Useful Implications of Low-dose Long-term Use of PDE-5 Inhibitors

Taymour Mostafa, MD

ABSTRACT

Introduction: Phosphodiesterase type 5 (PDE-5) hydrolyzes cyclic guanylate monophosphate (cGMP) specifically to 5’ GMP, promoting successful corporeal vascular relaxation and penile erection during sexual stimulation. Oral PDE-5 inhibitors such as sildenafil, vardenafil, tadalafil, and avanafil have provided noninvasive, effective, well-tolerated treatment for erectile dysfunction (ED) patients and, at the same time, stimulated both academic and clinical interests. Lately, some oral PDE-5 inhibitors were released as low-dose preparations with the concept of potential daily administration and long-term use.

Aim: To highlight the possible potential implications of low-dose long-term use of PDE-5 inhibitors.

Method: A systematic review was carried out until December 2015 based on a search of all concerned articles in MEDLINE, medical subjects heading (MeSH) databases, Scopus, The Cochrane Library, EMBASE, and CINAHL databases without language restriction. Key words used to assess the outcome and estimates for concerned associations were: PDE-5 inhibitors; erectile dysfunction; low-dose; long-term; sildenafil; tadalafil; vardenafil; avanafil.

Main Outcome Measures: Demonstrating different implications for low-dose long-term use of PDE-5 inhibitors.

Results: Low-dose and/or long-term use of PDE-5 inhibitors was shown to put forth beneficial sound effects in different medical implications with potentials that could be extended for different utilities. These implications included sexual, urogenital, cardiovascular, pulmonary, cutaneous, gastrointestinal, and reproductive, as well as neurological disorders. However, it is evident that most potential appliances were carried out experimentally on preclinical studies with off-label indications.

Conclusion: Making use of and exploring low-dose and/or long-term use of several PDE-5 inhibitors for their possible implications seem to be valuable in different medical disorders. Increased knowledge of the drug characteristics, comparative treatment regimens, optimal prescribing patterns, and well-designed clinical trials are needed before these agents can be recommended for use.

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Key Words: PDE-5 Inhibitors; Erectile Dysfunction; Low-Dose; Chronic Use; Sildenafil; Tadalafil; Vardenafil; Avanafil

INTRODUCTION

As the first-line treatment for erectile dysfunction (ED), oral phosphodiesterase type 5 inhibitors (PDE-5Is) are used worldwide with confirmed efficacy, tolerability, and couple satisfaction.1–3 Eleven groups of PDE isoenzymes were identified that can be grouped into 3 categories based on their substrate specificity. PDE-4, PDE-7, and PDE-8 selectively hydrolyze cAMP, whereas PDE-5, PDE-6, and PDE-9 hydrolyze cyclic guanosine monophosphate (cGMP). PDE-1, PDE-2, PDE-3, PDE-10, and PDE-11 possess dual specificity, acting on both cyclic adenosine monophosphate (cAMP) and cGMP.4,5

Specifically, PDE-5 hydrolyzes cGMP to 5’ GMP. This PDE family consists of a single PDE5 gene with 3 alternatively spliced PDE-5 isoforms (PDE-5A1, -5A2, and -5A3), differing only in the 5’ ends of their corresponding mRNAs and N-terminals. PDE-5, which specifically degrades cGMP, is relatively highly expressed in the corpus cavernosum. Thus, PDE-5Is, by blocking cGMP hydrolysis, potentiate the effects of cGMP, resulting in decreased intracellular calcium that leads to penile smooth muscle relaxation, vasodilatation with increased penile blood flow and erection.6–8

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Currently, 4 orally effective PDE-5Is are approved by the US Food and Drug Administration (sildenafil, vardenafil, tadalafil, and avanafil), whereas others are under clinical development (Table 1, Figure 1).

Sildenafil was the first, being released at 1998. It reaches its maximal concentration in the plasma ($T_{\text{max}}$) at 60 minutes on empty stomach with a duration of action of 4–6 hours.

Vardenafil was approved at 2003 with $T_{\text{max}}$ of 60 minutes on empty stomach with a duration of action extending up to 7 hours. It has also an oral-dispersible tablet (ODT) formula that dissolves in the mouth in seconds. Lately, vardenafil incorporated into a nano-sized lipid vesicular matrix as a transdermal film was thought to avoid first-pass metabolism in the liver, to decrease the erectogenic dose and to reduce adverse effects.

Tadalafil was released at 2003 with $T_{\text{max}}$ of 120 minutes and characterized with longer duration of action, reaching up to 36 hours and not being affected with food.

Avanafil was approved in 2012. It is formulated as self-nanoemulsifying drug delivery system, reaching $T_{\text{max}}$ within 30 to 45 minutes on an empty stomach and 1.25 hrs if a high-fat meal was ingested. Successful sexual attempts were established as early as 10 minutes, making it preferable for ED patients with multiple comorbidities.

