

**CURRENT AND EMERGING USES OF PHOSPHODIESTERASE 5 INHIBITORS.****RAVINDRA S.BEEDIMANI <sup>\*1</sup> AND BHUVANESHWARI KALMATH<sup>2</sup>**<sup>1</sup>*Department of Pharmacology, Kamineni Academy of Medical Sciences and Research Center, Hyderabad, Andhra Pradesh, India*<sup>2</sup>*Department of Oral Medicine and Radiology, Al-Badar Rural Dental College and Hospital, Gulbarga, Karnataka, India***ABSTRACT**

Phosphodiesterase 5 (PDE5) is a key enzyme involved in the regulation of cGMP-specific signaling pathways in normal physiological processes such as smooth muscle contraction and relaxation. Initially, PDE5 inhibitors were developed as potential antianginal agents, but early clinical results were disappointing and the focus of these drugs moved to the treatment of Erectile Dysfunction (ED) based on the findings that nitric oxide and cyclic guanosine monophosphate were important mediators of penile erection. The overall goal of this review is to provide a comprehensive understanding of the current and potential therapeutic roles of the PDE5 enzyme inhibitors. Novel PDE5 inhibitors are highly selective for the PDE5 isoenzyme, and this may translate into potential novel indications and fewer adverse systemic effects. Larger scale, well designed clinical trials are needed to ascertain the safety, efficacy and cost-effectiveness of PDE5 inhibitors in the future treatment of urological, cardiovascular, gastrointestinal, and central nervous system disorders.

**KEYWORDS:** Phosphodiesterase 5 inhibitors, Sildenafil, Erectile dysfunction, Pulmonary arterial hypertension

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## INTRODUCTION

Phosphodiesterase (PDE) constitutes a cyclic nucleotide group of enzymes that degrade the phosphodiester bond in the second messenger molecules 3'-5'-cyclic adenosine monophosphate (cAMP) and 3'-5'-cyclic guanosine monophosphate (cGMP). These enzymes are often referred to as class I cyclic nucleotide PDEs to differentiate them from class II cyclic nucleotide PDEs which to date have only been found in lower eukaryotes and are not as well characterized. The class II cyclic nucleotide PDEs includes DNases, RNases and phospholipases C and D which catalyze the hydrolysis of the phosphodiester backbone of DNA or RNA.

### **History and Nomenclature**

Different forms or subtypes of phosphodiesterases were initially isolated from rat brain by Uzunov and Weiss in 1972<sup>1</sup>. The advent of assays using radioactive substrate provided clear evidence that there were likely to be multiple forms of PDEs with different kinetic and regulatory properties. To date, at least 11 functional gene families named PDE1 to PDE11 have been identified<sup>2</sup>. Each gene PDEs family comprises one to four genes, and many of the genes generate multiple isoforms. The classification is based on amino acid sequences, enzyme regulatory properties, inhibitor specificity and tissue distribution<sup>2</sup>. Cellular localization of PDEs includes cytosol, plasma membranes, endoplasmic reticulum, nuclear membranes and the cytoskeleton. Their function is regulated by intracellular cyclic nucleotide concentration, phosphorylation, interaction with regulatory proteins, subcellular compartmentalization, and binding of Ca<sup>2+</sup>/calmodulin, as well as by changes in gene expression<sup>3</sup>. The standard nomenclature of PDEs designates PDE family by an Arabic numeral which is followed by a capital letter to represent the gene within a family. A second Arabic numeral indicates the splice variant derived from a single gene (e.g., PDE1C3: family 1, gene C, splicing variant 3)<sup>4</sup>. Any single cell type can express several different PDEs and the nature and localization of these PDEs then regulates the local concentration of cAMP or cGMP in the

cell. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are intracellular second messengers involved in the transduction of various physiologic stimuli and regulate multiple downstream physiological processes in a variety of tissues including vascular resistance, smooth muscles function, cardiac output, visceral motility, immune response, inflammation, neuroplasticity (new synapses based on experience), vision and reproduction. The intracellular level of cAMP is regulated by the balance of activity between adenylyl cyclase (AC), which is responsible for its formation and cyclic nucleotide PDE, which is responsible for its inactivation<sup>5</sup>. Changes in cAMP levels can be extremely variable, ranging from very short lived, lasting milliseconds as seen in olfactory neurons, to a more sustained duration of several hours, as seen in the effects of gonadotropin releasing hormones (GnRH) on anterior pituitary cells. In most cells, the capacity for hydrolysis of cyclic nucleotides by PDEs is in an order of magnitude greater than the maximum rate of synthesis of cAMP and cGMP and thus small reductions in the activity of PDEs can produce large increases in the level of cyclic nucleotides and significant changes in the activity of cAMP and cGMP dependent protein kinase<sup>6</sup>. The PDE5 enzyme is highly specific for cGMP and does not hydrolyze cAMP. Substrate selectivity is mediated through an intricate network of hydrogen bonding which is favorable for cGMP but unfavorable for cAMP in PDE5. In smooth muscle cells inhibition of PDE5 raises the cGMP concentration and can therefore increase relaxation of the smooth muscles. PDE5 has only one subtype, PDE5A, which has three well defined isoforms in humans called PDE5A1, PDE5A2 and PDE5A3. Formation of cGMP initiates several reactions in the body including activation of cGMP-gated cation channels, cGMP binding proteins and protein kinase G (PKG), conformational modification of allosteric sites and catalytic sites on specific PDE isoforms, and stimulation of certain multidrug transporter proteins<sup>7</sup>. The

effect on PKG reduces levels of calcium leading to relaxation of smooth muscles.

