Asian Journal of Andrology (2016) 18, 723–731

www.asiaandro.com; www.ajandrology.com

Open Access

REVIEW

Male Health

Clinical and preclinical treatment of urologic diseases with phosphodiesterase isoenzymes 5 inhibitors: an update

Wen-Hao Zhang, Xin-Hua Zhang

Phosphodiesterase isoenzymes 5 inhibitors (PDE5-Is) are the first-line therapy for erectile dysfunction (ED). The constant discoveries of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) cell-signaling pathway for smooth muscle (SM) control in other urogenital tracts (UGTs) make PDE5-Is promising pharmacologic agents against other benign urological diseases. This article reviews the literature and contains some previously unpublished data about characterizations and activities of PDE5 and its inhibitors in treating urological disorders. Scientific discoveries have improved our understanding of cell-signaling pathway in NO/cGMP-mediated SM relaxation in UGTs. Moreover, the clinical applications of PDE5-Is have been widely recognized. On-demand PDE5-Is are efficacious for most cases of ED, while daily-dosing and combination with testosterone are recommended for refractory cases. Soluble guanylate cyclase (sGC) stimulators also have promising role in the management of severe ED conditions. PDE5-Is are also the first rehabilitation strategy for postoperation or postradiotherapy ED for prostate cancer patients. PDE5-Is, especially combined with α-adrenoceptor antagonists, are very effective for benign prostatic hyperplasia (BPH) except on maximum urinary flow rate (Q_{max}) with tadalafil recently proved for BPH with/without ED. Furthermore, PDE5-Is are currently under various phases of clinical or preclinical researches with promising potential for other urinary and genital illnesses, such as priapism, premature ejaculation, urinary tract calculi, overactive bladder, Peyronie's disease, and female sexual dysfunction. Inhibition of PDE5 is expected to be an effective strategy in treating benign urological diseases. However, further clinical studies and basic researches investigating mechanisms of PDE5-Is in disorders of UGTs are required.

Asian Journal of Andrology (2016) **18**, 723–731; doi: 10.4103/1008-682X.167721; published online: 27 November 2015

Keywords: benign prostatic hyperplasia; erectile dysfunction; overactive bladder; phosphodiesterase isoenzymes 5 inhibitor; priapism; smooth muscle

INTRODUCTION

The cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important second messagers that play a central role in signal transduction and regulation of physiologic responses, such as smooth muscle (SM) contraction and relaxation, blood pressure control, neurotransmission, platelet aggregation, and disaggregation.[1,2] cAMP and cGMP are degraded by phosphodiesterase (PDE) isoenzymes, a heterogeneous group of hydrolytic enzymes. Today, 11 different PDE families have been identified with each family typically having several different isoforms and splice variants. Some types of PDE are specific for either cAMP or cGMP, and some degrade both. PDE11, for example, degrades both cAMP and cGMP, whereas PDE4 is specific for cAMP, and PDE5 is specific for cGMP.[1] Importantly, some PDE isoenzymes have been proven to be of pharmacological relevance with PDE5 inhibitors (PDE5-Is) widely studied and used. Sildenafil citrate was the first effective oral treatment for erectile dysfunction (ED). Its advent marked the milestone in the ED history.[3] Until now, there are six oral PDE5-Is commercially available, which are sildenafil (Viagra; Pfizer, New York, USA), vardenafil (Levitra, Staxyn; Bayer, West Haven, CT, USA), tadalafil (Cialis; Lilly, Indianapolis, USA), avanafil (Stendra; VIVUS Inc., CA, USA), udenafil (Zydena; Dong-A PharmTech, South Korea), and mirodenafil (Mvix; SK Chemical, South Korea) with mirodenafil and udenafil, and are only approved in Korea.[4,5] There are still several PDE5-Is under development, including JNJ-10280205, JNJ-10287069, lodenafil, and SLx-2101 with the purpose of offering safer and more effective options for ED suffers. All six PDE5-Is have an appropriate onset of action, duration and a success rate at least 65% for ED (**Table 1**) and newly developed compounds may contain certain advantages over sildenafil, such as higher selectivity for PDE5 compared with other isozymes, faster onset, longer duration of effect, and absence of food effect on absorption, which consequently, allowing more flexibility in sexual activity.[5–7] Besides corpus cavernosum (CC), PDE5 is also expressed in urinary tract and mediated relaxation of related SM. Inhibition of this enzyme would have a clinical benefit in the management of many benign urological diseases other than ED, such as lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH), priapism, premature ejaculation (PE), urinary tract

Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan City 430071, Hubei Province, P.R. China.
Correspondence: Dr. XH Zhang (zxhmd2000@yahoo.com)
Received: 05 February 2015; Revised: 11 June 2015; Accepted: 16 September 2015

Table 1: Characteristics of commercially available phosphodiesterase type 5 inhibitors

	Sildenafil	*Vardenafil*	*Tadalafil*	*Udenafil*	*Mirodenafil*	*Avanafil*
Dosage (mg)	25, 50, and 100 $Dose_{max}$ 100 daily	2.5, 5, 10, and 20 $Dose_{max}$ 20 daily	2.5, 5, 10, and 20 $Dose_{max}$ 20 daily	100, 200 $Dose_{max}$ 200 daily	50, 100 $Dose_{max}$ 100 daily	50, 100 $Dose_{max}$ 200 daily
Time to maximum plasmaconcentration (T_{max}, min)	30–60	30–60	120	60–90	75	30–45
Elimination half-life time ($T_{1/2}$, h)	4–8	4–8	17.5	11–13	2.5	3–5
Efficacy (%)	>65	>65	>65	>65	>65	>65
Side-effects	Headache, flushing, and dyspepsia	As for sildenafil	Flushing, back pain, and general myalgia	Flushing, nasal congestion, ocular hyperemia, and headache	Flushing, headache, nausea, and eye redness	Headache, flushing, nasal congestion, nasopharyngitis, and back pain
Food and alcohol interaction	Interacts with food. No alcohol interaction	As for sildenafil	No food or alcohol interaction	No food or alcohol interaction	No food or alcohol interaction	Interacts with food

calculi, overactive bladder (OAB), Peyronie's disease (PD), and female sexual dysfunction (FSD). In current review, we update the potentials of PDE5-Is for treating the aforementioned urological disorders.

ERECTILE DYSFUNCTION

PDE5-Is are the first-line therapy for ED. The efficacy and safety of sildenafil, vardenafil, tadalafil, and avanafil have been confirmed by a multitude of clinical trials involving thousands of ED patients with broad-spectrum etiology worldwide.[8–11] Also, several reviews pooled these evidence and documented the effectiveness of PDE5-Is.[4,6,7,12] In the present review, we focus on daily dosing, rehabilitation, and combined therapy with PDE5-Is.

Daily dosing versus on-demand

Compared to on-demand administration, daily dosing of PDE5-Is is supposed to have a more satisfactory effect and be a salvage to unresponsive individuals. In a 26-week, open-label crossover study of 145 ED patients using either on-demand 20 mg tadalafil or daily 10 mg tadalafil showed that daily tadalafil had a significantly higher international index of erectile function (IIEF) score and success intercourse rate. Furthermore, 72% patients preferred daily 10 mg tadalafil at the end of the study. Moreover, the incidence and severity of adverse events were not increased with daily treatment.[13] Another clinical trial including 112 ED subjects showed that sildenafil 50 mg nightly for 1 year can improve spontaneous erection in men with mild-to-moderate arteriogenic ED. In the subsequent nonmedicated period, 60.4% men had normal IIEF score (≥26) in daily dosing group while only 8.2% was observed for on-demand treatment.[14] Similar effect was found by a number of other studies. Also, psychogenic ED patients with high expectation of performance anxiety often become more anxious when they have to plan sexual activity with on-demand PDE5-Is. Daily dosing regimen would avoid scheduled sexuality and related distress. Consequently, erection, and overall sexual satisfaction would be improved.

