Tadalafil in the treatment of erectile dysfunction; an overview of the clinical evidence

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Abstract: Prevalence and severity of erectile dysfunction (ED) increase with aging and are often associated with illnesses, like diabetes mellitus, heart disease, and hypertension, pathologically characterized by endothelial dysfunction and whose prevalence increases with age. The assumption that ED is mainly a neurovascular disease is supported by the evidence that specific phosphodiesterase type 5 (PDE5) inhibition produces an efficient erection in a wide range of ages and conditions. The availability of specific PDE5 inhibitors has enabled the development of effective treatment strategies, in this contest, tadalafil may be considered as the least "typical" PDE5 inhibitor. In clinical trials, tadalafil significantly enhanced, in patients of different ages, all efficacy outcomes across disease etiologies and severities. With an effectiveness lasting up to 36h, tadalafil allows patients to choose when to have sexual activities without the need to time it, showing positive feedback in terms of quality of life related to the treatment. Headache and dyspepsia were the most frequent side-effects of tadalafil, followed by back pain, nasal congestion, myalgia, and flushing, but the impact that long time action could have on effectiveness and safety is not yet entirely defined. The aim of this article is to critically review the available evidence from the tadalafil clinical research program and give the physician a rational approach for intervention in the treatment of ED and related diseases.

Keywords: tadalafil, PDE5 inhibitors, erectile dysfunction, aging, sexual behavior

Introduction

Epidemiological studies suggest that ED is a common disorder in men, affecting up to 52% of men between the age of 40 and 70 years (Feldman et al 1994). Consistent with increasing life expectancies, the prevalence and the severity of ED increases in the elderly because of the aging process and related organic, iatrogenic and social problems (Feldman et al 1994; Parazzini et al 2000; Derby et al 2001; Kubin et al 2003). Meanwhile, a decline of testosterone (T) level is observed with age (Harman et al 2001), even though this phenomenon may be largely dependent on interindividual variability (Mazur 1998; Morley 2001). It is noteworthy that basal and dynamic peak cavernosal velocity at Penile Doppler Ultrasonography (PDU) examination is reduced in older patients (Corona et al 2004), and the pathophysiology of erectile dysfunction in this patient group mainly includes chronic ischemia, which triggers the deterioration of cavernous smooth muscle and the development of corporeal fibrosis. Generally, ED is associated with illnesses with a common basis of endothelial dysfunction, like diabetes mellitus, heart disease, and hypertension, whose prevalence increases with age (Virag et al 1985; Feldman et al 1994; Aversa et al 2002). The neural and endothelium-dependent mechanisms that would normally cause relaxation in corporal smooth muscle are impaired in tissue collected from men with diabetes and ED (Saenz De Tejada et al 1989). This body of knowledge leads to the assumption that ED is mainly a neurovascular disease (Virag et al 1985; Sullivan et al 2001), and

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is strongly supported by the evidence that specific PDE5 inhibition enhances vasodilatation in the corpus cavernosum (Ballard et al 1998) producing an efficient erection in a wide range of ages and conditions (Frajese and Pozzi 2003). Since the introduction of sildenafil, remarkable progress has been made in the treatment of erectile dysfunction. At present, inhibition of PDE5 with oral agents appears to be the treatment of choice (Kubin et al 2003). The critical role of PDE5 in penile erection and the availability of the new specific and potent inhibitors, tadalafil and vardenafil, have enabled the development of effective treatment strategies. PDE5 inhibitors are a safe and efficacious option for most elderly patients, and now represent first-line therapy also for their socio-economic impact (Anastasiadis et al 2002). An efficacious erectogenic effect by drugs is defined as an erection adequate for vaginal penetration and leading to successful intercourse. Nevertheless, considering the frequent association of sexual and medical problems in the aged, a holistic approach toward the treatment of ED should include counseling, adjustment of lifestyle, and modification of risk factors, such as medication, overweight, smoking, alcohol consumption, and lack of exercise (Meuleman 2002).

Due to its peculiar chemical and pharmacokinetics properties (essentially half-life), tadalafil may be considered as the least "typical" among the current generation of PDE5 inhibitors (Montorsi et al 2004). Providing more flexibility in dosing and more continuity in pharmacological action, tadalafil may ameliorate both sexual behavior and physiological processes leading to penile erection. This can be reflected on both efficacy and safety issues of the therapy of ED, in short as well as in long-term treatment. While the discovery of sildenafil opened a new era, mainly defeating the "impotence" of physicians in treating ED, the availability of tadalafil seems to give new perspectives as far as the treatment strategy and cure of ED is concerned.

