Review – Sexual Medicine

Daily Administration of Phosphodiesterase Type 5 Inhibitors for Urological and Nonurological Indications

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Abstract

Objectives: Although the discovery of phosphodiesterases (PDEs) was made soon after the identification of cyclic adenosine monophosphate nearly half a century ago, their true importance in medicine has taken many decades to be realised. The recognition of the important role PDE enzymes play and the impact of altering intracellular cyclic nucleotide levels became significant for most urologists and clinicians in the early 1990s with the discovery of sildenafil, a PDE5 inhibitor (PDE5-I). Once approved around the world, on-demand use of PDE5-Is became the gold standard. Recently, the potential beneficial effects of PDE5-Is on the pulmonary, vascular, and other systems has led to examination of alternative dosing regimens. In this review, we have synthesised the available published peer-reviewed literature to provide a critical contemporary view of evolving indications for PDE5-Is and how alternative dosing regimens may impact on sexual and other functions.

Methods: MEDLINE search of all peer-reviewed English literature for the period 1990–2007.

Results: The plethora of articles detailing potential uses of PDE5-I in multiple fields of medicine was uncovered. Use of alternative dosing regimens shows great promise across a number of clinical indications, including post–radical retropubic prostatectomy, pulmonary hypertension, endothelial dysfunction, and salvage of on-demand PDE5-I non-responders.

Conclusions: Use of PDE5-I on a daily basis may evolve into a major form of drug administration both for men with erectile dysfunction and for those with a myriad of other conditions shown to benefit from this approach.

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1. Introduction

A wealth of clinical experience supports oral PDE5-I as safe and efficacious agents of choice for treatment of erectile dysfunction (ED) in most men [1–4]. Reported efficacy rates of 60–70% are reported; however, therapeutic success is often lower in subpopulations identified as more difficult to treat, including diabetics, severe vasculogenic ED, and post–radical retropubic prostatectomy (RRP) patients [5,6]. Real or perceived lack of spontaneity or treatment flexibility, adverse effects, or improper administration/use may also limit patient satisfaction. Patient-identified criteria for success—namely

![PDE5i Target Organs](image-url)

Fig. 1 – Primary clinical indications for daily PDE5-I regimens.
Table 1 – Summary of potential benefits and limitations to urological and nonurological clinical use of daily PDE5-Is

<table>
<thead>
<tr>
<th>Indication</th>
<th>Potential benefits</th>
<th>Limitations</th>
<th>Selected references</th>
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</thead>
<tbody>
<tr>
<td><strong>Erectile dysfunction</strong></td>
<td>Salvage of on-demand nonresponders</td>
<td>Extended term follow-up limited—safety and efficacy profiles require further elucidation</td>
<td>Clinical: [6–8,10,11,13–15,30,36,47,48,51,56,71,73,147,149,150]</td>
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<tr>
<td></td>
<td>Disease modification</td>
<td>Disease modification—attractive concept but evidence-based data limited</td>
<td></td>
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<tr>
<td></td>
<td>May approximate more natural sexual function</td>
<td>No evidence of tachyphylaxis to date but longer follow-up needed</td>
<td>Patient cost</td>
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<td></td>
<td>Randomized, placebo-controlled trials demonstrate efficacy and safety for erectile dysfunction of various etiologies</td>
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<tr>
<td><strong>Benign prostatic hyperplasia/LUTS</strong></td>
<td>Meaningful symptomatic improvements noted in well-designed trials</td>
<td>Mechanism of action for BPH/LUTS unknown</td>
<td>Clinical: [80–90,144–146,148]</td>
</tr>
<tr>
<td></td>
<td>Decrease in IPSS</td>
<td>Trials limited with regards to duration of treatment and follow-up</td>
<td>Basic science: [91]</td>
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<tr>
<td></td>
<td>Flow remains similar to pretreatment</td>
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<td></td>
<td>May use in conjunction with alpha-blockers to modulate several proposed pathophysiological targets</td>
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<td><strong>Priapism</strong></td>
<td>Alleviate recurrent priapism without interfering with normal erectile function</td>
<td>Primarily animal study evidence</td>
<td>Clinical: [59–61,95]</td>
</tr>
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<td></td>
<td>Scientific basis for PDE5-I mechanism of action</td>
<td>Limited, although promising clinical reports</td>
<td>Basic science: [60,61,96]</td>
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<td></td>
<td></td>
<td>Further investigation (controlled trials) needed to validate and fully characterise PDE5-I therapeutic effect</td>
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<tr>
<td><strong>Premature ejaculation</strong></td>
<td>Improvement of overall sexual function</td>
<td>Role of PDE5-Is unclear</td>
<td>Clinical: [97–101,103]</td>
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<td></td>
<td>Prolong intravaginal ejaculation latency time</td>
<td>Conflicting data</td>
<td>Basic science: [102]</td>
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<tr>
<td></td>
<td>May be more efficacious in combination with SSRI (example paroxetine) and psychological-behavioural counselling</td>
<td>Little to support on-demand or daily PDE5-Is for lifelong PE and normal erectile function</td>
<td></td>
</tr>
<tr>
<td><strong>Peyronie’s disease</strong></td>
<td>Reversal of plaque or fibrosis</td>
<td>Data limited to animal study of Peyronie’s disease-like plaques</td>
<td>Basic science: [104]</td>
</tr>
<tr>
<td><strong>Pulmonary hypertension</strong></td>
<td>PDE5-Is approved for clinical use</td>
<td>Long-term efficacy and safety data continue to be accrued</td>
<td>Clinical: [19,74–76,79,105–112,115–118]</td>
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<td></td>
<td>Well-designed, large-scale clinical trials demonstrating treatment effect</td>
<td>Early COPD and secondary PH data only</td>
<td>Basic science: [33,113–114]</td>
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<td></td>
<td>Improvements in functional pulmonary arterial hypertension parameters, haemodynamics, and exercise capacity</td>
<td>Agent-specific characteristics required each PDE5-1 to be evaluated separately</td>
<td></td>
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<tr>
<td></td>
<td>Evolving data suggests PDE5-1 role for COPD and secondary pulmonary hypertension</td>
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<tr>
<td><strong>Systemic hypertension</strong></td>
<td>Known vasodilators</td>
<td>Limited randomized, placebo-controlled, double-blind data available</td>
<td>Clinical: [119,64,120,121,122,143,144]</td>
</tr>
<tr>
<td></td>
<td>Single-agent or combination therapy</td>
<td></td>
<td>Basic science: [123–124]</td>
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<td></td>
<td>Role may also be defined for renal injury-induced hypertension</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cardioprotection and endothelial function</strong></td>
<td>Potential reduction of morbidity and mortality of ischaemia-reperfusion injury</td>
<td>Limited primarily to animal evidence and early human study</td>
<td>Clinical: [28,31,32,58,62,115,125,132–134]</td>
</tr>
</tbody>
</table>
cure, pleasure, partner satisfaction, naturalness, and reliability—may not be fulfilled by on-demand dosing because sexual activity is linked to drug administration [7,8].