PDE-5Is’ extensive achievement in treating ED has led to increased interest in investigating their effects as potential therapeutic agents in diverse medical conditions apart from their famed erectogenic action. This spectrum includes cardiotonics, vasodilators, smooth muscle relaxants, antidepressants, antiarrhythmics, antiasthmatics, and agents for improving learning and memory, etc.

Lately, the concept of low-dose use of PDE-5Is was introduced first for treating ED as an extra administration option closer to the couples preference for spontaneous rather than planned sexual activity. In this context, accumulated data indicated that low-dose use of PDE-5Is or their long-term use could provide additional potential benefits and/or improved treatment responses in diverse medical implications (Table 2).

### SEXUAL IMPLICATIONS

#### 1. ED

Several studies demonstrated that low-dose tadalafil, once daily, is both effective and well tolerated compared with on-demand use. It allows the patients and their partners to disconnect its administration from sexual activity, thereby enabling them to return to the sex life they had before the onset of ED. Wrishko et al predicted that 5 mg tadalafil once daily maintained therapeutic concentrations throughout the 24-hour dosing interval based on pharmacodynamic and pharmacokinetic data.

In this context, McMahon reported on daily tadalafil open-label, flexible-dose (10 or 20 mg) in 112 ED men who failed to respond to 20 mg tadalafil on at least 6 occasions. These subjects exhibited substantial improved International Index of Erectile Function-Erectile Function (IIEF-EF) domain scores from 10.3 at baseline to 14.9 after the 4-week on-demand treatment and to 23.1 after 12 weeks of daily dosage. Also, McMahon carried out an open-label crossover trial comparing 12 weeks of tadalafil (10 mg daily vs 20 mg on-demand) in 145 men with ED, in which the baseline IIEF-EF score 14.6 was increased to 23.3 in the on-demand arm and 26.4 in the daily dose arm.

Porst et al evaluated the efficacy of 5 mg or 10 mg of tadalafil daily in a multicenter, randomized, double-blinded, placebo-controlled study on 293 men for 12 to 15 weeks. Both doses significantly improved EF, with a mean change in IIEF-EF domain scores of 9.7, 9.4, and 0.9 for the 5 mg, 10 mg, and placebo groups, respectively. Porst et al also reported that tadalafil 5 mg daily for up to 2 years is tolerated and effective in men with ED, with improved mean IIEF domain, intercourse satisfaction, and overall satisfaction. Positive responses were reported for 95.7% of the global assessment question 1 (GAQ.

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### Table 1. Chemical and Pharmacokinetic Data of FDA-approved PDE-5Is

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
<th>Avanafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>Viagra</td>
<td>Levitra</td>
<td>Cialis</td>
<td>Stendra</td>
</tr>
<tr>
<td>Available doses (mg)</td>
<td>25, 50, 100</td>
<td>2.5, 5, 10, 20</td>
<td>2.5, 5, 10, 20</td>
<td>50, 100, 200</td>
</tr>
<tr>
<td>Chemical data</td>
<td>C22H30N6O4</td>
<td>C23H32N6O4S</td>
<td>C22H29N6O4</td>
<td>C23H26CIN7O3</td>
</tr>
<tr>
<td>Molecular mass</td>
<td>474,600 g/mol</td>
<td>488,604 g/mol</td>
<td>389,404 g/mol</td>
<td>483,951 g/mol</td>
</tr>
<tr>
<td>Pharmacokinetic data</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Protein binding</td>
<td>90%</td>
<td>95%</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4, CYP2C9 (liver)</td>
<td>CYP3A4 (liver)</td>
<td>CYP3A4 (liver)</td>
<td>CYP3A4 (liver)</td>
</tr>
<tr>
<td>Biological half-life</td>
<td>3–4 hours</td>
<td>4–5 hours</td>
<td>17.5 hours</td>
<td>5 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Feces (80%), urine (13%)</td>
<td>Biliary</td>
<td>Feces (&gt;60%), urine (&gt;30%)</td>
<td>Feces (&gt;62%), urine (&gt;21%)</td>
</tr>
</tbody>
</table>
improved erection) and 92.1% of GAQ2 (improved ability to engage in sexual activity).

In their work, Rajfer et al.\textsuperscript{30} reported that both 2.5 mg or 5 mg of tadalafl daily in ED men over 24 weeks were superior to placebo, as the mean IIEF-EF score was increased by 6.1 with 2.5-mg tadalafl and by 7.0 with 5mg tadalafl compared to 1.2 points with placebo. Shabsigh et al.\textsuperscript{31} pointed that ED men on daily tadalafl experienced a high rate of reliable efficacy with successful attempts. Also, Kang et al.\textsuperscript{32} concluded that 5 mg of tadalafl daily over 8 weeks is effective in improving EF without adverse effects in ED men, in whom IIEF-5 scores significantly increased from 11.3 at baseline to 16.9. Similarly, udenafil (not approved yet by FDA) showed significantly improved EF among ED patients when administered at 50 mg or 75 mg/day for 12 weeks.\textsuperscript{33}

Porst et al.\textsuperscript{34} demonstrated that daily tadalafl (2.5 and 5 mg) is both effective and well-tolerated even after failure of on-demand use because of its longer efficacy, allowing a more spontaneous sexual life. Also, Huang et al.\textsuperscript{35} showed that daily tadalafl 5 mg for 6 to 8 weeks improved endothelial function and erectile hardness with an effectiveness rate of 96.1% in treating ED patients and significantly improved IIEF-5 scores compared with pretreatment scores.