A clinical pharmacological approach to the effective and safe use of tadalafil

The mechanism of action leading to penile erection involves inhibition of PDE5, the major cyclic guanosine monophospate (cGMP) hydrolyzing enzyme located in the vascular smooth muscle cells of corpus cavernosum. Sexual stimulation triggers the release of the endothelium dependent relaxing factor nitric oxide (NO) (Saenz De Tejada 1989), stimulating through the protein kinase G the release of guanylyl cyclase with an increase of intracellular cGMP, thus causing a decrease in intracellular calcium and, ultimately, the relaxation of trabecular erectile tissues and the dilatation of the helicine artery of the penis (Burnett et al 1992). The increase in blood flow causes the engorgement of the sinusoidal spaces of the corpora cavernosa, the tunica albuginea compresses the subtunical venules that drain the corpora and reduces the venous outflow increasing penile blood pressure and causing erection (NIH 1992). This mechanism acts primarily to maintain the tumescence phase, whereas neuronal-derived NO is mainly active in the induction of erectile function (Moreland et al 2001). Inhibiting PDE5 prolongs the effects of nerve stimulation. Tadalafil, like the PDE5 inhibitors sildenafil and vardenafil, competitively blocks the cGMP hydrolysis by PDE5, thereby fostering cGMP accumulation and the relaxation of vascular smooth muscle. Increased concentrations of cGMP produce higher PDE5 promoter activities (Lin et al 2002). cGMP accumulation stimulates cGMP degradation, but the pharmacological PDE5 inhibition blocks this negative feedback process. Thus, with PDE5 inhibitors, erection develops in a physiologic manner and only with sexual stimulation.

Chronic PDE inhibition, via the persistent activation of PDE5 promoters, may up-regulate PDE expression and, therefore, be associated with the development of drug tachyphylaxis (Moreland et al 1999). It has been shown that in the trabecular smooth muscle of the rat penis, sildenafil moderately down-regulated PDE5 (Ferrini et al 2004). The clinical long–term consequences of chronic PDE5 inhibition are still unknown. It has been reported that 20% of long-term sildenafil responders required increased dosages, while 17% discontinued because of loss of efficacy (El Galley et al 2001). It is also possible that the positive erectile response obtained with chronic administration may be related to functional tissue modifications involving up-regulation of either muscarinic receptors, or the transduction mechanism leading to the activation of endothelial NO synthase (Behr Roussel et al 2004). As PDEs are expressed in different tissues, selectivity is a prerequisite for therapeutic application of PDE inhibitors. Tadalafil is selective for PDE5 and minimally inhibits PDE6 (Angulo et al 2001), which works for visual transduction in the retina. With respect to PDE5, a 780-fold greater concentration of tadalafil is needed to inhibit PDE6, and a 14-fold greater concentration to inhibit PDE11, an enzyme with unknown physiological function. Tadalafil's nonselectivity with respect to PDE1 (expressed in the brain, myocardium, and vascular smooth

muscle cells), may result in vasodilatation and tachycardia (Bischoff 2004).

Tadalafil is rapidly absorbed with the maximum plasma concentration occurring at 2.0 h, the extended terminal half life being 17.5 h (Patterson et al 2001; Rosen et al 2001). The rate and extent of absorption of tadalafil is not altered by food ingestion, age, diabetes, or mild to moderate hepatic insufficiency (Patterson et al 2001). The earliest significant time from dosing to erectogenic effect, objectively determined by a stopwatch in a placebo-controlled design, is 16 minutes with tadalafil 20 mg, and 30 minutes with the dose of 10 mg (Rosen et al 2004). This demonstrates that effective plasma level is achieved before reaching the maximum plasma concentration. Nevertheless, most men would require more time for tadalafil to be optimally effective; in particular, patients with severe ED or older patients should be encouraged to optimize the period of sexual stimulation.

In healthy subjects, over a range of 2.5–20 mg, tadalafil's systemic exposure increases proportionally with the dose. Steady state plasma concentrations are attained within 5 days of once-daily dosing, with an exposure that is approximately 1.6-fold greater than after a single dose (Eli Lilly 2006).

The clinical evidence: efficacy of tadalafil in ED

The most important outcome for an ED therapy is the patient's perception of success (Hanson-Divers et al 1998). When patients with ED experience a successful intercourse after treatment, they feel cured of their problem. Furthermore, they express the desire of unplanned, unpremeditated or spontaneous sexual intercourse. In this sense, one possible use of the self-administered questionnaire International Index of Erectile Function – Erectile Function domain (IIEF-EF) score is to ascertain whether patients return to normal erectile function after treatment, with scores of 26–30 representing the normal ranges (Rosen et al 1999; Mulhall 2003). Integrated analysis of data from phase III trials demonstrated that tadalafil, at doses from 5 mg to 20 mg versus placebo, significantly improved erectile function (EF) by all measures. In particular, 50%–65% of patients, regardless of ED severity at baseline, returned to normal erectile function with almost 60%–90% of success rate at intercourse attempts during active treatment.

