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PRACTITIONERS’ SECTION
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NEWS

Trademarks Acknowledged
Erectile dysfunction (ED) is defined as a persistent inability to maintain penile erection sufficient for normal sexual activity. It has been reported that more than 20 million men worldwide are treated with PDE (phosphodiesterase)-5 inhibitors, and about $2 billion per year are spent on it.[10] Cardiovascular diseases like hypertension, hyperlipidemia, diabetes mellitus and obesity are the important predictors of ED. Endothelial dysfunction is proposed to be the underlying cause of ED, just like coronary artery disease. Sildenafil was originally developed to treat angina pectoris but later on was recognized as novel treatment option for impotence. To date, sildenafil has been the most extensively studied PDE (phosphodiesterase)-5 inhibitor. Currently two more PDE-5 inhibitors, tadalafil and vardenafil, are under study. Newer compounds have certain advantages over sildenafil, including greater selectivity for PDE-5 compared with other isoenzymes, absence of effect of food on absorption, faster onset and longer duration of action. PDE-5 inhibitors are emerging as novel therapeutic tools with a potential to protect or enhance endothelial function in humans and to selectively improve regional blood flow. The FDA has recently approved a reformulation of sildenafil for the treatment of pulmonary arterial hypertension. Raynaud’s phenomenon, respiratory disorders with ventilation/perfusion mismatch, congestive cardiac failure, hypertension and stroke are the other conditions in which PDE-5 inhibitors are being tried. It is hoped that this group of drugs will soon emerge as a novel weapon in the armamentarium against various cardiovascular and pulmonary diseases. 

Key words: Pulmonary arterial hypertension, Raynaud’s disease, sildenafil, tadalafil, vardenafil

Figure 1: Pathophysiology of erectile dysfunction and mechanism of action of phosphodiesterase-5 inhibitors

### ABSTRACT

Cardiovascular diseases like hypertension, hyperlipidemia, diabetes mellitus and obesity are the important predictors of erectile dysfunction (ED). Endothelial dysfunction is proposed to be the underlying cause of ED, just like coronary artery disease. Sildenafil was originally developed to treat angina pectoris but later on was recognized as novel treatment option for impotence. To date, sildenafil has been the most extensively studied PDE (phosphodiesterase)-5 inhibitor. Currently two more PDE-5 inhibitors, tadalafil and vardenafil, are under study. Newer compounds have certain advantages over sildenafil, including greater selectivity for PDE-5 compared with other isoenzymes, absence of effect of food on absorption, faster onset and longer duration of action. PDE-5 inhibitors are emerging as novel therapeutic tools with a potential to protect or enhance endothelial function in humans and to selectively improve regional blood flow. The FDA has recently approved a reformulation of sildenafil for the treatment of pulmonary arterial hypertension. Raynaud’s phenomenon, respiratory disorders with ventilation/perfusion mismatch, congestive cardiac failure, hypertension and stroke are the other conditions in which PDE-5 inhibitors are being tried. It is hoped that this group of drugs will soon emerge as a novel weapon in the armamentarium against various cardiovascular and pulmonary diseases.

### PRACTITIONERS’ SECTION

**NOVEL PHOSPHODIESTERASE-5 INHIBITORS: CURRENT INDICATIONS AND FUTURE DIRECTIONS**

**RASHMI SHARMA**

Pathophysiology of ED and endothelial dysfunction/mechanism of action of PDE-5 inhibitors [Figure 1][3-4]

In response to sexual stimulation, nitric oxide (NO) gets released from the endothelial cells within the corpus cavernosum, causing activation of guanylate-cyclase and resulting in formation of cyclic-guanosine-monophosphate (cGMP). Activation of the NO-cGMP pathway results in trabecular smooth muscle relaxation, leading to increased blood flow into the penis with pooling of blood in sinuses; and increase in corpus cavernosum pressure, resulting in penile erection. The same NO-cGMP pathway is also important in endothelium-derived dilatation of arteries in systemic, coronary and pulmonary vessels. NO also limits vascular recruitment of leukocytes by inhibiting pro-inflammatory cytokines, chemokines and leukocyte-adhesion molecules. It also limits vascular thrombosis and smooth muscle proliferation. Hence a patient with ED (due to dysfunction of NO-cGMP pathway) is at risk to develop CAD.