The concept of daily dosing or chronic administration was introduced in an effort to provide a treatment alternative for nonresponders to on-demand PDE5-Is and to more closely approximate “natural” erectile function [7,9–12]. These PDE5-I schedules have also been investigated for other urological and nonurological indications including pulmonary and systemic hypertension, cardioprotection, and endothelial dysfunction (Fig. 1). In this review, we synthesized the available literature to provide a critical contemporary view of evolving indications for PDE5-Is and how alternative dosing regimens may impact on sexual and other functions (Table 1).

2. Methods

MEDLINE search of all peer-reviewed English literature for 1990–2007 was performed for search terms phosphodiesterase inhibitors, sildenafil, vardenafil, and tadalafil. Critical analysis of the existing literature on PDE5-Is with alternative dosing and uses was performed; all reports were included in the review with emphasis on methodologically sound articles determined to be most clinically meaningful.

3. Results—erectile dysfunction

3.1. Daily dosing of PDE5 inhibitors for erectile dysfunction

Mirone et al [13] reported the first comparative trial of alternative dosing, investigating treatment efficacy and patient preference for 20-mg tadalafil taken on-demand versus 3 times per week, over a 6-wk study period. This study demonstrated that 42.2% of men preferred scheduled dosing versus 57.8% for on-demand; both treatment regimens were well tolerated and efficacious.

More recent studies have demonstrated that chronic dosing may be advantageous versus on-demand regimens, offering a valuable treatment option for ED. McMahon [10] reported upon the efficacy, safety, and tolerability of on-demand 20-mg versus daily dosed 10-mg tadalafil in 145 men with mild to severe ED of various etiologies. Primary outcome measures included changes from baseline in the erectile function domain of the International Index of Erectile Function (IIEF) and the proportion of “yes” responses to questions 2 (successful penetration) and 3 (successful completion of intercourse) of the Sexual Encounter Profile (SEP), in addition to a Global Assessment Question (GAQ) administered at completion of this 26-wk study. Patients receiving on-demand and daily tadalafil experienced a significant

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Potential benefits</th>
<th>Limitations</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Decreased microalbuminuria</td>
<td>Significance and mechanism of decreased microalbuminuria yet to be determined</td>
<td>Basic science: [138]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Decreased type-2 diabetic morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Modulate temperature-sensitive digital vasospasm</td>
<td>Limited clinical data</td>
<td>Clinical: [139]</td>
</tr>
<tr>
<td></td>
<td>Small, well-designed clinical trial supports decreased frequency and shorter duration of effects</td>
<td>Mechanism of PDE5-I incompletely understood</td>
<td></td>
</tr>
<tr>
<td>Altitude sickness</td>
<td>Treatment and prevention of high-altitude pulmonary oedema</td>
<td>Limited clinical data</td>
<td>Clinical: [140–142]</td>
</tr>
<tr>
<td></td>
<td>Prevent rapid progression to death</td>
<td>Extended daily-use trials not performed to date</td>
<td></td>
</tr>
</tbody>
</table>

