Tadalafil in the treatment of lower urinary tract symptoms and erectile dysfunction

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In the aging male, erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) are common conditions that have been shown to be related. As life expectancy increases, treatments that target both ED and LUTS will prove increasingly valuable over the coming years. Phosphodiesterase type 5 (PDE5) inhibitors are used primarily to treat ED. Recently, studies have shown that improvements in LUTS are also seen with PDE5 inhibitor treatment. In particular, the PDE5 inhibitor tadalafil may be beneficial owing to its unique long-acting pharmacokinetic properties. We review the current literature to provide an insight into how tadalafil could provide symptomatic relief from ED and LUTS.

Lower urinary tract symptoms & benign prostatic hyperplasia.

Benign prostatic hyperplasia (BPH) is one of the most common conditions affecting men, having a major impact on the health of aging men and, as a consequence, upon health economics [1]. Numerous post-mortem histological studies into the prevalence of the disease have concluded that the prevalence of BPH increases with age [2], with BPH not being identified in men younger than 30 years of age. In these studies, in men aged 21–30 years, the normal prostate was 20 ± 6 g in weight, and this weight remained unchanged with increasing age unless BPH developed. In the fourth decade of life, BPH was found in 8% of specimens, and by the sixth decade of life, histological BPH was identifiable in 50% of males.

The most important determinant of this disease, however, is a measure of the symptoms that patients experience, termed lower urinary tract symptoms (LUTS). These include increased urinary frequency, urgency, hesitancy, incomplete emptying and a weak urinary stream [3]. In a series of clinical studies of 2113 men aged 40–79 years who were randomly selected from Olmstead county (MN, USA) [4], the prevalence of LUTS and the relationship to prostatic size, and other measures of lower urinary tract function, were measured [5]. In this population, the point prevalence (the proportion of men within this population with a set of symptoms measured at a point in time) of moderate to severe LUTS showed a clear correlation with age, such that the prevalence rose from 13% in men aged 40–49 years up to 28% in those aged 70–79 years [6]. Correlation with prostatic size as assessed by transrectal ultrasonography showed that the odds ratio of having moderate to severe LUTS was 3.4 in prostates greater than 50 g, compared with men with prostates less than 50 g. There was also evidence of deterioration in other measures of lower urinary tract function. For example, as age increased, the mean urinary flow rate decreased from approximately 20.5 ml/s for men aged 40–44 years to 11.5 ml/s for men aged 75–79 years at a rate of approximately 2 ml/s for each decade.

This cohort of men was followed longitudinally for a number a years. Prostate volumes increased by 1.9%/year [7] and the average increase in International Prostate Symptom Score (IPSS) was 0.18 points/year [8]. Men in their fifties had increases in IPSS of 0.05 points/year and men in their seventies had increases of 0.44 points/year. Age and prostate size are therefore risk factors for symptomatic BPH. LUTS in the aging male population is a significant problem that is worthy of focused attention.

The medical treatment of LUTS at present includes 5-α-reductase inhibitors to reduce prostate size to influence the obstructive component of bladder outflow obstruction. The smooth muscle tone of the bladder neck, prostate and urethra can be reduced by α-adrenergic receptor antagonists, thus reducing the dynamic component of bladder outflow obstruction. These two drug classes in monotherapy or in combination have been shown to provide symptomatic benefit to patients with LUTS [9]. Until recently, no other drug class has shown similar benefits.

Relationship of erectile dysfunction & lower urinary tract symptoms

Erectile dysfunction (ED) is also a problematic condition of the aging male. In the Massachusetts Male Aging Study, 52% of men aged 40–70 years

Keywords: benign prostatic hyperplasia, BPH, ED, erectile dysfunction, lower urinary tract symptoms, LUTS, PDE5 inhibitors, tadalafil

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had some degree of ED, rising from 39% of men aged 40 years to 67% of men aged 70 years [10]. This relationship with age is confirmed in other epidemiological studies of ED. In a cross-sectional study of 2476 men aged 25–70 years [11], the prevalence of ED was 18.9%, rising from 8.5% of men aged 25–39 years to 48% of men aged 60–70 years. These and other studies demonstrated that risk factors for ED include cardiovascular conditions such as diabetes, hypertension and heart disease. However, in addition, there is commonly an association with LUTS, as was demonstrated in the latter study. In this study, the age-adjusted odds ratio for ED in men with LUTS was 2.67 compared with men without LUTS. Age-adjusted odds ratios for diabetes and hypertension were lower (1.98 and 1.72, respectively). This association between ED and LUTS has been demonstrated in several other studies in men from several different countries and regions [12–15].

The mechanisms by which these symptom complexes are associated are as yet unclear, but there is evidence that the association is independent of age. In the Multi-National Survey of the Ageing Male-7 study (MASM-7) [13], men aged 50–80 years in the USA and six European countries were surveyed regarding their LUTS and ED using validated symptom scores. A total of 12,815 returned surveys were evaluated. A strong relationship between ED and increasing severity of LUTS (odds ratio 8.9 for severe versus mild LUTS) was reported and was independent of diabetes, hypertension, cardiac disease, hypercholesterolemia, geography and age. Biological plausibility for this causal relationship has been well described in a recent review article [16]. Currently, four theories exist:

- Nitric oxide synthase (NOS)/NO theory
- Autonomic hyperactivity and metabolic syndrome hypothesis
- Rho-kinase activation/endothelin pathway
- Pelvic atheroscelorosis

The NOS/NO theory is currently gathering growing interest as agents already in clinical use for ED act by modifying this pathway. Given that both ED and LUTS are so common in aging men, and also given that life expectancy is increasing, treatments that target both these symptoms will prove increasingly valuable over the coming years. Inhibitors of the enzyme phosphodiesterase type 5 (PDE5) have been used for several years to treat ED, but in recent years there has been the suggestion that they may also be valuable in the treatment of LUTS.

In 1998, Goldstein and colleagues published the effects of sildenafil (Viagra®) in the treatment of ED [17], demonstrating efficacy and safety when taken, on demand, 1 h before planned sexual activity. Currently, three highly efficacious and safe PDE5 inhibitors are available to clinicians to treat ED. These are sildenafil, vardenafil (Levitra®) and tadalafil (Cialis®). We review the current literature to provide an insight into how tadalafil could provide symptomatic relief from ED and LUTS.