There are 30%–35% of ED patients who fail to respond or are dissatisfied with PDE5-Is on-demand treatment.[15] Severe arterial diseases, diabetes mellitus, and neurological diseases may contribute to the unresponsiveness. Daily dosing of PDE5-Is can be attempted as a salvage therapy. In a study including 112 men with moderate to severe ED of various etiologies and unresponsive to on-demand PDE5-Is, patients experienced a significant mean increase of IIEF score by 12.8 and 8.2 from baseline and from on-demand tadalafil with 12-week daily tadalafil (10 mg), respectively. This study indicated that on-demand tadalafil nonresponders can be salvaged with daily dosing.[16] Evidence from basic science has shown that PDE5-Is daily dosing may improve endothelial function that is one of the main initial factors involved in erectile process. It was found that chronic use of vardenafil increased endothelial nitric oxide synthase (eNOS) and SM α-actin protein level in cavernous tissue of diabetic rats, revealing chronic PDE5-Is may have an alleviative effect on improvement of endothelial function.[17] Also, long-term sildenafil treatment reduced the corporal collagen content, partially reversed the aging-related fibrosis and loss of SM in the CC[18] and decreased the oxidative stress-associated tissue damage at the same time in rat model.[19] Furthermore, a significant protection from penile length loss was recently found in patients with daily tadalafil in a multicenter randomized clinical trial (RCT) which suggests that chronic PDE5-Is treatment may contribute to the maintenance of cavernosal tissue integrity.[20] However, an RCT with vardenafil showed the improvement of erectile function (EF) did not differ between patients with daily dosing and on-demand therapy.[21] Moreover, drug tachyphylaxis evoked by daily dosing has also been concerned. Some *in vitro* studies showed that chronic PDE5 inhibition upregulated PDE5 expression and decreased the effect of PDE5-Is,[22] but another study did not observe PDE5 upregulation for a long-term tadalafil *in vivo* treatment.[23] Thus, PDE5-Is tachphylaxis remains unclear. Overall, daily PDE5-Is may have a potential role as a standard first-line treatment for ED with satisfactory efficacy and mild side effects but its utility will be limited by the cost. More clinical studies should be carried out.

Penile rehabilitation

Prostate cancer (PCa) is a relatively prevalent disease, and in some Western countries, it is the leading type of malignant tumor diagnosed in males.[24] Widely recognized treatments for localized PCa are radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, and androgen deprivation therapy. ED is the most common complication in patients undergoing these treatment strategies, which can have a significant negative impact on patients' health-related QoL and wellbeing.[25] Even when bilateral nerve-sparing RP (NSRP) procedures are performed, around 15%–80% of men experience postoperative ED.[26,27] Cavernosal nerve injury, vascular injury and SM damage which caused by surgical and radiant invasion are fundamental factors leading to posttreatment ED. The aforementioned insights into the pathophysiology of this kind of ED have led to the development of penile rehabilitation strategies, which is defined as the use of any drug or device at or after treatment to maximize EF recovery, including PDE5-Is, intracavernosal injections, intraurethral alprostadil, vacuum constriction devices (VCDs), neuromodulatory therapy, or a combination of these treatments.[28,29] PDE5-Is are more commonly used in rehabilitation programs than other treatment options and are often the first line of treatment.[30,31]

Post radical prostatectomy

In different trials, the response rate to sildenafil treatment ranged from 50% to 75% among patients underwent nerve-sparing surgery.[32,33] An RCT conducted in Europe and the USA showed that 71% of the patients treated with tadalafil 20 mg had an improvement of their EF after bilateral NSRP, compared to 24% of that in placebo group. Also, patients taking tadalafil had 52% rate of successful intercourse attempts, which was significantly higher than the 26% rate obtained with placebo.[34] Results from another RCT with PCa men who underwent NSRP at 50 international centers showed that both daily tadalafil and on-demand tadalafil could improve post-NSRP ED, with daily dosing more effective in ameliorating EF, maintaining penile length and protecting against structural changes due to neuropraxia. However, the unassisted erection was not enhanced during drug-free washout period.[20] However, another study reported that men using vardenafil on a regular rehabilitation schedule showed no better effect than men who used PDE5-Is on-demand.[35] This contrasting result could be attributed to the different pharmacokinetic characteristics of these two PDE-Is. The half-life time of tadalafil is approximately 4-fold longer than vardenafil, which may contribute to the better effectiveness of tadalafil on penile rehabilitation. Many factors influence the severity of postoperative ED and rehabilitative efficacy of PDE5-Is, including patient age, tumor stage, preoperative potency, length of time following surgery, surgical types, and the experience of surgeon. The integrity of cavernosal nerve after surgery is also extremely important since PDE5-Is improve EF depending on the peripheral release of NO from cavernosal nerve terminals. Controversies still exist in a number of other clinical trials on the rehabilitative efficacy of PDE5-Is. The meta-analysis from Candy *et al.*[36] showed oral PDE5-Is were effective in the medium term (up to 4 months) when used to treat ED subsequent to EBRT and bilateral or unilateral NSRP for PCa. However, no significant differences were found in their comparisons of the PDE5-Is dose, or between patients with unilateral and bilateral NSRP. They attributed these observations to too few patients in each subgroup. Recently, we performed a meta-analysis and confirmed the efficacy and safety of PDE5-Is in treating post bilateral NSRP ED in subjects suffering PCa.[37] In our subgroup comparisons, there was a trend that higher dose, longer course of treatment, on-demand dosing and sildenafil were associated with more efficacy of PDE5-Is, but these trends were not sufficient to demonstrate statistical differences.[37] The lack of statistical significance could also be accounted for insufficient patient numbers in the trials included.

Post radiotherapy

Besides surgical treatment, radiotherapy that includes EBRT and brachytherapy is common treatment modalities. Even with brachytherapy, the irradiation affects only a very precise and localized area, 24%–50% of the patients complained ED according to different literature.[38,39] A double-blind, placebo-controlled, cross-over study confirmed the efficacy and safety of tadalafil in treating three-dimensional conformal external beam radiotherapy (3D-CRT) induced ED.[40] Similar effect was observed for brachytherapy. An open-label, nonrandomized study showed that brachytherapy induced ED is as amenable to sildenafil treatment as ED from other causes.[38] However, as far as the short-term follow-up and limited patients involved, more large-scale and long-term clinical trials should be done to further clarify the efficiency and safety of PDE5-Is in treating radiotherapy-related ED.

In general, early penile rehabilitation can increase the arterial flow and tissue oxygenation that interrupt the gradual apoptotic loss of corpus cavernosum smooth muscle (CCSM) and endothelial cell.[41] However, the advantage of PDE5-Is over placebo in these clinical data may not reflect the real rehabilitative effect of PDE5-Is, as the majority of patients after post-PCa treatment experience severe ED. The efficacy of PDE5-Is in this population would not be expected to be high as in the general ED subjects. In Brock's study, only 28% severe ED patients had successful intercourse at the end of treatment.[42] As for providing sound practical advice for the use of PDE5-Is for post PCa-treatment ED, such as when to initiate, what dosage, duration of treatment, selection criteria, and which drug is most efficacious, more clinical trials are required.