PDE5-I, phosphodiesterase type 5 inhibitor; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; SSRI, selective serotonin reuptake inhibitor; PE, premature ejaculation; COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension.
mean improvement of 8.3 and 11.9 points in the IIEF, respectively ($p < 0.001$), with daily-dose mean changes significantly higher versus on-demand tadalafil ($p < 0.05$). SEP3 was answered “yes” in 69% and 84% of patients in on-demand and daily tadalafil groups, respectively, compared with 30% at baseline ($p < 0.001$). Successful completion of sexual intercourse was also statistically higher for daily tadalafil than for on-demand tadalafil ($p < 0.05$), with both treatments well tolerated. On the basis of these results, McMahon concluded that treatment with daily tadalafil was associated with a significantly higher IIEF erectile function domain score and completion of successful intercourse compared with on-demand tadalafil.

Porst et al [7] reported a randomised, double-blind, placebo-controlled, parallel-group, 12-wk daily-dose study consisting of 268 men. Groups were divided 1:2:2 to placebo, tadalafil 5 mg, and tadalafil 10 mg taken once daily in this study with primary outcome measures of changes in the IIEF erectile function domain (IIEF-EF), Sexual Encounter Profile diary questions 2 (SEP2, successful penetration) and 3 (SEP3, successful completion of intercourse), and treatment tolerability. Patients in placebo and tadalafil 5 mg or 10 mg groups reported score changes of 0.9, 9.7, and 9.4 for the IIEF-EF, successful penetration for 11.2%, 36.5%, and 39.4% of intercourse attempts, and completion rates of and 13.2%, 45.5%, and 50.1%, respectively. At the conclusion of the study, 28.3%, 84.5%, and 84.6%, respectively, reported improved erections, whereas 8.3%, 51.5%, and 50.5% demonstrated “no ED” (defined as IIEF 26–30), respectively. All comparisons between tadalafil and placebo were significant ($p < 0.001$). Adverse events included dyspepsia, headache, back pain, upper abdominal pain, and myalgia; however, only 8 treated patients discontinued because of adverse events.

Recently, Buvat et al [14] presented data from a randomised, double-blind, placebo-controlled, 12-wk study of 268 men assigned to once-a-day placebo, or 5 mg or 10 mg tadalafil; those treated with once-daily tadalafil were more satisfied with the hardness of their erections (SEP 4) and overall sexual experience (SEP 5) versus men receiving placebo.

These studies support previously published data by Olsson et al [11] assessing the efficacy and tolerability of sildenafil for treating ED of psychogenic and mixed psychogenic/organic etiology. Patients were randomised in a double-blind, fixed-dose manner to placebo ($n = 95$) or sildenafil 10 mg ($n = 90$), 25 mg ($n = 85$), or 50 mg ($n = 81$) once daily for 28 d. Patients receiving sildenafil had significantly more grade 3 (rigidity sufficient for penetration) or grade 4 (fully rigid) erections per week than patients receiving placebo ($p < 0.001$). Patients treated with sildenafil noted significant improvements compared with placebo for frequency, hardness, and duration of erections ($p < 0.01$), satisfaction ($p < 0.05$), and significant improvement in the partners’ own sex lives ($p < 0.001$). Adverse events were mostly mild to moderate in nature. The most common adverse events were headache, dyspepsia, flushing, myalgia, arthralgia, and flu syndrome. Discontinuations due to treatment-related adverse events, most commonly headache, dyspepsia, flushing, and myalgia, ranged from 1.1% to 6.2% for sildenafil and 4.2% for placebo.

3.2. **Salvaging nonresponders to on-demand PDE5-I therapy**

Currently, 30–35% of patients fail to respond or are dissatisfied with treatment; as a consequence of inadequate patient education, incorrect PDE5-I usage, unrecognised hypogonadism, severity of ED at presentation, and psychosocial factors [15,16]. PDE5-I salvage strategies include patient education, lifestyle changes, correction of modifiable risk factors, dose adjustment or switch of PDE5-I agents, androgen replacement, psychosexual or relationship counseling, and progression to second- or third-line treatment options [17].

McMahon [9] has reported results for efficacy and safety of daily tadalafil in 112 men with moderate to severe ED previously unresponsive to on-demand tadalafil. Compared with pretreatment and on-demand scores, 10-mg daily dosing resulted in a mean improvement of 12.8 and 8.2 from respective IIEF baseline scores ($p < 0.001$), and 58% of intercourse attempts (SEP 3) were successfully completed ($p < 0.001$). Improved erections were reported by 69% of men compared with 42% of men using on-demand tadalafil. Daily tadalafil proved an effective salvage strategy for previous nonresponders.