Basic science

Pharmacology of PDE5 inhibitors in penile smooth muscle

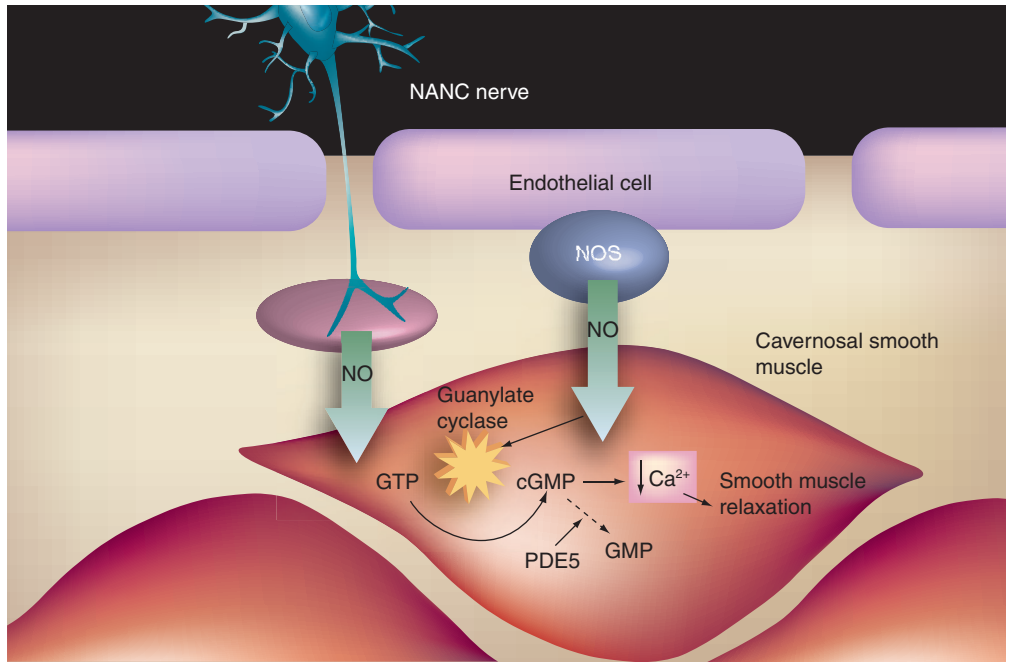
Penile erection is caused by the relaxation of penile vascular smooth muscle, leading to an accumulation of blood within cavernosal tissue [18,19]. Smooth muscle tone in the corpus cavernosum of the penis is influenced by the NO–cyclic GMP (cGMP) signaling pathway [20,21]. Sexual stimulation leads to NO release from parasympathetic nonadrenergic, noncholinergic (NANC) neurons in the penis and from the endothelial cells lining the penile vasculature [22–25]. Upon entry to the smooth muscle cell, NO stimulates the enzyme guanylate cyclase to convert GTP to cGMP, which in turns acts as a second messenger to relax the smooth muscle cell. PDE5 is a critical component that modulates levels of intracellular cGMP by hydrolyzing cGMP to GMP [26]. Inhibitors of PDE5 maintain intracellular levels of cGMP, thus enhancing the NO-mediated response of corpus cavernosum to sexual stimulation (**Figure 1**). PDE5 inhibitors therefore augment the maintenance of penile erection.

Pharmacology of PDE5 inhibitors in the lower urinary tract

While the pharmacology of the PDE5 inhibitors in penile tissue is well understood, the possible effects on LUTS, bladder outflow obstruction (BOO) and/or benign prostatic hyperplasia (BPH) depend on the expression of the components of the NO–cGMP signaling pathway within the lower urinary tract. At present, there are only limited data in this area.

Werkström and colleagues demonstrated the presence of PDE5, cGMP and a downstream effector of muscle contraction, c-GMP-dependent protein kinase 1 (PGK1), within both human and animal urethral tissue [27]. While there was immunoreactivity to cGMP, PKG1 and PDE5 in both human female urethra and pig urethra,

Figure 1. Pharmacology of PDE5 in the cavernosal smooth muscle cell.



NO from NANC nerves and NOS within endothelial cells causes stimulation of guanylate cyclase. Active cGMP causes a decrease in intracellular calcium and subsequent smooth muscle relaxation. Hydrolysis of cGMP to inactive GMP is facilitated by PDE5.
NANC: Nonadrenergic, noncholinergic; NOS: Nitric oxide synthase; PDE5: Phosphodiesterase type 5.

there was much stronger immunoreactivity for PDE5 in human tissue. PDE5 inhibitors, including tadalafil, resulted in relaxation of urethral smooth muscle strips, and the administration of PDE5 inhibitors also resulted in increased levels of cGMP.

PGK1 expression has also been demonstrated in human prostate tissue by immunohistochemistry and western blot analysis [28]. Donor tissue was sourced from patients undergoing radical surgery for prostate cancer. PGK1 was shown to be co-localized with cGMP, suggesting a role for the NO–cGMP pathway in human prostate.

Ückert described PDE5 expression in normal human prostate obtained from patients undergoing radical surgery for localized prostate cancer [29]. The PDE5 inhibitor sildenafil caused relaxation of prostate smooth muscle strips.

Studies of prostate smooth muscle cells in culture suggest that PDE5 inhibitors may also inhibit cell proliferation. BPH is characterized by excessive stromal cell proliferation [30]. Adolfsson and colleagues demonstrated concentration-dependent sildenafil inhibition of lysophosphatidic acid-stimulated DNA replication [31], as measured by showing changes in the incorporation of thymidine in human-cultured prostate stromal cells. Guh *et al.* showed that the NO donor sodium nitroprusside also inhibited the proliferation of human prostate stromal cells in culture [32]. Finally, a recent key paper confirmed the antiproliferative and muscle-relaxant effects of PDE5 inhibitors in rat prostate muscle strips and in human prostate stromal cells [33]. Sildenafil, vardenafil and tadalafil all reduced the contraction of rat prostate muscle strips in a concentration-dependent manner and also significantly attenuated serum-induced human prostate stromal cell proliferation.

LUTS can also be a result of bladder dysfunction either in isolation or in association with BPH. PDE5 expression has been shown in human bladder [34], but inhibition of PDE5 has been shown not to affect bladder muscle function in animal and human detrusor muscle [35,36].

Pharmacokinetics of tadalafil

Tadalafil is a potent and reversible inhibitor of PDE5 [37]. It is selective for PDE5 compared with the other ten isoforms of PDE. At high concentrations there is some inhibition of PDE11, although the physiological function of PDE11 is, as yet, unclear. Tadalafil has pharmacokinetic properties

Box 1. The SEP diary questions.