In the community-based Massachusetts Male Aging Study (MMAS) (Feldman et al 1994), 52% of 1290 men aged 40 to 70 years were found to have some degree of ED. The probability was 9.6% in the whole sample, and higher in men aged 60–69 years (40%) and in those treated for heart diseases (39%), diabetes (28%), or hypertension (15%). This indicates that ED is often a symptom present in cardiovascular disease and diabetes. Analogously, in the majority of the studies reported in this review the population selected is similar, as far as age and causes of ED are concerned, to that of MMAS.

With the purpose of assessing efficacy and safety of tadalafil in the treatment of ED, an integrated analysis of five randomized double-blind placebo controlled parallel group trials was conducted (Brock et al 2002). An update of this analysis has been made with six newest tadalafil studies including an additional group of 1215 men with ED (Carson et al 2004). The final analysis included eleven studies with 2102 patients (mean age 56 years, age range 22–88 years) who had a minimum 3-month history of mild (36%), moderate (27%), or severe (33%) ED, of organic (58%), psychogenic (12%), or mixed etiology (31%). Hypertension, diabetes mellitus, and hyperlipidemia were the most common comorbidities.

The subjects were randomly allocated to a 12-week treatment with placebo (n=638) or tadalafil at fixed daily doses of 2.5 mg (n=74), 5mg (n=151), 10 mg (n=321), and 20 mg (n=1143). The doses of 2.5 mg and 5 mg were included only in the "five studies analysis". Treatment was self administered as needed before sexual intercourse with no restrictions on food or alcohol intake or timing of sexual activity. Exclusion criteria were impotence due to radical prostatectomy, pelvic surgery, penile deformities, or recent history of stroke or spinal cord trauma, severe cardiovascular diseases and/or clinically significant renal or hepatic insufficiency. Men treated with nitrates, antiandrogens or cancer chemotherapy agents were also excluded from study participation. The international index of erectile function (IIEF) (Rosen et al 1999), that includes the domains of EF, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction, was used to globally evaluate EF. In particular, ED severity in the EF domain is scored mild (22–25), moderate (11–21), and severe (≤10) (Cappelleri et al 1999). The diary Sexual Encountered Profile (SEP) that consists of 6 and 4 yes/no questions to be answered by the patient and the partner respectively, and Global Assessment Question (GAQ) related to improvement of erections and ability to engage in sexual activity, were also administered at baseline and following treatment to evaluate the effect of therapy on successful completion of intercourse and satisfaction. Compared with placebo, tadalafil significantly

enhanced, in a dose-dependent manner, in patients of different ages, all efficacy outcomes across disease etiologies and severities. The primary efficacy outcome measure was the EF domain that consists of 6 questions with possible score range from 1 (worse function) to 30 (normal function). The score increase was <0.1 for placebo, and respectively 3.2, 4.6, 6.5, and 8.6 for tadalafil 2.5 mg, 5 mg, 10 mg, and 20 mg ($p<0.05$–0.001 vs placebo). Two other co-primary efficacy variables were the mean changes from baseline to end-point on the ability in penetration and length of erection for a successful intercourse, measured by questions 2 ("were you able to insert your penis into your partner's vagina?") and 3 ("did your erection last long enough for you to have successful intercourse?") of the SEP diary. The change of positive response to the questions 1 and 2 significantly increased from 2.3% and 8% for placebo, to 15% and 20%, 16% and 22%, 24% and 34%, 30% and 46% respectively, for tadalafil 2.5 mg, 5 mg, 10 mg, and 20 mg ($p<0.001$ vs placebo). Across all patients on tadalafil 10 mg and 20 mg, 71% and 84% reported improved erection (GAQ) versus 33% in the placebo group. The total number of successful attempts, as a proportion of the total number of attempts made, was 61% and 72% respectively, compared with 34% of placebo ($p<0.001$). Both 20 mg and 10 mg doses were significantly better than placebo in improving patients' EF. Based on the cause of ED, there was a similar trend in the IIEF–EF domain score improvements, with the 20 mg group that had numerically greater mean changes across all severity groups than the 10 mg group. The greatest percentage of tadalafil treated patients having normal EF at end-point were those with mild baseline ED, followed by those with moderate and severe ED.