Hatzimouratidis et al [18] investigated the efficacy of 20-mg vardenafil daily, as well as tadalafil 20 mg every other day, over a 2-wk period, in a group of PDE5-I nonresponders [18]; 18.2% and 11.1%, respectively, converted to responders. No side-effect or safety issues were identified for this, or the previously discussed McMahon [10] and Porst et al [7] studies. Continuous dosing of PDE5-Is has been shown to significantly improve treatment outcome measures; although data on the systemic effects of prolonged continuous administration for the three PDE5-Is is limited primarily to clinical trials of sildenafil for pulmonary hypertension [19], chronic therapy is well tolerated and thought to improve
various aspects of endothelial and haemodynamic function [20].

3.3. **Mechanisms for treatment effects of once-daily PDE5-I dosing**

On the basis of currently available evidence, it is possible that endothelial dysfunction and systemic cardiovascular pathology are modulated by chronic PDE5-I use, resulting in improved erectile function owing to effects upon both local and systemic targets [6]. Endothelium-dependent cavernosal responses were potentiated by an 8-wk course of subcutaneous sildenafil (60 mg/kg) given daily [21]. In this study, Behr-Roussel et al concluded that chronic sildenafil may regulate the transduction pathway, leading to the activation of endothelial nitric oxide synthase (eNOS), but has no effect on nitric oxide (NO) bioavailability or on the cyclic guanosine monophosphate (cGMP) pathway; therefore, they eliminated tachyphylaxis as an unwanted byproduct of prolonged PDE5-I exposure. Long-term continuous sildenafil (20 mg/kg for 45 d) in aged rats, as reported by Ferrini et al [22], facilitated reversal of aging-related cavernosal fibrosis, prevented loss of corporal smooth muscle, and stimulated nitric oxide synthase-2A. Chronic sildenafil treatment (20 mg/kg) for 3 wk showed greater improvement for rats with impaired baseline erectile function (aged) versus young healthy rats [23]. This phenomenon was further investigated by Musicki et al [24], who concluded that, under preconditions of erectile impairment, long-term PDE-1 augments erectile function through Akt-dependent eNOS phosphorylation. Furthermore, it was observed that the lack of erectile enhancement in young rats by long-term PED5 inhibition might relate to restrained NO signalling by PDE5 upregulation, lack of incremental Akt and eNOS phosphorylation, and heightened Rho-kinase signalling in the penis.

PDE5-Is have also been shown to confer favourable effects upon systemic endothelial dysfunction, which is clearly associated with ED [25–27]. Cardiovascular risk factors such as hypertension, diabetes, smoking, dyslipidaemia, and the metabolic syndrome can cause endothelial damage, leading to impaired NO release or increased endothelial “stickiness,” which often leads to progressive atherosclerosis. Rosano et al [28] demonstrated improved endothelial function in men with increased cardiovascular risk using chronic tadalafil treatment. In this study of 32 men, flow-mediated dilation (FMD) of the brachial artery, nitrate/nitrite ratios, and endothelin-1 (vasoconstrictor) responded positively to PDE5-I treatment. Halcox et al [29] reported sildenafil use improved epicardial coronary artery dilation, lessened endothelial dysfunction, and inhibited platelet activation in men with various vascular risk factors, whereas Vlachopoulos et al [30] demonstrated abrogation of smoking-induced acute decreases in FMD of the brachial artery. These studies provide the experimental support for the chronic administration of PDE5-I [31–33]. Mechanistic studies also suggest that PDE5-Is may exert endothelial and cardioprotective effects via activation of protein kinase C/ERK signalling, opening of mitochondrial adenosine triphosphate–sensitive potassium channels, or modulation of the hormonal milieu [34–36].

3.4. **Difficult to treat populations: diabetes**

As early as 1998, Price et al [12] described daily use of sildenafil for ED in diabetic men. Twenty-one men were enrolled in a double-blind, placebo-controlled, three-way crossover study; daily diary records of erectile activity and a global efficacy question were used to evaluate once-daily dosing versus placebo for 10 d. Sildenafil increased the number of erections considered sufficiently rigid for vaginal penetration compared with placebo ($p = 0.0005$); 50% and 52% of patients treated with 25 and 50 mg of sildenafil reported improved erection quality compared with 10% of those receiving placebo ($p < 0.05$). Several lines of basic research support the use of chronic PDE5-Is in diabetics. PDE5-I administration attenuated the development of ED in diabetic rats, in association with improved endothelial function as measured by thoracic aorta relaxation in vitro and measurement of plasma endothelin-1 levels [37]. Oral sildenafil (5 mg/kg) given daily for 3 wk to streptozotocin-induced diabetic rats preserved both penile expression of neuronal NOS and erections compared with controls [38]. Other proposed mechanisms of action include antioxidant activities, upregulation of diminished central NO effects, enhanced vasodilation response, and prevention of diabetes-induced tissue damage [39–42].