- SEP 1: Were you able to achieve some erection?
- SEP 2: Were you able to insert your penis into your partner's vagina?
- SEP 3: Did your erection last long enough to successfully complete intercourse?
- SEP 4: Were you satisfied with the hardness of your erection?
- SEP 5: Were you satisfied overall with this sexual experience?

The SEP diary records the responses to the above questions. If any 'No' responses were recorded then subsequent questions were analyzed as 'No' responses.
SEP: Sexual Encounter Profile.

unlike other PDE5 inhibitors in clinical use [38]. At the highest recommended dose taken orally (20 mg), the maximum plasma concentration was reached after 2 h, with a half-life of 17.5 h. Bioavailability was unaffected by food, BMI, age, gender or smoking. Patients with diabetes or hepatic impairment tolerated a 10 mg oral dose with no clinically significant changes in tadalafil pharmacokinetics. Patients with end-stage renal failure showed serum levels of the major metabolite, methylcatechol glucuronide, three-times higher than healthy patients [39].

Clinical effects of tadalafil in men with erectile dysfunction

Efficacy

The efficacy and safety of on-demand tadalafil were first described by Padma-Nathan and colleagues in a multicenter, double-blind, placebo-controlled study [40]. A total of 179 men with at least a 3-month history of ED were randomized to receive placebo or tadalafil 2, 5, 10 and 25 mg. Each patient group was well matched for age, ethnicity and weight. Severity of ED was assessed at baseline using the International Index of Erectile Function (IIEF) [41]. This is a validated symptom scoring system that summarizes recent sexual encounters. It has been adopted as the 'gold standard' measure for assessing efficacy in clinical trials of ED [42,43]. Average IIEF scores were equal across all groups. At randomization, patients were also given sexual encounter diaries (or Sexual Encounter Profiles [SEP]), a five-question survey assessing individual sexual encounters (**Box 1**). Patients were then instructed to take one dose 'on demand' when intercourse was planned at a maximum frequency of once daily over 21 days, but no more than 14 doses. Repeat IIEF scores were obtained and SEP diaries collected at 7 days into treatment and at the end of the treatment period.

Tadalafil 5 and 10 mg caused significant increases in IIEF questions 3 and 4, erectile function domain scores and SEP questions 3 and 4 over placebo (**Table 1**). Tadalafil 2 mg caused variable increases and 25 mg caused no further increases compared with 10 mg tadalafil. Thus, this initial study of tadalafil 5- and 10-mg on demand caused significant proportions of patients with ED to be able to have successful intercourse.

In a subsequent integrated analysis of 11 randomized, double-blind, placebo-controlled, parallel-arm trials [44], statistically significant changes from baseline to endpoint measures over placebo were seen in patients taking tadalafil 10 and 20 mg (**Table 2**). Tadalafil is efficacious at both 10 and 20 mg for almost all patients, and its effects can last from 30 min up to 36 h [45,46].

Safety & adverse effects of tadalafil

PDE5 inhibitors are well tolerated. In the previously described integrated analysis of 11 randomized, double-blind, placebo-controlled studies [44], only 1.3, 1.6 and 3.2% of patients taking placebo, tadalafil 10 mg, and tadalafil 20 mg, respectively, discontinued medication during the study. The most common adverse events were headache, dyspepsia and back pain, while nasopharyngitis, myalgia, flushing, nasal congestion and pain in a limb were seen less frequently. These effects probably reflect the presence of PDE5 in other tissues [47]. The occasional visual disturbances (not including nonarteritic anterior ischaemic optic neuropathy [NAOIN]) seen with sildenafil are not seen with tadalafil, reflecting the minor inhibition of PDE6 (involved in visual perception in the retina) that is seen at high doses with sildenafil [48]. This inhibition is not seen with tadalafil. NAOIN is rare and associated with all three PDE5 inhibitors in case reports, but its causal relationship has yet to be established [49].

As discussed earlier, PDE5 inhibitors augment the NO–cGMP pathway. Nitrates, such as nitroglycerin, isosorbide mononitrate and isosorbide dinitrate, are used to treat angina by vasodilatation of coronary artery smooth muscle, and they also increase intracellular cGMP. As a result, when taken in combination, PDE5 inhibitors and nitrates can cause symptomatic hypotension [50]. Consequently, the use of PDE5 inhibitors is contraindicated in men taking organic nitrate medications. According to the Princeton II consensus [51], it has been recommended that if a patient has taken a short-acting PDE5 inhibitor (sildenafil or vardenafil), nitrates can be restarted 24 h after the last PDE5 dose [52]. As tadalafil is a long half-life agent, a study suggests that at least 48 h should elapse between the last tadalafil dose and readministration of a nitrate [53].

Table 1. Effect of tadalafil on responses to IIEF and SEP.

	Placebo (n = 35)	Tadalafil 2 mg (n = 35)	Tadalafil 5 mg (n = 37)	Tadalafil 10 mg (n = 36)	Tadalafil 25 mg (n = 36)
IIEF question 3	2.5 ± 0.3	3.5 ± 0.3	4.2 ± 0.2	4.1 ± 0.2	4.2 ± 0.2
Change	-0.3 ± 0.2	0.6 ± 0.2*	1.2 ± 0.2‡	1.0 ± 0.2‡	1.3 ± 0.2‡
IIEF question 4	2.4 ± 0.2	3.1 ± 0.3	3.7 ± 0.2	4.0 ± 0.2	4.0 ± 0.2
Change	0.2 ± 0.2	0.8 ± 0.2	1.4 ± 0.2‡	1.7 ± 0.2‡	1.7 ± 0.2‡
IIEF EFD	14.7 ± 1.2	19.3 ± 1.5	22.9 ± 1.0	23.6 ± 1.1	24.2 ±1.2
Change	1.0 ± 0.9	4.1 ± 1.1§	7.3 ± 1.0‡	7.8 ± 1.2‡	9.4 ± 1.2‡
SEP 3 and 4	26.6%	45.7%	61.7%¶	69.8%#	70.2%**

IIEF scores are mean ± standard error at the end of treatment. Change represents the change in scores from baseline. SEP 3 and 4 represents the percentage of patients answering yes up to question 4 of SEP diaries.

**p ≤0.005 versus placebo, based on comparison of the least-squared means.*

‡p ≤0.0005 versus placebo, based on comparison of the least-squared means.

§p ≤0.05 versus placebo, based on comparison of the least-squared means.