To evaluate the efficacy of tadalafil in men with ED by demographic and ED characteristics, Lewis and colleagues (2005) extended post-hoc the analysis of the "eleven double-blind trials" (Carson et al 2004). In particular, etiology, severity, duration, presence of comorbid conditions such as obesity, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, depression, benign prostatic hyperplasia (BPH), or concomitant treatment with antihypertensive or antidepressant drugs have been considered. Younger patients (<65 years) had numerically better scores than older patients on each of the efficacy measures, although the differences were small after accounting for the slightly better baseline characteristics in younger patients. When age was considered, the percentage of patients attaining normal EF at end-point (IIEF–EF domain ≥26) was significantly superior in the younger treatment groups ($p<0.001$). Overall, tadalafil proved to be effective in improving erectile function across a variety of patient demographics and illness characteristics including ED etiology, duration, severity, comorbidity, and concomitant treatments. Obesity is generally associated with increased risk of medical conditions such as diabetes mellitus, hypertension, depression or cardiovascular diseases, and BPH. This was reflected in these ED studies with 66% of obese patients (Body Mass Index [BMI] >30) affected from these concomitant illnesses in comparison to the BMI <30 subjects that were affected by 53% ($p<0.001$). The obese subgroup had a statistically nonsignificant lower score on each of the efficacy measures with respect to the rest of the sample. The group of patients with organic ED etiology had lower baseline scores on both IIEF–EF and SEP-Q3 and accounts for the 67% of severe ED compared with the mixed (25%) and psychogenic subgroups (8%). As already expected (Emmick et al 2002; Saenz De Tejada et al 2002), whether affected from diabetes or hypertension, these subgroups had lower baseline and end-point scores. Both tadalafil doses showed statistically greater improvement than placebo for each ED severity level, with more pronounced amelioration in the moderate and severe ED patients because of the lower baseline scores. The subgroups of patients with comorbid conditions taking tadalafil 20 mg showed significant improvements from baseline to end-point.

Early treatment success may be important in enhancing self-confidence to continue successful treatment. An integrated post-hoc analysis of the "five double-blind studies" (Brock et al 2002) examined the first dose success, the cumulative success by dose and the maintenance of success among men taking tadalafil (Shulman et al 2004). The SEP diary questions assessed these three perspectives. With the first dose, significantly greater proportions of men taking tadalafil 10 mg and 20 mg versus placebo achieved successful erection (SEP-Q1: 85% and 90% vs 66% respectively), successful penetration (SEP-Q2: 74% and 79% vs 47% respectively), successful intercourse (SEP-Q3: 56% and 67% vs 31 % respectively), and were satisfied overall with their sexual experience (SEP-Q5: 36% and 47% vs 15%, respectively; all $p<0.001$). Regardless of the ED severity or patient age, continued dosing increased the proportion of men achieving first success, reaching a plateau between dose 4th and 8th at approximately 95% (SEP-Q2), 90% (SEP-Q3), and 81% (SEP-Q5). After first-dose success, success rate in a 12-week period was significantly greater for men taking tadalafil versus placebo (SEP-Q2: 85% and

91% vs 75%; SEP-Q3: 81 and 88% vs 64%, respectively; p<0.001). Note the high proportion of patients attaining initially a successful erection while on placebo. This success was not maintained under the measures of successful penetration, intercourse, and satisfaction.

In a large population of men from Central and Eastern Europe and Eastern Mediterranean (mean age 52 years; range 21–82 years), after 12 weeks of on demand treatment, tadalafil 20 mg versus placebo has confirmed its superior efficacy, also after stratification of IIEF–EF severity class from mild and moderate to severe (Skoumal et al 2004). Tadalafil patients achieved a normal IIEF–EF score at endpoint, compared with 16% of placebo patients (p<0.001), and compared with placebo, have a significantly higher end-point and a greater change from baseline across all domains of IIEF. The same conclusions on tadalafil 20 mg were yielded in similar trials with populations of different ethnicity (Allen et al 2004; Carson et al 2005). In particular, in a multicentric trial conducted both in Italy and UK (Eardley et al 2004), involving nearly 41% of severe ED patients (mean age 53; range 26–78 years), tadalafil 20 mg on-demand improved mean EF domain scores by 11.1, versus 0.4 of placebo (p<0.001), with 74% of successful intercourse attempts compared with 30% of placebo. This is the largest numerical improvement observed in the IIEF–EF domain with tadalafil. Tadalafil significantly improved IIEF satisfaction domain and GAQ overall effect on erection (82% vs 23%) and sexual activity (79% vs 17%). These results mirror those observed in the "five studies analysis" (Brock et al 2002).