In humans, Desouza et al [43] reported the acute and prolonged effects of sildenafil on brachial artery FMD, an index of NO-dependent endothelial function that is impaired in patients with type 2 diabetes. In this double-blind, placebo-controlled crossover trial in 16 patients, treatment with sildenafil 25 mg daily for 2 wk and testing 24 h after the final dose resulted in a mean FMD increase of 14% ($p = 0.01$). Subsequently, improvements in FMD were also demonstrated for tadalafil 20 mg taken every other day [29]. Although endothelium-dependent FMD improved in both studies, further investigations
are required to determine the clinical implications of this measure for patients with type 2 diabetes.

### 3.5. Difficult to treat populations: post-RRP

Despite advances in operative technique, erectile function is frequently compromised in men undergoing RRP for prostate cancer [6]. Injury to the neurovascular bundle initiates progressive corporal smooth muscle apoptosis and increased fibrosis, inducing veno-occlusive dysfunction. The landmark report by Montorsi et al [44] demonstrated that early ED treatment helps preserve erectile function following RRP. Several studies have been performed in an effort to define the role of PDE5-Is as a part of a penile rehabilitation program [45–49]; as evidenced by the number of ongoing trials, clinical data about potential mechanisms and patient outcomes for chronic use in this patient group remain incomplete [50]. Further data are also required to define which role, if any, daily PDE5-Is may have in men undergoing non–nerve-sparing procedures.

Despite the limitations of available data, evidence suggests that daily use of a PDE5-I merits careful consideration. Schwartz et al [51] reported on 40 volunteers who had undergone RRP and were treated with every-other-day sildenafil for 6 mo; after the treatment period, cavernosal biopsy demonstrated smooth muscle preservation at 50 mg, and decreased levels of fibrosis and substantially increased smooth muscle content at 100 mg doses [51]. Up to 6-fold increases in the return of spontaneous erections for men treated with nightly sildenafil versus placebo have also been reported [52].

Animal studies provide further support for daily PDE5-I therapy in this group of patients. Vignozzi et al [53] recently reported their findings of protection against cavernous tissue protein and messenger RNA (mRNA) changes, and preservation of PDE5 expression and tadalafil efficacy after a 3-mo treatment course of daily tadalafil (2 mg/kg) following bilateral cavernous neurotomy in the rat. Using a similar rat model, Ferrini et al [54] demonstrated that long-term vardenafil may prevent veno-occlusive dysfunction after RRP by preserving smooth muscle content and inhibiting corporal fibrosis, possibly by an effect on inducible NOS (iNOS), as evidenced by increased iNOS and proliferating cell nuclear antigen expression (smooth muscle cell replication), with functional normalisation of the dynamic infusion cavernosometry drop rate and smooth muscle-to-collagen ratio. Daily-use sildenafil has also demonstrated the ability to protect against structural changes secondary to cavernous nerve injury and to preserve erectile function in the rat [55].

### 3.6. Disease modification

The unique mechanisms of action for PDE5-Is and their varied pharmacological properties have encouraged investigation for potential “disease modification” or “cure” via chronic therapy [56].

Sighinolfi et al [57] observed an extended response to chronic PDE5-I treatment using sildenafil for up to 20 mo; peak systolic velocity before and after treatment were compared, demonstrating a 10.5% improvement (p < 0.001). Modulation of the NO signalling pathways is proposed as the primary mechanism for these effects. Carreta et al [58] demonstrated that chronic and non–on-demand treatment with tadalafil induced spontaneous resumption of erections, likely through improvement of endothelial function. Although promising, evidence-based data are limited and direct evidence to confirm these hypotheses is required.

Potential nonurological targets for disease modification with chronic PDE5-I therapy include endothelial dysfunction, pulmonary and essential hypertension, and cardioprotection against ischaemia-reperfusion injury or drug-induced toxicity [19,28,62–64].

### 3.7. Tachyphylaxis

PDE5 gene expression in the penis may be modulated by influences including PDE5-regulated NO/cGMP molecular signalling and the androgen milieu [61,65–68]. Although it has been suggested that tachyphylaxis may occur with extended use, this hypothesis remains unproven on the basis of existing clinical trial data [50,68].

Daily dose PDE5-I therapy and excessive cGMP accumulation may upregulate PDE5 expression [69,70]. The clinical sequelae of tachyphylaxis secondary to these mechanisms should include increased dosage requirements for efficacy. However, a review of more than 1000 men using sildenafil for ED demonstrated low tachyphylaxis potential and dropout rates; subsequent studies have corroborated these findings [9,71]. Nonurological applications for daily PDE5-I use have also reported longer-term (up to 20 mo) satisfactory safety, efficacy, and tolerability data [27,57,72–75]. Several animal studies have shown no evidence of tachyphylaxis [21,67,76–78].

