REVIEW

A once-daily dose of tadalafil for erectile dysfunction: compliance and efficacy

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Abstract: Selective phosphodiesterase type 5 inhibitors (PDE5Is) have revolutionized the treatment of erectile dysfunction (ED) in men. As an on-demand treatment, PDE5Is have excellent efficacy and safety in the treatment of ED due to a broad spectrum of etiologies. Nevertheless, these drugs do have side-effect profiles that are troublesome to some patients, eg, headache, dyspepsia, myalgia, etc. Furthermore, many patients and their partners dislike the necessity of on-demand treatment for ED, citing a desire for greater spontaneity with sexual interactions. In 2008, approximately 10 years after the release of the first commercially available PDE5I, a paradigm shift in the management of ED occurred with the approval of once-daily dose of tadalafil by the US Food and Drug Administration for the management of ED. The prolonged half-life of tadalafil lends itself well to this dosing regimen and conveys the advantage of separating medication from sexual interactions; lower dose therapy also carries the theoretical benefit of lower incidence of side effects. In this study, we review the current state of the art with respect to this new management strategy for ED, highlighting published reports of the efficacy and tolerability of the daily dose tadalafil regimen.

Keywords: PDE5 inhibitor, on-demand therapy, side effects, daily dosing

Introduction

Erectile dysfunction (ED) is defined as the persistent and/or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual intercourse.[1] This problem is prevalent throughout the world and is strongly associated with age-related comorbidities; hence, the incidence of ED will likely increase dramatically as the world's population ages.[2] ED is associated with substantial psychological distress for both men and their partners and has been clearly linked to cardiovascular health problems both as a comorbid condition and as a sentinel event for serious vascular diseases in the future.[2–5]

In this modern era, selective phosphodiesterase type 5 inhibitors (PDE5Is) are the mainstay of treatment for ED.[6] These medications are highly efficacious, are well tolerated, and have very favorable safety profiles. In the United States, 3 PDE5Is are currently available; sildenafil (Viagra®, Pfizer), vardenafil (Levitra®, Bayer), and tadalafil (Cialis®, Lilly-ICOS).[7] Each of these drugs is highly efficacious in the management of ED although pharmacokinetic and side-effect profiles differ and results for each drug may vary for individual men.[7,8] Another PDE5I, udenafil, has been approved for use in South Korea, and a number of novel PDE5Is are currently in various stages of development.[9,10]

Tadalafil was approved for use in the United States in November 2003, after both sildenafil and vardenafil were approved.[11] Tadalafil differs from the other 2 PDE5Is

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in that the absorption does not appear to be influenced by the intake of fatty meals or alcohol.[11] Peak serum concentration is attained about 2 hours postdose rather than 1 hour as occurs with the other 2 PDE5Is.[12] Tadalafil is also unique in that it has a long elimination half-life of approximately 18 hours.[13] The potential advantage of this prolonged duration of action is that the other medications can be separated temporally from sexual activity.[14] The theoretical impact of this pharmacokinetic property is that sexual spontaneity may be more easily restored using this medication.[15] However, the prolonged half-life of tadalafil also makes it more prone to long-lasting adverse effects (such as headache) relative to the other PDE5Is, with up to 30% of men on tadalafil treatment reporting side effects lasting greater than 12 hours.[16] Importantly, chronic dosing of tadalafil has not been shown to lead to upregulation of PDE5 in human penile tissue,[17] an effect that has been observed in rat penile tissue exposed continuously to high doses of sildenafil.[18] This difference may theoretically make tadalafil less likely than sildenafil to lose its efficacy over time due to tachyphylaxis.

There has long been a substantial interest in routine dosing of PDE5Is as a new and novel approach to the management of ED. The advantage of daily dosing for management of ED is the complete separation of medication use from sexual activity.[14,19] Furthermore, routine low-dose exposure may diminish overall drug exposure in men who engage in sexual intercourse more than twice weekly and may minimize side effects in men who have trouble tolerating higher doses of the PDE5I.[19,20]

The prolonged half-life of tadalafil makes it ideally suited for daily dosing and attainment of steady-state serum levels.[21,22] In the multicenter, randomized, Scheduled Use versus on-demand Regimen Evaluation (SURE) study, 4,262 men with ED were treated with 20 mg of tadalafil 3 times weekly or 20 mg on-demand in a 12-week cross-over design. At follow-up, more than 60% of men in both arms reported normalization of erectile function. More than 70% of men in both groups reported ability to successfully penetrate and complete sexual intercourse relative to 21% at baseline. There were no differences in success rate between routine and on-demand dosing for any efficacy parameter.[23] There was a substantial difference in the timing of intercourse between the treatment arms, with 53% of attempts in the on-demand arm and 29% of attempts in the routine dose arm occurring within 4 hours of dosing.[24] This suggests that greater flexibility with respect to timing was possible in the routine dose group. Although efficacy data did not demonstrate a difference, the 3 times a week dosing regimen for tadalafil

was preferred only by 43% of enrolled patients.[25] Although on-demand therapy was preferred by a majority of men, it was apparent that routine dosing was also a good option for a substantial minority of subjects.

The SURE study was 1 of the first of many studies investigating the utility of chronic dosing for tadalafil. These efforts culminated, in 2008, in US Food and Drug Administration's approval of tadalafil at a 2.5-mg or 5-mg daily dose for the management of ED.[11,19] This paradigm shift in the management of ED represented not only a new way to treat the condition but also a change in our conception of the disorder; ED is no longer strictly a situational problem in need of on-demand treatment but rather is a chronic condition that can be managed with routine-dose pharmacotherapy.

In this study, we will discuss the current state of the art for daily dose of tadalafil in the management of ED from the studies published before April 2010. The particular areas of investigation will include safety, efficacy, and compliance. Routine-dose tadalafil is also under investigation for a number of non-ED conditions;[26–28] however, in the interest of conciseness, we will focus our attention on indications related to erectile function.

Methods

A literature review was conducted to obtain all publications pertaining to routine-dose tadalafil. The search terms used on PubMed included *tadalafil*, *ED*, *daily dosing*, *routine dosing*, and *Cialis*. Manuscripts were identified and selected based on their relevance to the subject matter of daily dose tadalafil for ED. Selected manuscripts were read and critically reviewed. Particular attention was directed to manuscripts based on randomized, double-blind, placebo-controlled studies (RDBPCSs).

Physiology of penile erection

To understand the action of PDE5 inhibitors, it is necessary to have some familiarity with the molecular mechanisms of penile erection. Briefly, sexual stimulation induces nitric oxide (NO) release from endothelial cells and nonadrenergic and noncholinergic neurons. NO activates the cellular enzyme guanylate cyclase, which cleaves guanosine triphosphate into cyclic guanosine monophosphate (cGMP). cGMP in turn activates a series of downstream G proteins, which collectively lead to a decline in intracellular calcium content and subsequent smooth muscle relaxation. With muscular relaxation, there is a dilation of the cavernous arteries and corporal sinusoids of the penis, leading to enhancement of blood flow.[29]

PDE5 is the enzyme primarily responsible for the hydrolysis of cGMP in the penis.[30] Inhibition of PDE5 leads to persistent vasodilation and maintenance of penile blood flow by sustaining a high level of cGMP in the cavernous tissues and arteries.[30] It is important to note that PDE5I do not spontaneously produce vasodilation; sexual stimulation is required for potentiation of erection with PDE5I. For this same reason, the efficacy of these drugs tends to be less in patients with conditions in which NO activity (and subsequent production of cGMP) is low or absent, such as diabetes or after pelvic surgery.[31,32]