Likewise, Xu et al.\textsuperscript{36} showed obvious increase in IIEF-5 scores and peak systolic velocity (PSV) of the cavernosal artery on 43 arterial ED on tadalafl 5 mg after supper on alternate days for 4 weeks. Li et al.\textsuperscript{37} demonstrated significant increases in the self-esteem and relationship questionnaire and IIEF-5, with improved nocturnal penile tumescence after 5 mg/day tadalafl for 12 weeks compared with the baseline. In their study, Chen et al.\textsuperscript{38} concluded that oral tadalafl improved PSV and penile erection in ED patients, where the patients with PSV >15 cm/s can be medicated at 5 mg dose, and those with PSV <15 cm/s at 10 mg dose or more on alternate days. Goldfischer et al.\textsuperscript{39} demonstrated that tadalafl 5 mg daily significantly improved sexual function in men with partial response to on-demand PDE-5Is therapy vs placebo irrespective of testosterone (T) levels. Also, Kim et al.\textsuperscript{40} showed that tadalafl 2.5 mg or 5 mg/day is a feasible alternative to as-needed therapy in ED men.

### 2. Sexual Quality of Life

Tadalafl 5 mg daily as ED treatment was demonstrated to improve overall satisfaction for both partners with high concordance among couples in their responses to the man’s ED treatment. In addition, significant improvement in sexual relationship, confidence, self-esteem, and overall relationship were correlated with EF improvement.\textsuperscript{41-43}

### 3. Combined PDE-5I Medication

It is suggested that combined PDE-5I medication can better improve EF, especially for patients with severe ED. Cui et al.\textsuperscript{44} evaluated the efficacy of long-term low-dose tadalafl combined with sildenafil in the early stage of ED treatment; 1:1 to tadalafl 5 mg/day or once daily combined with sildenafil 50 mg as needed. Total IIEF-5 scores of patients with severe ED and Question 2 scores of patients with moderate and severe ED in combined medication group were significantly higher than in the tadalafl alone group. The percentage of “yes” responses to SEP4, SEP5, and partner’s SEP3 were improved significantly in the combined medication group without adverse events.

### 4. ED-No Sexual Life

ED-no sexual life (ED-NS) is the inability to have enough penile erection hardness and duration for enough confidence in attempting coitus for more than 6 months. Zhang et al.\textsuperscript{45} investigated 35 ED-NS patients (17 to 35 years of age) on oral tadalafl 5 mg/day for 3 months who were followed for another 3 months. The patients’ Self-estimation Index of Erectile Function-No Sexual Life scores were 43.2 after medication and 42.1 at 3 months after drug withdrawal compared with 21.2 before treatment.
5. Psychogenic ED
Huang et al. investigated the effect of low-dose daily de-escalatory administration of tadalafil on 84 psychogenic ED patients for 2 months compared with on-demand medication as controls. The rate of therapeutic effectiveness was significantly higher in the observation group than controls (95.2% vs 86.5%).

6. Avoid PDE-5Is’ Side Effects
About 25% of ED patients on sildenafil experience headaches, including cluster headaches that could be resolved by prescribing low-dose vardenafil or tadalafil instead. Also, sildenafil should be used as single dose 25 mg/48 hr with protease inhibitors, especially ritonavir, as anti-retrovirals reduce metabolism of sildenafil in the liver, resulting in abnormally high levels in the body. In addition, low-dose PDE-5Is appear to be efficacious and well tolerated in patients on renal dialysis or hepatic failure.

7. Anejaculation
Jin et al. assessed anejaculation (AE) in 55 patients randomized on Yangjing capsule (once 5 pills, tid) and low-dose tadalafil (5 mg, qd alt, 1 h before bedtime) compared with oral ephedrine (25 mg before bedtime) as controls for 1 to 3 months. The patients were advised to do sexual stimulation, to reduce the frequency of sexual intercourses and to quit masturbation. The total effectiveness rate was 83.34% compared with 40% in controls, demonstrating that Yangjing capsule plus low-dose tadalafil are effective for treating functional AE.

8. ED Post Bone Marrow Transplantation
ED is a recognized complication of bone marrow transplantation (BMT). Chatterjee et al. studied 8 male recipients of BMT presented with hypogonadism, ED, diminished libido, and ejaculatory disorders. All patients received intramuscular testosterone cypionate (250 mg 4 weekly) for 6 months and 50 to 100 mg sildenafil orally, 1 to 2 times/week. All patients
responded favorably, suggesting that this combined therapy is an effective approach in recipients of high-dose therapy presenting with ED after transplant.

