimulating hormone and luteinizing hormone) [19].

Q: Has priapism been reported with tadalafil therapy?

In the over 100 clinical trials completed to date (involving more than 12,000 patients) no reports of priapism have been observed. Rare reports of priapism have been reported following the administration of other PDE5 inhibitors. There have been rare reports of priapism in post-marketing surveillance of tadalafil. PDE5 inhibitors should be prescribed with caution in patients who have conditions that might predispose them to priapism (sickle cell anemia, multiple myeloma, or leukemia).

Q: What effects does tadalafil have on vision?

Visual side effects associated with tadalafil are rare, likely due to tadalafil's low affinity for PDE6. In the analysis of 11 integrated randomized, double-blind, placebo-controlled trials lasting 12 weeks [23], there were no reports of “blue vision” among the 1464 men taking tadalafil. In a long-term safety study involving 1173 men taking tadalafil for 18 to 24 months [50], one episode of “blue vision” was reported.

Q: Can my patients take tadalafil with statins?

Yes, tadalafil may be prescribed in men taking statins (HMG-CoA reductase inhibitors) to lower cholesterol. Co-administration of tadalafil with statins is well tolerated with no evidence of increased adverse events, including back pain and myalgia. Also, in a clinical pharmacology study there was no clinically significant pharmacokinetic interaction when tadalafil and lovastatin (Mevacor[®]) were co-administered. Specifically tadalafil 20 mg did not increase plasma concentrations of lovastatin.

In an integrated placebo-controlled tadalafil database involving 2945 subjects, 388 men (13.2%) received statins simultaneously with study drug. The relatively high proportion of men treated with statins in this population of males with erectile dysfunction is not surprising, because hyperlipidemia is a prominent risk factor for ED. A detailed analysis of this large population of men taking tadalafil concomitantly with HMG-CoA reductase inhibitors has indicated that the administration of statins does not increase the relative risk of back pain, myalgia, or pain in limb in tadalafil-treated patients (10 and 20 mg) relative to placebo-treated patients.

Q: Does tolerance (tachyphylaxis) occur with long-term use of tadalafil?

No, there have been no reports or evidence showing tachyphylaxis or tolerance with long-term tadalafil therapy. *Tachyphylaxis* is the rapid, progressive decrease in response to a given dose following repetitive administration of the drug. *Tolerance* is the reduction in response to the drug after repeated administrations over time, the result being that a higher dose is required to produce the same effect that

was once obtained at a lower dose. In a clinical study of patients using tadalafil 10 – 100 mg daily for three weeks, [51] no patients withdrew due to tachyphylaxis (perceived sudden lack of efficacy). In another clinical study of patients taking tadalafil on an ‘as needed’ (PRN) basis for 6 months, significant improvements in erectile function were demonstrated on all efficacy variables at both 3 and 6 months. In addition the mean change from baseline of intercourse success observed in the initial 3 months of therapy were similar to that observed in the final 3-month treatment period. The consistent efficacy at these two time points suggests that there is no tolerance to tadalafil over time. Furthermore, the low rate of discontinuations due to lack of efficacy in a long-term (18 to 24 months), open-label safety study provides further support to that observation [50].

Q: Is sexual activity safe in men with cardiovascular disease?

Cardiac disease and erectile dysfunction frequently coexist. Sexual activity, being physical activity, carries a potential cardiac risk for those patients with pre-existing cardiac disease. This risk may include the triggering of a myocardial infarction due to the increase in cardiac workload associated with sexual activity. Therefore, it is generally considered unwise for any patient with unstable cardiovascular disease to engage in sexual activity, regardless of whether they have taken a PDE5 inhibitor. Unstable cardiovascular disease is defined as: unstable or refractory angina; uncontrolled hypertension; congestive heart failure (Class III or IV); very recent MI (<2 weeks); high-risk arrhythmias; obstructive cardiomyopathies; moderate-to-severe valvular disease [52]. Sexual intercourse requires 3 to 4 METS (Metabolic Equivalent of the Tasks) of energy expenditure. This energy requirement is approximately equivalent to walking at a rate of 3 MPH (or one mile in 20 minutes on level ground) [53].