Regardless of the degree of ED, tadalafil 20 mg every other day for one month has been shown to improve endothelial function in patients with increased cardiovascular risk (Rosano et al 2004), since endothelial damage is a common marker of diseases of the cardiovascular system. The benefit was sustained two weeks after treatment discontinuation and was associated with an increase in nitrite/nitrate levels and a decrease in endothelin-1. Age itself is an important risk factor for vascular disease and ED, and thereby endothelial dysfunction. In elderly patients (60–70 years) affected by ED, with slight or no signs of carotid disease, resumption of spontaneous erections was obtained with chronic tadalafil 20 mg administered for three months on alternate days. One month after withdrawal from dosing, spontaneous improvement in sexual function was reported in 55%–65% of patients unaffected from carotid disease and in 16% of those with increase of carotid intimal thickness (Caretta et al 2005). Nocturnal penile tumescence rigidity monitoring and PDU parameters were inversely related to different degrees of carotid wall alteration and showed a significant improvement in those patients with atherosclerotic plaques, probably due to the amelioration of endothelial function during treatment.

A retrospective analysis of pooled data from 12 placebo-controlled trials was conducted to characterize the efficacy and safety of tadalafil in men with diabetes mellitus (Fonseca et al 2004). Baseline characteristics of ED severity, assessed by IIEF–EF, scored 12.6 in diabetics and 15 in nondiabetics (p<0.001). These scores correlated inversely with glycosylated hemoglobin (HbA1c) levels. Regardless of glycemic control and diabetic therapy, tadalafil 10 mg and 20 mg, compared with placebo, improved all primary efficacy outcomes in all patients. The subgroup receiving tadalafil 20 mg experienced a mean improvement of 7.4 in the IIEF–EF domain score from baseline versus 0.9 for placebo (p<0.001), reporting a 53% average of successful intercourse attempts, compared with 22% for placebo.

Tadalafil 20 mg was effectively administered in the treatment of 303 men suffering from ED following bilateral nerve sparing radical retropubic prostatectomy (Montorsi, Padma-Nathan, et al 2004). Compared with placebo, a greater improvement on all the evaluated end-points was reported. IIEF–EF domain score increased by 5.3 (p<0.001 vs placebo), and positive response for SEP-Q2 and Q3 was for 54% and 41% of patients. A subgroup of patients with at least a post-operative tumescence, meaning a post-surgical minimal cavernous innervation damage, reported an increase of 5.9 points on the IIEF–EF and of 69% and 52% on SEP-Q2 and Q3.

In a randomized blind cross-over trial for the treatment of ED in 30 male spinal cord-injured patients (mean age 34.6, range 21–60 years) tadalafil 10 mg was compared with sildenafil 50 mg (Del Popolo et al 2004). In these patients, either psychogenic erections or reflexive spinally elicited erections or both are necessary for PDE5 inhibitor response. Tadalafil and sildenafil allowed patients to achieve erections whit a mean total score on IIEF of 17.82 and 15.75 (increase from baseline of 58.41% and 40%) respectively. No significant differences were observed up to 12 h, while, as expected, normal sexual functioning and improved overall sex satisfaction up to 24 h post-dosing was better for tadalafil compared with sildenafil (p<0.01).

The clinical evidence: safety of tadalafil in ED

Most of the side effects reported in the clinical trials are dose-dependent and consistent with the vasodilatatory effect of PDE-5 inhibition. When tadalafil was administered on an on-demand basis headache and dyspepsia were the most frequent symptoms, followed by back pain, nasal congestion, myalgia, and flushing. Subgroup analyses have revealed no differences between incidences of adverse events in tadalafil-treated men over 65 years compared with the younger group. No relevant differences in the frequency and pattern of side-effects have been reported when tadalafil was schedully administered (eg, three times per week, or daily). The daily administration of tadalafil was well tolerated with headache, dyspepsia, facial flushing, nasal congestion, and backache as the most frequently reported adverse events (McMahon 2004). In the "eleven trials analysis" (Carson et al 2004), adverse events leading to study discontinuation account for 3.2% of patients taking tadalafil 20 mg, 1.6% of patients taking tadalafil 10 mg and 1.3% of patients on placebo. Respectively, 51%, 58%, and 39% of the subjects experienced at least one or more unwanted symptoms. Side-effects were generally mild to moderate and decreased in frequency during continued treatment. While no significant laboratory or electrocardiographic changes were assessed, the most common treatment-emergent adverse events were headache (15%, 12%, 5% respectively), dyspepsia (8%, 7%, 1% respectively), back pain/myalgia (8%, 11%, 3% respectively), nasopharyngitis and nasal congestion (4%, 11%, 5% respectively), flushing (3%, 3%, 1% respectively), pain in limb (3%, 3%, 1% respectively).