9. Female Sexual Dysfunction

Angulo et al.61 concluded that potentiating the NO pathway by vardenafil improves vascular sexual responses and overcomes the inhibitory effects of acutely administered antidepressants on female genital vascular responses. van der Made et al.2,53 investigated the combination of T and vardenafil on increased sensitivity for sexual cues and physiological sexual responding in women with hypoactive sexual desire disorder. In women who did not suffer childhood sexual abuse (CSA), T appears to activate central sexual mechanisms resulting in higher vaginal pulse amplitude under the combination of T and vardenafil. However, women who suffered CSA showed no alterations in their physiological sexual responses.

10. Recurrent Priapism

Burnett et al.54–56 demonstrated that long-term, continuous PDE-5Is therapeutic regimen in recurrent ischemic priapism is successful in alleviating, controlling, and resolving recurrences with unchanged erectile function.

11. Morning Erection

Aversa et al.57 indicated that long-term use of tadalafil improved endothelial function with dramatic increase in morning erections and sustained effects after its discontinuation that determines better oxygenation to the penis.

12. Experimental Cavernous Effects

Mostafa et al.58,59 pointed to the pronounced antiapoptotic and antioxidant effects of frequent low-dose sildenafil and/or tadalafil combined with T for 12 weeks on the cavernous tissues of aged diabetic rats, where alternate sildenafil/tadalafil with/without T showed further improvement. Also, Helmy and Senbel60 concluded that low-dose sildenafil (5 mg/kg/day) results in antioxidant properties in long-term use being increased if combined with vitamin E (80 IU/day) in age-associated ED.

Mostafa et al.61 associated tadalafil (0.09 mg/200 g) daily for 2 months in induced diabetic rats with substantial improved structure of penile cavernous tissue, increased smooth muscles and elastic tissue, decreased fibrous tissue, and functional enhancement of the erectile function. Also, Wu et al.62 concluded that a continuous low dose of tadalafil can improve the function and structure of cavernous vascular endothelium. Similarly, Hotta et al.63 determined that long-term vardenafil could ameliorate impaired penile hemodynamics and maintained normal smooth muscle/collagen ratio in cavernous tissues for acute arteriogenic ED in rats induced by ligating bilateral internal iliac arteries from 1 week after ligature.

UROGENITAL IMPLICATIONS

1. Benign Prostatic Hyperplasia

PDE-5Is have a favorable impact in patients with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).64–66 The similarities between the pathophysiologcal mechanisms of LUTS and ED include NO/cGMP pathway, RhoA/Rho-kinase signaling, pelvic ischemia, and autonomic adrenergic overactivity.67 Ying et al.68 indicated that treatment of ED with LUTS due to BPH by sildenafil could improve urinary symptom scores, whereas Zhang and Park69 pointed to PDE-5Is efficacy for improving LUTS in BPH patients with/without ED. Also, Porst et al.70 showed meaningful reduction in total International Prostate Symptom Score (IPSS) on BPH symptoms as early as 1 week with achieved significance at 4 weeks by daily 5 mg tadalafil in a double-blind, placebo-controlled study for 12 weeks. Egerdie et al.71 also demonstrated the efficacy of daily 5 mg tadalafil on both ED and BPH.

Regarding concomitant use of PDE-5Is and alpha blockers, Kloner et al.72 reported that tadalafil augmented the hypotensive effects of alpha-blocker doxazosin but had little hemodynamic interaction with tamsulosin. Kaplan et al.73 showed that the combination of alfuzosin 10 mg and sildenafil 25 mg is safe and more effective than monotherapy with either agent to improve voiding in ED men with LUTS suggestive of BPH. Bechara et al.74 showed that tamsulosin 0.4 mg/day plus tadalafil 20 mg/day was more effective than tamsulosin 0.4 mg/day alone to improve LUTS and ED. Liguori et al.75 verified that combined therapy of alfuzosin 10 mg and tadalafil 20 mg for 12 weeks could improve ED and LUTS with significant upgrading in uroflowmetry measures and in IPSS, IIEF-EF scores, and quality of life assessments. Jin et al.76 indicated that combined therapy with sildenafil and doxazosin for ED and BPH/LUTS is safe and effective compared to sildenafil monotherapy. Lee et al.77 demonstrated that tadalafil 5 mg/day combined with alpha blockers have few adverse effects on hypotensive events and can improve LUTS and restore sexual function. Gacci et al.78 showed that the combination of tamsulosin and vardenafil for 12 weeks was well tolerated and more effective in improving both LUTS and erectile function compared with tamsulosin alone.

However, Tuncel et al.79 showed that the combination of tamsulosin only and sildenafil only was not superior to tamsulosin only to enhance voiding symptoms. Also, sexual function improvement was similar for both the combination and sildenafil only treatments. In their study, Goldfsicher et al.80 illustrated a trend for increased hemodynamic signs and symptoms in men taking nonuroselective α-blockers, most notably those taking doxazosin in these cases.