Accordingly, the physical demands of intercourse can generally be considered safe for a patient who can walk comfortably one mile in 20 minutes without notable symptoms.

Q: Is tadalafil safe in men with cardiovascular disease?

Tadalafil has an established safety profile including its cardiovascular safety profile. In

the more than 12,000 patients who have been exposed to tadalafil in clinical trials, the cardiovascular-related adverse events have been low and comparable to placebo-treated patients [54].

In tadalafil studies, about 15% of patients had hyperlipidemia, 20% had diabetes, and about 30% had hypertension [54]. Extensive evaluation of cardiac parameters did not demonstrate any clinically relevant cardiac events attributable to tadalafil. The incidence of adverse events associated with cardiovascular function (such as dizziness, syncope, or chest pain) was low, and tadalafil was not associated with an increased incidence of these events. Also, the incidence of myocardial infarction in tadalafil clinical trials was 0.33 per 100 patient years, which is no higher than that observed in the placebo-treated patients in the same set of trials (0.41 per 100 patient years) or in age-standardized male population (0.6 per 100 patient years) [55–57].

For tadalafil, the following groups of patients have not been studied: patients with a myocardial infarction within the last 90 days, patients with unstable angina, or angina occurring during sexual intercourse, patients with New York Heart Association Class 2 or greater heart failure in the last 6 months, patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension (>170/100 mm Hg), and patients with a stroke within the last 6 months. Thus, tadalafil should not be prescribed to this patient population.

Tadalafil has minimal effects on blood pressure and heart rate in healthy subjects [58]. At a dose of 100 mg, 5 times higher than the highest recommended dose, there were no clinically relevant effects of tadalafil on ventricular repolarization as assessed by QTc interval measurement [21,58]. Further, no adverse effects on myocardial blood flow or time to ischemia have been demonstrated in patients with coronary artery disease taking tadalafil [21].

Q: Can my patients take tadalafil with alpha-blockers?

Alpha-blockers are commonly used in the treatment of symptoms of benign prostatic hyperplasia (BPH) and some are indicated for hypertension. In the USA, tadalafil may be prescribed with tamsulosin 0.4 mg (Flomax[®])

daily, but is contraindicated with other alpha-blockers (e.g., doxazosin (Cardura[®]), terazosin (Hytrin[®]), prazosin (Minipress[™]), and alfuzosin hydrochloride (UroXatral[®])).

Tamsulosin: Tamsulosin is a selective alpha[1A]-adrenergic blocker commonly used to treat lower urinary tract symptoms (LUTS) and BPH symptoms. No significant blood-pressure lowering effect was seen in a study testing the interaction of tadalafil with tamsulosin 0.4 mg administered once-daily [59].

Doxazosin: In the USA, tadalafil is contraindicated with doxazosin and other alpha-adrenergic blockers (with the exception of tamsulosin 0.4 mg once daily). When tadalafil 20 mg was administered to healthy subjects taking doxazosin 8 mg daily, there was an augmentation of the blood-pressure lowering effect of doxazosin, and the number of subjects with potentially clinically significant standing blood pressure decreases was greater for the combination of doxazosin and tadalafil compared to the combination of doxazosin and placebo [60]. There were no cases of syncope.

Variation in label language: The contraindication with alpha-blockers is specific to the US label. Information regarding the concomitant use of alpha-blockers depends upon the country and the associated label for which such use is being considered. Please refer to the package insert pertaining to your locale when advising whether the concomitant use of tadalafil and alpha-blockers is contraindicated, “discouraged,” “not recommended,” or “used with caution.”

Q: Can tadalafil be prescribed to men with ED who are on one or more antihypertensives?

Tadalafil can be prescribed to men with ED who are on one or more antihypertensives, with the exception of those alpha-blockers which are used to treat hypertension. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are being treated with antihypertensive medications and taking a PDE5 inhibitor.