Combined therapy

PDE5-Is plus testosterone

Despite the efficiency of PDE5-Is, 30%–35% of the patients do not respond to PDE5-Is alone.[15] Given the important role of testosterone (T) in the sexual activity and decreased plasma level of T in unresponsive subjects, interest in T plus PDE5-Is therapy has increased in recent years. SM cell degeneration (apoptosis), adipose tissue and collagen fibers deposition in CC, and reduced expression of eNOS and neural nitric oxide synthase (nNOS) were confirmed in hypogonadism subjects by previous studies.[43–46] Upregulation of CCSM contractility was also found in castrated or diabetic animal models.[47–50] Also, we and others found that PDE5 in CC is T-dependent, which has an important clinical significance: when the unresponsiveness to PDE5-Is in an ED subject happens, androgen deficiency should be considered, and supplement of T may be an effective solution.[45,51,52] Indeed, a lot of clinical trials have demonstrated that T replacement therapy (TRT) can improve EF and the response to PDE5-Is in patients with ED and hypogonadism.[53–55] Furthermore, other studies have confirmed the beneficial effects of combination therapy in patients with comorbid conditions, like type II diabetes and obesity.[56,57] During clinical practice, all patients with ED should be evaluated for T levels before any therapy. If hypogonadism can be diagnosed, TRT should be prescribed first. Many patients may achieve successful erection with TRT alone. Moreover, other disorders related to hypogonadism, such as osteoporosis, dyslipidemia, obesity, and cardiovascular mortality, could be benefited from TRT. If necessary, PDE5-Is could be added for patients whose hypogonadism is resolved but ED remains. However, sometimes blood T level is not low enough for the diagnosis of hypogonadism and determination of bioactive T level is not available. For those ED sufferers, EF should be restored with PDE5-Is first, and TRT could be combined when PDE5-Is alone is ineffective.[58]

Soluble guanylate cyclase (sGC) stimulators/activators plus PDE5-Is

In addition to PDE5-Is, soluble guanylate cyclase (sGC) stimulators and sGC activators have been developed to target sGC directly and increase cGMP formation. sGC stimulators, such as BAY 60-4552, can bind to sGC and enhance the catalytic activity of sGC to increase cGMP formation NO-independently.[59] With using a cavernous nerve crush induced ED rat model, Oudot *et al*. showed the combination of intravenous injection of BAY 60-4552 and vardenafil produced synergistic beneficial effects on the erectile response to cavernosal nerve stimulation.[60] In the situation of the failure of sGC stimulators, the sGC activator, such as BAY 60-2770 can be helpful.[61] Unlike sGC stimulators, the sGC activators increase the catalytic activity of sGC directly when the enzyme is inactivated. In a rat model treated with 1H[1,2,4]oxadiazolo-[4,3-a] quinoxalin-1-one (ODQ), which inhibited sGC and made it insensitive to NO, the intracavernosal pressure (ICP) rise in response to intracavernosal injection of BAY 60-2770 were enhanced significantly while this ICP increase induced

by intracavernosal injection of the sGC stimulator BAY 41-8543 or NO-donor were not found.[62,63] These data suggest that sGC stimulators will potentially be useful when NO is inactivated, while sGC activators can be used as a salvage therapy when sGC is inactivated or oxidized and not responsive to NO or sGC stimulators. The combination of these agents with PDE5-Is would have a promising future in the management of severe ED conditions. A clinical trial on the treatment of ED using a combination of the sGC stimulator BAY 60-4552 and vardenafil has been completed by Bayer HealthCare, but the results are still not published.

BENIGN PROSTATIC HYPERPLASIA

Current oral therapies recommended by guidelines include α-adrenoceptor antagonists (α-blockers, ABs), 5α-reductase inhibitors (5ARIs), muscarinic receptor antagonists (MRAs) and a "new emerging treatment" PDE5-Is.[64,65] Recently, numerous clinical trials have investigated the efficacy of PDE5-Is for LUTS/BPH, while tadalafil was licensed in the USA and in European Union for treating LUTS/BPH with or without ED.[64,65] Recent studies suggested the potential significance of the NO/cGMP and adenylate cyclase (AC)/cAMP pathway in the control of prostate SM.[66,67] The presence of PDE5 in prostate has been confirmed by Ückert *et al*. and Fibbi *et al*. but controversy exists regarding the precise location of PDE5 within prostate.[68,69] We most recently showed that PDE5 distributed mainly in fibromuscular stroma cell as well as in endothelial and SM cells of blood vessels both in rat and human prostate (**Figure 1**, Zhang *et al*. unpublished data). Differences in the polyclonal antibodies and tissue source employed could explain the disparity. Using organ bath technique, we and others showed that exposure of isolated rat or human prostate tissue to PDE5-Is could produce a relaxation of the precontracted prostatic strips.[70–72] These preclinical studies support the use of inhibitors of PDE5 for treating LUTS/BPH.

Clinical evidence

The first clinical trial was conducted by Sairam *et al*.[73] in 2002 with sildenafil for treating LUTS/BPH/ED patients. After 3 months of treatment, there was a significant inverse relationship between international prostate symptom score (IPSS) and IIEF score suggesting that sildenafil both improved LUTS and ED. Since then, the effects of PDE5-Is on LUTS/BPH were extensively investigated, especially tadalafil, a long-acting PDE5-Is. Different doses of tadalafil (2.5, 5, 10, and 20 mg per day) have been evaluated in many high-quality RCTs, 5 mg and higher doses can relieve LUTS symptoms significantly. However, only tadalafil 5 mg once daily has been licensed for the treatment of LUTS with or without ED which was probably due to unnecessary higher dose will increase economic burden and potential drug-related side effects.[74–78] The majority of the studies demonstrated that PDE5-Is alone were efficacious on decreasing IPSS total score, storage subscore, and voiding subscore except on maximum urinary flow rate (Q_{max}). One RCT even showed that LUTS/BPH patients with daily tadalafil (5 mg) treatment had greater treatment satisfaction compared with daily tamsulosin (0.4 mg) therapy or placebo.[79] We recently performed a systematic review and network meta-analysis including 64 RCTs with 28 196 participants comparing the effectiveness of different oral drug therapies for LUTS/BPH.[80] As shown in **Figure 2**, our novel data showed that among all the drug treatments, PDE5-Is combined with ABs ranked highest in efficacy for decreasing the IPSS total score, storage subscore, and voiding subscore. ABs combined with 5ARIs ranked highest in efficacy for increasing of Q_{max}. ABs plus MRAs showed great effectiveness on improving storage symptoms. PDE5-Is alone also showed promising effect except on Q_{max}.[80] The results suggest combination therapies, especially ABs plus PDE5-Is, have the greatest efficacy for treatment of LUTS/BPH, which is the optimal approach for difficult-to-treat cases, especially for those who are reluctant to surgical procedures. In 2012, Gacci *et al*. conducted an extensive pair-wise meta-analysis on the use of PDE5-Is alone or in combination with ABs for the treatment of LUTS/BPH. They indicated that PDE5-Is could significantly improve LUTS and be a promising treatment for this disorder, although they were ineffective on Q_{max} either.[81] Gacci *et al*. explained that PDE5-Is concomitant relaxation of the detrusor muscle may counteract the relaxation of the prostate and bladder neck. However, for detrusor SM, the role of PDE5-Is may not just be limited to relaxation and the mechanism remains to be fully clarified.[82–84] Also, the combination of tadalafil and 5ARIs is an attractive approach for the management of LUTS/BPH, especially for patients have large volume prostate. Casabe *et al*. conducted a large-scale, randomized, double-blind study to evaluate this approach and reported that coadministration of tadalafil and finasteride achieved early amelioration of LUTS as well as an improvement EF.[85]