¶p ≤0.01 versus placebo.

#p ≤0.005 versus placebo.

***p ≤0.0002 versus placebo.*

IIEF: International Index of Erectile Function; EFD: Erectile Function Domain Score; SEP: Sexual Encounter Profile.

Data taken from [40].

Tadalafil in the treatment of ED after localized prostate cancer treatment

Radical retropubic prostatectomy (RRP) and radical external-beam radiotherapy (REBR) are treatments for localized carcinoma of the prostate. Each can cause post-treatment ED in men whose erections were normal previously. In surgical cases, this effect is likely to be caused by cavernosal nerve neuropraxia and smooth muscle hypoxia, despite nerve-sparing prostatectomy techniques.

Tadalafil improves erectile function in patients who have had both nerve-sparing RRP [54] and REBR [55], although the benefits in the surgical group are less marked than are usually seen in the broad population of men with ED. This probably reflects the loss of the innervation of the penile smooth muscle with the associated reduction in neuronal NO release. Montorsi and colleagues studied patients with ED 12–48 months following nerve-sparing RRP [54]. In a double-blind, randomized, placebo-controlled study, they showed that patients' erectile function significantly improved with tadalafil compared with placebo. This benefit was maximized in a subgroup of patients who had some spontaneous tumescence postoperatively. Incrocci and colleagues studied patients with ED 12–96 months after REBR [55]. Patients were randomized to receive tadalafil or placebo, and a statistically significant improvement in erectile function was seen in tadalafil-treated patients compared with placebo.

Treatment of erectile dysfunction in 'difficult-to-treat' patients

The treatment of ED in patient populations such as patients with diabetes mellitus, severe vascular disease or severe neurological disease with PDE5 inhibitors has been shown to be less successful [56]. For example, there is evidence that in men with diabetes, tadalafil has reduced efficacy [57]. Possible explanations could involve decreased expression or activity of neuronal or

Table 2. Effect of tadalafil on responses to IIEF and SEP in an integrated analysis of 11 separate studies.

	Placebo	Tadalafil 10 mg	Tadalafil 20 mg
IIEF EFD	15.3 (n = 616)	21.1 (n = 309)	23.2 (n = 1111)
Change	0.9	6.5 (p < 0.001)	8.6 (p < 0.001)
SEP 3	31% (n = 625)	58% (n = 311)	68% (n = 1119)
Change	8%	34% (p < 0.001)	46% (p < 0.001)

Pairwise comparisons between placebo and each treatment were adjusted by the method of Bonferroni.

IIEF EFD: International Index of Erectile Function Erectile Function Domain Score; SEP: Sexual Encounter Profile.

Data taken from [44].

endothelial NOS, impaired NO release or NO destruction precluding sufficient cGMP formation [56]. Clinical trials involving men with diabetes and ED nevertheless show significant proportions of men achieving successful intercourse with tadalafil and other PDE5 inhibitors [58–60]. A large, open-label, multicenter trial of patients with ED treated with tadalafil 20 mg showed that patients with two or more co-morbid conditions, such as diabetes, cardiovascular disease and hyperlipidemia, also had significantly increased end points, such as IIEF-EF domain scores and the mean percentage of positive responses to SEP3 from baseline [61].

Clinical effects of PDE5 inhibitors on lower urinary tract symptoms

Sildenafil

Sildenafil treatment of men with ED was first noted to improve LUTS in the men attending an andrology outpatient clinic [62]. In this small, nonrandomized study, patients were instructed to take sildenafil on demand prior to intercourse. With 3 months of optimal-dose sildenafil, LUTS (as assessed by the IPSS) improved significantly compared with baseline.

In a more recent randomized, double-blind, placebo-controlled trial, sildenafil improved both ED and urinary symptoms in men with concomitant ED and LUTS [63]. Men were included in this study if they had IPSS scores greater than 12 and EF domain of the IIEF scores less than 25. A total of 369 men from 41 centers across the USA were randomized to take either placebo or sildenafil. A 50-mg dose of study medication (placebo or sildenafil) was used every night for 30 min to 1 h prior to sexual activity for 2 weeks to ensure at least one daily dose. Dose escalation to 100 mg was offered and, if not tolerated, patients could choose to return to the 50 mg dose. A further 10 weeks of study medication was given. At the end of the treatment period, a significant increase in EF domain scores (i.e., an improvement in erectile function) was seen associated with a significant decrease in overall IPSS scores (i.e., an improvement in urinary symptoms). Sildenafil resulted in a decrease of 6.3 points (95% confidence interval (CI): 8.1–4.6) compared with a decrease of 1.9 (95% CI: 3.7–0.2) with placebo. It is of note that dynamic measures of prostatic bladder outflow obstruction, such a urinary flow rate, were unaffected by sildenafil treatment.

Vardenafil

A double-blind, placebo-controlled, randomized trial in men with LUTS is about to be published evaluating the effects of vardenafil [64]. Men with IPSS scores greater or equal to 13 were included. Vardenafil 10 mg twice-daily caused significant decreases in IPSS scores by 5.9 points compared with a decrease of 3.6 points with placebo. Vardenafil did not influence urinary flow rate. These data suggest the effect on IPSS scores is likely to be a class effect.

Tadalafil

A double-blind, placebo-controlled, randomized, multicenter trial in men with LUTS has recently been published evaluating the effect of tadalafil on LUTS in 479 men with LUTS secondary to BPH [65]. Men were included if they had IPSS scores greater than 12 and a maximum urinary flow rate (Q_{max}) between 4 and 15 ml/s on a voided volume greater than 125 ml. There was an extensive list of exclusion criteria, which included any man who had diseases that might affect lower urinary tract function, or prior surgery or radiotherapy for lower tract diseases. While men using 5-α-reductase inhibitors were excluded, men using α-blockers, anticholinergics, sympathomimetic medications, antihistamines, PDE5 inhibitors and herbal preparations were included, but underwent a 4-week washout period.

Patients were then given single-blind placebo for 4 weeks to demonstrate treatment compliance, following which they were randomized to placebo (n = 143) or tadalafil 5 mg (n = 138) for 6 weeks. A total of 19 patients discontinued during this period, ten in the placebo group and nine in the tadalafil group. The tadalafil dose was then escalated to 20 mg in the tadalafil group. A total of 251 patients completed the study, 126 in the placebo group and 125 in the tadalafil group, with both groups evenly matched for age, ethnicity, previous α-blocker use, severity of LUTS and presence of ED. Outcome measures included IPSS, urinary flow rates and IIEF EF domain scores.

