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REVIEW

Daily use of phosphodiesterase 5 inhibitors for erectile dysfunction and lower urinary tract symptoms

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Erectile dysfunction is a prevalent disorder that not only affects men with the disorder but also their partners. Significant improvements in the sexual health of these couples have been achieved with the introduction of phosphodiesterase 5 (PDE5) inhibitors. Currently PDE5 inhibitors are used on an on-demand basis. New evidence regarding the effects of PDE5 inhibitors on the underlying pathophysiologic processes that cause erectile dysfunction have sparked interest in the continuous dosing of these medications. We will discuss the biological background and the available clinical evidence for the continuous use of phosphodiesterase inhibitors in erectile dysfunction. Lastly, we will discuss the emerging clinical data for the use of daily PDE5 inhibitors in men with lower urinary tract symptoms.
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Introduction

Erectile dysfunction (ED) affects over 18 million couples in the United States alone.[1] The causes of ED involve psychiatric, hormonal, vascular and neurologic conditions. Psychiatric and hormonal imbalances are often effectively treated by correcting the underlying psychiatric disease or endocrinopathy. Vascular causes include those that affect the arterial inflow to the penis or its venous outflow. Neurological problems are often due to diabetes or other systemic diseases that are often difficult to cure. One of the most important neurological causes of ED is injury to the cavernosal nerves during pelvic surgery.[2] The use of phosphodiesterase 5 (PDE5) inhibitors on an on-demand basis has improved the sexual function of many of these patients but there continue to be others with minimal or no improvement.[3] There has been an increased interest in changing the dosing regimens using current phosphodiesterase (PDE) inhibitors in an attempt to improve the return of erectile function in these difficult-to-treat patients.[4,5]

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Pathophysiology of erectile dysfunction

For an erection to occur several physiologic processes and structures must function appropriately together. Injury to any one of these structures or processes can lead to ED. A physiologic erection is caused by cavernosal smooth muscle relaxation, cavernosal artery dilatation and venous outflow compression.[6] Therefore, injury to the smooth muscle, the arteries, or the venous outflow can all lead to ED. Venous outflow compression is a passive phenomenon dependent on the relaxation of the cavernosal smooth muscle and subsequent compression of the subtunical veins against the tunica albuginea. Thus, venous dysfunction is primarily a symptom of smooth muscle dysfunction. Cavernosal smooth muscle appears to be one of the most important variables in determining erectile function.

A decrease in the number of cavernosal smooth muscle cells has been noted in previous studies of ED.[7] Smooth muscle content is typically measured by acquiring cavernosal tissue from biopsies and staining them. The percentage area of the cavernosal

tissue that is composed of smooth muscle is then calculated with the aid of computerized digital image analysis. The more cavernosal smooth muscle tissue a subject has the less likely that the subject will suffer from ED. Another method used is quantitative immunohistochemical staining for acting or other smooth muscle proteins. Similarly, the more smooth muscle protein content, the less likely the subject will have ED.[8]

The most important neurotransmitter for cavernosal smooth muscle relaxation is nitric oxide.[9] Nitric oxide mediates production of guanosine monophosphate (cGMP), which causes a decrease in the intracellular levels of calcium, leading to cavernosal smooth muscle relaxation. A lack of bioavailable nitric oxide has been shown to be associated with decreased relaxation of cavernosal tissue in models of ED.[10] Nitric oxide is typically evaluated by measuring levels of nitric oxide synthase (NOS). In fact, gene transfer of endothelial NOS has been shown to improve erectile function in diabetic rat models.[11] Form these and other studies researchers have therefore started to focus on NOS and the content of smooth muscle as targets for measuring improvement in the different treatment options for ED.

Aging, diabetes and hypertension are known to have strong associations with the development of ED.[12] The collagen content within the cavernosal tissues has been studied in animal models. Salama *et al*.[13] reported on increased density of collagen bundles in aged and diabetic rat models. A similar study looking at the structural changes in the corpora cavernosum of hypertensive rats found similar results with respect to the increased collagen content. This second study also found that the elastic tissue within the corporeal bodies showed an inverse relationship with blood pressure.[14] Although changes in collagen content have been found in animal models of ED, human studies do not show such a clear relationship.[15] Fibrosis and increased collagen content do not appear to be as strong a predictor of erectile function as smooth muscle function or smooth muscle content.