Preclinical studies

The potential mechanisms of PDE5-Is in treating LUTS/BPH are multifactorial and not as ABs, which reducing urethral resistance

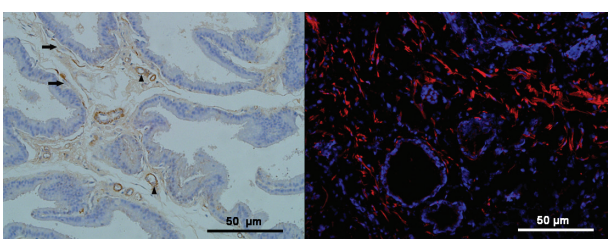

Figure 1: Phosphodiesterase type 5 (PDE5) expression and immunolocalization in rat and human tissues. Left: The rat prostatic gland section shows the main PDE5 immunostaining in fibromuscular stroma (black arrows) as well as in the endothelial and smooth muscle cells of blood vessels (black triangle). Right: Cy3-immunofluorescence (red) indicating the presence of PDE5 was abundantly observed in the fibromuscular stroma in human prostate. DAPI (blue) indicates nuclear staining.

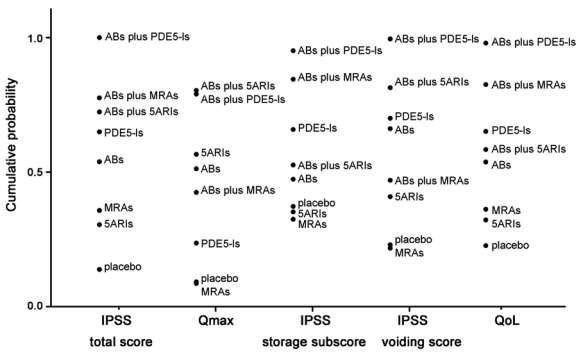

Figure 2: Cumulative probabilities of different kinds of oral drug therapies as measured by the included outcomes. The Bayesian approach could apply the rank probabilities of each drug therapy and the cumulative probability sum the rank probabilities to give an overall probability. Larger cumulative probability represents the better effect on the improvement of IPSS total score, Q_{max}, IPSS storage subscore, IPSS voiding score and QoL, which also represent the rank of the drug therapies. ABs: α-blockers; 5ARIs: 5α-reductase inhibitors; MRAs: muscarinic receptor antagonists; PDE5-Is: phosphodiesterase 5 inhibitors (Credited to Wang *et al*.[80]).

by attenuating the tension of SM fibers. Besides the expression and functional activity of PDE5 in bladder, urethra, and prostate,[69] Morelli *et al*. revealed that human vesicular-deferential artery (provides blood flow to prostate and bladder) and rat iliac artery (provides blood supply to the prostate) expressed high levels of active PDE5 and found that tadalafil increased prostate tissue oxygenation in spontaneously hypertensive rat through detecting the immunosignal of hypoxia markers.[86] However, the increase of prostate blood flow was not confirmed by an RCT that daily tadalafil (5 mg) was used 8 weeks for LUTS/BPH patients. This ineffectiveness may ascribe to low baseline blood flow in prostate and insufficient sensitivity of techniques.[87] In addition, they also found that *in vitro* treatment with tadalafil or vardenafil on human myofibroblast prostatic cells reduced interleukin 8 (IL-8) secretion induced by either tumor necrosis factor α (TNF-α) or metabolic factors, which indicated that PDE5-Is could blunt intraprostatic inflammation.[88] Also, Fibbi *et al.* showed that vardenafil enhanced dose-dependent antiproliferation induced by SNP (NO donor) and BAY 41-8543 (sGC stimulator) in prostatic SM cell.[69] Finally, Minagawa *et al.* showed that systemic administration of tadalafil reduced mechanosensitive afferent activities of both A δ- and C-fibres elicited by bladder distension in the rat.[89] Recently, men with LUTS/BPH were involved in an RCT assessing IPSS and Q_{max}, who were randomized to either placebo (n = 172) or tadalafil (5 mg; n = 171) or tamsulosin (0.4 mg n = 168). Subjects who took tadalafil and tamsulosin showed significant improvement in IPSS and Q_{max} versus placebo after 12 weeks of treatment. This international study showed that tadalafil 5 mg once daily for 12 weeks had the same effect with tamulosin 0.4 mg once daily in treating men with LUTS/BPH.[78] Similar result was found in another RCT accessing the efficacy and safety of daily tadalafil (10 mg), daily tamsulosin (0.4 mg) and combination in treating LUTS/BPH.[90] The significant improvement in Q_{max} with tadalafil in these studies contrast with the majority of previous studies on PDE5-Is for LUTS/BPH. The authors attributed this increase of Q_{max} possibly due to lower baseline Q_{max} in the treatment group compared with previous tadalafil studies, which could allow more room for improvement.[78] Another multicenter, well-designed clinical trial assessing the effect of UK-369,003 (a PDE5-I) on LUTS/BPH patients found the same change of Q_{max}, and high selectivity of this drug compared with other PDE5-Is could be a possible explanation for the significant increase of Q_{max}.[91] Indeed, the effect of PDE5-Is on Q_{max} remains controversial.

In summary, as shown in **Figure 3**, the plausible mechanisms of PDE5-Is in treating LUTS/BPH may be: (1) slight-to-moderate relaxation of muscle tone in prostate and bladder; (2) significant dilation of local blood vessels which provide adequate blood; (3) significant augmentation of oxygen perfusion to local organs; (4) inhibition of afferent nerve activity of bladder; (5) bluntness of intraprostatic inflammation; and (6) antiproliferation in prostate.

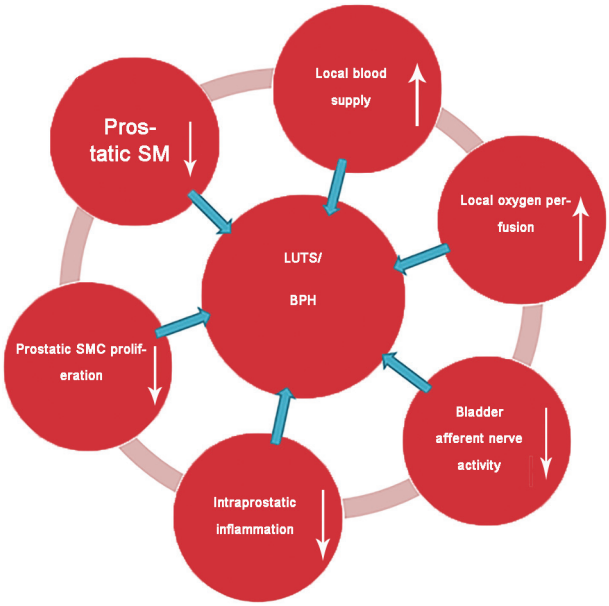

Figure 3: The plausible mechanisms of PDE5-Is in treating LUTS/BPH. This schematic depicts the possible mechanisms that PDE5-Is treat LUTS/BPH. PDE5-Is: phosphodiesterase 5 inhibitors; LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia.