Statistically significant decreases were seen in IPSS scores in patients receiving both 5-mg and 20-mg doses of tadalafil compared with placebo by analysis of covariance (ANCOVA) ($p < 0.001$), but not for IPSS-Quality-of-Life scores or uroflowmetry measures. The least-squares mean ± standard error of the mean decreases from baseline to endpoint measures

were 1.7 ± 0.5 for the placebo group and 3.8 ± 0.5 for the tadalafil group. In a subgroup of patients who were sexually active with ED (placebo group: 76; tadalafil group: 80), statistically significant increases in IIEF EF domain scores were also seen compared with placebo. No significant safety or tolerability issues were identified in the study. The effects of PDE5 inhibitors on IPSS are summarized in **Table 3**.

Current medical therapy for LUTS/BPH includes α-blockade and 5-α-reductase inhibitors, as discussed earlier. Comparison with the effect of α-blockers on LUTS should therefore be mandatory (**Table 4**). Hence, in a study of men with LUTS treated with the α-blocker alfuzosin or placebo, the mean change in IPSS at 12 weeks was 3.6 for alfuzosin 10 mg compared with 1.6 for placebo [66], and a meta-analysis of 11 studies comparing alfuzosin 10 mg with placebo showed decreases in IPSS by 5.4 for treatment and 3.6 for placebo [67]. These decreases in IPSS by α-blockers are comparable with decreases in IPSS by PDE5 inhibitors.

It is not clear at this time why an effect on symptom scores was seen without parallel improvements in urinary flow rate and other measures of lower urinary tract function.

What may a reduction in IPSS mean to patients in real life? It has been shown that an improvement in IPSS symptom scores influences the risk of serious outcomes of BPH progression. The Alf-One study was a 2-year, open-label, 'real-life' study of patients with LUTS taking alfuzosin in a general-practice setting [68]. Patients with an IPSS that was stable or worsening at the end of the study had a greater risk of acute urinary retention than those who had an improvement, even with a modest improvement [69]. Therefore, improvements in IPSS mean that patients will not only see improvements in symptoms, but also the prevention of serious outcomes such as acute retention of urine. Clearly, long-term efficacy studies need to confirm PDE5 effects on BPH progression.

Given that there is an improvement in sexual function with PDE5 inhibitors that is not seen with α-blockers, and given the epidemiological association between ED and LUTS, there would appear to be a possible place for these drugs in the treatment of LUTS in aging men.

Combination of PDE5 inhibitors & α-blockers

Given the differing mechanisms of action, it is conceivable that PDE5 inhibitors taken in combination with α-blockers could elicit a dual effect enhancing symptom relief from LUTS. A small, randomized, open-label, three-arm study comparing sildenafil 25 mg, alfuzosin 10 mg and both in combination has recently addressed this question [70]. Significant decreases from baseline in IPSS scores were seen with 12 weeks of daily treatment in all three arms of the trial, while combination treatment greater enhanced decreases in IPSS than either monotherapy. Although not placebo-controlled, this study shows promising results with no serious safety concerns.

Safety is paramount when combining treatments. Both PDE5 inhibitors and α-blockers can induce hypotension, and their co-administration must be regarded with caution. Studies have evaluated the combined effect of tadalafil and α-blockers (**Table 5**) [71,72]. Clinically significant decreases in blood pressure were seen with doxazosin in combination with tadalafil [72]. Decreases in supine and standing blood pressure persisted at 10 h and peaked at 2 h. Combination of tadalafil 20 mg plus doxazosin 8 mg caused 28% of patients' standing systolic blood pressure (SSBP) to decrease below 85 mmHg and by a decrease of 30 mmHg. Doxazosin plus placebo caused only 6% of patients to decrease their SSBP to below 85 mmHg, and 12% of patients to decrease their SSBP by 30 mmHg. In all patients, the mean maximal post-baseline decrease in SSBP was significantly greater after doxazosin plus tadalafil than doxazosin plus placebo, with a mean difference of 9.8 mmHg (95% CI: 4.1–15.5). Serious adverse events were recorded in two patients: an episode of dizziness and an episode of vertigo.

Table 3. The effect of PDE5 inhibitors on IPSS scores in patients with lower urinary tract symptoms.

	Sildenafil 50–100 mg o.d.	Vardenafil 10 mg b.d.	Tadalafil 20 mg o.d.
Treatment IPSS change	-6.3	-5.9	-3.8 ± 0.5
Placebo IPSS change	-1.9	-3.6	-1.7 ± 0.5

Clearly significant improvements in IPSS over placebo are a class effect.
b.d.: Twice daily; IPSS: International Prostate Symptom Score; o.d.: Once daily; PDE5: Phosphodiesterase type 5.

Table 4. Comparison of the effects of tadalafil 20 mg versus the α-blocker alfuzosin 10 mg in a single study and in a meta-analysis on IPSS scores in patients with lower urinary tract symptoms.

	Tadalafil 20 mg	Alfuzosin 10 mg	Alfuzosin 10 mg (MA)
Treatment IPSS change	-3.8 ± 0.5	-3.6	-5.4
Placebo IPSS change	-1.7 ± 0.5	-1.6	-3.6

Comparable improvements in IPSS are clearly shown.
IPSS: International Prostate Symptom Score; MA: Meta-analysis.
Data taken from [65–67].

Tadalafil 20 mg plus tamsulosin 0.4 mg did not significantly decrease SSBP. The mean difference in maximal post-baseline decreases in SSBP between tadalafil plus tamsulosin and placebo plus tamsulosin was 2.3 mmHg (95% CI: -4.1–8.7). Tadalafil 20 mg plus alfuzosin 10 mg again did not significantly decrease SSBP [71]. The mean difference in maximal post-baseline decreases in SSBP between tadalafil plus alfuzosin and placebo plus alfuzosin was 4.4 mmHg. These studies are small and have been carried out in healthy, normotensive men. Long-term, placebo-controlled efficacy and safety studies of these combinations in populations of men with LUTS need to be performed to fully evaluate their role in treatment.