Assessing efficacy of ED treatments

When interpreting data on efficacy in the ED literature, it is essential to be familiar with the existing validated instruments for assessment of treatment response. The International Index of Erectile Function (IIEF) is the most widely used quantitative validated scale for studies of ED treatments. Consisting of 15 items covering 5 domains of male sexual function, it is most commonly utilized to assess the change in erectile function after treatment.[33] Six items of the IIEF pertain directly to erectile function and comprise the IIEF erectile function domain (IIEF-EF or IIEF-6; score range 5–30).[33] A score of 26–30 points on the IIEF-EF is generally consistent with normal erectile function, with progressively lower scores indicative of ED of worsening severity (22–25 = mild ED, 17–21 = mild to moderate ED, 11–16 = moderate ED, and ≤10 = severe ED).[34] Additional domains of sexual function assessed by the IIEF include sexual desire, intercourse satisfaction, orgasmic function, and overall satisfaction.[33] Although similar but distinct instruments for the assessment of ED (such as the IIEF-5 or Sexual Health Inventory for Men) are also used in both clinical and research contexts, most studies of daily dose tadalafil to date are relied mostly on IIEF-EF domain scores.

The sexual encounter profile (SEP) questions are also common end points for studies of ED treatments.[35] Designed as diary entries to be made after each attempt at sexual intercourse, the SEP profile consists of 5 questions, each of which is primarily dependent on an affirmative response to the prior question. The SEP questions are in the following order – SEP1: "During sexual activity, did your penis become erect?" SEP2: "Whether you were able to insert your penis into your partner's vagina?" SEP3: "Did your erection last long enough for you to have a successful intercourse?" SEP4: "Are you satisfied with the hardness of your erection?" SEP5: "Are you overall satisfied with this sexual experience?"[35] Although the instruments are subjective in nature, they do encompass the efficacy of any given drug treatment in a simple "yes" and "no" fashion.

The IIEF and SEP questionnaires investigate sexual function specifically. Different instruments must be utilized to assess the influence of ED treatment on relationship factors and other interpersonal variables. The self-esteem and relationship (SEAR) quality survey is a validated tool for the assessment of the 2 domains of relationship quality: sexual relationship and confidence, which are further subdivided into SEAR quality subdomains.[36] SEAR scores are typically normalized to a 0–100 range, with higher scores indicating better relationship functioning or confidence.[36]

Pharmacology of tadalafil

Tadalafil in a β-carboline-based type 5 phosphodiesterase inhibitor, with a piperazinedione ring formed from a modification of the hydantoin ring seen on sildenafil.[37] The molecular structure of tadalafil, a heterocyclic nitrogen-containing double-ring system with a central ring, mimics cGMP. This allows for competitive binding to the catalytic site of PDE5.[37] Tadalafil is approximately 700 times more selective for PDE5 relative to PDE6 (the PDE isoform found in the retina).[11] Furthermore, tadalafil has approximately 1/50th to 1/100th the affinity of sildenafil or vardenafil for PDE6.[38] This selectivity most likely underlies the much lower incidence of visual side effects from tadalafil as compared with the other commercially available PDE5Is.[39] However, tadalafil does have relatively high affinity for PDE11, an isoform found in skeletal muscle, which is considered to be related to the higher incidence of myalgia and back pain in patients on tadalafil therapy relative to sildenafil and vardenafil.[16]

The prolonged half-life of tadalafil is due to the low volume of distribution, slow hepatic clearance, and approximately 80% bioavailability.[11,12] Upon administration, it reaches the maximum plasma concentration in 2 hours. Although peak concentrations take 2 hours, the onset of action has been reported within 15 minutes of dosing and the efficacy may persist for up to 36 hours.[15,40] It has been speculated that retention of PDE5I in cells but not serum and/or continuation of cellular effects from PDE5I may lead to persistent erection-potentiating activity even after its serum levels have declined.[41] Tadalafil is metabolized by CYP450 3A4 to a catechol metabolite; subsequently, it is further metabolized to its circulatory metabolite, methylcatechol glucuronide. Excretion is primarily in feces, with about one-third of the metabolized drug excreted in the urine.[11]

Tadalafil has linear pharmacokinetics over the dose range of 2.5–20 mg.[12] A steady state of tadalafil is reached after 5 days of daily administration, with a plasma concentration that is roughly 1.6 times higher than that of a single dose.[12] In

other words, cumulative plasma exposure at steady state of a 5-mg daily dose corresponds roughly to an 8-mg on-demand dose.[42] In a study simulating pharmacokinetics of daily dose tadalafil, a dosage of 5 mg once daily was estimated to lead to a trough serum concentration of 55 ng/mL, which corresponds to 90% PDE5 inhibition *in vitro*. This therapeutic target is acknowledged to correspond with clinical efficacy of drugs and, therefore, serves as a reasonable surrogate marker for concentrations likely to produce an erectogenic effect.[20] At steady state, the peak plasma concentration of 5 mg administered once daily is less than that of 10 or 20 mg taken 2–3 times per week.[20] It is implied from these data that men who experience side effects from higher serum concentrations of tadalafil may benefit from the lower peak concentrations seen with the daily dose therapy while sacrificing little in the way of efficacy. Interestingly, when daily dosing of 2.5–5 mg has been compared with on-demand dosing at 10–20 mg for tadalafil, the frequency of headaches has generally been 3–5 times less in the daily treatment arms.[43] However, the caveat is that men who require greater serum concentrations for therapeutic effect (ie, those with more severe ED) may be better served by the higher peak concentrations obtained with on-demand dosing.

Certain substances known to inhibit CYP450 (such as ketoconazole, erythromycin, protease inhibitors, and grapefruit juice) may slow the excretion of tadalafil, and therefore, patients taking these should consider on-demand therapy exclusively or the lowest possible daily dose (2.5 mg).[11] Patients with hepatic impairment are also generally advised to start at the lowest dose possible; pharmacokinetic studies have suggested delayed excretion of the drug in patients with moderate or severe renal impairment.[44] For patients with these conditions, therapy with on-demand tadalafil may be safer although low dose (2.5 mg daily) may be an option in some cases. Caution should also be exercised when prescribing daily dose of tadalafil to patients with a history of coronary artery disease. As nitrates are strictly contraindicated in patients on PDE5I, consideration must be given to the risk of administering a PDE5I with a prolonged half-life, which would tend to complicate standard therapy for angina symptoms.[45] This important contraindication is due to the synergistic effect of nitrates (an exogenous source of NO) coupled with decreased degradation of the NO downstream effector cGMP by PDE5I. This synergistic effect may lead to drastic decreases in blood pressure that could be life threatening.[45]

Efficacy of daily dose tadalafil

There have been numerous trials of tadalafil as a routine dose therapy. Many of the published reports have included analyses of existing older data sets with new statistical methods or primary outcome measures. A summary of all publications derived from RDBPCSs is presented in Table 1. Statistical significance is set at $P \leq 0.05$ for all of the studies detailed below unless otherwise noted.