PRIAPISM

Among men with sickle cell disease, the prevalence of priapism is more than 40%.[92,93] This disorder is poorly understood from a pathophysiologic standpoint, and thus effective treatments are still lacking. Recently, we established a novel, rat priapism model induced by intracavernous injection of myosin specific inhibitor blebbistatin. At various time point of 2 h, 4 h, 4- day, and 7-day prolonged erection, the major contractile and relaxant molecules were determined in CC. Importantly, this model showed CC contractile molecules including PDE5 upregulated, and relaxation molecules downregulated with ICP reversible in the early compensated stage while these pathways were opposite (contraction decrease and relaxation increase, ICP irreversible) in the later decompensated stage with eventual severe fibrosis and atrophy.[94] Champion *et al.* also demonstrated that the disturbance of NO/cGMP pathway mediating penile erection plays an important role in priapism.[95] This dysregulation specifically involves the decreased expression of PDE5 in CC. The excessive amount of cGMP accounts for the prolonged erectile tissue relaxation that manifests as priapism.[95,96] This discovery makes PDE5 a novel molecular target for treatment. Burnett *et al.* reported serial clinical trials that long-term, low-dose sildenafil or tadalafil treatment reduced the frequency and duration of disordered erection in men with recurrent priapism.[97] In these trials, the initial dose of sildenafil was 25 mg daily with escalation up to 50 mg daily, and doses of tadalafil at 5–10 mg 3 times a week. Only one patient with severe recurrent episodes did not respond to treatment. The findings are encouraging and support the useful role of PDE5-Is against mild or moderate priapism. They hypothesized that continuous, long-term, low-dose PDE5-Is treatment may achieve an upregulation of PDE5 gene (although reversible) and reset the PDE5 expression in penile tissue, which would control the excessive cGMP signaling associated with priapism.[22,98] Recently, Burnett *et al.* conducted the first double-blind, placebo-controlled RCT including 13 patients to assess the efficacy and safety of sildenafil in prevention of recurrent ischemic priapism associated with sickle cell disease.[99] Although no significant difference was found between sildenafil and placebo at the end of phase 1 study, a reduction in priapism episodes was observed in the majority of patients participating in the open-label phase. Also, an overall 4-fold fewer priapism-related hospital visits occurred among patients adherent to therapy than those who were nonadherent or receiving placebo. These results suggested a beneficial role of PDE5-Is in the management of priapism. It should be noted that PDE5-Is therapy should be started when the penis is in its flaccid state and not during an acute episode. Current use of PDE5-Is for treatment of recurrent priapism is contraindicated by the labeled indications and multicenter, and placebo-controlled RCTs are underway to further evaluate the potential of PDE5-Is for this disorder.

PREMATURE EJACULATION

PE is another very common sexual disorder among males with a prevalence of 20%–30%. It is a multicomponent dysfunction, including anxiety, penile hypersensitivity, and serotonin receptor dysfunction.[100] The treatment of PE has been primarily focused on behavioral therapy, topical anesthetics, and selective serotonin reuptake inhibitors (SSRIs). However, none of them is reliable. The importance of the NO/cGMP pathway in the control of the ejaculatory apparatus such as seminal vesicle (SV) and vas deferens (VD) has been previously reported.[101–103] It was also reported that the adrenergic tension of isolated human SV strip was dose-dependently attenuated by the NO-donating compounds, PDE1-I, PDE4-I, and PDE5-I.[102–104] Recently, several clinical trials have demonstrated PDE5-Is is effective in treating PE subjects. Fourteen clinical studies assessed PDE5-Is treatment as monotherapy or combination therapy with SSRI for PE were reviewed, among them, seven found that PDE5-Is was helpful for PE,[105–111] whereas two did not.[112,113] Five other studies[114–118] demonstrated that the combined use of PDE5-Is and SSRI led to significantly improved results regarding intravaginal ejaculation latency time (IELT) and overall sexual satisfaction when compared with SSRI monotherapy. Sildenafil was the main PDE5 agent that was used at a usual dosage of 50 mg. Based on these studies, it seems that PDE5-Is are promising options against PE by mechanism of relaxing the SM of VD, SV, prostate, and prolonging the duration of erection and increasing confidence, finally overall sexual satisfaction. A meta-analysis conducted by Asimakopoulos *et al.* showed an overall positive effect for the use of PDE5-Is as monotherapy or as components of a combination regimen in the treatment of PE, however, considering the lack of a unique PE definition as well as the lack of appropriate endpoints for outcome evaluation of a placebo control arm, these results should be considered with caution.[119] Overall, on-demand dapoxetine remains the first line therapy for PE populations as PDE5-Is are not approved medications. If coexisting PE and ED, combined therapy is preferred.

PEYRONIE'S DISEASE

One of the most efficient treatments for PD is the prevention of fibrosis. No satisfactory medical treatments for PD are currently available. However, recent studies have been demonstrated that the NO/cGMP system plays an important role in antifibrotic mechanism.[120,121] Especially, the use of PDE5-Is as an antifibrotic modality has provided new insights into the management of PD. Ferrini *et al*. found long-term vardenafil treatment significantly decreased collagen I and III deposition and reduced the numbers of myofibroblasts in PD plaques in a rat model of PD.[122] A RCT conducted by Ozturk *et al*. found that 50 mg sildenafil daily for 12 weeks could significantly reduce penile plaques.[123] However, this first clinical study has a lot of limitations, such as small patient population, nondouble-blind design, and short study duration. Despite the promising role of PDE5-Is in PD therapy, its utility may be restricted to the early stage since the progression of PD plaque to fibrosis and calcification cannot be hampered by PDE5-Is alone. More preclinical studies and clinical trials are needed.

OTHER DISEASES

Many basic investigations also support the use of PDE5-Is in treating other urogenital disorders, such as urinary tract calculi, OAB, and FSD although clinical data are still lacking. Stief *et al*. showed that ureteral tissue contained NO-containing nerves within the smooth musculature[124] and suggested that ureteral relaxation may involve the NO/cGMP pathway. Regarding OAB, inhibition of PDE5 may also become an intriguing approach since both LUTS and urge urinary incontinence symptoms originate within the bladder and are characterized by detrusor overactivity.[125] The occurrence and hydrolytic activity of PDE5 in human clitoral CC and vagina have been discovered,[126,127] and it is expected that PDE5-Is may improve vaginal and clitoral blood flow and facilitate arousal and orgasm in women as the same mechanism of treating ED. However, the results pooled from clinical trials in which PDE5-Is were used against FSD were not encouraging,[128,129] which probably due to the psychological influence in female sexual behavior. We believe PDE5-Is may have a promising potential in the management of this disease and more preclinical and clinical studies should be carried out.

CONCLUSION

On-demand PDE5-Is are efficacious for most cases of ED while daily dosing and combination with T are recommended for refractory cases. sGC stimulators also have promising role in the management of severe ED conditions. PDE5-Is are also the first rehabilitation strategy for postoperation or postradiotherapy ED for PCa patients. PDE5-Is, especially combined with ABs, are very effective for LUTS/BPH except on Q_{max} with tadalafil recently proved for BPH with/without ED in the USA and European Union. Furthermore, PDE5-Is are currently under various phases of clinical or preclinical researches with promising potential for other urinary and genital illnesses, such as priapism, PE, PD, urinary tract calculi, OAB, and FSD. The potential uses of PDE5-Is for indications outside the scope of sexual medicine are intriguing. However, further clinical studies and basic researches investigating mechanisms of PDE5-Is in disorders of UGTs are required.

COMPETING INTERESTS

All authors declared that they have no competing interests.

ACKNOWLEDGMENTS

This study is supported by National Natural Science Foundation of China (No. 81270843 and No. 81160086).