Future PDE5 inhibitors

Several PDE5 inhibitors are in development, and data so far show similar efficacy rates for the treatment of ED. Avanafil [73–76] and SK3530 [77] both show similar pharmacokinetics, efficacy and safety to the short-acting PDE5 inhibitors sildenafil and vardenafil, while udenafil [78,79] has a longer half-life of approximately 10 h. SLx-2101 is a PDE5 inhibitor with a unique property. It is metabolized to SLx-2081, which continues to be active, giving an increased half-life similar to tadalafil. In an animal model, therapeutic levels were seen for longer than 24 h [80]. A double-blind, randomized, dosing study in healthy male volunteers showed peak plasma levels at 1 h for SLx-2101 and 2.8 h for SLx-2081, with half-lives of 8–13 h and 9–14 h, respectively [81]. No clinical trial to date has been published to show the effects of SLx-2101 in patients with ED.

Conclusion

Tadalafil has a significantly longer half life than other PDE5 inhibitors, and is well suited to once-daily administration. Indeed, it has recently been licensed in Europe for daily dosing in the treatment of ED, where it has good efficacy and tolerability at a dose of 5 mg/day [82].

In the treatment of BPH/LUTS, a number of end points are relevant, namely symptoms, quality of life, urodynamic parameters and progression. At present, while we understand the effects of α-blockers and 5-α-reductase inhibitors upon all these end points [9], we only have limited data relating to the PDE5 inhibitors. Promising early data have shown that tadalafil improves symptoms from BPH (LUTS), and this is almost certainly a class effect. No effects on measures such as peak urinary flow rate are seen with any PDE5 inhibitor.

Preclinical data suggests that the effects of PDE5 inhibitors may simply be the NO–cGMP pathway causing relaxation of prostatic smooth muscle. The antiproliferative effects of PDE5 inhibitors may become a more important effect if long-term PDE5 inhibitor use can be shown to reduce the risk of clinical progression of BPH. PDE5 inhibitors may influence LUTS through a yet unrecognised pathway; however, it seems unlikely to be an effect on bladder muscle function.

Further research is needed to clarify the place of PDE5 inhibitors in general, and tadalafil in particular, in the treatment of LUTS, and to clarify whether combination with currently available drugs such as α-blockers provides any advantage for patients with LUTS.

Table 5. The mean maximal post-baseline decrease in standing systolic blood pressure in healthy, normotensive men treated with tadalafil and three different α-blockers versus placebo and the same three α-blockers.

	Tadalafil 20 mg plus doxazosin 8 mg	Tadalafil 20 mg plus tamsulosin 0.4 mg	Tadalafil 20 mg plus alfuzosin 10 mg
Mean difference vs placebo	9.8 mmHg 95% CI: 4.1–15.5	2.3 mmHg 95% CI: -4.1–8.7	4.4 mmHg (not significant)

Financial & competing interests disclosure

I Eardley is a consultant and speaker for Lilly, Pfizer and Bayer-Schering. The authors have no other relevant affiliations or financial involvement with any organization or ntity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript, apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor with a longer half-life (17.5 h) compared with other PDE5 inhibitors.
- Tadalafil effectively treats erectile dysfunction, with an onset of action from approximately 60–90 min and duration of action of up to 36 h.
- Although still effective, the efficacy of tadalafil is reduced in men with diabetes and men who have undergone radical prostatectomy when compared with other groups of men with erectile dysfunction.
- Tadalafil is well tolerated with minimal adverse effects, which include headache, dyspepsia and back pain.
- Tadalafil is contraindicated for patients taking nitrates.
- Tadalafil effectively improves lower urinary tract symptoms in men with benign prostatic hyperplasia, but not peak urinary flow rates.
- Tadalafil is safe to take with alfuzosin and tamsulosin but combination with doxazosin should be considered with caution.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Kirby R: Benign prostatic hyperplasia. *BMJ* 318(7180), 343–344 (1999).
2. Berry SJ, Coffey DS, Walsh PC *et al.*: The development of human benign prostatic hyperplasia with age. *J. Urol.* 132(3), 474–479 (1984).
3. Wei JT, Calhoun E, Jacobsen SJ: Urologic diseases in America project: benign prostatic hyperplasia. *J. Urol.* 173(4), 1256–1261 (2005).
4. Girman CJ, Panser LA, Chute CG *et al.*: Natural history of prostatism: urinary flow rates in a community-based study. *J. Urol.* 150(3), 887–892 (1993).
5. Chute CG, Panser LA, Girman CJ *et al.*: The prevalence of prostatism: a population-based survey of urinary symptoms. *J. Urol.* 150(1), 85–89 (1993).
6. Girman CJ, Jacobsen SJ, Guess HA *et al.*: Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. *J. Urol.* 153(5), 1510–1515 (1995).
7. Rhodes T, Girman CJ, Jacobsen SJ, Roberts RO, Guess HA, Lieber MM: Longitudinal prostate growth rates during 5 years in randomly selected community men 40 to 79 years old. *J. Urol.* 161(4), 1174–1179 (1999).
8. Jacobsen SJ, Girman CJ, Guess HA, Rhodes T, Oesterling JE, Lieber MM: Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. *J. Urol.* 155(2), 595–600 (1996).
9. McConnell JD, Roehrborn CG, Bautista OM *et al.*: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N. Engl. J. Med.* 349(25), 2387–2398 (2003).
10. 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.* 151(1), 54–61 (1994).
11. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I *et al.*: Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. *J. Urol.* 166(2), 569–574 (2001).
12. Boyle P, Robertson C, Mazzetta C *et al.*: The association between lower urinary tract symptoms and erectile dysfunction in four centres: the UrEpik study. *BJU Int.* 92(7), 719–725 (2003).
13. Rosen R, Altwein J, Boyle P *et al.*: Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). *Eur. Urol.* 44(6), 637–649 (2003).
14. Li MK, Garcia LA, Rosen R: Lower urinary tract symptoms and male sexual dysfunction in Asia: a survey of ageing men from five Asian countries. *BJU Int.* 96(9), 1339–1354 (2005).
15. Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group: Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J. Urol.* 169(6), 2257–2261 (2003).
16. McVary K: Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathophysiology. *BJU Int.* 97(Suppl.) 223–228 (2006).

• **This review is of particular interest as it discusses the relevant literature behind the relationship between lower urinary tract symptoms (LUTS) and sexual dysfunction.**

17. Goldstein I, Lue TF, Padma-Nathan H *et al.*: Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N. Engl. J. Med.* 338(20), 1397–1404 (1998).