Tadalafil has been studied with concomitant use of antihypertensive medications because many patients who experience erectile dysfunction also have hypertension. Specific

drug-interaction studies, examining the use of tadalafil and commonly prescribed oral antihypertensive agents, and extensive safety data from patients taking tadalafil and oral antihypertensives concomitantly, demonstrate that tadalafil is generally safe in patients receiving one or more concomitant antihypertensive agents [61,62].

Studies have been conducted to test the interaction of tadalafil with antihypertensive agents including amlodipine besylate (Norvasc[®]), metoprolol (Toprol-XL[®]), bendroflumazide, enalapril maleate (Vasotec[®]), or angiotensin II receptor blockers. No clinically significant interactions were observed [62].

Q: Some of my patients with ED taking tadalafil also have ischemic heart disease. Can I prescribe PRN nitrate therapy in case they have chest pain?

No. All PDE5 inhibitor therapy including tadalafil are *contraindicated* in men taking any form of organic nitrates including sublingual and long-acting nitroglycerin. PDE5 inhibitors potentiate the hypotensive effect of nitrates. Nitrate therapy, even if PRN, should not be prescribed and patients should be instructed to discard any leftover nitroglycerin tablets while on PDE5 inhibitor therapy. Patients with ischemic heart disease who wish to take a PDE5 inhibitor for the treatment of their ED should be counseled that in case they have chest pain they should seek immediate medical care, they should not take nitroglycerin, and they should inform the health care provider that they are on a PDE5 inhibitor, and when they last took it. Though nitrates are highly effective in relieving pain associated with myocardial ischemia, they do not alter long-term survival [63–65].

Q: If my patient has chest pain while on tadalafil, how should he be treated in the emergency room?

Administration of nitrates to a patient on any PDE5 inhibitor, including tadalafil, is contraindicated. Physicians and paramedics need to be aware of this potentially serious interaction. Thus, if a patient presents with chest pain, it will be imperative to question whether the patient has used a PDE5 inhibitor and the

timing of any such use. In a drug-interaction study, the hemodynamic interaction between tadalafil and sublingual nitroglycerin lasted 24 hours, but was not seen at 48 hours [66]. If the man has taken tadalafil within 48 hours, then organic nitrates should not be given. If nitrates are deemed medically necessary in a life-threatening situation 48 hours or more after the use of tadalafil, they should be administered under medical supervision with hemodynamic monitoring. If the chest pain is secondary to myocardial ischemia, then treatment other than nitrates should be instituted immediately. These include beta-blockers, calcium channel blockers, morphine, oxygen, aspirin, heparin, percutaneous coronary intervention, and/or thrombolytic therapies. Physician judgment should guide the selection of the most appropriate treatment modality for the patient.

According to ACC/AHA guidelines, where there is no contraindication, antiplatelet therapy should be initiated with aspirin early in the emergency care of patients with acute coronary syndrome [67]. Tadalafil does not potentiate the increase in bleeding time caused by aspirin.

Q: Can tadalafil be taken with amyl nitrate?

No. Amyl nitrate, often referred to as “pop-pers,” is an organic nitrate. All PDE5 inhibitors

including tadalafil are contraindicated in the presence of ANY organic nitrate. Men should be counseled that amyl nitrate and butyl nitrate, which may be abused recreationally, are organic nitrates and are therefore also contraindicated.

Continued Learning

Q: Where can I find additional information about tadalafil?

Additional information about tadalafil is available at regulatory websites, including websites for the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or from regulatory agencies in your country. You can find additional information on the Internet at the official Cialis website: <http://www.cialis.com>.

There are also several good books available, in addition to the articles referenced herein: Jackson, *Sex, the Heart and Erectile Dysfunction*; Eardley and Sethi, *Erectile Dysfunction: Current Investigation and Management*; and Shabsigh, *Back to Great Sex: Overcome ED and Reclaim Lost Intimacy*.

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