REFERENCES

1 Conti M, Jin SL. The molecular biology of cyclic nucleotide phosphodiesterases. *Prog Nucleic Acid Res Mol Biol* 1999; 63: 1–38.
2 Mayer B. Nitric oxide/cyclic GMP-mediated signal transduction. *Ann N Y Acad Sci* 1994; 733: 357–64.
3 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, *et al.* Oral sildenafil in the treatment of erectile dysfunction. Sildenafil study group. *N Engl J Med* 1998; 338: 1397–404.
4 Bruzziches R, Francomano D, Gareri P, Lenzi A, Aversa A. An update on pharmacological treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors. *Expert Opin Pharmacother* 2013; 14: 1333–44.
5 Katz EG, Tan RB, Rittenberg D, Hellstrom WJ. Avanafil for erectile dysfunction in elderly and younger adults: differential pharmacology and clinical utility. *Ther Clin Risk Manag* 2014; 10: 701–11.
6 Shamloul R, Ghanem H. Erectile dysfunction. *Lancet* 2013; 381: 153–65.
7 Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. *Int J Clin Pract* 2006; 60: 967–75.
8 Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. *Urology* 2002; 60: 12–27.
9 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, *et al.* Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. *Urology* 2003; 61: 8–14.
10 Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, *et al*. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002; 168: 1332–6.
11 Goldstein I, McCullough AR, Jones LA, Hellstrom WJ, Bowden CH, *et al*. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med* 2012; 9: 1122–33.
12 Cui YS, Li N, Zong HT, Yan HL, Zhang Y. Avanafil for male erectile dysfunction: a systematic review and meta-analysis. *Asian J Androl* 2014; 16: 472–7.

13 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: 415–25.
14 Sommer F, Klotz T, Engelmann U. Improved spontaneous erectile function in men with mild-to-moderate arteriogenic erectile dysfunction treated with a nightly dose of sildenafil for one year: a randomized trial. *Asian J Androl* 2007; 9: 134–41.
15 McMahon CN, Smith CJ, Shabsigh R. Treating erectile dysfunction when PDE5 inhibitors fail. *BMJ* 2006; 332: 589–92.
16 McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004; 1: 292–300.
17 De Young LX, Domes T, Lim K, Carson J, Brock GB. Endothelial rehabilitation: the impact of chronic PDE5 inhibitors on erectile function and protein alterations in cavernous tissue of diabetic rats. *Eur Urol* 2008; 54: 213–20.
18 Ferrini MG, Kovanecz I, Sanchez S, Vernet D, Davila HH, *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: 915–23.
19 Lagoda G, Jin L, Lehrfeld TJ, Liu T, Burnett AL. FK506 and sildenafil promote erectile function recovery after cavernous nerve injury through antioxidative mechanisms. *J Sex Med* 2007; 4: 908–16.
20 Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, *et al.* Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). *Eur Urol* 2014; 65: 587–96.
21 Zumbe J, Porst H, Sommer F, Grohmann W, Beneke M, *et al.* Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the RESTORE study. *Eur Urol* 2008; 54: 204–10.
22 Lin G, Xin ZC, Lue TF, Lin CS. Up and down-regulation of phosphodiesterase-5 as related to tachyphylaxis and priapism. *J Urol* 2003; 170: S15–8.
23 Vernet D, Magee T, Qian A, Nolazco G, Rajfer J, *et al.* Phosphodiesterase type 5 is not upregulated by tadalafil in cultures of human penile cells. *J Sex Med* 2006; 3: 84–94.
24 Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005; 16: 481–8.
25 Kundu SD, Roehl KA, Eggener SE, Antenor JA, Han M, *et al.* Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. *J Urol* 2004; 172: 2227–31.
26 Lee R, Penson DF. Treatment outcomes in localized prostate cancer: a patient-oriented approach. *Semin Urol Oncol* 2002; 20: 63–73.
27 Zippe CD, Raina R, Thukral M, Lakin MM, Klein EA, *et al.* Management of erectile dysfunction following radical prostatectomy. *Curr Urol Rep* 2001; 2: 495–503.
28 Briganti A, Montorsi F. Penile rehabilitation after radical prostatectomy. *Nat Clin Pract Urol* 2006; 3: 400–1.
29 Mulhall JP. The role and structure of a postradical prostatectomy penile rehabilitation program. *Curr Urol Rep* 2009; 10: 219–25.
30 Wang R. Penile rehabilitation after radical prostatectomy: where do we stand and where are we going? *J Sex Med* 2007; 4: 1085–97.
31 Giuliano F, Amar E, Chevallier D, Montaigne O, Joubert JM, *et al.* How urologists manage erectile dysfunction after radical prostatectomy: a national survey (REPAIR) by the French urological association. *J Sex Med* 2008; 5: 448–57.
32 Raina R, Lakin MM, Agarwal A, Mascha E, Montague DK, *et al.* Efficacy and factors associated with successful outcome of sildenafil citrate use for erectile dysfunction after radical prostatectomy. *Urology* 2004; 63: 960–6.
33 Zippe CD, Jhaveri FM, Klein EA, Kedia S, Pasqualotto FF, *et al.* Role of viagra after radical prostatectomy. *Urology* 2000; 55: 241–5.
34 Montorsi F, Nathan HP, McCullough A, Brock GB, Broderick G, *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* 2004; 172: 1036–41.
35 Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, *et al.* Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008; 54: 924–31.
36 Candy B, Jones L, Williams R, Tookman A, King M. Phosphodiesterase type 5 inhibitors in the management of erectile dysfunction secondary to treatments for prostate cancer: findings from a Cochrane systematic review. *BJU Int* 2008; 102: 426–31.
37 Wang X, Wang X, Liu T, He Q, Wang Y, *et al.* Systematic review and meta-analysis of the use of phosphodiesterase type 5 inhibitors for treatment of erectile dysfunction following bilateral nerve-sparing radical prostatectomy. *PLoS One* 2014; 9: e91327.
38 Merrick GS, Butler WM, Lief JH, Stipetich RL, Abel LJ, *et al.* Efficacy of sildenafil citrate in prostate brachytherapy patients with erectile dysfunction. *Urology* 1999; 53: 1112–6.
39 Merrick GS, Butler WM, Wallner KE, Galbreath RW, Anderson RL, *et al.* Erectile function after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2005; 62: 437–47.
40 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* 2006; 66: 439–44.
41 Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res* 1998; 10: 113–20.
42 Brock G, Nehra A, Lipshultz LI, Karlin GS, Gleave M, *et al.* Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. *J Urol* 2003; 170: 1278–83.
43 Aversa A, Bruzziches R, Spera G. A rationale for the use of testosterone "salvage" in treatment of men with erectile dysfunction failing phosphodiesterase inhibitors. *Endocrinologist* 2005; 15: 99–105.
44 Ferreira FT, Dambros M, Bisogni S, Dambros MC, Scolfaro MR, *et al.* Effects of testosterone supplementation on prevention of age-related penile remodeling. *Aging Male* 2014; 17: 12–7.
45 Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med* 2006; 3: 382–404.
46 Blute M, Hakimian P, Kashanian J, Shteynshluyger A, Lee M, *et al.* Erectile dysfunction and testosterone deficiency. *Front Horm Res* 2009; 37: 108–22.
47 Zhang XH, Melman A, Disanto ME. Update on corpus cavernosum smooth muscle contractile pathways in erectile function: a role for testosterone? *J Sex Med* 2011; 8: 1865–79.
48 Wingard CJ, Johnson JA, Holmes A, Prikosh A. Improved erectile function after Rho-kinase inhibition in a rat castrate model of erectile dysfunction. *Am J Physiol Regul Integr Comp Physiol* 2003; 284: R1572–9.
49 Vignozzi L, Morelli A, Filippi S, Ambrosini S, Mancina R, *et al.* Testosterone regulates RhoA/Rho-kinase signaling in two distinct animal models of chemical diabetes. *J Sex Med* 2007; 4: 620–30.
50 Zhang X, Kanika ND, Melman A, DiSanto ME. Smooth muscle myosin expression, isoform composition, and functional activities in rat corpus cavernosum altered by the streptozotocin-induced type 1 diabetes. *Am J Physiol Endocrinol Metab* 2012; 302: E32–42.
51 Zhang XH, Morelli A, Luconi M, Vignozzi L, Filippi S, *et al.* Testosterone regulates PDE5 expression and *in vivo* responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol* 2005; 47: 409–16.
52 Morelli A, Filippi S, Mancina R, Luconi M, Vignozzi L, *et al.* Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology* 2004; 145: 2253–63.
53 Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2008; 179: S97–102.
54 Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, *et al.* Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 2011; 8: 284–93.
55 Yassin DJ, Yassin AA, Hammerer PG. Combined testosterone and vardenafil treatment for restoring erectile function in hypogonadal patients who failed to respond to testosterone therapy alone. *J Sex Med* 2014; 11: 543–52.
56 Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male* 2003; 6: 94–9.
57 Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003; 6: 1–7.
58 Jannini EA, Isidori AM, Aversa A, Lenzi A, Althof SE. Which is first? The controversial issue of precedence in the treatment of male sexual dysfunctions. *J Sex Med* 2013; 10: 2359–69.
59 Lasker GF, Pankey EA, Kadowitz PJ. Modulation of soluble guanylate cyclase for the treatment of erectile dysfunction. *Physiology (Bethesda)* 2013; 28: 262–9.
60 Oudot A, Behr-Roussel D, Poirier S, Sandner P, Bernabe J, *et al.* Combination of BAY 60-4552 and vardenafil exerts proerectile facilitator effects in rats with cavernous nerve injury: a proof of concept study for the treatment of phosphodiesterase type 5 inhibitor failure. *Eur Urol* 2011; 60: 1020–6.
61 Evgenov OV, Pacher P, Schmidt PM, Hasko G, Schmidt HH, *et al.* NO-independent stimulators and activators of soluble guanylate cyclase: discovery and therapeutic potential. *Nat Rev Drug Discov* 2006; 5: 755–68.
62 Zhao Y, Brandish PE, Di Valentin M, Schelvis JP, Babcock GT, *et al.* Inhibition of soluble guanylate cyclase by ODQ. *Biochemistry* 2000; 39: 10848–54.
63 Lasker GF, Pankey EA, Frink TJ, Zeitzer JR, Walter KA, *et al.* The sGC activator BAY 60-2770 has potent erectile activity in the rat. *Am J Physiol Heart Circ Physiol* 2013; 304: H1670–9.
64 Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, *et al.* EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2013; 64: 118–40.
65 McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, *et al.* Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011; 185: 1793–803.
66 Takeda M, Tang R, Shapiro E, Burnett AL, Lepor H. Effects of nitric oxide on human and canine prostates. *Urology* 1995; 45: 440–6.