Various mechanisms responsible for deficiency of NO in endothelial dysfunction or ED are oxidative stress due to hypercholesterolemia, diabetes or aging, inactivation of NO by advance glycation end products in diabetics, increased expression of arginase II enzyme responsible for degradation of amino-acid L-arginine (precursor of NO), low androgen levels leading to decreased expression of endothelial and neuronal NO synthase (NOS) and over-expression of Rho/ Rho kinase, a cellular signaling enzyme responsible for negative regulation of NOS. PDE-5 inhibitors enhance erectile function by inhibiting the breakdown of cGMP by the enzyme PDE-5.

### PDE-5 inhibitors

Sildenafil was originally tested as treatment of angina pectoris. However, it was found to have little effect in phase-I trial. Erection and priapism were reported as adverse effects in male subjects. This led to the study of this agent as novel treatment option for impotence. To date, sildenafil has been the most extensively studied PDE-5 inhibitor. Currently two more PDE-5 inhibitors, tadalafil and vardenafil, are under study. Newer compounds have certain advantages over sildenafil, including (1) greater selectivity for PDE-5, (2) absence of effect of food on absorption, (3) faster onset and (4) longer duration of action [Table 1].[7-13] PDEs have been identified throughout the vasculature. PDE-1, PDE-4 and PDE-5 are found predominantly in the human saphenous vein samples; and PDE-1 to PDE-5 in the
mesenteric artery samples. Both PDE-3 and PDE-5 isozymes are present in the smooth muscle and platelets. PDE-5 is likely also present in the cardiac tissue. The PDE-6 isoenzyme has tissue distribution in the retina, and PDE-11 is found predominantly in skeletal muscles, the heart, vascular muscles and visceral muscles. Tadalafil has the least effect on PDE-6, and hence it is not associated with visual disturbances of blurring and effect on PDE-6, and hence it is not associated with high fat diet high fat diet

### Clinical trials

In clinical trials, men with mild-to-severe ED of psychiatric, organic or mixed etiology have experienced significant improvement with sildenafil therapy [Table 2]. A multi-center, randomized, double-blind, placebo-controlled, parallel-group study of 348 men (mean age 57 years) with ED was conducted in Europe and the United States. Patients were stratified by baseline severity of ED and then randomly allocated within the severity group (using the Erectile Function domain score of the International Index of Erectile Function) to receive tadalafil 20 mg (n = 175) or placebo (n = 173) at 2 to 4 weeks' intervals, during which they were requested to attempt sexual intercourse approximately 24 or 36 h after tadalafil or placebo dosing. The proportion of successful intercourse attempts at 24 and 36 h was significantly greater with tadalafil than with placebo (P < 0.001). However, the incidences of headache, flushing, dyspepsia and myalgia were significantly greater in the tadalafil group than in the placebo group (P < 0.05). However, in comparison studies, tadalafil is preferred to sildenafil (50/100 mg) by men with ED, possibly because of its longer duration of action. In an open-label, crossover study of sildenafil and tadalafil (taken as needed), out of 367 men with ED (mean age 54 years), 29% of men chose sildenafil and 71% chose tadalafil for ED therapy during an 8-week extension after 12 weeks of therapy for each drug. However, sildenafil and tadalafil were both effective and well tolerated. In a retrospective pooled subgroup analysis of randomized, double-blind, placebo-controlled studies, men with ED from the general population received either placebo or vardenafil 5, 10 or 20 mg over 12 weeks. It was observed that vardenafil is an effective alternative to sildenafil for ED treatment.