McMahon 2004: daily tadalafil for ED

McMahon[21] published one of the first reports of daily dose tadalafil for ED in 2004. In this open-label flexible dose evaluation, 112 men with ED of various causes who had failed to respond completely to 20-mg dosage of tadalafil on at least 6 occasions and endorsed a SEP3 affirmative response rate of less than 30% were enrolled. These men were treated with 20 mg of tadalafil on demand for 4 weeks, followed by a 4-week washout period; they were subsequently treated with a 12-week, 10- or 20-mg flexible daily dose of tadalafil. One hundred and one men completed the study; there was a substantial improvement in mean IIEF-EF domain scores from 10.3 at baseline to 14.9 after the 4-week on-demand treatment and to 23.1 after 12 weeks of daily dose therapy. The mean IIEF-EF domain score was significantly higher relative to both of the earlier time points after the daily dose phase. Affirmative responses to SEP2 were 21% at baseline and increased to 28% after on-demand therapy and 66%/62% for daily therapy with 10/20 mg, respectively. Affirmative responses to SEP3 were 14% at baseline and increased to 21% after on-demand therapy and 58%/52% for daily therapy with 10/20 mg, respectively. Importantly, IIEF-EF domain scores normalized (>26) in 41% and 32% of men treated with daily dose therapy compared with none after the on-demand phase.[21]

McMahon 2005: daily tadalafil for ED

A follow-up, randomized, open-label cross-over trial by McMahon[46] compared 12 weeks of tadalafil dose (10 mg daily vs 20 mg on-demand) in 145 men with ED of at least 6 months duration and SEP3 positivity less than 50%. Of them, 122 completed the study. The baseline IIEF-EF score was 14.6; this score increased significantly to 23.3 and 26.4 at follow-up in the on-demand and daily dose arms, respectively. Affirmative responses to SEP2 were 36% at baseline and increased to 73% for on-demand therapy and 85% for daily therapy. Affirmative responses to SEP3 were 30% at baseline and increased to 67% for on-demand therapy and 80% for daily therapy. The IIEF-EF domain score normalized (>26) in 57% and 73% of men treated with on-demand therapy and daily dose, respectively. Daily dosing was preferred by 72% of the patients compared with 28% preferring on-demand treatment.[46]

Table 1 Efficacy of tadalafil once daily from randomized controlled trials

Study	Design	Subjects	Treatment	End points	Findings
Porst et al[42]	RDBPCSs	293 men with ≥3 month history of ED	Tadalafil 5 mg or 10 mg daily for 12 wk	IIEF-EF domain score, SEP2, SEP3	Tadalafil significantly improved EF relative to placebo regardless of baseline ED severity
Rajfer et al[47]	RDBPCSs	287 men with ≥3 month history of ED	Tadalafil 2.5 mg or 5 mg daily for 24 wk	IIEF-EF domain score, SEP2, SEP3	Tadalafil significantly improved EF relative to placebo regardless of baseline ED severity, with the 5 mg group experiencing numerically greater improvements than the 2.5 mg group
Hatzichristou et al[49]	RDBPCSs	298 men with ≥3 month history of diabetes (type 1 or type 2) and ED	Tadalafil 2.5 mg or 5 mg daily for 12 wk	IIEF-EF domain score, SEP2, SEP3	Significant improvements in erectile function seen across all ED and diabetes subgroups treated with tadalafil
Porst et al[48]	1- and 2-y extensions of 2 RDBPCSs	234 men with ED who completed a 12-wk treatment period and 238 men with ED who completed a 24-wk treatment period, all enrolled in open-label extensions	Tadalafil 5 mg or 10 mg daily for 12 wk, and tadalafil 2.5 mg or 5 mg daily for 24 wk	Safety: adverse event incidence, ECGs, clinical laboratory measures; efficacy: IIEF-EF, -IS, -OS, GAQ1, GAQ2	No treatment-related serious adverse events or meaningful changes in clinical measures, normal EF attained by >50% of patients from both arms
Rubio-Aurioles et al[52]	RDBPCSs	342 men with ≥3 month history of ED and their female partners	Tadalafil 5 mg daily for 12 wk	IIEF-EF domain score, SEP2, SEP3, SQoL domain	Tadalafil-treated couples more likely to report sexual quality of life comparable to what was experienced before ED onset
Seftel et al[53]	RDBPCSs	264 men with ≥3 month history of ED and their partners who met criteria for inclusion in this follow-up arm of this study	Tadalafil 5 mg daily for 12 wk	IIEF-EF domain score, SEP2, SEP3, SQoL domain	Men treated with tadalafil had significant changes in EF, confidence, self-esteem, overall relationship, and partner's satisfaction
Porst et al[50]	Post hoc analysis of a phase 2–3 RDBPCS	581 men with ED from study focused on BPH-LUTS	Tadalafil 2.5 mg, 5 mg, 10 mg, or 20 mg daily for 12 wk	IIEF-EF domain score, IPSS, peak urinary flow rate, and postvoid residual volume	Tadalafil significantly improved IIEF and IPSS scores independent of all other factors
Shabsigh et al[35]	Post hoc analysis of 2 RDBPCSs	450 men with ≥3 month history of ED	Tadalafil 2.5 mg or 5 mg daily for 12 wk	Reliability (no. of "yes" responses to SEP3 after initial attempt)	5 mg group had increased rates of reliability, intercourse success, and satisfaction

Abbreviations: ECG, electrocardiogram; ED, erectile dysfunction; EF, erectile function domain; GAQ1, Global Assessment Question 1; GAQ2, Global Assessment Question 2; IIEF, International Index of Erectile Function; IIEF-EF, International Index of Erectile Function-erectile function domain; IIEF-IS, International Index of Erectile Function-Intercourse satisfaction domain; IIEF-OS, International Index of Erectile Function-Overall satisfaction domain; IPSS, International Prostate Symptoms Score; RDBPCSs, randomized, double-blind, placebo-controlled studies; SEP, sexual encounter profile; SQoL, Sexual Quality of Life Domain of the Sexual Life Quality Questionnaire.

Porst 2006: daily tadalafil for ED

Porst et al[42] evaluated the efficacy and safety of once-daily dosing of 5 and 10 mg tadalafil in a multicenter, parallel group RDBPCS of 293 men with ED, with treatment lasting 12–15 weeks. The protocol was completed by 234 (87.3%) men, with medication compliance greater than 93%. Both the 5-mg and 10-mg doses significantly improved erectile function, with a mean change in IIEF-EF domain score of +9.7, +9.4, and +0.9 for the 5 mg, 10 mg, and placebo groups, respectively. The results remained similar when men with IIEF-EF domain scores within the range of normal (>26) at baseline were excluded. The mean percentage of per-patient SEP2 affirmative responses was significantly higher in men in both the treatment arms (79.4%, 81.2%, and 51.7% for 5 mg, 10 mg, and placebo groups, respectively). Similarly, the mean percentage of per-patient SEP3 affirmative responses was higher in treated men (67.2%, 72.8%, and 36.7% for 5 mg, 10 mg, and placebo groups, respectively).[42]

Rajfer 2007: daily tadalafil for ED

Rajfer et al[47] reported a multicenter, RDBPCS of tadalafil dosed at 2.5 or 5 mg daily vs placebo in men with ED over 24 weeks. The protocol was completed by 238 men of the 287 enrolled (83%). Tadalafil was found to be superior to placebo at both dosages for all primary efficacy end points; specifically, the mean IIEF-EF domain score increased by 6.1 and 7.0 points in the tadalafil 2.5 and 5 mg arms, respectively, relative to an increase of 1.2 points in the placebo arm. The mean change in affirmative response to SEP2 was 24%, 26%, and 5% for 2.5 mg, 5 mg, and placebo, respectively. The mean change in affirmative response to SEP3 was 31%, 35%, and 10% for 2.5 mg, 5 mg, and placebo, respectively. Tadalafil also produced significant changes in other end points assessed by the IIEF, including intercourse satisfaction, sexual confidence, and overall satisfaction with sexual life.[47]