67 Drescher P, Eckert RE, Madsen PO. Smooth muscle contractility in prostatic hyperplasia: role of cyclic adenosine monophosphate. *Prostate* 1994; 25: 76–80.
68 Ückert S, Oelke M, Stief CG, Andersson KE, Jonas U, *et al.* Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. *Eur Urol* 2006; 49: 740–5.
69 Fibbi B, Morelli A, Vignozzi L, Filippi S, Chavalmane A, *et al.* Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med* 2010; 7: 59–69.
70 Ückert S, Sormes M, Kedia G, Scheller F, Knapp WH, *et al.* Effects of phosphodiesterase inhibitors on tension induced by norepinephrine and accumulation of cyclic nucleotides in isolated human prostatic tissue. *Urology* 2008; 71: 526–30.
71 Ückert S, Kuthe A, Jonas U, Stief CG. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. *J Urol* 2001; 166: 2484–90.
72 Zhang X, Zang N, Wei Y, Yin J, Teng R, *et al.* Testosterone regulates smooth muscle contractile pathways in the rat prostate: emphasis on PDE5 signaling. *Am J Physiol Endocrinol Metab* 2012; 302: E243–53.
73 Sairam K, Kulinskaya E, McNicholas T, Boustead G, Hanbury D. Sildenafil influences lower urinary tract symptoms. *BJU Int* 2002; 90: 836–9.
74 McVary KT, Roehrborn CG, Kaminetsky JC, Auerbach SM, Wachs B, *et al.* Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2007; 177: 1401–7.
75 Egerdie RB, Auerbach S, Roehrborn CG, Costa P, Garza MS, *et al.* Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. *J Sex Med* 2012; 9: 271–81.
76 Porst H, McVary KT, Montorsi F, Sutherland P, Elion-Mboussa A, *et al.* Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. *Eur Urol* 2009; 56: 727–35.
77 Yokoyama O, Yoshida M, Kim SC, Wang CJ, Imaoka T, *et al.* Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men. *Int J Urol* 2013; 20: 193–201.
78 Oelke M, Giuliano F, Mirone V, Xu L, Cox D, *et al.* Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol* 2012; 61: 917–25.
79 Oelke M, Giuliano F, Baygani SK, Melby T, Sontag A. Treatment satisfaction with tadalafil or tamsulosin vs placebo in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH): results from a randomised, placebo-controlled study. *BJU Int* 2014; 114: 568–75.
80 Wang X, Wang X, Li S, Meng Z, Liu T, *et al.* Comparative effectiveness of oral drug therapies for lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and network meta-analysis. *PLoS One* 2014; 9: e107593.
81 Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, *et al.* A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 2012; 61: 994–1003.
82 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* 1996; 24: 129–34.
83 Fujiwara M, Andersson K, Persson K. Nitric oxide-induced cGMP accumulation in the mouse bladder is not related to smooth muscle relaxation. *Eur J Pharmacol* 2000; 401: 241–50.
84 Kajioka S, Nakayama S, Seki N, Naito S, Brading AF. Oscillatory membrane currents paradoxically induced via NO-activated pathways in detrusor cells. *Cell Calcium* 2008; 44: 202–9.
85 Casabe A, Roehrborn CG, Da Pozzo LF, Zepeda S, Henderson RJ, *et al.* Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *J Urol* 2014; 191: 727–33.
86 Morelli A, Sarchielli E, Comeglio P, Filippi S, Mancina R, *et al.* Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. *J Sex Med* 2011; 8: 2746–60.
87 Pinggera GM, Frauscher F, Paduch DA, Bolyakov A, Efros M, *et al.* Effect of tadalafil once daily on prostate blood flow and perfusion in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: a randomized, double-blind, multicenter, placebo-controlled trial. *Urology* 2014; 84: 412–9.
88 Vignozzi L, Gacci M, Cellai I, Morelli A, Maneschi E, *et al.* PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. *Prostate* 2013; 73: 1391–402.
89 Minagawa T, Aizawa N, Igawa Y, Wyndaele JJ. Inhibitory effects of phosphodiesterase 5 inhibitor, tadalafil, on mechanosensitive bladder afferent nerve activities of the rat, and on acrolein-induced hyperactivity of these nerves. *BJU Int* 2012; 110: E259–66.
90 Singh DV, Mete UK, Mandal AK, Singh SK. A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. *J Sex Med* 2014; 11: 187–96.
91 Tamimi NA, Mincik I, Haughie S, Lamb J, Crossland A, *et al.* A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia. *BJU Int* 2010; 106: 674–80.
92 Adeyoju AB, Olujohungbe AB, Morris J, Yardumian A, Bareford D, *et al.* Priapism in sickle-cell disease; incidence, risk factors and complications – An international multicentre study. *BJU Int* 2002; 90: 898–902.
93 Berger R, Billups K, Brock G, Broderick GA, Dhabuwala CB, *et al.* Report of the American Foundation for Urologic Disease (AFUD) thought leader panel for evaluation and treatment of priapism. *Int J Impot Res* 2001; 13 Suppl 5: S39–43.
94 Zhang X, Melman A, DiSanto M. Pathophysiology of priapism with varied duration: a novel rat model study using the myosin II specific inhibitor blebbistatin(Abstract). *J Urol* 2011; 185: e452.
95 Champion HC, Bivalacqua TJ, Takimoto E, Kass DA, Burnett AL. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. *Proc Natl Acad Sci U S A* 2005; 102: 1661–6.
96 Yuan J, Desouza R, Westney OL, Wang R. Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl* 2008; 10: 88–101.
97 Burnett AL, Bivalacqua TJ, Champion HC, Musicki B. Feasibility of the use of phosphodiesterase type 5 inhibitors in a pharmacologic prevention program for recurrent priapism. *J Sex Med* 2006; 3: 1077–84.
98 Burnett AL, Bivalacqua TJ, Champion HC, Musicki B. Long-term oral phosphodiesterase 5 inhibitor therapy alleviates recurrent priapism. *Urology* 2006; 67: 1043–8.
99 Burnett AL, Anele UA, Trueheart IN, Strouse JJ, Casella JF. Randomized controlled trial of sildenafil for preventing recurrent ischemic priapism in sickle cell disease. *Am J Med* 2014; 127: 664–8.
100 McMahon CG, Abdo C, Incrocci L, Perelman M, Rowland D, *et al.* Disorders of orgasm and ejaculation in men. *J Sex Med* 2004; 1: 58–65.
101 Ückert S, Waldkirch ES, Sonnenberg JE, Sandner P, Kuczyk MA, *et al.* Expression and distribution of phosphodiesterase isoenzymes in the human seminal vesicles. *J Sex Med* 2011; 8: 3058–65.
102 Seftel AD. Expression and functional activity of phosphodiesterase type 5 in human and rabbit vas deferens. *J Urol* 2005; 174: 1043.
103 Machtens S, Ckert S, Stief CG, Tsikas D, Frlich JC Jr, *et al.* Effects of various nitric oxide-donating drugs on adrenergic tension of human seminal vesicles *in vitro*. *Urology* 2003; 61: 479–83.
104 Ückert S, Bazrafshan S, Scheller F, Mayer ME, Jonas U, *et al.* Functional responses of isolated human seminal vesicle tissue to selective phosphodiesterase inhibitors. *Urology* 2007; 70: 185–9.
105 Abdel-Hamid IA, El-Naggar EA, El-Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res* 2001; 13: 41–5.
106 Aversa A, Pili M, Francomano D, Bruzziches R, Spera E, *et al.* Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. *Int J Impot Res* 2009; 21: 221–7.
107 Tang W, Ma L, Zhao L, Liu Y, Chen Z. [Clinical efficacy of Viagra with behavior therapy against premature ejaculation]. *Zhonghua Nan Ke Xue* 2004; 10: 366–7, 70.
108 Mathers MJ, Klotz T, Roth S, Lummen G, Sommer F. Safety and efficacy of vardenafil versus sertraline in the treatment of premature ejaculation: a randomised, prospective and crossover study. *Andrologia* 2009; 41: 169–75.
109 Mattos RM, Srougi M. Tadalafil and fluoxetine in premature ejaculation: prospective, randomized, double-blind, placebo-controlled study. *Urol Int* 2008; 80: 162–5.
110 Gokce A, Demirtas A, Halis F, Ekmekcioglu O. *In vitro* measurement of ejaculation latency time (ELT) and the effects of vardenafil on ELT on lifelong premature ejaculators: placebo-controlled, double-blind, cross-over laboratory setting. *Int Urol Nephrol* 2010; 42: 881–7.
111 Gokce A, Halis F, Demirtas A, Ekmekcioglu O. The effects of three phosphodiesterase type 5 inhibitors on ejaculation latency time in lifelong premature ejaculators: a double-blind laboratory setting study. *BJU Int* 2011; 107: 1274–7.
112 McMahon CG, Stuckey BG, Andersen M, Purvis K, Koppiker N, *et al.* Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med* 2005; 2: 368–75.
113 Atan A, Basar MM, Tuncel A, Ferhat M, Agras K, *et al.* Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. *Urology* 2006; 67: 388–91.
114 Salonia A, Maga T, Colombo R, Scattoni V, Briganti A, *et al.* A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol* 2002; 168: 2486–9.
115 Wang WF, Wang Y, Minhas S, Ralph DJ. Can sildenafil treat primary premature ejaculation? A prospective clinical study. *Int J Urol* 2007; 14: 331–5.
116 Hosseini MM, Yarmohammadi H. Effect of fluoxetine alone and in combination with sildenafil in patients with premature ejaculation. *Urol Int* 2007; 79: 28–32.