Biological evidence supporting the use continuous PDE5 inhibitors

Animal studies have shown that daily administration of PDE5 inhibitors can lead to improvements in the physiologic functioning of the erectile tissue. De Young *et al*.[16] demonstrated that intracavernosal pressure in rats treated with daily sildenafil was improved significantly from the control groups. These results were corroborated in a similar study looking at a novel PDE5 inhibitor in which the rats treated with the highest dose were found to have increased cavernosal pressures during electrostimulation of the cavernosal nerves.[17] This group was also able to show decreased transforming growth factor (TGF)-β1 expression in a subsequent study with higher doses of the PDE inhibitor. This implies that PDE5 inhibitors may prevent fibrosis of the corporal tissue in men with ED by decreasing the release of the profibrotic growth factor TGF-β1. PDE5 inhibitors are thought to have an antifibrotic effect on the corporal tissue by inducing NOS. The increased levels of cGMP are thought to downregulate TGF-β1 protein expression and its downstream effects such as myofibroblast differentiation.[18]

Other animal studies have shown that the chronic use of PDE5 inhibitors can potentially improve smooth muscle content and function in several models of ED as well. A study looking at a cavernosal nerve injury model found that vardenafil was able to improve smooth muscle function as measured by NOS and smooth muscle content. Interestingly, this study also found that vardenafil increased cell replication of the smooth muscle as measured by immunohistochemical staining of proliferating cell nuclear antigen.[19] Additionally, a decrease in the cellular apoptotic rate was not seen. Vardenafil appears to increase proliferation of smooth muscle cells but does not prevent apoptosis of these cells. This may indicate a rationale for the chronic administration of PDE5 inhibitors. Another study in an aged rat model with daily use of PDE inhibitors showed very similar results.[20] Lastly, in diabetic models of ED increased smooth muscle function with chronic therapy has also been found.[21]

Clinical evidence supporting the use of daily PDE5 inhibitors

To date several animal studies have found that the physiologic, morphologic and cellular changes that occur in ED can be further improved with chronic administration of PDE5 inhibitors. Emerging clinical evidence indicates that this may also be the case in humans. When initiating new dosing strategies, overall safety is always a primary concern. Like all medical treatments PDE5 inhibitors have side effects that can potentially harm some of its users. The safety of potentially vulnerable patients to chronic therapy has been evaluated extensively. Debusk *et al*.[22] evaluated patients with stable angina for 12 weeks and found no increase in serious adverse effects. Similarly, Katz *et al*.[23] found that subjects with stable heart failure tolerated the medications without an increase in serious cardiac events.

Long-term treatments are more costly and require more effort to study. Fortunately, tachyphylaxis with PDE5 inhibitors does not appear to occur. Muscki *et al*.[24] used a scheduled dosing regimen and

measured PDE5 expression and erection physiology after chronic treatment with sildenafil. In this study the maximal intracavernosal pressure after sildenafil did not significantly decrease after long-term treatment. The activity of the PDE enzyme continued to be suppressed at similar efficacy as well. Both of these results support other evidence that tachyphylaxis does not occur with chronic treatment.

It is well established that fewer patients achieve adequate erectile function after radical prostatectomy.[25] Therefore, postprostatectomy patients have become a main target for new dosing regimens. Previous studies focusing on vacuum erection devices and alprostadil injections have found that continuous dosing improves return of erectile function.[26,27] Montorsi *et al.*[26] measured a spontaneous erection rate of 67 versus 20% for those subjects who where initiated on the early frequent dosing of alprostadil injections in comparison to the control group. Although scheduled treatment with alprostadil injections and vacuum erection devices have been found to be beneficial, the invasiveness and inconvenience of these treatments do not make them ideal candidates for further study.

PDE inhibitors are less invasive and much easier to administer. Nandipati *et al.*[28] showed that with a combination of scheduled sildenafil tablets and alprostadil injections the incidence of venous leak was diminished. Almost 50% of these patients were also able to achieve a spontaneous erection without treatment after the termination of the study. Schwartz *et al.*[29] treated postprostatectomy subjects with every other night sildenafil for 6 months and determined that the smooth muscle content within the cavernosal tissue was maintained. More impressively, the group taking the larger 100 mg dose had a significant improvement in the amount of smooth muscle content when compared to there own preoperative levels. This is the only study we are aware of that sampled cavernosal tissue after continuous treatment. The results are very encouraging and indicate that erectile function could potentially be stabilized after radical prostatectomy.