Porst 2008: daily tadalafil in 1- to 2-year open-label, follow-up studies

In a report on open-label extensions from 2 prior daily tadalafil trials,[42,47] the mean IIEF-EF domain was found to improve from 13.7 at study baseline to 24.1 at the end of the 1-year extension and from 14.0 at baseline to 24.8 at the end of the 2-year extension. Of interest, the mean IIEF-EF domain score declined to near-baseline level (16.0), following discontinuation of tadalafil at the end of the 1-year open-label extension period. IIEF-EF domain scores of greater than 26 were attained by 58% of subjects in both the trials (117 of 202 and 78 of 135 for the 1- and 2-year extensions, respectively). In the 1-year extension period, 114 of the 117 who normalized their erectile function continued into the ED treatment-free period; only 25% (28 of 114) maintained normal erectile function 4 weeks after discontinuing tadalafil. Only 3% (8 of 234) and 16% (39 of 238) of men in the 1-year and 2-year open-label extension periods, respectively, discontinued the treatment based upon a perceived lack of efficacy. The majority of men who discontinued had severe ED at baseline (7.5% [7 of 8] and 71.8% [28 of 39], respectively).[48]

Shabsigh 2010: reliability of daily tadalafil

Shabsigh et al[35] reported on the reliability profile of tadalafil using data pooled from 2 prior studies[42,47] of daily dose tadalafil vs placebo in men with ED. Reliability was defined as the rate of affirmative response to SEP3 after the initial attempt at intercourse after started receiving the study drug. Men in the 2.5 mg and 5 mg groups were significantly more likely to report successful intercourse (46% and 55%, respectively) on their initial attempt compared with 29% of men in the placebo group. Similarly, men in both the 2.5 mg and 5 mg groups were significantly more likely to report an affirmative response to SEP5 (overall satisfaction with sexual experience) relative to placebo-treated men (27%, 39%, and 15%, respectively). Only the 5 mg group was significantly more likely to report affirmative response to SEP4 (satisfaction with erection hardness, 41%, 27%, and 17% for 5 mg, 2.5 mg, and placebo groups, respectively) during their initial attempt.[35]

On analysis of subsequent attempts (the reliability analysis) at intercourse in all men who had initial success (affirmative SEP3), men in the 5 mg group (but not the 2.5 mg group) were significantly more likely to report consistent success relative to placebo-treated men (86%, 74%, and 70% in 5 mg, 2.5 mg, and placebo groups, respectively). However, men in both treatment arms were significantly more likely to endorse affirmative responses to SEP4 and SEP5 with repeat attempts than placebo-treated men. Among men with mild (IIEF > 17) or moderate ED (IIEF-EF 11–16), those treated with the 5-mg dose were significantly more likely to report successful intercourse on subsequent attempts; this effect was not noted for men with mild or moderate ED treated with 2.5-mg dose, and no significant difference between dose and reliability was noted for men with severe ED (IIEF ≤ 10).[35]

Among men who were unsuccessful on their first attempt at intercourse (negative SEP3), a significantly greater proportion in both treatment arms reported affirmative response to SEP3 (52%, 58%, and 37% for 5 mg, 2.5 mg, and placebo among initial nonresponders) and SEP5 (49%, 52%, and 32%

for 5 mg, 2.5 mg, and placebo). The 5 mg group reported significantly greater SEP4 rates relative to placebo (54%, 48%, and 34% in the 5 mg, 2.5 mg, and placebo groups, respectively). In contrast to what was observed for reliability in initial responders to tadalafil, in the initial nonresponders group, the 5-mg dose was significantly more likely to lead to successful subsequent intercourse than placebo, irrespective of baseline ED severity. Initial nonresponders (younger than 65 years) were significantly more likely to report successful intercourse at both tadalafil dosages relative to placebo-treated men (younger than 65 years). There were no significant differences in the rate of response in men older than 65 in this cohort, but the relatively small sample size for this age group in the non-initial responder group (n = 35 among 3 arms) likely underlies the failure to attain statistical significance.[35]

Hatzichristou 2008: daily tadalafil in diabetic men

Hatzichristou et al[49] investigated the efficacy of daily dose tadalafil (2.5 and 5 mg) in diabetic men with ED in a multi-center, 24-week RDBPCS. The protocol was completed by 254 men of the 298 enrolled (85% completion). Tadalafil was found to be significantly superior to placebo at both dosages for all primary efficacy end points; specifically, the mean IIEF-EF domain score increased by 4.8 and 4.5 points in the tadalafil 2.5 and 5 mg arms, respectively, relative to a 1.3 point increase in the placebo arm. The mean change in affirmative response to SEP2 was 20%, 29%, and 5% for 2.5 mg, 5 mg, and placebo groups, respectively. Mean change in affirmative response to SEP3 was 26%, 25%, and 8% for 2.5 mg, 5 mg, and placebo groups, respectively. Tadalafil also produced significant changes in other end points, including intercourse satisfaction, sexual confidence, and overall satisfaction with sexual life. This study also investigated serum biomarkers for diabetes (hemoglobin A1c) and inflammation, including C-reactive protein, nitrotyrosine, intracellular adhesion molecule-1, and vascular adhesion molecule-1. No significant changes were noted for these serum parameters.[49]

Porst 2009: tadalafil for lower urinary tract symptoms, effects on erectile function

Porst et al[50] published a post hoc analysis of sexually active men from a phase 2–3, multinational RDBPCS in men with ED and lower urinary tract symptoms (LUTS), considered to be secondary to benign prostatic enlargement, who were given placebo, 2.5 mg, 5 mg, 10 mg, or 20 mg tadalafil daily for a 12-week treatment period. Of the 581 subjects who started the

study, 85% completed the entire protocol. Although the focus of this investigation was on LUTS, IIEF-EF domain scores were noted to improve significantly at all time points (4, 8, and 12 weeks), with mean change from baseline at the 12-week time point $+5.4 \pm 1.0$ for 2.5 mg group, $+6.8$ mg ± 1.0 for 5 mg group, $+7.9 \pm 1.0$ for 10 mg group, and $+8.2 \pm 1.0$ for the 20 mg group vs $+2.0 \pm 1.0$ for placebo. Importantly, the frequency of sexual intercourse attempts was not significantly different between the treatment groups throughout the study. No significant differences in response were noted between various subgroups stratified by baseline age, body mass index, LUTS severity, serum prostate-specific antigen value, prior α-blocker use, and prior ED therapy. Among men with IIEF-EF scores less than 26 at baseline, normalization of IIEF-EF domain scores was attained at the conclusion of the study in 21.2% (24/113), 34.2% (40/117), 42.5% (51/120), 40.0% (46/115), and 14.0% (16/114) of men in the 2.5 mg, 5 mg, 10 mg, 20 mg, and placebo groups, respectively, with no explicit comment made on statistical significance in this study. Tadalafil appeared to have beneficial effects on LUTS severity at all dosages although this was not associated with any clinically significant changes in objective urodynamic parameters (urine flow rate and postvoid residual [PVR] urine volume), with the exception of a statistically significant (but likely clinically meaningless) increase in PVR volume in the 2.5 mg group relative to the placebo group.[50]

Partner preference studies

The impact of tadalafil daily dosing on female partners' satisfaction with sexual activity has also been a topic of recent interest and research. A partner preference study of on-demand sildenafil vs tadalafil indicated that 79% of female partners preferred tadalafil, citing a more relaxed approach to sexual intimacy and greater flexibility with respect to timing of intercourse.[51] Based on this, it may be inferred that the flexibility of completely separating medication from sexual activity (as is the case for daily dose therapy) would be appealing to many female partners of men with ED.