117 Chen J, Mabjeesh NJ, Matzkin H, Greenstein A. Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology* 2003; 61: 197–200.
118 Lee WK, Lee SH, Cho ST, Lee YS, Oh CY, *et al*. Comparison between on-demand dosing of dapoxetine alone and dapoxetine plus mirodenafil in patients with lifelong premature ejaculation: prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Sex Med* 2013; 10: 2832–41.
119 Asimakopoulos AD, Miano R, Finazzi Agro E, Vespasiani G, Spera E. Does current scientific and clinical evidence support the use of phosphodiesterase type 5 inhibitors for the treatment of premature ejaculation? A systematic review and meta-analysis. *J Sex Med* 2012; 9: 2404–16.
120 Ferrini MG, Vernet D, Magee TR, Shahed A, Qian A, *et al*. Antifibrotic role of inducible nitric oxide synthase. *Nitric Oxide* 2002; 6: 283–94.
121 Gonzalez-Cadavid NF, Rajfer J. Treatment of Peyronie's disease with PDE5 inhibitors: an antifibrotic strategy. *Nat Rev Urol* 2010; 7: 215–21.
122 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: 625–33.
123 Ozturk U, Yesil S, Goktug HN, Gucuk A, Tuygun C, *et al*. Effects of sildenafil treatment on patients with Peyronie's disease and erectile dysfunction. *Ir J Med Sci* 2014; 183: 449–53.
124 Stief CG, Ückert S, Truss MC, Becker AJ, Machtens S, *et al*. A possible role for nitric oxide in the regulation of human ureteral smooth muscle tone *in vitro*. *Urol Res* 1996; 24: 333–7.
125 Chapple CR, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. *Eur Urol* 2006; 49: 651–8.
126 Oelke M, Hedlund P, Albrecht K, Ellinghaus P, Stief CG, *et al*. Expression of cAMP and cGMP-phosphodiesterase isoenzymes 3, 4, and 5 in the human clitoris: immunohistochemical and molecular biology study. *Urology* 2006; 67: 1111–6.
127 D'Amati G, di Gioia CR, Bologna M, Giordano D, Giorgi M, *et al*. Type 5 phosphodiesterase expression in the human vagina. *Urology* 2002; 60: 191–5.
128 Caruso S, Intelisano G, Lupo L, Agnello C. Premenopausal women affected by sexual arousal disorder treated with sildenafil: a double-blind, cross-over, placebo-controlled study. *BJOG* 2001; 108: 623–8.
129 Kaplan SA, Reis RB, Kohn IJ, Ikeguchi EF, Laor E, *et al*. Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. *Urology* 1999; 53: 481–6.