### 3.8. Potential barriers to the treatment of ED with daily dosing

Patient cost represents the primary barrier to treatment using an every-day dosing schedule [50].
Unlike pulmonary hypertension, for which sildenafil may provide a net cost savings compared with inhaled or intravenous medications [79], daily PDE5-I use may be limited by high costs, given the average intercourse frequency of five to six times per month [6]. Should lower-dose daily administration provide attractive efficacy and safety profiles compared with on-demand use, and equivalent net monthly cost approach, chronic PDE5-I use may become an important treatment option [50].

4. Results—other urological conditions

4.1. Lower urinary tract symptoms

The proposed links between lower urinary tract symptoms (LUTS) and ED include changes in the NOS and cGMP pathways in the prostate and penis, Rho-kinase activation, endothelin pathway modulation, autonomic hyperactivity and changes secondary to pelvic atherosclerosis [80–84]. Further, the rationale for further study of potential PDE5-I treatment for BPH and LUTS is underpinned by the presence of PDE5 isoenzymes in the transition zone of the human prostate, along with PDE4 and PDE11, and the roles of cGMP and cAMP as controls of prostate physiology as reported by Sairam et al, demonstrating improved International Prostate Symptom Score (IPSS) and sexual function scores after treatment with sildenafil [85,86].

Data demonstrating efficacy of PDE5-I use in men with LUTS with and without accompanying ED shows promise. In a study of 48 men with on-demand sildenafil, Mulhall et al [87] reported 60% improved their IPSS score, with 35% demonstrating at least a 4-point improvement. Subsequently, McVary et al [88] assessed the safety and efficacy of tadalafil dosed once daily (5 mg initially, dose escalation to 20 mg) in 281 men for the treatment of LUTS; in this double-blind, placebo-controlled study, IPSS decreased 7.1 for tadalafil versus 4.5 for placebo. In a double-blind, randomised, placebo-controlled study [89] of 369 men, once-daily dosing of 50 and 100 mg sildenafil was shown to improve IPSS scores by 6.32 (vs. 1.93 placebo; p < 0.0001) and resulted in a 71.2% treatment satisfaction rate compared with 41.7% for placebo (p < 0.0001).

No change in flow rate was measured in these studies, potentially indicating a new, as yet unidentified, pathophysiological mechanism not involving prostatic smooth muscle relaxation [87–89]. Filippi et al [90] have reported on PDE5 expression and activity in the human bladder and PDE5-I effects both in vitro and in vivo. Sildenafil, tadalafil, and vardenafil blocked 70% of the total cGMP catabolising activity in the bladder. Results demonstrated that PDE5-Is regulate bladder smooth muscle tone and strongly limit NO/cGMP signalling, providing a possible therapeutic option for bladder dysfunction targeting irritative LUTS. Tinel et al [91] also tested PDE5-Is in this capacity using organ-bath experiments and a partial bladder outlet obstruction rat model in vivo. They identified PDE5 mRNA expression in the bladder, followed by the urethra and prostate, confirming expression in tissues generally held responsible for LUTS. PDE5-Is also induced significant relaxation of these tissues, inhibited the proliferation of human prostate stromal cells, and reduced the irritative symptoms of BPH/LUTS in vivo.

Combination therapy consisting of daily 25-mg sildenafil and 10-mg alfuzosin has been reported by Kaplan et al [80]. Patients were randomised to either agent alone, or combined, in this 12-wk, open-label, randomised, single-centre study; PDE5-I alone resulted in a 16.9% decrease in IPSS score (compared with 15.6% and 24.1% for alfuzosin and combination treatments, respectively).

4.2. Priapism, premature ejaculation, and Peyronie’s disease

4.2.1. Priapism

An increased understanding of the pathological mechanisms responsible for ischemic priapism has identified PDE5-Is as possible modulatory agents for underlying penile smooth muscle PDE dysregulation [59–61]. Current guidelines emphasise the use of established clinical interventions for presentations of high-risk episodes (greater than 4 h); reactive management is usually successful in the acute setting, but does not prevent further episodes [4,92]. However, the opportunity for chronic PDE5-I therapy exists for men who are known to have prodromal symptoms in the form of short-lived attacks, also known as stuttering priapism, which often heralds subsequent major and possibly permanently debilitating episodes [93,94].