In a comprehensive review on the cardiovascular effects of tadalafil, a safety assessment of more than 4000 subjects who received the drug during clinical studies was performed (Kloner et al 2003). When tadalafil 10 mg and 20 mg was administered to healthy subjects, minimal, but statistically significant differences over placebo in standing systolic (SBP) and diastolic blood pressure (DBP) were observed. Tadalafil 20mg administered daily for 26 weeks in healthy volunteers or in subjects with mild ED (age ≥45 years) did not result in significant changes in sitting SBP or DBP. A small decrease in standing SBP and DBP has been reported in patients with chronic stable angina treated with different doses of tadalafil (5 mg and 10 mg), however, these changes were greater and statistically significant with respect to placebo in the so called "outlier patients", in whom a decrease of >30 mm Hg in SBP or >20 mm Hg in DBP from baseline was recorded.

An update on thirty-five placebo-controlled and eight open clinical trials of tadalafil demonstrated no increased risk of cardiovascular adverse events such as myocardial infarction, cerebrovascular events or cardiac mortality (Jackson et al 2004).

The evidence that duration of action for tadalafil is well beyond the elimination half-life, advises for a careful monitoring of its long-term effect. However, the duration of side-effects has not been measured in the majority of the studies. Due to the potential for a clinically significant decrease in blood pressure, the major contraindications of the PDE5 inhibitors are concomitant use with nitrates or molsidomine-containing medications, because of the increased sensitivity to nitroglycerin (Dishy et al 2001). Interaction between grapefruit juice and sildenafil, tadalafil, or vardenafil may cause serious systemic vasodilatation (Bailey and Dresser 2004), and we do suggest such a possibility with alcohol as well (Frajese and Pozzi 2005). Since men with ED have high incidence of cardiovascular disease, diabetes mellitus and BPH, they are likely to be taking medications that affect blood pressure like the alpha-blockers terazosin and doxazosin (Simonsen 2002). Tadalafil augmented the hypotensive effects of doxazosin, but had little hemodynamic interaction with tamsulosin, a drug prescribed for BPH (Kloner et al 2004). The long-term safety and tolerability of tadalafil 10–20 mg in the treatment of erectile dysfunction has been assessed, evaluating in a 18–24 month open extension trial in 1173 subjects (mean age 57, range 23–83 years) (Montorsi, Verheyden, et al 2004). Notably, 74% of patients were taking concomitant medication for comorbid conditions, including diabetes mellitus (30.5%) and hypertension (29.5%). After three months, 72% of patients had chosen the 20mg dose. 173 (14.7%) of men discontinued because of perceived lack of efficacy over 18–24 months of treatment. 234 (20%) and 493 subjects (42%) completed 18 and 24 months of treatment respectively. The total tadalafil exposure was 1676 patient-years. Headache (15.8%), dyspepsia (11.8%), nasopharyngitis (11.4%) and back pain (8.2%) were the most common treatment emergent side-effects. Consistent with the low affinity of tadalafil for PDE6, only 1 patient complained of cyanopsia (blue vision). The rate of discontinuation due to adverse events was 6.3%. No clinically significant laboratory, or electrocardiographic findings, or changes in vital signs, or serious adverse events (8.6%), or major safety concerns were causally associated with tadalafil administration.

Back pain or myalgia or both appearing as a consequence of PDE5 inhibition was experienced by 8.3%–9.4% of men taking tadalafil 10–20 mg. The potential mechanism of this side effect remains unknown. The underlying symptoms include diffuse bilateral lower lumbar gluteal, thigh, or thoracolumbar muscular discomfort, exacerbated by recumbency. The integrated analysis of ten placebo-controlled tadalafil studies, including 1846 patients (Seftel et al 2005), showed that laboratory markers of inflammation or muscle damage and renal plasma flow were unchanged with respect to baseline, and no lumbar or gluteal myositis was evidenced by positron emission tomography scan or magnetic resonance imaging.

Across tadalafil clinical trials no impairment of blue-green color discrimination was detected, and color vision alterations were rare (0.1%) (Eli Lilly 2006). Chronic tadalafil administration has no detrimental effect on human spermatogenesis or reproductive hormones (Ellstrom et al 2003).

Treatment strategies and effect on sexual behavior

Although efficacy and safety are two important characteristics when choosing a pharmacological treatment for ED, the ideal therapy should be reliable during maintenance. Furthermore, beyond erection and penetration, intercourse success and overall satisfaction needs have to be considered. The primary goal in the treatment of ED should be the restoration of sexual life rather than merely the achievement of a penile erection.