2. Penile Rehabilitation

Bannowsky et al.81,82 and Mevcha et al.83 reported that low-dose sildenafil (25 mg) at night for rehabilitation after nervesparing radical prostatectomy (NSRP) led to a significant
improvement/acceleration of EF recovery. Also, Nakano et al. analyzed the post-NSRP EF with 10 or 20 mg vardenafil at least once weekly for 12 months. The proportion of patients that recovered EF in those undergoing penile rehabilitation was significantly greater than those without penile rehabilitation (60% vs 38.2%). Later, Bannowsky et al. reported that daily low-dose vardenafil (5 mg/day) escalation had improved recovery of EF after unilateral NSRP, whereas doubling the dosage did not. Similarly, Tang et al. reported that tadalafter treatment.

Similarly, Tang et al. reported that vardenafil 10 mg twice/week and prostate brachytherapy gave high rates of stability and dose-dependent manner. 0.5 and 2 mg/kg/day can alleviate testicular I/R injury in a time- and dose-dependent manner.

Conversely, Pavlovich et al. showed that erectile recovery up to 1 year after NSRP did not differ between previously potent men who use sildena nightly compared with on-demand. Experimentally, Kovanecz et al. concluded that lower-dose continuous long-term sildena maintained reversed corporal veno-occlusive dysfunction (CVOD) in a bilateral cavernosal nerve resection rat model. Kovanecz et al. added that long-term single daily oral tadalafl has a similar effect to that of sildenafl or vardenafil in preventing corporal fibrosis and CVOD caused by cavernosal nerve damage in rats through a cGMP-related mechanism independent of inducible NOS induction.

3. Prostate Brachytherapy

Pahlajani et al. reported that early use of sildenafl after prostate brachytherapy maintained EF at 6 and 12 months, where ED can be a side-effect within the first 12 months after treatment. Pugh et al. reported that periprocedural tadalafl 10 mg twice/week and prostate brachytherapy gave high rates of sexual potency preservation. At 24-months follow-up, 72% of these men reported erections firm enough for coitus and 56% were potent. Of men with potency at baseline, 89% had erection firm enough for coitus and 76% remained potent 24 months after treatment.

4. Testicular Torsion

Yildiz et al. showed that intraperitoneal low-dose sildenafl was beneficial in reducing testicular injury after unilateral testicular torsion/detorsion (T/D) in rats created by rotating the right testis 720° in a clockwise direction for 2 hours. Yildiz et al. added that low-dose sildenafl before detorsion prevents ischemia/reperfusion (I/R) cellular damage through reduced reactive oxygen species and supported antioxidant enzymes. Yildiz et al. reported that low-dose sildenafl in these cases prevents increased MDA and NO levels and decreased glutathione peroxidase activity, whereas high-dose sildenafl had no effect. Also, Wu et al. reported that tadalafl 0.5 and 2 mg/kg/day can alleviate testicular I/R injury in a time- and dose-dependent manner.

5. Chronic Renal Disease

Rodriguez-Iturbe et al. reported that sildenafil treatment prevented hypertension and deterioration of renal function, reduced histologic damage, inflammation and apoptosis, delayed the onset of proteinuria, and preserved renal capillary integrity. Delayed sildenafil treatment failed to improve proteinuria and glomerulosclerosis but ameliorated hypertension and azotemia with potential clinical value in the treatment of chronic renal disease.

6. Ovarian Torsion

Yurtcu et al. concluded that low- and high-dose vardenafil are effective in attenuating induced I/R ovary injury.

7. Interstitial Cystitis

Chen et al. showed that interstitial cystitis (IC) symptom indices scores and urodynamic index were significantly improved on daily low-dose (25 mg) sildenafil for 3 months compared with placebo at baselines at weeks 4, 6, 8, 10, and 12, and 3 months after treatment.

8. Peyronie’s Disease

Chung et al. assessed the efficacy of tadalafl 2.5 mg/day for 6 months in remodeling isolated septal scar with higher IIEF-5 scores in 69% of their patients, compared with 10% in the controls.

CVD5: Low-dose Long-term Use

CARDIOVASCULAR IMPLICATIONS

Low dose and long term uses of PDE-5Is demonstrated diverse cardiovascular implications.

1. Heart Failure

Botha et al. showed that intravenous PDE-5Is in patients with end-stage congestive heart failure (HF) had reduced systemic and pulmonary vascular resistance with a suitable hemodynamic profile. In chronic HF, Bussotti et al. demonstrated that sildenafil increases exercise performance, improves lung mechanics and gas diffusion, and prevents exercise-induced pulmonary edema formation, probably by restoring NO pathways.

2. Congenital Heart Disease

Zeng et al. reported that sildenafil (25 mg, 3 times daily) is effective and safe for pulmonary arterial hypertension (PAH) secondary to atrial septal defects, ventricular septal defects, or patent ductus arteriosus. Fraisse et al. showed that intravenous sildenafil reduced PAH and shortened time to extubation for immediate postoperative pediatric patients undergoing congenital heart surgery. Zhang et al. added that iloprost combined with low-dose tadalafl effectively reduced pulmonary vascular resistance, increased 6-minute walking test and improved
cardiopulmonary function in adult congenital heart disease patients with severe PAH.