Another group who may benefit significantly from daily dosing would be nonresponders to on-demand PDE5 inhibitor therapy. Patients with previous failure of PDE5 inhibitors are currently counseled on more invasive options such as injection, intraurethral and surgical therapies. McMahon *et al.*[5] found that a significant proportion of patients who were previously considered tadalafil nonresponders were salvaged with a scheduled dosing treatment plan. Those patients placed on tadalafil 10 mg every 3 days were able to achieve intercourse 58% of the time with this change. Changing the type of PDE5 inhibitors for nonresponders has typically had less drastic results.[30] Another difficult-to-treat group are patients with comorbidities such as coronary artery disease and diabetes. Mirone *et al.*[31] compared two different dosing regimens in 4262 subjects. The majority of the subjects had at least one of the above comorbidities. The scheduled tadalafil group had more attempted sexual encounters than the on-demand group. Importantly, the dosing regimen was also found to be safe.

Another important factor for some couples is convenience and spontaneity.[31,32] Daily dosing tadalafil can achieve plasma levels greater than on-demand dosing after as few as 5 days.[33] Porst *et al.*[34] evaluated PDE5 naive patients and found that the 5 and 10 mg daily doses were well tolerated and achieved excellent results in comparison to placebo. Rajfer *et al.*[35] also found that daily dosing with tadalafil may allow patients to decrease their dose while achieving similar improvements in erectile function. In this study the daily doses were decreased to 2.5 and 5 mg while still achieving significant improvements and a reasonable side effect profile. The Porst and Rajfer studies were limited because they did not include an on-demand treatment arm. One clinical study by McMahon *et al.*[36] did compare these two groups. McMahon *et al.* compared 20 mg of on-demand therapy with 10 mg daily. The subjects with daily dosing had better International Index of Erectile Function (IIEF) scores and 15% more subjects were able to successfully have intercourse with their partners in comparison to the on-demand group. Indeed, there is some evidence that daily dosing may provide increased convenience and improved efficacy while still maintaining a minimal side effect profile (Table 1).

Another emerging use for daily dosing of PDE5 inhibitors is in the treatment of lower urinary tract symptoms. McVary *et al.*[37] randomized 369 patients with lower urinary tracts symptoms and ED to daily sildenafil or placebo. There were significant improvements in both erectile function and lower urinary tract symptoms in the sildenafil group. The improvements in the lower urinary tract symptoms were comparable to treatments with α-blockade. The use of daily tadalafil in comparison to placebo has also yielded similar results.[38] Kaplan *et al.*[27] compared alfuzosin and sildenafil in patients with both lower urinary tract symptoms and ED. Mean International Prostate Symptom Score (IPSS) and IIEF scores were most improved in the group who had combination therapy. Because there was no placebo group in this trial, a placebo-controlled trial will be necessary before determining if the combination therapy is indeed the most efficacious. As in previous studies with PDE5 inhibitors, there was no improvement in postvoid residuals or flow rates with sildenafil. The mechanism of PDE5 inhibitors to improve lower urinary tract symptoms therefore appears to be different from that of α-blockers. PDE has been found in the prostate of humans but the majority of PDE5 has been found in the glandular stroma.[39] Smooth muscle cGMP protein-dependent kinases have also been found in the transition zone

Table 1 Clinical evidence for scheduled dosing of PDE5 inhibitors

Study/author	*Type of PDE5-I*	*Dose (mg)*	*Regimen (daily, other scheduled)*	*Effect*	
				ED (IIEF etc.)	*LUTS (IPSS etc.)*
Schwartz *et al.*[29]	Sildenafil	50, 100	Every other day	Cavernosal smooth muscle content of 42.82 and 56.85% in the sildenafil 100 mg and placebo group, respectively ($P<0.05$)	
Nandipati *et al.*[28]	Sildenafil and alprostadil	50	Daily	IIEF-5 score of 10.5 from a baseline of 5.2 with sildenafil alone ($P<0.05$). Decreased incidence of venoocclusive disease	
McMahon *et al.*[36]	Tadalafil	10	Every 3 days	IIEF score improvement of 8.2 and 12.8 with on-demand and daily dosing, respectively ($P<0.001$). 58% of on-demand nonresponders were salvaged with scheduled dosing	
Mirone *et al.*[31a]	Tadalafil	20	Every 3 days	IIEF final scores of 24.6 and 24.8 with on-demand and scheduled dosing, respectively	
Porst *et al.*[34a,b]	Tadalafil	5, 10	Daily	IIEF score improvement of 9.7 and 0.9 with tadalafil 5 mg and placebo, respectively	
Rajfer *et al.*[35a,b]	Tadalafil	2.5, 5	Daily	IIEF score improvement of 6.1 and 7.4 with tadalafil 2.5 and 5 mg, respectively ($P<0.001$)	
McMahon *et al.*[4]	Tadalafil	10	Daily	IIEF score improvement of 8.3 and 11.9 with on-demand and daily dosing, respectively ($P<0.001$)	
McVary *et al.*[37a,b]	Sildenafil	100	Daily		IPSS score improvement of 6.3 and 1.9 on sildenafil and placebo, respectively ($P<0.001$)
McVary *et al.*[38a,b]	Tadalafil	20	Daily		IPSS score improvement of 7.1 and 4.5 on tadalafil and placebo, respectively ($P<0.001$)
Kaplan *et al.*[27a]	Sildenafil	25	Daily		IPSS score improvement of 2 points from baseline ($P<0.03$)