### Table 1: Comparative pharmacokinetics and pharmacodynamics of sildenafil, vardenafil and tadalafil[9-12]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>(1-[4-ethoxy-3-(6,7-dihydro-1-methoxy-7-oxo-6-propyl-1H-pyrazolo [4,3-g]pyrimidin-5-yi)]phenyl)sulfonyl)4-methylpiperazine</td>
<td>(2-[3-ethyl-5-isopropyl-phenyl]-3-[3-ethyl-1H-indol-2-yl]pyrazole)</td>
<td>(1-[4-ethoxy-3-(6,7-dihydro-1-methoxy-7-oxo-6-propyl-1H-pyrazolo [4,3-g]pyrimidin-5-yi)]phenyl)sulfonyl)4-methylpiperazine</td>
</tr>
<tr>
<td>Selectivity for PDE-5 Selective over PDE1 to 4 (80 to 19,000-fold) and PDE6 (10-fold) Selective over PDE1 (257-fold), PDE2-4 (&gt;1500 folds) and retinal PDE5 over PDE1 to PDE4 Selective over PDE1 (257-fold), PDE2-4 (&gt;1500 folds) and retinal PDE5 over PDE1 to PDE4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with food Decreased absorption with high fat diet Headache, myalgia, dyspepsia, back pain, flushing, visual disturbances, nonarteritic anterior ischemic optic neuropathy, high-sensitivity skin reactions, anemia leucopenia</td>
<td></td>
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<tr>
<td>Adverse drug reactions Flushing, headache, hypotension, myalgia, dyspepsia, back pain, flushing, visual disturbances, nonarteritic anterior ischemic optic neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interactions -Not to be given with in four hours of organic nitrates. -Additional fall in blood pressure with common antihypertensive drugs. -Contraindicated in patients on alpha blockers. -Interaction with drugs causing inhibition (protease inhibitors) and induction (rifampicin) of cytochrome P450 enzyme.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trough plasma drug concentration 4.9-10.5 ng/ml (sildenafil) 9.05 µg/lt (vardenafil) 378 µg/lt (tadalafil)</td>
<td>6.7-10.7 ng/ml (sildenafil) 10-17 µg/lt (vardenafil) 20-40 µg/lt (tadalafil)</td>
<td>6.7-10.7 ng/ml (sildenafil) 10-17 µg/lt (vardenafil) 20-40 µg/lt (tadalafil)</td>
<td></td>
</tr>
<tr>
<td>Tmax 1.2 hrs 2 hrs 3 hrs</td>
<td>1.2 hrs 2 hrs 3 hrs</td>
<td>1.2 hrs 2 hrs 3 hrs</td>
<td></td>
</tr>
<tr>
<td>Cmax 20 ng/ml (sildenafil) 78 ng/ml (vardenafil) 200 ng/ml (tadalafil)</td>
<td>20 ng/ml (sildenafil) 78 ng/ml (vardenafil) 200 ng/ml (tadalafil)</td>
<td>20 ng/ml (sildenafil) 78 ng/ml (vardenafil) 200 ng/ml (tadalafil)</td>
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</tr>
<tr>
<td>Tmax 4.5-9.5 hrs 2 hrs 4.0 hrs 1.0-2.0 hrs 3 hrs 2 hrs</td>
<td>4.5-9.5 hrs 2 hrs 4.0 hrs 1.0-2.0 hrs 3 hrs 2 hrs</td>
<td>4.5-9.5 hrs 2 hrs 4.0 hrs 1.0-2.0 hrs 3 hrs 2 hrs</td>
<td></td>
</tr>
<tr>
<td>Cmax 9.0 µg/l (10 mg) 20.9 µg/l (20 mg) 37.8 µg/l</td>
<td>9.0 µg/l (10 mg) 20.9 µg/l (20 mg) 37.8 µg/l</td>
<td>9.0 µg/l (10 mg) 20.9 µg/l (20 mg) 37.8 µg/l</td>
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<tr>
<td>Tmax 1.2 hrs 2 hrs 3 hrs</td>
<td>1.2 hrs 2 hrs 3 hrs</td>
<td>1.2 hrs 2 hrs 3 hrs</td>
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<tr>
<td>Cmax 1044 ng/ml (sildenafil) 1000 ng/ml (vardenafil) 2000 ng/ml (tadalafil)</td>
<td>1044 ng/ml (sildenafil) 1000 ng/ml (vardenafil) 2000 ng/ml (tadalafil)</td>
<td>1044 ng/ml (sildenafil) 1000 ng/ml (vardenafil) 2000 ng/ml (tadalafil)</td>
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</table>