3. Cardioprotection

In isolated rat heart model, Das et al reported that sildenafil pretreatment within a narrow dose range (0.001 mg to 0.5 mg/kg) provided significant cardioprotection from I/R injury evidenced by improved ventricular recovery, reduced incidence of ventricular fibrillation and decreased myocardial infarction. du Toit et al showed that pretreatment with low-dose sildenafil (20 to 50 nM) could increase myocardial cGMP levels and protect the heart against I/R injury with decreased infarct size. Similarly, Elrod et al demonstrated that treatment with 0.06 mg/kg sildenafil 5 minutes before reperfusion significantly reduces myocardial infarct size. Also, Kolettis et al showed experimentally that sildenafil regimen effect on left ventricular function after I/R is strongly evident after acute pretreatment with a low dosage.

4. Flow-mediated Dilatation

Impaired flow-mediated dilatation (FMD) is partly attributable to hyporesponsiveness of cGMP-mediated vasorelaxation effector mechanisms in the vascular smooth muscle. Katz et al demonstrated that acute effect with sildenafil 25 mg single dose increased endothelium-dependent FMD in the brachial artery of patients with chronic HF compared with placebo after release of transient arterial occlusion. In their study, Desouza et al assessed the acute and prolonged effects of a low-dose sildenafil (25 mg) on FMD in ED patients with type 2 diabetes. After 1 hour, FMD increased the brachial artery dilatation by 15% without change in the placebo group. After daily treatment for 2 weeks, the mean FMD was increased to 14% vs 9% in the placebo group and persisted for at least 24 hours after the last dose.

5. Orthotopic Heart Transplantation

Maruszewski et al performed a short-term outcome analysis of orthotopic heart transplantation in 6 patients with PAH treated perioperatively with oral sildenafil 50 mg followed by 50 or 25 mg t.i.d after transplantation, then discontinued 10 to 14 days with stepwise reduction. Perioperative sildenafil was associated with good short-term outcomes in the majority of patients (4/6), reducing pulmonary resistance and pressure with a low rate of hemodynamic instability.

6. Allograft Vasculopathy

Ziqiang et al explored the effects of tadalafil on allograft vasculopathy in male Brown-Norway rats that supplied aorta grafts for male Lewis rats divided into 3 groups; saline placebo controls, low-dose tadalafil (0.5 mg/kg/day), and high-dose tadalafil (1.0 mg/kg/day) for 8 weeks. Treatment with tadalafil significantly alleviated the neointimal thickness and attenuated graft arteriosclerosis of aortas compared with the controls.

PULMONARY IMPLICATIONS

1. Pulmonary Arterial Hypertension

PAH is a chronic and disabling condition characterized by elevated pulmonary vascular resistance and mean pulmonary arterial pressure. Current treatment guidelines recommend tadalafil for patients with WHO functional class II or III PAH. In a placebo-controlled clinical trial, tadalafil demonstrated improved exercise capacity, as measured by the 6-minute walking distance, decreased incidence of clinical worsening, increased quality of life, and improved cardiopulmonary hemodynamics. Kothari et al reported that low-dose sildenafil is of clinical benefit in 14 patients with severe PAH in improving clinical condition and exercise performance. Similarly, Vida et al evaluated the efficacy of a low dose of 0.5 mg/kg sildenafil in 10 PAH patients daily for 3 months with improved functional capacity. The efficacy of sildenafil 20 mg and 40 mg doses in patients with chronic obstructive pulmonary disease (COPD)-associated PAH demonstrated the mean PAH pressure, and improved pulmonary hemodynamics at rest and during exercise with inhibited hypoxic vasoconstriction.

In younger age, Barst et al randomized 235 children (≥8 kg) with PAH for low-, medium-, or high-dose sildenafil or placebo orally 3 times/day for 16 weeks and reported hemodynamic improvement with medium and high doses. Also, Shah and Ohlsson reported the efficacy and safety of sildenafil in treating persistent PAH in neonates, with a steady improvement after the first dose with reduced mortality.

2. Eisenmenger Syndrome

This syndrome comprises pulmonary vascular disease associated with intra-cardiac shunting, cyanosis, and polycythemia. Mukhopadhyay et al treated 16 cases with tadalafil (1 mg/kg) daily for 12 weeks with decreased mean pulmonary vascular resistance and improved mean systemic oxygen saturation immediately and for 12 weeks.