Applied daily in a manner not associated with stimulatory conditions, PDE5-Is have been shown to alleviate recurrent priapism without interfering with normal erectile function [95]. Burnett et al [61] have further reported their experience for seven patients with repeated episodes of prolonged erections not associated with sexual stimulation, and noted that daily doses of 25 to 50 mg, as well as tadalafl 10 mg every other day, resulted in safe, efficacious, and tolerable control of priapism (patients followed up to 24 mo). PDE5-Is used in a...
long-term, continuous fashion cause a heightened basal amount of cGMP in the penis, which progressively re-establishes normal PDE5 expression and activity, and counters the altered NO signalling responsible for priapism [96]. Further investigation in the form of controlled trials is needed to validate and fully characterise PDE5-I therapeutic profiles in this context.

4.2.2. Premature ejaculation

Available studies provide conflicting data regarding the role of PDE5-Is for the treatment of premature ejaculation (PE). Sildenafil, in combination with paroxetine, prolongs intravaginal ejaculation latency time (IELT) and, when combined with paroxetine and psychological-behavioural counseling, has shown some effectiveness in nonresponders to other treatments [97,98]. However, others have demonstrated an absence of superiority compared with placebo or combination treatment with topical anesthetics [99].

The proposed mechanism for PDE5-I modulation of PE pathophysiology focuses on both central and peripheral inhibition of vas deferens, seminal vesicle, prostate, and urethral contractions [50, 100–102]. However, there is no convincing evidence at this time to support on-demand or daily PDE5-Is in the treatment of men with lifelong PE and normal erectile function. Further well-designed controlled studies are required, especially with daily or on-demand selective serotonin reuptake inhibitors, which have previously shown promise in this group of patients [103].

4.2.3. Peyronie's disease

Vardenafil has been shown to slow and reverse the early stages of a Peyronie's disease (PD)-like plaque in the rat, with some amelioration of more advanced plaques [104]. In this study reported by Ferrini et al, 45 cumulative days of once-daily (1 and 3 mg/kg) treatment resulted in reduced collagen/smooth muscle and collagen III/I ratios, and myofibroblasts and tumour growth factor-beta1-positive cells, and selectively increased the apoptotic index in the PD-like plaque. However, no clinical data for this application are available at this time.

5. Results—nonurological indications

5.1. Pulmonary hypertension

The use of extended, daily-dose PDE5-Is for the treatment of various forms of pulmonary hypertension (PH), including primary arterial hypertension (PAH), chronic thromboembolic PH, and portal-pulmonary hypertension, has gained rapid acceptance in clinical practice owing to safety, therapeutic efficacy, and cost-effectiveness [79,105–112].

The major source of NO production in lung is eNOS, which is located in the vascular endothelium and the airway epithelium [113,114]. Rossi et al [115] reported sildenafil effects on pulmonary and endothelial function, demonstrating significant reductions of mean pulmonary artery pressure and arteriolar resistances, as well as improved endothelial-dependent vasodilation and reduced plasma concentrations of endothelin-1.

Sildenafil is currently licensed for the treatment of pulmonary arterial hypertension, having demonstrated improvements in World Health Organization functional PAH parameters, haemodynamics, and exercise capacity in landmark studies [105]; vardenafil and tadalafil have also shown sustained pulmonary vasodilation and satisfactory safety profiles in early trials [106,116]. PDE5-I agent-specific characteristics have also been shown. For example, although vardenafil demonstrated most rapid onset of effect, selectivity for pulmonary circulation was not seen as for sildenafil and tadalafil, whereas improved arterial oxygenation has been observed only for sildenafil to date [116].

Encouraging initial data have also been reported for PDE5-I treatment of chronic obstructive pulmonary disease and secondary pulmonary hypertension due to chronic heart failure in patients undergoing cardiac transplantation [117,118].

5.2. Systemic hypertension

PDE5-Is are known vasodilators and may offer therapeutic potential as a treatment of essential hypertension and blood pressure (BP) [119,64]. Oliver et al reported the first randomised, double-blind, study of a PDE5-I for this purpose, showing a reduction in BP similar to that of other antihypertensives [120,121]. These results correspond to previously reported class effects of PDE5-Is on BP, namely that decreases in arterial pressure average 9/8 mm Hg (systolic and diastolic, respectively) at rest [122]. Early animal evidence also provides insight into chronic hypertension induced by renal injury, as deficient NO production and activity were evidenced by downregulation of endothelial, neuronal, and inducible NOS, and soluble guanylate cyclase in the injured kidney of the rat [122]. Given that PDE5 is the dominant isoform in the kidney, Bai et al [123] concluded that PDE5-Is might serve as a potential modulator of secondary renal sympathetic activation.
5.3. Cardioprotection and endothelial function