### Table 2: Important clinical evidences with phosphodiesterase-5 inhibitors

<table>
<thead>
<tr>
<th>Study design</th>
<th>Drugs</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel-group study on 348 men with ED[10]</td>
<td>Sildenafil and tadalafil (taken as needed)</td>
<td>Significant improvement in ED therapy during an 8-week extension after 12 weeks of therapy for each drug</td>
</tr>
<tr>
<td>Two phase study on 600 patients[12]</td>
<td>Sildenafil and vardenafil Vs placebo</td>
<td>Vardenafil increased erectile function than placebo</td>
</tr>
<tr>
<td>Randomized double-blind, placebo controlled crossover trial on 150 men with ED and CAD[13]</td>
<td>Sildenafil Vs placebo</td>
<td>On exercise similar effects on BP, HR, exercise capacity, exercise induced wall motion abnormality on echocardiogram, dyspnoea, angina and ejection fraction in both groups</td>
</tr>
<tr>
<td>Randomized study on 108 patients with chronic stable angina.[20]</td>
<td>Sildenafil Vs placebo</td>
<td>No difference in time to 1 mm of ST-segment depression or in total exercise time between two groups. Sildenafil significantly prolonged time to angina</td>
</tr>
<tr>
<td>A study on 41 men with reproducible stable angina.[21]</td>
<td>Sildenafil Vs placebo</td>
<td>Vardenafil had no effect on total exercise treadmill time or time to first awareness of angina and change in peak exercise BP and HR as compared to placebo</td>
</tr>
<tr>
<td>Double-blind, placebo-controlled randomized study on 278 patients with symptomatic PAH.[22]</td>
<td>Sildenafil Vs placebo</td>
<td>Sildenafil improved significantly erectile capacity, WHO functional class and hemodynamics (P&lt;0.001) as compared to placebo</td>
</tr>
<tr>
<td>Randomized, controlled, open-label trial Inhaled NO and 50 mg of sildenafil plus iloprost</td>
<td>50 mg of sildenafil plus iloprost was most effective, followed by 12.5 mg of sildenafil plus iloprost</td>
<td></td>
</tr>
<tr>
<td>A study, on a cohort of 6 patients with severe PH secondary to chronic thromboembolic disease.[23]</td>
<td>Sildenafil</td>
<td>Sildenafil produced improvement in mean PAP, mean PCWP, MRC dyspnoea score, NYHA class and gas transfer after 6 weeks of therapy</td>
</tr>
<tr>
<td>A 2-week open-label study on 7 patients with primary and 33 with secondary Raynaud’s disease.[24]</td>
<td>Vardenafil 10 mg twice daily</td>
<td>In 28 (70%) a highly significant increase after 2 weeks in DBP at room temperature (30.0%) and a cold exposure test (35.1%) was observed. Duration, number and severity of disease-related attacks were reduced in 60%, 50% and 53% patients respectively</td>
</tr>
</tbody>
</table>

ED - Erectile dysfunction, CAD - Coronary artery disease, BP - Blood pressure, HR - Heart rate, PAH - Pulmonary artery hypertension, PH - Pulmonary hypertension, LPA - Left pulmonary artery, PAP - Pulmonary artery pressure, PCWP - Pulmonary capillary wedge pressure, MRC - Medical Research Council, NYHA - New York Heart Association, DBF - Digital blood flow
effective and generally well-tolerated treatment for ED, irrespective of age. The most common treatment-emergent adverse events were headache, rhinitis, flushing and dyspepsia, which were mild to moderate, transient and unrelated to age.[16]

In a two-phase study, during the open-label phase of 1 week with 10 mg single dose of vardenafil, out of total 600 patients, 87% patients were reported with a vardenafil, and 74% patients reported maintenance of erection. Whereas, during the double-blind phase of the study, the reliability of penetration and maintenance rates for patients was significantly greater with vardenafil compared with placebo during 12 weeks of the therapy.[19] Headache and flushing were the frequently reported adverse events with vardenafil use in this study.[19]

**PDE-5 inhibition and cardiovascular safety concerns**

PDE-5 inhibitors have potential direct effects on the cardiovascular system, like effects on plaque vulnerability, arrhythmogenicity, myocardial contractility and decrease in peripheral resistance (or systemic pressure, whichever term the authors prefer). Their potential indirect effect may include increased myocardial oxygen demand, effects on sympathetic tone and arrhythmogenicity. Concerns have been raised that these effects might contribute to the development of myocardial infarction (MI) or ischemia, arrhythmia and sudden death.[20] However, the results of various studies have suggested that PDE-5 inhibitors do not contribute to development of MI or angina on their own.[21]