CUTANEOUS IMPLICATIONS

1. Raynaud’s Phenomenon

Raynaud’s phenomenon (RP) is excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers or toes. In a randomized controlled trial in RP patients unresponsive to other vasodilators, Fries et al reported that sildenafil (50 mg) twice daily for 4 weeks reduces the mean frequency, duration of Raynaud attacks and increases capillary blood flow velocity. Baumbeckel et al showed that tadalafil use in RP is an effective option if not responding to sildenafil. Caglayan et al pointed that patients with primary or secondary RP on vardenafil (10 mg) twice daily exhibited significant increase after 2 weeks in digital blood flow at room temperature and during cold exposure test with reduced total daily duration, number, and severity of attacks.
In their study, Kamata et al\textsuperscript{125} assessed RP in 3 patients with mixed connective tissue disease and 3 patients with systemic sclerosis on sildenafil, vardenafil, or tadalafil measuring fingertip temperature by thermography before and 120 minutes after administration. For longer effects, vardenafil was administered daily for 12 weeks. Compared with preadministration of sildenafil, vardenafil, and tadalafil, the mean fingertip temperature increased by 2.17°C, 3.47°C, and 3.59°C in 120 minutes, whereas in the vardenafil 12-week trial, the mean fingertip temperature increased by 3.04°C, 7.96°C, and 3.32°C from baseline.

2. Digital Ulcers

Digital ulcers in progressive systemic sclerosis are often refractory to therapy where chronic aggressive course can lead to loss of involved acral limbs. Ambach et al\textsuperscript{126} described a 73-year-old woman with dramatic worsening of her ulcerations despite maximum conventional therapy. Switching therapy to bosentan (endothelin receptor antagonists) and sildenafil in low-dose regimens yielded complete healing of these ulcers. Also, Wollina et al\textsuperscript{127} reported improved chronic leg ulcers by combining sildenafil 20 mg 3 times/day and repeated application of a porcine small intestinal submucosal acellular matrix.

3. Palmar-Plantar Erythrodysesthesia

Meadows et al\textsuperscript{128} evaluated the efficacy of sildenafil cream for treating palmar-plantar erythrodysesthesia (PPE) on 9 subjects randomized to receive 0.5 mL of 1% topical sildenafil cream twice daily to the left or right extremities and placebo cream on the opposite extremity. Improved foot pain was reported in 5/9 subjects and in 3/8 subjects for hand pain.

4. Diffuse Cutaneous Systemic Sclerosis

Gheita et al\textsuperscript{129} presented a case of a 40-year-old female patient with diffuse cutaneous systemic sclerosis who presented with progressive dyspnea, choking sensation, cough, abdominal distension, constipation and dysphagia to solids, reduced muscle power, and multiple purpuric eruptions on the legs. Sildenafil 50 mg/day resulted in marked improve of dyspnea, skin tightness, small vessel vasculitic rash, with dramatic improved PAH.

5. Wound Healing

Farsaei et al\textsuperscript{130} demonstrated the beneficial effects of sildenafil in wound healing in 15 animal studies, 7 case reports, and 2 clinical studies in various conditions of skin flaps, grafts and anastomosis. In this context, Samy et al\textsuperscript{131} studied the possible benefit of combining biodegradable polymers with sildenafil in wound healing, showing that the spray-dried chitosan/sildenafil powder and its gel form are promising wound healing promoters.

6. Pressure Ulcer

Pressure ulcer (PrU)-related hospitalization and mortality are critical issues in medical and surgical patients. Farsaei et al\textsuperscript{132} was the first to evaluate effects of topical sildenafil (10%) ointment daily on PrU healing in humans. Decreases in PrU grades were significantly higher and their surface areas in sildenafil group were significantly reduced compared with controls at day 14 compared with placebo group. These effects were attributed to improved microvascular reperfusion in the skin and soft tissue.

7. Skin Flap Survival

Breuer et al\textsuperscript{133} investigated oral tadalafil on random flap survival measured 8 cm \( \times \) 2.5 cm raised on the backs of 37 male rats divided into controls, low-dose (10 mg/kg), and high-dose (20 mg/kg) groups once preoperatively and every day postoperatively for 7 doses. Average flap survival at 7 days and 14 days was 77% and 77% in controls, 82% and 81% in the low-dose-group, and 81% and 80% in the high-dose group, respectively.

GASTROINTESTINAL IMPLICATIONS

1. Esophageal Spasm

Esophageal spasm is presented with dysphagia and chest pain. Fox et al\textsuperscript{134} provided open-label sildenafil treatment for 2 patients with severe, treatment-resistant symptoms associated with esophageal spasm. Dysphagia and chest pain were resolved during this therapeutic trial and the efficacy was preserved on maintenance treatment of 25 to 50 mg sildenafil b.i.d. without side effects.

2. Chronic Anal Fissure

Hyperonticity of the internal anal sphincter (IAS) is involved in the pathogenesis of anal fissure. Sildenafil was shown to relax augmented tone of human IAS in vitro. Torrabadella et al\textsuperscript{137} showed that topical 10% sildenafil significantly reduces anal sphincter pressure in these patients, whereas Marino and Bottalico\textsuperscript{138} pointed that tadalafil 5 mg/day improves the symptoms of chronic anal fissure.