Rubio-Aurioles 2009: patients' or partners' satisfaction with daily tadalafil

Rubio-Aurioles et al[52] reported on partners' satisfaction in a multicenter, parallel group RDBPCS of 5 mg tadalafil daily vs placebo for 12 weeks for men with ED, most of whom had the condition for more than 1 year. A total of 342 couples were enrolled, and 307 couples (90%) completed the 12-week protocol. Of note, partners were prescreened using the Female Sexual Function Index (FSFI); partners with FSFI total scores

less than 26.55 (suggestive of high risk of female sexual dysfunction) were excluded from the subsequent analysis. Mean IIEF-EF score at baseline was 15.8 and 15.1 in the tadalafil and placebo arms, respectively. Approximately, half of each group had mild ED (IIEF-EF score of 17+) at baseline. Men treated with tadalafil endorsed significantly greater improvements in IIEF-EF score (+7.9 vs +0.7 in the treatment and placebo groups) and changed to an affirmative response to SEP2 (29% and 3%, respectively) and SEP3 (46% vs 11%, respectively). Men and their partners in the treatment group reported significantly greater improvements in sexual quality of life and quality of treatment relative to placebo-treated couples based on validated instruments. With respect to specific facets of sexual life, patients and partners treated with tadalafil 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.[52]

Seftel 2009: treatment satisfaction and improvement in relationship quality in couples treated with daily tadalafil

In a follow-up data set based on the prior work reported by Rubio-Aurioles et al,[52] Seftel et al[53] reported on variables pertaining to overall sexual satisfaction in tadalafil-treated men and their female partners. Men who received tadalafil were significantly more satisfied with treatment compared with placebo (75% vs 51%, respectively), as measured by the sexual life quality questionnaire; female partners also endorsed significantly greater satisfaction with tadalafil as opposed to placebo (73% vs 55%, respectively). There was a significantly greater change in mean sexual life quality in the tadalafil-treated men relative to controls (+39 vs +12, respectively) and in female partners of treated men relative to partners of controls (+32 vs +5, respectively). The percentage of affirmative responses to SEP4 and SEP5 was significantly greater in the tadalafil group (57% and 56%, respectively) compared with placebo group (20% and 20%, respectively), when all intercourse attempts were considered. When only "successful intercourse attempts" (defined as affirmative response to SEP3) were considered, subjects in the tadalafil group reported significantly more affirmative responses to SEP4 and SEP5 (77% and 74%, respectively) relative to placebo group (56% and 52%, respectively). The mean increase from baseline intercourse satisfaction and overall satisfaction (as determined by the IIEF) was significantly greater in the tadalafil group (+3 and +3, respectively) vs placebo group

(+0.5 and +0.1, respectively).[53] Tadalafil-treated men also manifested significantly greater improvements on SEAR domains relative to placebo-treated men, with mean change in self-esteem of +34 vs +5 and mean change in confidence of +25 vs +3, respectively. Changes in IIEF-EF scores in the tadalafil and placebo arms positively correlated with all SEAR domains.[53] The partners of tadalafil-treated men were on the whole more likely to report an affirmative response to the partner SEP3 question relative to the control men (70% vs 37%, respectively). More importantly, improvements in the IIEF-EF of tadalafil-treated men were positively correlated to the satisfaction with treatment in their female partners.[53]

Althof 2010

Althof et al[54] combined the results of the studies on 5-mg daily dosage of tadalafil (n = 473 couples) by Rubio-Aurioles et al[52] and Porst et al[42] to verify that daily dose tadalafil has a high degree of efficacy in managing ED and improving sexual quality of life for both patients and partners.[54] There was strong concordance between both patients' and partners' assessment of erection, penetration capacity, and overall sexual satisfaction.[54]

Summary statement of efficacy

It is clear from numerous high-quality studies that tadalafil as a daily dose is highly efficacious in the management of ED from a variety of causes. It is also clear that daily dose of tadalafil will have a beneficial effect on the sexual relationship between partners.

Side-effect profile of daily dose tadalafil

Side effects from daily dose tadalafil in clinical trials have generally been mild, with 54%–80% of reported events mild in nature and with no more than a third of events moderate in severity.[21,42] Serious side effects have not been reported in some studies; in studies where serious events occurred, the effect was considered not to be related to the study drug itself.[42,52] Although the effects may be mild, it should be noted that the prolonged half-life of tadalafil may tend to produce side effects of longer duration compared with PDE5I with shorter half-lives.[16] Steady-state kinetics have been observed in daily dose tadalafil, with the steady-state levels being roughly 1.6 times greater than those of a single dose. Although this might lead to a greater incidence of side effects, this dosing regimen may permit lower dosing overall.[19,20] A summary of reported incidence of the most commonly reported side effects in RDBPCSs is presented in Table 2.

Table 2 Side-effect profile

Study	Headache	Dyspepsia	Back pain	Myalgia
McMahon et al[21]	8.7% (10 mg)	8.7% (10 mg)	4.3% (10 mg)	0% (10 mg)
	13.6% (20 mg)	6.1% (20 mg)	4.5% (20 mg)	4.5% (20 mg)
	16.1% (on-demand)	9.8% (on-demand)	6.3% (on-demand)	4.5% (on-demand)
McMahon et al[46]	8.0% (10 mg daily)	10.7% (10 mg daily)	6.7% (10 mg daily)	4.0% (10 mg daily)
	17.1% (20 mg as-needed)	12.9% (20 mg as-needed)	4.3% (20 mg as-needed)	4.3% (20 mg as-needed)
Porst et al[42]	6.4% (5 mg)	5.5% (5 mg)	3.7% (5 mg)	2.8% (5 mg)
	10.5% (10 mg)	11.4% (10 mg)	9.5% (10 mg)	6.7% (10 mg)
	7.4% (placebo)	3.7% (placebo)	3.7% (placebo)	0.0% (placebo)
Rajfer et al[47]	3.1% (2.5 mg)	4.2% (2.5 mg)	5.2% (2.5 mg)	4.2% (2.5 mg)
	1.0% (5 mg)	1.0% (5 mg)	2.1% (5 mg)	1.0% (5 mg)
	3.2% (placebo)	1.1% (placebo)	3.2% (placebo)	2.1% (placebo)
Hellstrom et al[55]	16% (20 mg)	8% (20 mg)	11% (20 mg)	8% (20 mg)
	2% (placebo)	1% (placebo)	3% (placebo)	1% (placebo)
Donatucci et al[43]				
1-y extension phase	9%	9%	7%	–
2-y extension phase	2%	4%	5%	–
Porst et al[48]				
1-y extension phase	9.0%	9.0%	6.8%	–
2-y extension phase	2.1%	3.8%	5.0%	–
Porst et al[50]	3.5% (2.5 mg)	0.9% (2.5 mg)	1.8% (2.5 mg)	1.8% (2.5 mg)
	3.4% (5 mg)	4.3% (5 mg)	0.9% (5 mg)	0.9% (5 mg)
	5.0% (10 mg)	1.7% (10 mg)	4.2% (10 mg)	3.3% (10 mg)
	1.7% (20 mg)	2.6% (20 mg)	5.2% (20 mg)	2.6% (20 mg)
	3.5% (placebo)	0% (placebo)	0.9% (placebo)	0% (placebo)

In a report on open-label extension of tadalafil, 53% of subjects reported at least 1 adverse event in 1 year and 73% within 2 years of therapy.[48] Generally, the incidence of these side effects declines over time on chronic therapy.[48] The rate of consistent bothersome side effects (headache, back pain, dyspepsia, etc) of on-demand therapy with tadalafil has not been measured to be greater than 10%.[43] Discontinuation rates due to the side effects of medication are reportedly between 1% and 6%[21,42,46–48,52] although higher rates of discontinuation (~10%) have been reported in studies in which men received 20 mg of tadalafil daily for months on end.[55]