In a randomized double-blind, placebo-controlled crossover trial in 150 men with ED and CAD, BP (blood pressure), HR (heart rate), exercise capacity, exercise-induced wall-motion abnormality on echocardiogram, dyspnea, angina and ejection fraction were similar during exercise in both the group of patients – those receiving sildenafil and those receiving placebo.[22] In another study by Jackson in 108 patients with chronic stable angina, no difference in time to 1 mm of ST-segment depression or in total exercise time was reported between sildenafil and placebo groups.[23] However, sildenafil significantly prolonged time to angina compared to placebo, suggesting a possible beneficial effect in men with chronic stable angina.[23] In a study in 41 men with reproducible stable angina, vardenafil had no effect on total exercise treadmill time or time to first awareness of angina and change in peak exercise BP and HR as compared to placebo.[24] However, duration of ST-segment depression ≥1 mm was significantly prolonged in the vardenafil group.[24]

Tadalafil 20 mg daily dosing after 26 weeks in a randomized double-blind, placebo-controlled, parallel group study in healthy volunteers or subjects with mild ED showed no significant effect on SBP (systolic blood pressure) or DBP (diastolic blood pressure) in comparison to the placebo.[8] In another placebo-controlled three-way crossover study in 51 patients with chronic stable angina, after 2 h of single oral dose of 5 mg or 10 mg of tadalafil, a decrease in standing mean DBP of >20 mmHg was observed; whereas a mean decrease in SBP of >30 mmHg was seen with only tadalafil 10 mg treatment.[9] However, no significant symptomatic hypotensive effects were reported with its use. As with sildenafil, drug interactions with antihypertensive drugs and organic nitrates are also reported with use of tadalafil and vardenafil. Tadalafil may cause transient hypotension, and organic nitrates should not be taken for at least 48 h after taking the last dose of tadalafil. Using organic nitrates within this time frame may increase the risk of life-threatening hypotension.[11]

**Uses of PDE-5 inhibitors beyond ED**

Premature ejaculation.[25,26] In the age range of 18-59 years, premature ejaculation (PE) represents the predominant sexual dysfunction affecting 28.5% of men. Selective serotonin reuptake inhibitors (SSRIs) offer a treatment strategy; however, the SSRIs are frequently associated with reduced desire and erectile dysfunction. The concomitant use of SSRIs and sildenafil may therefore represent an appropriate approach for PE. The possible mechanism may be that an improved erection (firmness, duration or both) resulting from the PDE-5 inhibitor provides inhibition of ejaculation via down-regulation of receptors involved in somatosensory latency times. A reduction in performance anxiety may exist on a subconscious level. There is limited evidence to support role for PDE-5 inhibitors in the treatment of acquired PE in men with comorbid erectile dysfunction. Controlled clinical trials are required to clarify the role of PDE-5 inhibitors in this subgroup of men with acquired PE.

Anorgasmia in women:[27] SSRI antidepressants commonly produce iatrogenic sexual dysfunction. Sildenafil (100 mg) and vardenafil (10 mg) have been used to reverse SSRI-induced anorgasmia in women. At this point, vardenafil has been approved by the Food and Drug Administration only for use in men. Further studies in women with primary or secondary sexual dysfunction may reveal other populations and medical conditions that could benefit from vardenafil treatment.

Heart failure (HF) and pulmonary arterial hypertension (PAH)

HF is characterized by pulmonary arterial vasoconstriction that is thought to be caused by relative deficiencies of vasodilators such as NO and exaggerated production of vasoconstrictors such as endothelin. PDE-5 is abundant in the pulmonary vasculature, where it catalyzes cGMP, the second messenger of NO. Inhibition of PDE-5 has been shown to lower pulmonary vascular resistance in HF by augmenting local cGMP.[28] Recent studies also suggest that PDE-5 inhibitors may have antihypertropic effects, exerted through increased myocardial cGMP signaling, which could be of additional benefit in patients with heart failure.[29] In an animal study, the effect of sildenafil on the calcium signaling of isolated pulmonary artery smooth muscle cells and the reactivity of pulmonary artery (PA) obtained from chronic hypoxia-induced pulmonary hypertensive rats was compared with that in control (normoxic) rats. It was found that sildenafil is a potent pulmonary artery relaxant, and it normalizes chronic hypoxia-induced increases in resting [Ca2+][i] in smooth muscle cells and basal tone of PA.[30]
as compared with placebo after 12 weeks of therapy.[31] These patients were then treated with 80 mg sildenafil thrice a day in a long-term extension trial, which was conducted over a 2-year period. The increase in the 6-minute walk distance achieved after 3 months in the placebo-controlled phase was maintained even after 1 year of therapy.[32]