•• **First published randomized trial showing the benefits of phosphodiesterase type 5 (PDE5) inhibitors for patients with erectile dysfunction.**

18. Lue TF, Takamura T, Schmidt RA *et al.*: Hemodynamics of erection in the monkey. *J. Urol.* 130(6), 1237–1241 (1983).
19. Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J: Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem. Biophys. Res. Commun.* 170(2), 843–850 (1990).
20. Kim N, Azadzoi KM, Goldstein I, Saenz de Tejada I: A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. *J. Clin. Invest.* 88(1), 112–118 (1991).
21. Rajfer J, Aronson WJ, Bush PA *et al.*: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. *N. Engl. J. Med.* 326(2), 90–94 (1992).

22. Burnett AL, Lowenstein CJ, Bredt DS, Chang TS, Snyder SH: Nitric oxide: a physiologic mediator of penile erection. *Science* 257(5068), 401–403 (1992).
23. Knispel HH, Goessl C, Beckmann R: Nitric oxide mediates relaxation in rabbit and human corpus cavernosum smooth muscle. *Urol. Res.* 20(4), 253–257 (1992).
24. Trigo-Rocha F, Hsu GL, Donatucci CF, Lue TF: The role of cyclic adenosine monophosphate, cyclic guanosine monophosphate, endothelium and nonadrenergic, noncholinergic neurotransmission in canine penile erection. *J. Urol.* 149(4), 872–877 (1993).
25. Trigo-Rocha F, Aronson WJ, Hohenfellner M, Ignarro LJ, Rajfer J, Lue TF: Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. *Am. J. Physiol.* 264(2 Pt 2), H419–H422 (1993).
26. Francis SH, Turko IV, Corbin JD: Cyclic nucleotide phosphodiesterases: relating structure and function. *Prog. Nucleic Acid Res. Mol. Biol.* 65, 1–52 (2001).
27. Werkström V, Svensson A, Andersson KE, Hedlund P: Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. *BJU Int.* 98(2), 414–423 (2006).
28. Waldkirch ES, Uckert S, Langnase K *et al.*: Immunohistochemical distribution of cyclic GMP-dependent protein kinase-1 in human prostate tissue. *Eur. Urol.* 52(2), 495–501 (2007).
29. Uckert S, Küthe A, Jonas U, Stief CG: Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. *J. Urol.* 166(6), 2484–2490 (2001).
30. Shapiro E, Becich MJ, Hartanto V, Lepor H: The relative proportion of stromal and epithelial hyperplasia is related to the development of symptomatic benign prostate hyperplasia. *J. Urol.* 147(5), 1293–1297 (1992).
31. Adolfsson PI, Ahlstrand C, Varenhorst E, Svensson SP: Lysophosphatidic acid stimulates proliferation of cultured smooth muscle cells from human BPH tissue: sildenafil and papaverin generate inhibition. *Prostate* 51(1), 50–58 (2002).
32. Guh JH, Hwang TL, Ko FN, Chueh SC, Lai MK, Teng CM: Antiproliferative effect in human prostatic smooth muscle cells by nitric oxide donor. *Mol. Pharmacol.* 53(3), 467–474 (1998).
33. Tinel H, Stelte-Ludwig B, Hütter J, Sandner P: Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. *BJU Int.* 98(6), 1259–1263 (2006).

• **Important study showing the effects of sildenafil, vardenafil and tadalafil on human prostate preparations *in vitro*.**

34. Truss MC, Uckert S, Stief CG, Kuczyk M, Jonas U: Cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the human detrusor smooth muscle. I. Identification and characterization. *Urol. Res.* 24(3), 123–128 (1996).
35. Truss MC, Uckert S, Stief CG, Forssmann WG, Jonas U: Cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the human detrusor smooth muscle. II. Effect of various PDE inhibitors on smooth muscle tone and cyclic nucleotide levels *in vitro*. *Urol. Res.* 24(3), 129–134 (1996).
36. Longhurst PA, Briscoe JA, Rosenberg DJ, Leggett RE: The role of cyclic nucleotides in guinea-pig bladder contractility. *Br. J. Pharmacol.* 121(8), 1665–1672 (1997).
37. Brock GB, McMahon CG, Chen KK *et al.*: Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J. Urol.* 168(4 Pt 1), 1332–1336 (2002).
38. Forgue ST, Patterson BE, Bedding AW *et al.*: Tadalafil pharmacokinetics in healthy subjects. *Br. J. Clin. Pharmacol.* 61(3), 280–288 (2006).
39. Forgue ST, Phillips DL, Bedding AW *et al.*: Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br. J. Clin. Pharmacol.* 63(1), 24–35 (2007).

• **References 38 and 39 show the novel pharmacokinetic properties of tadalafil.**

40. Padma-Nathan H, McMurray JG, Pullman WE *et al.*: On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. *Int. J. Impot. Res.* 13(1), 2–9 (2001).

• **First evidence published showing the benefits of tadalafil for patients with erectile dysfunction.**

41. Rosen RC, Cappelleri JC, Gendrano N III: The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int. J. Impot. Res.* 14(4), 226–244 (2002).
42. Cappelleri JC, Siegel RL, Osterloh IH, Rosen RC: Relationship between patient self-assessment of erectile function and the erectile function domain of the international index of erectile function. *Urology* 56(3), 477–481 (2000).
43. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49(6), 822–830 (1997).
44. Carson CC, Rajfer J, Eardley I *et al.*: The efficacy and safety of tadalafil: an update. *BJU Int.* 93(9), 1276–1281 (2004).

•• **Meta-analysis showing the efficacy and safety of tadalafil.**

45. Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R: Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. *Urology* 62(1), 121–125 (2003).
46. Young JM, Feldman RA, Auerbach SM *et al.*: Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US trial. *J. Androl.* 26(3), 310–318 (2005).
47. Küthe A, Mägert H, Uckert S, Forssmann WG, Stief CG, Jonas U: Gene expression of the phosphodiesterases 3A and 5A in human corpus cavernosum penis. *Eur. Urol.* 38(1), 108–114 (2000).
48. Stockman A, Sharpe LT, Tufail A, Kell PD, Ripamonti C, Jeffery G: The effect of sildenafil citrate (Viagra) on visual sensitivity. *J. Vis.* 7(8), 4 (2007).
49. Danesh-Meyer HV, Levin LA: Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association? *Br. J. Ophthalmol.* 91(11), 1551–1555 (2007).
50. Webb DJ, Freestone S, Allen MJ, Muirhead GJ: Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist. *Am. J. Cardiol.* 83(5A), 21C–28C (1999).
51. Jackson G, Rosen RC, Kloner RA, Kostis JB: The second Princeton consensus on sexual dysfunction and cardiac risk: new guidelines for sexual medicine. *J. Sex. Med.* 3(1), 28–36 (2006).