Abbreviations: ED, erectile dysfunction; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PDE5-I, phosphodiesterase 5 inhibitors.
[a]Randomized trial.
[b]Placebo-controlled trial.

of the prostate.[40] Filipi *et al.*[41] measured PDE in bladder tissue. They also found that a PDE-resistant cGMP analog, SP-8-Br-PET-cGMPS, induced a consistent antiproliferative and relaxing effect in bladder tissue. The relaxant tissue and antiproliferative effects on the bladder may lead to a better understanding in how PDE5 inhibitors improve urinary symptoms. Despite the presence of PDE in bladder and prostatic tissues the exact mechanism responsible for the improvement in urinary symptoms has yet to be determined. A possible next step would be to study PDE5 inhibitors in women with urinary symptoms. Evaluating if PDE5 inhibitors can improve urinary symptoms in women may help localize their site of primary action.

Conclusion

There is mounting evidence that daily dosing is preferential in several groups of patients. The groups that will most likely benefit from daily dosing range from postprostatectomy patients to those with concomitant lower urinary symptoms. The biologic evidence for continuous treatment for ED is significant but the mechanism for why PDE5 inhibitors improve lower urinary tract symptoms is unknown. Further clinical studies are needed to determine what groups will most benefit from this new dosing option.

References

1 Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007; **120**: 151.
2 Miller DC, Sanda MG, Dunn RL, Montie JE, Pimentel H, Sandler HM *et al.* Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005; **23**: 2772.
3 Raina R, Lakin MM, Agarwal A, Mascha E, Montague DK, Klein E *et al.* Efficacy and factors associated with successful outcome of sildenafil citrate use for erectile dysfunction after radical prostatectomy. *Urology* 2004; **63**: 960.
4 McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004; **1**: 292.
5 Carson C, Shabsigh R, Segal S, Murphy A, Fredlund P, Kuepfer C *et al.* Efficacy, safety, and treatment satisfaction of tadalafil versus placebo in patients with erectile dysfunction evaluated at tertiary-care academic centers. *Urology* 2005; **65**: 353.