In another randomized controlled open-label trial in 30 patients with severe PAH (n = 16), chronic thromboembolic pulmonary hypertension (n = 13) or pulmonary hypertension due to aplasia of the left pulmonary artery (n = 1), all classified as New York Heart Association class III or IV, all patients received inhaled NO and aerosolized iloprost (inhaled dose, 2.8 microg) followed by 12.5 mg of oral sildenafil or 50 mg of sildenafil or 12.5 mg or 50 mg of sildenafil plus inhaled iloprost. It was found that 50 mg of sildenafil plus iloprost was most effective, followed by 12.5 mg of sildenafil plus iloprost.[32] Iloprost alone and 50 mg of sildenafil were almost equally effective but were less potent than the combination regimen. However, the least potent treatment was 12.5 mg of sildenafil and NO. Thus the results of this study clearly indicated that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost to cause strong pulmonary vasodilatation in both severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

In a study conducted in pediatric patients of idiopathic PAH in New York Heart Association functional class III or IV with severe idiopathic PAH unresponsive to conventional therapy, all patients achieved a good therapeutic response, with improvement by at least one functional class, and presented an increase in systemic arterial oxygen saturation; five patients showed a decrease in the ratio of pulmonary systolic pressure to systemic systolic pressure and improvement in the 6-minute walking test without any major side effects at 4 to 36 months of follow-up with sildenafil therapy.[33] However, one patient died because of sudden withdrawal of drug. Hence patients should be advised against the withdrawal of sildenafil without medical supervision.[33] In a study of six patients with severe pulmonary hypertension secondary to chronic thromboembolic disease, which was not amenable to pulmonary thromboendarterectomy and right ventricular dysfunction, sildenafil produced improvement in mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, MRC (Medical Research Council) dyspnea score, and gas transfer after 6 weeks of therapy.[34] Hence oral sildenafil in a patient with severe secondary pulmonary hypertension and right ventricular dysfunction could be an attractive therapeutic option as it is an oral formulation and the cost of treatment would be lower as compared to NO.[35] Based on the very favorable mid- and long-term effects of oral sildenafil, the FDA approved it (20 mg t.i.d. dose) in 2005 for the treatment of patients suffering from PAH.[35]

Eisenmenger syndrome: It refers to patients with pulmonary vascular disease associated with intracardiac shunting, commonly at ventricular level, who become cyanotic and polycytemic as increasing pulmonary vascular resistance results in right-to-left flow through the shunt.[36] In a clinical trial, 16 symptomatic Eisenmenger syndrome patients (mean age = 25±8.9 years) were treated with a single dose of tadalafil (1 mg/kg body weight up to a maximum of 40 mg) daily for 12 weeks.[37] There was a significant decrease in mean pulmonary vascular resistance immediately (P < 0.005 after 90 min vs. baseline) and at 12 weeks (P = 0.03 vs. 90 min). A ≥20% decrease in pulmonary vascular resistance was seen in 81.25% of the patients, and these were defined as responders.[37] The mean systemic oxygen saturation improved significantly both immediately (P < 0.005) and at 12 weeks (P < 0.02 vs. 90 min) without a significant change in systemic vascular resistance. The mean World Health Organization functional class improved from 2.31±0.47 to 1.25±0.44 (P < 0.0001), and the 6-minute walk distance improved from 344.56±119.06 to 387.56±117.18 m (P < 0.001).[37] In a case report, concomitant use of sildenafil and L-arginine produced significant improvement in clinical and hemodynamic condition of a pregnant woman with severe pulmonary hypertension due to Eisenmenger syndrome.[38] However, sildenafil in patients with Eisenmenger syndrome has a potential to cause a reduction in pulmonary blood flow and an increase in cyanosis as a result of even mild systemic vasodilatation and consequent increased right-to-left shunting.[39] Hence larger trials are required to establish the safety of sildenafil in patients with Eisenmenger syndrome.