Myocardial ischaemia-reperfusion injury contributes significantly to morbidity and mortality [124]. PDE5-Is have shown great promise in animal studies as a possible cardioprotective pharmacological agent via several potential pathways; cardioprotection may occur through NO generated from eNOS/iNOS, activation of protein kinase C/ERK or protein kinase G signalling, opening of mitochondrial ATP-sensitive potassium channels, attenuation of cell death resulting from necrosis and apoptosis, and increased Bcl2/Bax ratios through NO signalling in adult cardiomyocytes [34,62,125–126]. Sildenafil, vardenafil, and tadalafil have all demonstrated decreased infarct size after ischaemia-reperfusion in animal models, providing overwhelming evidence for cardioprotective effects [32,126–135]. Gori et al [131] have also reported human in vivo results for 10 healthy male volunteers, confirming the ability of oral sildenafil to induce potent protection against ischaemia- and reperfusion-induced endothelial dysfunction via opening of K\textsubscript{ATP} channels [131]. Chronic PDE5-Is have been shown to increase endothelium-dependent flow-mediated vasodilation in chronic heart failure and to improve endothelium function in at-risk cardiac patients and among those with altered endothelial function [27,28,132–134]. Forresta et al [135] demonstrated that chronic tadalafil and vardenafil improve endothelial function and increase the number of circulating endothelial progenitor cells (EPCs). EPCs are thought to contribute to endothelial repair and neovascular repair, and increased levels are associated with lowered risk for cardiac death [136,137]. Altogether, daily use of PDE5-Is for cardioprotection and modulation of endothelial dysfunction is supported by animal and early clinical data; eventual clinical use of these agents may represent a significant advance in cardiovascular medicine should pivotal trials establish an expanded PDE5-I role in cardiac health.

5.4. Other indications

5.4.1. Diabetes

There is currently little data available on the effects of long-term PDE5-I use in patients with type-2 diabetes. However, Grover-Paez et al [138] reported that sildenafil taken daily (50 mg) for 30 d diminished microalbuminuria.

5.4.2. Raynaud’s phenomenon

The effects of PDE5-Is on temperature-sensitive digital vasospasms, known as Raynaud’s phenomenon, was recently reported by Fries et al [139] who demonstrated decreased frequency and shorter duration of attacks coupled with a 4-fold increase in mean capillary flow velocity in this double-blind, placebo-controlled, fixed-dose (sildenafil 50 mg twice daily) crossover study over 4 wk.

5.4.3. Altitude sickness

Early data suggests that PDE5-Is may have a role in the treatment and prevention of high altitude pulmonary edema, a devastating illness at high altitudes that is characterised by a rapid progression to death [140–142]. Extended, daily-use PDE5-Is trials in this cohort have not been performed to date.

6. Safety of daily PDE-5 inhibitor use

Although the safety of this class of agents has been indisputably established for the treatment of ED on an on-demand basis, there remains a paucity of data on the long-term effects of chronic PDE5-I use. Studies that are available for extended use indicate maintained treatment benefit (no tachyphylaxis) with minimal, well-tolerated side-effects as described previously in this review [79,105–110]. Randomised, placebo-controlled assessment of daily tadalafil for 26 wk did not demonstrate meaningful differences in systolic and diastolic BP between groups, suggesting no significant deterioration after chronic use [143]. Co-administration with selective α\textsubscript{1}-adrenergic blockers is safe, as long as directions for the use of both medications are followed [144–148]. The influence of daily administration of PDE5-Is on the occurrence of rare adverse events, such as nonarteritic ischaemic optic neuropathy, remains to be elucidated [149]. The patient should be informed of commonly anticipated side-effects, such as flushing, headache, congestion, and so forth, as well as the current gap in a complete understanding of the potential ramifications of extended-term daily PDE5-I use.

Cardiac safety for PDE5-Is has been clearly established [150]. Although all three approved PDE5-Is are contraindicated in men using or requiring nitrates for cardiovascular disease, the concern about daily PDE5-I use always raises concern about co-administration in cases of cardiac emergency. Based on nearly 10 yr of clinical experience among thousands of men with ED and cardiovascular risk factors, a cardiac event should be managed at all times in an appropriate environment with little concern related to long- or short-acting PDE5-Is.
7. Conclusions

The use of daily dosing of PDE5-I may prove to be highly significant, given the emerging data on endothelial function, LUTS, smooth preservation, general vascular health, and its potential to salvage erectile function in populations of men not responding to on-demand PDE5-I. Cost and tolerability may limit its widespread early application among large groups of individuals until and unless these added values can be conclusively demonstrated.

Among the cohorts of men most likely to benefit from this approach are those who have both ED and LUTS. In this large subset of men aged 40 years or older, the ability to relieve two dysfunctions that significantly impact their quality of life may prove to be too attractive to ignore. At present, despite a rapidly growing cache of reports indicating the potential of PDE5-Is, well-designed large prospective studies producing robust data are needed prior to this approach becoming a standard of care.

Conflicts of interest

Gerald B. Brock: Consultant/advisor, meeting participant/lecturer, and owns stock in Pfizer, Lilly, Bayer, GlaxoSmithKline, and Schering.

Anthony J. Bella: Consultant/advisor and meeting participant/lecturer; Pfizer Inc, Eli Lilly Inc, and American Medical Systems.

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