The most common side effects of daily dose tadalafil include headache (1%–14%), dyspepsia (1%–11%), facial flushing (7%–8%), nasal congestion (6%–7%), back pain (2%–11%), myalgias (1%–5%), abdominal pain (3%–9%), and dizziness (1%–4%).[21,42,46,47,52] In some studies, side effects were more common at higher dosages of tadalafil,[42,49,55] but this dose–response relationship was not confirmed in every study.[21,50] In at least 1 study, there was no significant difference in the rate of side effects between the treatment and the placebo arms,[52] but other studies suggested that flushing, dyspepsia, back pain, abdominal pain, and myalgia were more frequent with tadalafil than placebo.[42,49,50]

Tadalafil and hemodynamics

Tadalafil has been shown to have a favorable cardiovascular risk profile, with no significant indications of worsening ischemia, unstable hemodynamics, electrocardiogram changes, worsening of clinical laboratory parameters, or increase in serious cardiovascular events in men using the drug or placebo.[11,20,47,48] Tadalafil has not been shown to be associated with QT prolongation.[56] There have been no reports of increased mortality in men on tadalafil.[11] It is important, however, to reemphasize that the nitrate use is a strict contraindication to PDE5I therapy.[45]

In 2 small randomized controlled trials of short (<1 month) duration, the influence of daily dose of 5 mg tadalafil on hemodynamic parameters in healthy men given α blockers (doxazosin or tamsulosin; n = 45 and 39, respectively) was assessed. There was essentially no change in the mean standing systolic blood pressure or the heart rate between placebo- and tadalafil-treated men on either α blocker. One man, in both the tamsulosin and the doxazosin 4-mg arms experienced a standing systolic blood pressure of <85 mm Hg while taking tadalafil; this rate did not differ significantly from what was observed in placebo-treated men.[57] Generally, studies have been congruous with this one, suggesting a very low rate of clinically significant hypotension with tadalafil with or without α blockers; this effect held true regardless of the dosing regimen (on-demand, daily, etc).[58]

In an open-label extension of 2 prior trials of daily dose tadalafil, no clinically significant abnormalities on electrocardiogram or laboratory measures were observed in the general population of men on tadalafil. Of 472 men who participated, 36 subjects (8% of total) reported serious adverse effects, which resulted in hospitalization, life-threatening complications, or disability. In 9 of these 36 subjects, (25%) a total of 10 cardiovascular events occurred, including cerebrovascular accident, coronary artery disease, myocardial infarction, atrial fibrillation, worsening of hypertension, angina, and syncope. Eight of these occurred in patients with prior cardiac histories. None of these adverse effects was considered tadalafil-related by the authors.[48]

Ophthalmology effects of daily dose tadalafil

A study of ophthalmological effects of daily placebo vs daily dose tadalafil (5 mg) or sildenafil (50 mg) in 244 subjects (194 of whom completed the 6-month protocol) detected a significantly higher increase in β-wave amplitude during electroretinographic response to flash in light-adapted eyes for tadalafil relative to placebo. There were no other significant differences in the rate of ophthalmological abnormality or in the morbidity from drug treatment at study conclusion and 4–6 weeks after cessation of treatment. Additional parameters assessed included the combined electroretinographic response to flash after darkness adaptation, visual acuity, color discrimination, visual-field testing, and intraocular pressure. The only ophthalmological adverse event was a retinal artery occlusion in 1 patient in the placebo arm.[38] Based on the relatively similar results, the authors concluded that there is no evidence to suggests clinically relevant side effects from this daily dose regimen.

Daily tadalafil and semen parameters

In the largest and longest duration study of tadalafil and its affect on male reproduction, Hellstrom et al[55] investigated the influence of high-dose (20 mg) daily tadalafil for 9 months, with a 6-month follow-up in men older than 45 years of age. All men enrolled had normal values for testosterone, gonadotropins, and semen parameters that were within the World Health Organization reference ranges. This double-blind, placebo-controlled, randomized, noninferiority trial enrolled 253 men, 191 (75%) of whom completed the 9-month protocol and 179 (70%) of whom completed the 6-month follow-up. The geometric mean sperm concentration was significantly lower in tadalafil-treated men at 9-month follow-up, 54.3 M/mL vs 63.4 M/mL in placebo, although

after adjustment for multiple comparisons, the difference was no longer strictly significant ($P = 0.06$) and was not apparent after 6-month wash-out. A 50% decline in sperm concentration was reported in 2 (2%) of placebo-treated men compared with 12 (13%) of tadalafil-treated men at 9-month follow-up. Although the difference was substantial, it did not meet the criteria for inferiority given the upper 95% confidence interval for proportion of subjects with a greater than 50% decline on concentration was 17.5%, less than the 20% prescribed for inferiority. Interestingly, the mean ejaculatory frequency was significantly higher in men who experienced a greater than 50% drop in sperm concentration compared with those who did not (5.4 times per week vs 2.9 times per week, respectively). After 6 months of drug wash-out, sperm concentrations returned to baseline in 8 of 12 men treated with tadalafil and 1 of 2 treated with placebo.[55] Fertility may not be a concern for many men taking tadalafil, and the study by Hellstrom et al[55] did not conclusively demonstrate a negative influence on sperm parameters; indeed, it is possible that the much higher ejaculatory frequency in men who experienced a greater than 50% decline in sperm concentration was responsible for the results observed. Furthermore, the doses used in this study were much higher than those recommended for daily dose therapy. Be that as it may, the trend toward a decline in sperm concentration in some men is of note and should be kept in mind by men taking tadalafil who are concerned about conceiving children.

Daily tadalafil and serum androgen levels

In the study of semen parameters by Hellstrom et al,[55] it was determined that the mean change in serum testosterone after 9 months of daily dose tadalafil (20 mg) was significantly higher in the treatment group relative to the placebo group ($P = 0.01$ before adjustment and $P = 0.03$ after adjustment for multiple comparisons). Mean serum of luteinizing hormone (LH) was also significantly higher ($P = 0.05$) in the treatment group at the 9-month time point; this relationship was not significant after the adjustment for multiple comparisons ($P = 0.21$). Free testosterone level was not found to be affected by the treatment.[55] Although strict clinical and statistical significance for difference in serum testosterone was not met, it is somewhat intriguing to speculate that tadalafil might have some sort of impact (either direct or indirect) on testosterone levels by a centrally mediated mechanism involving LH secretion because of the absence of a local effect on the testes themselves as noted by the authors.[55] Although this explanation is strictly hypothetical, enhancement of erectile and sexual functions may have led to secondary changes

in neurochemical modulation of testosterone secretion by psychogenic mechanisms. To our knowledge, this effect has not been confirmed and this finding may be worthy of further investigation and verification.

Miscellaneous and potential side effects of tadalafil

Although the clinical relevance is not entirely clear, a single 20-mg dose has been shown to produce detectable electro-encephalographic changes in up to 34% of healthy men.[59] Animal studies have demonstrated a blunting of the cerebral vasoconstrictive response to hyperbaric oxygen therapy and subsequent lowering of seizure threshold in tadalafil-treated rats.[60] The clinical relevance of these findings is unclear, but these may be important topics for future research. PDE5Is have also been associated with sudden sensorineural hearing loss,[61] and studies of audiometric properties in men and experimental animals using sildenafil or vardenafil have suggested changes in hearing.[62,63] Although we are not aware of any published studies directly linking tadalafil to hearing changes, the possibility of a PDE5I class effect on hearing must be considered and taken seriously by patients and providers.