Raynaud’s disease: Treatment for Raynaud’s phenomenon currently includes the use of calcium-channel blockers, infused prostanoids and alpha-2 blockade. However, a growing number of uncontrolled trials indicated the efficacy of sildenafil for the treatment of digital ulceration and Raynaud’s phenomenon in patients with scleroderma with or without pulmonary hypertension.[40,41] In a randomized controlled trial in patients unresponsive to other vasodilators, sildenafil treatment (50 mg given twice daily) for 4 weeks reduced the mean frequency and duration of Raynaud attacks and lowered the mean Raynaud’s condition score significantly.[42] Moreover, capillary blood flow velocity increased in each individual patient, and the mean capillary flow velocity of all patients more than quadrupled after treatment with sildenafil.[40]

In a 2-week open-label study, 7 patients with primary and 33 with secondary Raynaud’s disease were recruited and advised to take vardenafil 10 mg twice daily.[43] In 28 (70%) patients with reduced digital blood flow, a highly significant increase after 2 weeks in digital blood flow at room temperature (30.0%) and in blood flow during a cold exposure test (35.1%) was observed.[41] The total daily duration, number and severity of attacks were reduced in 24 (60%), 20 (50%) and 21 (53%) patients respectively.[41] Responses were similar in smokers and nonsmokers and in those with primary versus secondary Raynaud’s disease. As calcium-channel blockers and PDE-5 inhibitors exert their vasodilative properties through distinct mechanisms, it is possible that combination therapy may enhance the effect of either agent alone.

While PDE-5 inhibitors have predilection for certain vascular beds (pulmonary circulation, corpus cavernosum), they might be differentially expressed in the remodeled vasculature of digital ulcers as opposed to the non-affected regions of the systemic circulation in patients of
Raynaud’s phenomenon. This could explain the reported benefits in patients with Raynaud’s phenomenon and provide good rationale to further examine the utility of PDE-5 inhibitors in this condition.

**Pulmonary hypertension associated with ventilatory disorders**

In pulmonary hypertension associated with interstitial lung disease, systemic administration of vasodilators increases the blood flow to low- or non-ventilated areas of the lung by interfering with the physiological hypoxic vasoconstrictor mechanism. This worsens preexistent ventilation(V)/ perfusion(Q) mismatch and increases shunt flow. However, sildenafil has selectivity for well-ventilated lung areas, resulting in improvement, rather than deterioration, of gas exchange. Various studies investigating the effects of sildenafil administration in acute and chronic conditions of hypoxic pulmonary hypertension confirmed its potential to reverse pulmonary pressures and also confirmed the beneficial effects of sildenafil on exercise performance, under these conditions. Hence sildenafil has therapeutic potential in patients suffering from pulmonary hypertension due to chronic hypoxia, as it occurs in various chronic diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease and obstructive sleep apnea.

**Cerebral circulation** Various studies have examined the role of the NO-cGMP pathway in the brain. Inhibition of hippocampal NOS can result in impairment in object recognition. Sildenafil significantly improves neurovascular coupling, and the initial blood flow response to cortical activity is mainly governed by stimulation of the NO system. It has been observed that sildenafil can reduce the size of the infarction area in an experimental rodent model and can significantly increase cGMP levels and induce neurogenesis in a model of neuronal growth. Hence it has been proposed that sildenafil has a therapeutic potential in cerebral ischemic disorders.

**Antinoceptive agent**

In an animal study using carrageenan-induced hyperalgesia in rats and the acetic-acid–induced writhing test in mice, local administration of sildenafil exhibited a dose-dependent antinoceptive effect. Co-administration of sildenafil significantly enhanced the antinoceptive effect of morphine. However, pretreatment with N(G)-nitro-L-arginine methyl ester (an NO synthesis inhibitor), methylene blue (gunalyl cyclase inhibitor) or naloxone (opioid receptor antagonist) blocked the effect of a sildenafil-morphine combination. Hence it has been suggested that opioid receptor and NO-cGMP mechanisms are involved in the combined antinoceptive effect. Further, sildenafil produced antinociception per se and increased the response of morphine, probably through the inhibition of cGMP degradation.

**Irritable bowel syndrome (IBS)**

NO is a major inhibitory neurotransmitter in gastrointestinal tract. Sildenafil causes relaxation of smooth muscles in various organs by increasing levels of NO. In a study of 17 patients of IBS with ED, there was improvement noted in their IBS symptoms with 37.5 mg/day dose, with significant improvement at the maximum dose for ED symptoms.