An important characteristic of tadalafil is its prolonged period of responsiveness. In prescribing a therapy for ED, the long lasting effect of the drug may not be the most important issue. Tadalafil is unique to the PDE5 inhibitors available because of its efficacy up to 36 h after dosing. This should release from the need to plan sexual activities and therefore favor spontaneity.

In a study designed to assess whether tadalafil 20 mg was associated with a treatment effect discriminated from placebo (Porst et al 2003), a greater proportion of successful intercourse attempts up to 36 hours post-tadalafil dose compared with placebo at 24 h and 36 h was reported. Fifty-three percent versus 29% ($p<0.001$) of successful intercourse attempts according to SEP-Q3 was undertaken up to 24 h, and 59% versus 28% ($p<0.001$) within 36 h after dosing.

In a randomized prospective placebo-controlled trial, the chronological distribution of sexual intercourse was evaluated (De Rose et al 2005). Tadalafil 20 mg administered twice a week resulted in a significant change of sexual attitude with the highest percentages of successful intercourse after 6–12 h (35%), and 12–24 h (28%) from dosing. It should be mentioned that 5% and 2% of intercourse were recorded up to 48 h and 60 h, while none of the placebo patients has reported sexual intercourse over 16 h. Recovery of spontaneous night, awakening, and day long erections at the rate of 78% was also reported. Besides the quality of sexual intercourse, these results showed an improvement of sexuality in the broadest sense. Unfortunately, due to the low mean age of patients enrolled (46 years), it is difficult to extrapolate this data to elderly patients.

When taken on demand, tadalafil 20 mg versus placebo allows a range of 62%–74% (vs 0%–33%) of successful intercourse attempt rate up to 36 h ($p<0.001$ up to 24 h; $p=0.017$ up to 36 h) (Allen et al 2004; Seftel et al 2005).

Patients on tadalafil changed their sexual behavior significantly when on an alternate dose regimen (3 times/week) and had sexual attempts distributed over a wide period of time post dosing (Mirone et al. 2005). The on-demand regimen versus scheduled use was evaluated in 4262 patients in a cross-over open-label study conducted to assess patient's choice of treatment regimens. Overall, both regimen were effectives with a normal IIEF–EF domain score (≥26) achieved by 60.2% and 62.3% of patients, and a 72.6% and 74.4% mean per patient intercourse success rate. A preference for the on-demand administration was expressed by 57.8% of patients. An analysis of preferences based on comorbidities associated with ED (Moncada et al 2005) showed that the on demand regimen was preferred in each subgroup except for the depressed patients, in which 53% expressed preference for the 3 times/week treatment. It was concluded that the patient's choice of treatment regimens is not exclusively determined by demographics or clinical features, but is possibly related to individual cultural and psychosocial factors. Forty seven percent of the attempts on the on-demand regimen and 71% on the 3 times/week treatment were performed by patients more than 4h post-dosing. The efficacy of tadalafil 20 mg was more than 70% (mean-per-patient) success rate regardless of the time interval post-dosing. Since age is a potential influencing factor on sexual habits, a subgroup analysis of age was performed. On three cohorts of patients aged <40, 40–65, and >65 years, overall 52%–56% of attempts were performed within 4h post-dosing with on-demand regimen and 68%–71% of attempts beyond 4h post-dosing with the 3 times/week interval. In all the three groups the evening

was the preferred time for sexual activity, but with increasing age fewer weekend attempts (about 51%, 48%, and 45% respectively) and more morning attempts were observed on the 3 times/week regimen (about 13%, 22% and 28% for patients aged >65 years). Moncada and collegues (2005) commented that this behavior may be a general response to a less pronounced perception of a deadline to engage in sexual activity and to the major availability of time for sexual activity in the older patients and their partners.

Similar results emerged from the post-hoc analyses (Shabsigh et al 2005) assessing the time from dosing to sexual intercourse attempts of the "eleven double-blind trials" (Carson et al 2004) and of the double-blind studies conducted in eastern Europe (Hatzichristou et al 2005). Regardless of age, ED severity or previous experience with sildenafil, most patients attempted sexual intercourse 12–36 h after one dose of tadalafil and did not adhere to a fixed schedule of intimacy.

In several clinical studies for the treatment of ED, a significant greater efficacy of PDE5 inhibitors in the younger with respect to older subjects (89.1% vs 65.7%; $p<0.01$) has been reported (Tsujimura et al 2002). The progression of endothelium dysfunction and of penile vascular disease, androgen deficiency, reduced sexual desire and appealing, and psychogenic issues are often the reason for a low response to PDE-5 inhibition (McMahon 2004).