Future directions for daily dose tadalafil therapy

"Penile rehabilitation" refers to treatments intended to restore functional penile erection after some sort of physiological insult, typically radical pelvic surgery; PDE5Is are the mainstay of penile rehabilitation therapy at present.[64,65] There exists substantial controversy regarding the true efficacy of penile rehabilitation, with the largest multicenter trial, to date, suggesting no long-term impact with the PDE5I vardenafil as either a routine or on-demand treatment despite several smaller studies of other PDE5Is suggesting benefit.[66–68]

Although the clinical efficacy of PDE5I for penile rehabilitation remains open to debate, basic science research has generally indicated favorable outcomes in animal models.[69,70] Tadalafil seems a logical choice for rehabilitative therapy given its prolonged duration of action; if indeed PDE5I exerts a protective or salubrious effect on penile tissues, a prolonged duration of exposure seems most likely to produce the desired results. When consulting basic science literature on PDE5I, it is important to recognize that the metabolism of PDE5I in rodents is much more rapid than in humans, and hence, proportionally large doses must be given to determine the therapeutic effects.[71]

A 2006 study of rats treated with 2 mg/kg tadalafil daily for 3 months after cavernous nerve transection (a model system for radical pelvic surgery induced ED) indicated that treated rats had superior erectile hemodynamics, as assessed by cavernous nerve electrostimulation with real-time measurement of intracavernous pressure. Molecular studies indicated that declines in erectile function after cavernous nerve injury were associated with the decreased smooth muscle to collagen ratio in the corporeal tissues and evidence of hypoxia. Tadalafil treatment was found to ameliorate the decline in smooth muscle to collagen ratio and to restore oxygenation; this was associated with superior vasodilatory activity of tissues obtained from treated rats for *in vitro* studies. The authors theorized that the maintenance of corporeal oxygenation is the underlying mechanism of action in the tadalafil-treated group.[72]

A similar study of daily dose tadalafil administered retrolingually (5 mg/kg/d) vs placebo in rats subjected to cavernous nerve transection indicated that treated rats had greater erectile response to papaverine and maintenance of normal veno-occlusive capacity during penile caversonometry 45 days after injury, signifying less venous leak. Treated animals also had greater content of smooth muscle, less collagen deposition, and lower levels of apoptosis, all suggestive of better tissue integrity.[73]

The majority of published reports on penile rehabilitation to date have been on the other 2 PDE5Is that are commercially available. However, in 1 small, open-label human trial, tadalafil was investigated as a penile rehabilitation agent. Twenty men with ED were randomized to 20 mg of tadalafil either every other day or on demand (maximum 8 doses per month) for 4 weeks in an open-label cross-over fashion. At 4-week follow-up, a significant increase (+8.3%) was noted in mean flow-mediated dilation of the cavernous artery in the every other day group. Furthermore, the mean peak systolic blood pressure in the flaccid state was also significantly increased in the every other day group. On the molecular level, every other day treatment led to significant declines in vascular cellular adhesion molecule, C-reactive protein, and endothelin-1, all of which are known to be associated with vasoconstriction and/or inflammation. None of these theoretically beneficial effects was observed in the on-demand portion of the study.[74]

Although the evidence at this time is scanty, it is tantalizing to speculate that daily therapy with a PDE5I such as tadalafil may produce beneficial humoral and tissue effects, which tend to be erection protective. More research is required to determine what role these drugs may play in maintenance of sexual health rather than simple treatment of sexual problems.

Conclusion

Tadalafil is the first ED treatment approved for daily dosing. This represents an important change in our conception of ED as a disorder and has the potential to dramatically alter the way we approach this prevalent and vexing concern. Although not necessarily the optimal management schema for every man with ED, this exciting dosing option has the potential to expand our capacity to care for men with ED in a novel and unprecedented direction.

Disclosure

Alan W Shindel has served as a nonfiduciary consultant for Boeheringer-Ingelheim.

References

1. NIH Panel on Impotence. NIH Consensus Conference: Impotence. *JAMA*. 1993;270:83–90.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994;151:54–61.
3. Feldman HA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts Male Aging Study. *Prev Med*. 2000;30(4):328–338.
4. Miner MM, Kuritzky L. Erectile dysfunction: a sentinel marker for cardiovascular disease in primary care. *Cleve Clin J Med*. 2007; 74 Suppl 3:S30–S37.
5. Fisher WA, Eardley I, McCabe M, Sand M. Erectile dysfunction (ED) is a shared sexual concern of couples II: association of female partner characteristics with male partner ED treatment seeking and phosphodiesterase type 5 inhibitor utilization. *J Sex Med*. 2009;6(11):3111–3124.
6. Tsertsvadze A, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med*. 2009;151(9):650–661.
7. Carson CC. PDE5 inhibitors: are there differences? *Can J Urol*. 2006; 13(Suppl 1):34–39.
8. Ljunggren C, Hedelin H, Salomonsson K, Stroberg P. Giving patients with erectile dysfunction the opportunity to try all three available phosphodiesterase type 5 inhibitors contributes to better long-term treatment compliance. *J Sex Med*. 2008;5:469–475.
9. Paick JS, et al. The efficacy and safety of udenafil, a new selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction. *J Sex Med*. 2008;5:946–953.
10. Shindel AW. 2009 update on phosphodiesterase type 5 inhibitor therapy part 2: updates on optimal utilization for sexual concerns and rare toxicities in this class. *J Sex Med*. 2009;6(9):2352–2364;quiz 2365–2366.
11. Coward RM, Carson CC. Tadalafil in the treatment of erectile dysfunction. *Ther Clin Risk Manag*. 2008;4:1315–1330.
12. Forgue ST, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol*. 2006;61:280–288.
13. Eardley I, Cartledge J. Tadalafil (Cialis) for men with erectile dysfunction. *Int J Clin Pract*. 2002;56:300–304.
14. Hanson-Divers C, Jackson SE, Lue TF, Crawford SY, Rosen RC. Health outcomes variables important to patients in the treatment of erectile dysfunction. *J Urol*. 1998;159(5):1541–1547.
15. Porst H, et al. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. *Urology*. 2003;62(1):121–125; discussion 125–126.
16. Taylor J, Baldo OB, Storey A, Cartledge J, Eardley I. Differences in side-effect duration and related bother levels between phosphodiesterase type 5 inhibitors. *BJU Int*. 2009;103(10):1392–1395.
17. Vernet D, et al. Phosphodiesterase type 5 is not upregulated by tadalafil in cultures of human penile cells. *J Sex Med*. 2006;3:84–94; discussion 94–95.
18. Lin G, Xin ZC, Lue TF, Lin CS. Up and down-regulation of phosphodiesterase-5 as related to tachyphylaxis and priapism. *J Urol*. 2003;170:S15–S18; discussion S19.
19. Costa P, Grivel T, Gehchan N. Tadalafil once daily in the management of erectile dysfunction: patient and partner perspectives. *Patient Prefer Adherence*. 2009;3:105–111.
20. Wrishko R, Sorsaburu S, Wong D, Strawbridge A, McGill J. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. *J Sex Med*. 2009;6:2039–2048.
21. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med*. 2004;1:292–300.
22. Mirone V, et al. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. *Eur Urol*. 2005;47:846–854; discussion 854.
23. Costa P, et al. Predictors of tadalafil efficacy in men with erectile dysfunction: the SURE study comparing two dosing regimens. *J Sex Med*. 2006;3:1050–1058.
24. Moncada I, et al. Sexual intercourse attempt patterns with two dosing regimens of tadalafil in men with erectile dysfunction: results from the SURE study in 14 European countries. *J Sex Med*. 2005;2:668–674.
25. Buvat J, et al. Efficacy and safety of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: Scheduled Use vs. On-Demand Regimen Evaluation (SURE) study in 14 European countries. *J Sex Med*. 2006;3:512–520.
26. Affuso F, Palmieri EA, Di Conza P, Guardasole V, Fazio S. Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension. *Int J Cardiol*. 2006;108:429–431.
27. Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol*. 2008;180:1228–1234.
28. Rosato E, et al. Plasma adrenomedullin and endothelin-1 levels are reduced and Raynaud's phenomenon improved by daily tadalafil administration in male patients with systemic sclerosis. *J Biol Regul Homeost Agents*. 2009;23:23–29.
29. Lue TF. Erectile dysfunction. *N Engl J Med*. 2000;342:1802–1813.
30. Corbin JD. Mechanisms of action of PDE5 inhibition in erectile dysfunction. *Int J Impot Res*. 2004;16 Suppl 1:S4–S7.
31. El-Sakka AI, Lin CS, Chui RM, Dahiya R, Lue TF. Effects of diabetes on nitric oxide synthase and growth factor genes and protein expression in an animal model. *Int J Impot Res*. 1999;11:123–132.
32. Miles CL, et al. Interventions for sexual dysfunction following treatments for cancer. *Cochrane Database Syst Rev*. 2007;CD005540.
33. Rosen RC, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49:822–830.
34. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology*. 1999;54:346–351.
35. Shabsigh R, et al. Reliability of efficacy in men with erectile dysfunction treated with tadalafil once daily after initial success. *Int J Impot Res*. 2010;22(1):1–8.
36. Cappelleri JC, et al. Development and validation of the self-esteem and relationship (SEAR) questionnaire in erectile dysfunction. *Int J Impot Res*. 2004;16:30–38.
37. Francis SH, Turko IV, Corbin JD. Cyclic nucleotide phosphodiesterases: relating structure and function. *Prog Nucleic Acid Res Mol Biol*. 2001;65:1–52.
38. Cordell WH, et al. Retinal effects of 6 months of daily use of tadalafil or sildenafil. *Arch Ophthalmol*. 2009;127:367–373.
39. Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. *Int J Impot Res*. 2004;16(Suppl 1): S11–S14.