3. Congenital Diaphragmatic Hernia

Keller et al\textsuperscript{139} described a case of chronic pulmonary hypertension in a 7-week-old infant with congenital diaphragmatic hernia who was mechanically ventilated from birth and dependent on low-dose inhaled NO but still unstable, with systemic right ventricular pressures leading to oxygen desaturation. Continued oral sildenafil 0.3 mg/kg/12 hr led to successful discontinuation of the inhaled therapy and improvement. Similarly, Rocha et al\textsuperscript{140} reported an improved survival rate for congenital diaphragmatic hernia due to the use of high-frequency oscillation ventilation and sildenafil.

4. Liver Regeneration

Yardimci et al\textsuperscript{141} concluded that sildenafil accelerates hepatic regeneration after 70% partial hepatectomy in young female rats divided into controls (G1) on intraperitoneal saline; 10 \( \mu \)g/kg
sildenafil low-dose (G2), and 100 μg/kg high-dose sildenafil (G3). Hepatic regeneration and mitosis rate were significantly greater in G2 and G3 than the controls.

REPRODUCTIVE IMPLICATIONS

1. Uterus

She et al. demonstrated enhanced endometrial thickness in 70% of patients on vaginal sildenafil (25 mg, 4 times/day) for 3 to 10 days in infertile women with poor endometrial development. Hale et al. investigated uterine volumetric blood flow (UVF) and vascular impedance in nonpregnant, nulliparous women on placebo or sildenafil (25 or 100 mg) during the luteal phase. Sildenafil showed increased UVF and decreased resistance index over a 3-hour monitoring period. Also, Malinova et al. investigated the role of 25 mg sildenafil vaginally plus 100 to 150 mg Serophene orally on endometrial thickness and uterine volume in anovulatory infertility with increased mean endometrial thickness and endometrial volume.

2. Recurrent Miscarriage

Jerzak et al. evaluated the effect of sildenafil (25 mg intravaginal, 4 times/day) for 36 days on peripheral natural killer (NK)-cell activity in 38 women with a history of recurrent miscarriage (RM) and 37 healthy women. NK-cell activity was significantly decreased and endometrial thickness was significantly increased.

3. Poor Ovarian Response

The use of sildenafil as an adjunct to controlled ovarian hyperstimulation (COH) protocols was shown to enhance ovarian response in women with poor ovarian response. Trakakis et al. presented a case of a 37-year-old woman not responding to COH with the sole use of gonadotropins as a part of intracytoplasmic sperm injection cycle, with the combination of recombinant follicle stimulating hormone and human menopausal gonadotropins for 13 days, without follicular growth. Addition of oral sildenafil 50 mg/day for 5 doses was shown to improve ovarian response and retrieval of 10 oocytes then 3 embryos that were transferred with successful pregnancy.

4. Sperm Functions

Many studies demonstrated a significant increase in sperm motility and viability both in vivo and in vitro at low concentrations, which was reduced at high concentrations. 

NEUROLOGICAL IMPLICATIONS

1. Peripheral Neuropathy

Peripheral neuropathy (PN) is a common complication of diabetes. Hackett reviewed 5 patients with diabetic PN or severe peripheral vascular disease reporting improved symptoms on regular or daily dosing with PDEIs. The authors attributed that improvement to the action of these drugs on endothelial dysfunction via improved blood supply to the vasa nervorum.

2. Cognitive Functions

Oz beyli et al. investigated the effects of sildenafil pretreatment and chronic exercise on anxiety and cognitive functions. Sildenafil pretreatment or exercise exerts a protective effect against acute stress and improves cognitive functions by decreasing oxidative damage. Also, several reports have demonstrated that cognitive function can be restored in mouse models of Alzheimer’s disease after administration of sildenafil or tadalafil, which are capable of passing the blood-brain barrier.

3. Hepatic Encephalopathy

Ammonia is a byproduct of protein metabolism in the body that can cross the blood-brain barrier. Elevated ammonia levels are toxic to the brain. Arafa et al. reported that sildenafil has a protective effect on the brains of hyperammonemic rats due to cytoprotective, antioxidant and antiapoptotic effects, increased cGMP, and enhanced proper metabolism of fats that suppresses oxygen radical generation and prevents brain oxidative damage. The authors shed a light on the therapeutic modulation of the NO–cGMP pathway that might have clinical applications to improve brain functions in patients with hyperammonemia or clinical hepatic encephalopathy.

4. Antinociception Effects

Gediz et al. investigated the peripheral antinociceptive effects of vardenafil on carrageenan-induced nociception in rats, and the role of calcium besides the l-arginine–NO–cGMP pathway in these effects. Local administration of vardenafil produced a dose-dependent antinociceptive effect. The authors suggested that vardenafil may offer a new therapeutic tool to treat pain that probably result from L-arginine dysfunction via improved blood supply to the vasa nervorum.

CONCLUSION

Low-dose and long-term use of different PDE-5Is in different formulations might pave the way to numerous beneficial medical implications for the welfare of the human beings with outstanding overall efficacy and tolerability. However, it is evident that most potential appliances were carried out experimentally in preclinical studies with off label indications. Therefore, increased knowledge of the drug characteristics, comparative treatment regimens, optimal prescribing patterns, and well-designed clinical trials are needed before these agents can be recommended for use.
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