**PDE-5 inhibitors and concomitant use of other drugs**

All three drugs are vasodilators and are contraindicated with concomitant administration of nitrates, since significant hypotension can result. However, the use of a PDE-5 inhibitor following a dose of a short-acting nitrate such as sublingual glyceryl trinitrate or sublingual (or transdermal) isosorbide dinitrate may be permissible, provided the use of the short-acting nitrate is infrequent and has preceded by not less than 8 (preferably 24) h the intention of using the PDE-5 inhibitor. Moreover, PDE-5 inhibitors should be used cautiously with α-blockers, with lower starting doses administered when one drug is added to the other. Vardenafil can cause an increased QT interval, and its use with class IA and class III antiarrhythmic drugs should be avoided. Wide use of PDE-5 inhibitors in combination with recreational club drugs such as methylenedioxymethamphetamine (MDMA, Ecstasy), γ-hydroxybutyrate (GBH, ‘date rape’ drug), ketamine and amyl nitrate is an important concern. Such patients will be at heightened risk for cardiovascular complications. Drugs like erythromycin, ketoconazole,itraconazole, grapefruit juice, etc. (which are potent inhibitors of cytochrome P450-CYP 3A4) reduce metabolism of tadalaflu, sildenafil and vardenafil. Hence their dose should be reduced in presence of concomitant use of CYP3A4 inhibitors.

Sildenafil was initially developed as an agent for the treatment of hypertension and angina. However, it has subsequently evolved into a revolutionary new oral treatment for ED. Sildenafil has been on the market since 1998, and the other two PDE-5 inhibitors were approved by the FDA in 2003. PDE-5 inhibitors are emerging as novel therapeutic tools with a potential to protect or enhance endothelial function in humans and to selectively improve regional blood flow. The FDA has recently approved a reformulation of sildenafil for the treatment of pulmonary arterial hypertension. PDE-5 inhibitors have also shown promise in treating severe Raynaud’s phenomenon, respiratory disorders with ventilation/ perfusion mismatch, congestive cardiac failure, hypertension and stroke. It is hoped that this group of drugs that became known as ‘sex pills’ will soon emerge as novel weapon in the armamentarium against various cardiovascular and pulmonary diseases.

**COUNSELING PATIENTS**

Consideration of clinically important therapeutic information about PDE-5 inhibitors, along with factors that lead to treatment failure, yields the basis for patient counseling about these drugs. Key counseling points for PDE-5 inhibitors for erectile dysfunction are the following:

- Sexual stimulation is necessary; the drug is not an aphrodisiac
- Faster onset of effect occurs on an empty stomach; avoid high-fat meals with sildenafil and vardenafil
- As the duration of effect is 4 h for sildenafil and vardenafil and up to 36 h for tadalaflu, wait for onset of effect
- Success increases with each use of the drug, even up to 6-8 attempts
- A higher dose may be necessary if the first dose is ineffective
- Make a follow-up appointment with the
prescribe if the drug is not effective
• Side effects are usually mild and transient – headache, flushing, gastrointestinal upset
• If prolonged erection (>4 h) occurs, contact the physician immediately
• Inquire if the patient is taking any drugs for his heart, blood pressure or prostate; if yes, follow up with specific questions about nitrates and α-blockers

Incorrect use of PDE-5 inhibitors accounts for most instances of treatment failure, whereas adverse effects and cost concerns rarely cause patients to discontinue therapy. Thus, instructions on proper use should be a high priority in patient counseling. Although many pharmacists will not have time to discuss all these issues with patients, being fully prepared to discuss these points will allow the pharmacist to tailor the first counseling discussion and to be able to respond to questions from patients or providers.

A final consideration is how treatment may affect the patient and his partner. The physical ability to have sex is only one element in the complex equation that determines whether or how often a patient has sexual relations. Merely restoring erections is usually not sufficient to restore a poor sexual relationship. Although PDE-5 inhibitors provide many couples the opportunity to resume sexual life, they may also cause or uncover relationship problems in couples who have become accustomed to the lack of sexual intercourse. Many men with erectile dysfunction are in relationships characterized by sexual apathy and avoidance. Reestablishing a satisfactory sexual relationship requires not only the physical ability to achieve an erection but resetting of the sexual equilibrium that may have been altered by chronic erectile dysfunction.

REFERENCES


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