• **Worldwide consensus on PDE5 inhibitors and cardiac risk. Of vital importance to all clinicians.**

52. Cheitlin MD, Hutter AM Jr, Brindis RG *et al.*: ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. *J. Am. Coll. Cardiol.* 33(1), 273–282 (1999).
53. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G: Time course of the interaction between tadalafil and nitrates. *J. Am. Coll. Cardiol.* 42(10), 1855–1860 (2003).

54. Montorsi F, Nathan HP, McCullough A *et al.*: Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. *J. Urol.* 172(3), 1036–1041 (2004).
55. Incrocci L, Slagter C, Slob AK, Hop WC: A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* 66(2), 439–444 (2006).
56. Sáenz de Tejada I: Therapeutic strategies for optimizing PDE-5 inhibitor therapy in patients with erectile dysfunction considered difficult or challenging to treat. *Int. J. Impot. Res.* 16(Suppl. 1), S40–S42 (2004).
57. Fonseca V, Seftel A, Denne J, Fredlund P: Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. *Diabetologia* 47(11), 1914–1923 (2004).
58. Sáenz de Tejada I, Anglin G, Knight JR, Emmick JT: Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 25(12), 2159–2164 (2002).
59. Lewis RW, Sadovsky R, Eardley I *et al.*: The efficacy of tadalafil in clinical populations. *J. Sex. Med.* 2(4), 517–531 (2005).
60. Vardi M, Nini A: Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. *Cochrane. Database. Syst. Rev.* (1), CD002187 (2007).
61. Goldstein I, Kim E, Steers WD *et al.*: Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: multiple observations in men with erectile dysfunction in National Tadalafil Study in the US. *J. Sex. Med.* 4(1), 166–175 (2007).
62. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB, Hanbury DC: Sildenafil influences lower urinary tract symptoms. *BJU Int.* 90(9), 836–839 (2002).
63. McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ, van den Ende G: Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J. Urol.* 177(3), 1071–1077 (2007).
64. Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E: A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur. Urol.* (2008) (Epub ahead of print).
65. McVary KT, Roehrborn CG, Kaminetsky JC *et al.*: Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J. Urol.* 177(4), 1401–1407 (2007).

•• **Important study of considerable interest, as this study clearly shows the benefits of tadalafil to patients with LUTS.**

66. Roehrborn CG: Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. *Urology* 58(6), 953–959 (2001).
67. MacDonald R, Wilt TJ: Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 66(4), 780–788 (2005).
68. Elhilali M, Emberton M, Matzkin H *et al.*: Long-term efficacy and safety of alfuzosin 10 mg once daily: a 2-year experience in 'real-life' practice. *BJU Int.* 97(3), 513–519 (2006).
69. Emberton M, Lukacs B, Matzkin H, Alcaraz A, Elhilali M, Vallancien G: Response to daily 10 mg alfuzosin predicts acute urinary retention and benign prostatic hyperplasia related surgery in men with lower urinary tract symptoms. *J. Urol.* 176(3), 1051–1056 (2006).
70. Kaplan SA, Gonzalez RR, Te AE: Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *Eur. Urol.* 51(6), 1717–1723 (2007).

• **Promising data to show an increased benefit to patients with LUTS taking a combination of a PDE5 inhibitor and an α-blocker.**

71. Giuliano F, Kaplan SA, Cabanis MJ, Astruc B: Hemodynamic interaction study between the α1-blocker alfuzosin and the phosphodiesterase-5 inhibitor tadalafil in middle-aged healthy male subjects. *Urology* 67(6), 1199–1204 (2006).
72. Kloner RA, Jackson G, Emmick JT *et al.*: Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 α-blockers, doxazosin and tamsulosin in healthy normotensive men. *J. Urol.* 172(5 Pt 1), 1935–1940 (2004).
73. Omori K, Mochida H, Fujishige K *et al.*: Avanafil has the potential for the treatment of erectile dysfunction with selective phosphodiesterase-5. *J. Sex. Med.* 3(Suppl. 3), 221–222 (2006) (Abstract MP-05-140).
74. Peterson C, Swearingen D: Pharmacokinetics of avanafil, a new PDE5 inhibitor being developed for erectile dysfunction. *J. Sex. Med.* 3(Suppl. 3), 253–254 (2006) (Abstract P-05-45).
75. Lewis RW, Hellstrom WJ, Gittelman M *et al.*: Rigiscan evaluation of TA-1790, a novel PDE5 inhibitor for the treatment of erectile dysfunction. *J. Urol.* 175(Suppl. 4), 316 (2006) (Abstract 1196).
76. Kaufman JM, Dietrich J: Safety and efficacy of avanafil, a new PDE5 inhibitor for treating erectile dysfunction. *J. Urol.* 175(Suppl. 4), 299 (2006) (Abstract 923).
77. Paick JS, Choi HK, Kim SC *et al.*: Efficacy and safety of oral SK3530 in the treatment of men in Korea with erectile dysfunction: a multi-center, randomized, double-blind, placebo-controlled, fixed dose, parallel group clinical trial. *J. Sex. Med.* 3(Suppl. 5), 393 (2006) (Abstract OR-032).
78. Kim JJ, Choi HK, Lee SW *et al.*: A Phase III study to evaluate the efficacy and safety of udenafil in Korean ED patients. *J. Sex. Med.* 3(Suppl. 3), 255 (2006) (Abstract P-05-49).
79. Park NC, Min KS, Paick JS: Efficacy of udenafil for the treatment of erectile dysfunction up to 12 hours after dosing. *J. Sex. Med.* 3(Suppl. 3), 180 (2006) (Abstract PS-02-013).
80. Sweetnam P, Campbell S, Grogan M *et al.*: SLx-2101, a novel long-acting phosphodiesterase-5 (PDE5) inhibitor for erectile dysfunction: *in vivo* and *in vitro* studies. *J. Sex. Med.* 3(Suppl. 3), 30 (2006) (Abstract 51).
81. Prince WT, Campbell AS, Tong W *et al.*: SLx-2101, a new long-acting PDE5 inhibitor: preliminary safety, tolerability, PK and endothelial function effects in healthy subjects. *J. Sex. Med.* 3(Suppl. 1), 29–30 (2006) (Abstract 50).

• **References 80 and 81 describe the pharmacokinetic properties of a new long-acting PDE5 inhibitor.**

82. Porst H, Giuliano F, Glina S *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.* 50(2), 351–359 (2006).