It was shown that while serum T and prolactin (PRL) were similar between young and elderly groups, mean serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations significantly differed below and over 65 years (5.2 and 8.7 mIU/mL vs 11.0 and 18.9 mIU/mL, respectively; $p<0.01$). This may be partly explained by the increasing number of pathologies observed with aging (Eisenhardt and Siffert 2003), although a significant role is played by the decline in gonadal (Mazur 1998; Aversa et al 2000; Derby et al 2001; Harman et al 2001) as well as in hypothalamic–pituitary functions (Pincus et al 1997). Older males secrete LH and T more irregularly, and jointly more asynchronously than younger males (Pincus et al 1996), although hormone levels fell in the normal range. On the other hand, androgens may influence sexual behavior by acting within the central nervous system, and through regulatory effects on several neurotransmitter systems, in particular dopamine and serotonin (Steers 2000). In the same way, both sexual desire and erectile function are responsive to testosterone and lack of sexual activity decreases T levels (Ahn et al 2002). There is a T threshold below which libido and sexual function are impaired, but no evidence of a correlation between ideational or erectile components of sexual function and T level in the normal range of circulating androgens has been reported before (see Rubinow and Schmidt 1996).

In a trial comparing sildenafil and tadalafil (Carosa et al 2004) in the treatment of ED, basal T and FT levels in the lower normal range, and LH level at the top of the normal range, were reversed during treatment. An LH reduction and a testosterone rise, well within the normal laboratory values, were observed. The T and FT increase in sildenafil patients was significantly lower than in those treated with tadalafil (4.7 ± 2.7 vs 5.1 ± 0.9, $p<0.001$). The full sexual intercourse frequency also significantly roused to a 4.9 ± 2.9/month intercourse rate for sildenafil and 6.9 ± 4.6/month ($p=0.04$) for tadalafil, because the longer half-life of the latter facilitates the higher frequency of intercourse, as was concluded by the study. Whether the observed changes in the hormonal pattern may be attributed to the increased sexual activity, or directly due to the PDE5 inhibition (eg, NO stimulates hypothalamic gonadotropin-releasing hormone [Kohsaka et al 1999], and inhibits PRL release in rats [Velardez et al 2000]) remains to be determined. However, no significant correlation between frequency of sexual intercourse and T level has been found by Goldstein and colleagues (1998*)* in aged ED patients.

The efficacy of PDE5 inhibitors is probably related to the extent and severity of ED. In patients suffering from ED with diabetes, or severe vasculogenic disease, or post-radical prostatectomy, a significantly reduced efficacy of these drugs was demonstrated in several experiences (Goldstein et al 1998; Emmick et al 2002; Saenz De Tejada et al 2002). Different salvage strategies have been applied in such cases (McMahon 2002; Atiemo et al 2003). In a clinical trial (McMahon 2004) involving subjects with ED of predominantly vasculogenic etiology, (mean age of 63; range 21–79 years), previously unresponsive to on-demand tadalafil, daily administration of tadalafil, at the flexible dose of 10–20 mg significantly enhanced all efficacy outcome variables. Improved erections at end-point were reported by 69% of men compared with 42% of men with on-demand tadalafil. A significant improvement in the IIEF–EF domain of 12.8 versus pre-treatment ($p<0.001$), and of 8.2 from on-demand tadalafil baseline ($p<0.001$) was reported. Sexual intercourse was successfully completed on 58% of attempts with daily tadalafil 10 mg compared with 21% at baseline, and 28% with on-demand tadalafil 20 mg ($p<0.001$). However, McMahon (2004) hypothesized that although the potential for tachyphylaxis (Moreland et al 1999) is probably

low for on-demand use of PDE5 inhibitors, the long lasting duration of tadalafil's effect and its chronic use may facilitate the loss of treatment efficacy.

Conclusions

With an effectiveness that lasts up to 36 h, tadalafil could provide nearly continuous coverage when taken on a regular basis, allowing patients and their partners to choose freely when to have sexual activities without the need of timing it. This property of tadalafil explains why patients suffering from ED showed positive feedback in terms of quality of life related to the treatment. Although various studies reported the superior pharmacokinetic properties of tadalafil compared with the other PDE5 inhibitors, this should be cautiously interpreted, especially in the elderly, because up to now it has not been entirely defined the impact that such a long lasting effect could have both on clinical effectiveness and safety, especially in the presence of comorbid conditions or other drugs. Nevertheless, the efficacy of tadalafil was demonstrated in patients of all ages across disease severities and etiologies with a broad range of outcomes, including improved erections, hardness, ability to penetrate the partner's vagina, maintenance of erection, intercourse satisfaction, and overall satisfaction. The treatment choices that are possible with tadalafil allow patients to take the drug on a regular basis and to regain satisfaction with sex life.

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