6 Lue TF, Takamura T, Schmidt RA, Palubinskas AJ, Tanagho EA. Hemodynamics of erection in the monkey. *J Urol* 1983; **130**: 1237.
7 Wespes E, Goes PM, Schiffmann S, Depierreux M, Vanderhaeghen JJ, Schulman CC. Computerized analysis of smooth muscle fibers in potent and impotent patients. *J Urol* 1991; **146**: 1015.
8 De Young L, Bella A, Howard J, Brock G. Arteriogenic erectile dysfunction alters protein expression within the cavernosal tissue in an animal model. *J Sex Med* 2005; **2**: 199.
9 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* 1990; **170**: 843.
10 Vernet D, Cai L, Garban H, Babbitt ML, Murray FT, Rajfer J *et al.* Reduction of penile nitric oxide synthase in diabetic BB/WORdp (type I) and BBZ/WORdp (type II) rats with erectile dysfunction. *Endocrinology* 1995; **136**: 5709.
11 Bivalacqua TJ, Usta MF, Champion HC, Adams D, Namara DB, Abdel-Mageed AB *et al.* Gene transfer of endothelial nitric oxide synthase partially restores nitric oxide synthesis and erectile function in streptozotocin diabetic rats. *J Urol* 2003; **169**: 1911.
12 Saigal CS, Wessells H, Pace J, Schonlau M, Wilt TJ, Urologic Diseases in America Project. Predictors and prevalence of erectile dysfunction in a racially diverse population. *Arch Intern Med* 2006; **166**: 207.
13 Salama N, Kagawa S. Ultra-structural changes in collagen of penile tunica albuginea in aged and diabetic rats. *Int J Impot Res* 1999; **11**: 99.
14 Jiang R, Chen JH, Jin J, Shen W, Li QM. Ultrastructural comparison of penile cavernous tissue between hypertensive and normotensive rats. *Int J Impot Res* 2005; **17**: 417.
15 Costa WS, Carrerete FB, Horta WG, Sampaio FJ. Comparative analysis of the penis corpora cavernosa in controls and patients with erectile dysfunction. *BJU Int* 2006; **97**: 567.
16 De Young L, Yu D, Freeman D, Brock GB. Effect of PDE5 inhibition combined with free oxygen radical scavenger therapy on erectile function in a diabetic animal model. *Int J Impot Res* 2003; **15**: 347.
17 Ahn GJ, Yu JY, Choi SM, Kang KK, Ahn BO, Kwon JW *et al.* Chronic administration of phosphodiesterase 5 inhibitor improves erectile and endothelial function in a rat model of diabetes. *Int J Androl* 2005; **28**: 260.
18 Ferrini MG, Kovanecz I, Nolazco G, Rajfer J, Gonzalez-Cadavid NF. Effects of long-term vardenafil treatment on the development of fibrotic plaques in a rat model of Peyronie's disease. *BJU Int* 2006; **97**: 625.
19 Ferrini MG, Davila HH, Kovanecz I, Sanchez SP, Gonzalez-Cadavid NF, Rajfer J. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. *Urology* 2006; **68**: 429.
20 Ferrini MG, Kovanecz I, Sanchez S, Vernet D, Davila HH, Rajfer J *et al.* Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol Reprod* 2007; **76**: 915.
21 Bivalacqua TJ, Usta MF, Champion HC, Leungwattanakij S, Dabisch PA, McNamara DB *et al.* Effect of combination endothelial nitric oxide synthase gene therapy and sildenafil on erectile function in diabetic rats. *Int J Impot Res* 2004; **16**: 21.
22 DeBusk RF, Pepine CJ, Glasser DB, Shpilsky A, DeRiesthal H, Sweeney M. Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease. *Am J Cardiol* 2004; **93**: 147.
23 Katz SD, Parker JD, Glasser DB, Bank AJ, Sherman N, Wang H *et al.* Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; **95**: 36.
24 Musicki B, Champion HC, Becker RE, Kramer MF, Liu T, Sezen SF *et al. In vivo* analysis of chronic phosphodiesterase-5 inhibition with sildenafil in penile erectile tissues: no tachyphylaxis effect. *J Urol* 2005; **174**: 1493.
25 Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW *et al.* Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the prostate cancer outcomes study. *JAMA* 2000; **283**: 354.
26 Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L *et al.* Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol* 1997; **158**: 1408.
27 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* 2007; **51**: 1717.
28 Nandipati K, Raina R, Agarwal A, Zippe CD. Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. *Int J Impot Res* 2006; **18**: 446.
29 Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol* 2004; **171**: 771.
30 Carson CC, Hatzichristou DG, Carrier S, Lording D, Lyngdorf P, Aliotta P *et al.* Erectile response with vardenafil in sildenafil nonresponders: a multicentre, double-blind, 12-week, flexible-dose, placebo-controlled erectile dysfunction clinical trial. *BJU Int* 2004; **94**: 1301.
31 Mirone V, Costa P, Damber JE, Holmes S, Moncada I, Van Ahlen H *et al.* An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. *Eur Urol* 2005; **47**: 846.
32 Hanson-Divers C, Jackson SE, Lue TF, Crawford SY, Rosen RC. Health outcomes variables important to patients in the treatment of erectile dysfunction. *J Urol* 1998; **159**: 1541.
33 Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; **61**: 280.
34 Porst H, Giuliano F, Glina S, Ralph D, Casabe AR, Elion-Mboussa A *et al.* Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006; **50**: 351.
35 Rajfer J, Aliotta PJ, Steidle CP, Fitch III WP, Zhao Y, Yu A. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. *Int J Impot Res* 2007; **19**: 95.
36 McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med* 2005; **2**: 415.
37 McVary KT, Monnig W, Camps Jr JL, 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* 2007; **177**: 1071.
38 McVary KT, Roehrborn CG, Kaminetsky JC, Auerbach SM, Wachs B, Young JM *et al.* Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2007; **177**: 1401.
39 Uckert S, Oelke M, Stief CG, Andersson KE, Jonas U, Hedlund P. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. *Eur Urol* 2006; **49**: 740.
40 Waldkirch ES, Uckert S, Langnase K, Richter K, Jonas U, Wolf G *et al.* Immunohistochemical distribution of cyclic GMP-dependent protein kinase-1 in human prostate tissue. *Eur Urol* 2007; **52**: 495.
41 Filippi S, Morelli A, Sandner P, Fibbi B, Mancina R, Marini M *et al.* Characterization and functional role of androgen-dependent PDE5 activity in the bladder. *Endocrinology* 2007; **148**: 1019.