40. Rosen RC, et al. Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. *J Sex Med*. 2004;1:193–200.

41. Francis SH, Morris GZ, Corbin JD. Molecular mechanisms that could contribute to prolonged effectiveness of PDE5 inhibitors to improve erectile function. *Int J Impot Res*. 2008;20:333–342.

42. Porst H, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2006;50:351–359.

43. Donatucci CF, et al. Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. *Curr Med Res Opin*. 2008;24:3383–3392.

44. Forgue ST, et al. Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol*. 2007;63:24–35.

45. Kloner RA, et al. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol*. 2003;42:1855–1860.

46. McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med*. 2005;2:415–425; discussion 425–427.

47. Rajfer J, et al. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. *Int J Impot Res*. 2007;19:95–103.

48. Porst H, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. *J Sex Med*. 2008;5:2160–2169.

49. Hatzichristou D, et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. *Diabet Med*. 2008;25:138–146.

50. Porst H, et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. *Eur Urol*. 2009;56:727–735.

51. Conaglen HM, Conaglen JV. Investigating women's preference for sildenafil or tadalafil use by their partners with erectile dysfunction: the partners' preference study. *J Sex Med*. 2008;5:1198–1207.

52. Rubio-Aurioles E, et al. Impact on erectile function and sexual quality of life of couples: a double-blind, randomized, placebo-controlled trial of tadalafil taken once daily. *J Sex Med*. 2009;6:1314–1323.

53. Seftel AD, et al. Improvements in confidence, sexual relationship and satisfaction measures: results of a randomized trial of tadalafil 5 mg taken once daily. *Int J Impot Res*. 2009;21:240–248.

54. Althof SE, et al. Impact of tadalafil once daily in men with erectile dysfunction-including a report of the partners' evaluation. *Urology*. 2010;75(6):1358–1363.

55. Hellstrom WJ, et al. An evaluation of semen characteristics in men 45 years of age or older after daily dosing with tadalafil 20 mg: results of a multicenter, randomized, double-blind, placebo-controlled, 9-month study. *Eur Urol*. 2008;53:1058–1065.

56. Beasley CM Jr, et al. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. *J Am Coll Cardiol*. 2005;46:678–687.

57. Guillaume M, Lonsdale F, Darstein C, Jimenez MC, Mitchell MI. Hemodynamic interaction between a daily dosed phosphodiesterase 5 inhibitor, tadalafil, and the alpha-adrenergic blockers, doxazosin and tamsulosin, in middle-aged healthy male subjects. *J Clin Pharmacol*. 2007;47:1303–1310.

58. Kloner RA, et al. Cardiovascular safety update of tadalafil: retrospective analysis of data from placebo-controlled and open-label clinical trials of tadalafil with as needed, three times-per-week or once-a-day dosing. *Am J Cardiol*. 2006;97:1778–1784.

59. Okuyucu EE, et al. EEG abnormalities during treatment with tadalafil, a phosphodiesterase type 5 inhibitor. *Neurol Res*. 2009;31:313–315.

60. Demchenko IT, Ruehle A, Allen BW, Vann RD, Piantadosi CA. Phosphodiesterase-5 inhibitors oppose hyperoxic vasoconstriction and accelerate seizure development in rats exposed to hyperbaric oxygen. *J Appl Physiol*. 2009;106:1234–1242.

61. Maddox PT, Saunders J, Chandrasekhar SS. Sudden hearing loss from PDE-5 inhibitors: a possible cellular stress etiology. *Laryngoscope*. 2009;119:1586–1589.

62. Hong BN, Yi TH, Kim SY, Kang TH. High dosage sildenafil induces hearing impairment in mice. *Biol Pharm Bull*. 2008;31:1981–1984.

63. Okuyucu S, Guven OE, Akoglu E, Ucar E, Dagli S. Effect of phosphodiesterase-5 inhibitor on hearing. *J Laryngol Otol*. 2009;123:718–722.

64. Magheli A, Burnett AL. Erectile dysfunction following prostatectomy: prevention and treatment. *Nat Rev Urol*. 2009;6:415–427.

65. Teloken P, Mesquita G, Montorsi F, Mulhall J. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. *J Sex Med*. 2009;6:2032–2038.

66. Montorsi F, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol*. 2008;54:924–931.

67. Bannowsky A, Schulze H, van der Horst C, Hautmann S, Junemann KP. Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. *BJU Int*. 2008;101:1279–1283.

68. Padma-Nathan H, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Int J Impot Res*. 2008;20:479–486.

69. Albersen M, Joniau S, Claes H, Van Poppel H. Preclinical evidence for the benefits of penile rehabilitation therapy following nerve-sparing radical prostatectomy. *Adv Urol*. 2008;594868.

70. Mulhall JP. Penile rehabilitation following radical prostatectomy. *Curr Opin Urol*. 2008;18:613–620.

71. Walker DK, et al. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. *Xenobiotica*. 1999;29:297–310.

72. Vignozzi L, et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. *J Sex Med*. 2006;3:419–431.

73. Kovanecz I, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. *BJU Int*. 2008;101:203–210.

74. Aversa A, et al. Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study. *Int J Impot Res*. 2007;19:200–207.