### **PHOSPHODIESTERASE 5 FAMILY**

PDE5 was originally identified, isolated, and characterized from platelets and later lungs<sup>8-10</sup>. PDE5 is highly specific for cGMP hydrolysis at low substrate levels and the existence of high affinity-binding sites for cGMP are recognized to be in the N-terminal regulatory GAF domains of the enzyme. Only one gene for PDE5 has been discovered. The PDE5 variants (PDE5A1-PDE5A3) differ at their N termini, and all three have unique first exons followed by a common sequence of 823 amino acids. The order of the first exons from the 5' end in the gene is PDE5A1, PDE5A3, and PDE5A2. PDE5A is generally considered to be a cytosolic protein<sup>8-11</sup>. PDE5A1 and PDE5A2 isoforms can be found in the brain, lungs, heart, liver, kidneys, bladder, prostate, urethra, penis, uterus and skeletal muscles<sup>12-14</sup>. PDE5A2 is more common than PDE5A1. PDE5A3 is only found in the heart, bladder, prostate, urethra, penis and uterus. The most established function of PDE5A is as a regulator of vascular smooth muscle contraction through regulation of cGMP. In the cavernosal smooth muscle of the penis, PDE5 inhibition enhances relaxation of smooth muscle by nitric oxide and cGMP and thereby stimulates penile erection<sup>8</sup>. PDE5 enzyme has also been reported in platelets, rod and cone photoreceptor cells of the retina, cerebellum, pancreas, placenta and colon, clitoral corpus cavernosum as well as vaginal smooth muscle<sup>15</sup>. PDE5 is also expressed in human intestinal cells whose activity is regulated by intracellular cGMP levels that increase on guanylyl cyclase C activation. Chemical reduction of PDE5 relieves auto-inhibition of enzyme functions, allosteric cGMP-binding activity is increased 10-fold, and catalytic activity is increased ~3-fold<sup>13</sup>.

### **APPROVED CLINICAL USES OF PDE-5 INHIBITORS**

#### **1. ERECTILE DYSFUNCTION (ED)**

Discovered out of a screening program for novel anti-allergy compounds, Zaprinast was the first characterized selective PDE5 inhibitor<sup>16</sup>. Lack of selectivity and potency

limited its progress in clinical trials, although it has been utilized in numerous experimental studies to illustrate the pharmacological consequences of inhibition of cGMP hydrolysis. Further investigation into structural ring systems led to the discovery of more effective compounds such as pyrazolopyrimidinone. Substitution of a propyl group for a methyl group on this system increased both the potency and affinity for PDE5<sup>11</sup>. Addition of a sulfonamide group led to sildenafil citrate, a compound with increased solubility and reduced lipophilicity. Sildenafil was originally intended to be used for cardiovascular disease but was not successful as anti-anginal drug in clinical trials probably because there are at least eleven different types of PDEs in different tissues of the body<sup>17</sup>. It however proved very successful at blocking the PDE-5 form, which was found in the corpora cavernosa erectile tissues of males. It was therefore diverted to use in erectile dysfunction (ED), creating a revolution in the treatment of ED. Many novel PDE5 inhibitors were later developed and these are mainly indicated for ED. Erectile dysfunction (ED) is defined as a deficiency in sustaining or maintaining enough penile erection for sexual intercourse for at least 6 months. Five oral PDE-5 inhibitors namely, Sildenafil (Viagra®), Tadalafil (Cialis®), Vardenafil (Levitra®), Udenafil (Zydena®) and Avanafil (Stendra®) are now approved for this indication. These drugs work by increasing intracellular cGMP to cause relaxation of penile vascular smooth muscle and enhance vasodilation resulting in augmentation of erection. They work in response to sexual stimulation<sup>18; 19</sup>. PDE5 inhibitors now constitute the standard treatment for erectile dysfunction in most settings, including diabetes mellitus. Individuals on antidepressants may experience sexual dysfunction, either as a result of their illness or as a result of their treatment<sup>19</sup>. Sildenafil improved sexual function in both men and women in this situation<sup>19</sup>. A side effect of concern with sildenafil reported in certain individuals involves a blurring or blue "tinting" of vision caused by the inhibitory effects of sildenafil on retinal PDE6<sup>19</sup>. Tadalafil and Vardenafil are more selective for PDE5 than PDE6

compared with Sildenafil. Newer PDE5 inhibitors appear to have fewer adverse effects like blurring or blue 'tinting' of vision. Occasional reports of haziness, and color abnormalities have also been described with vardenafil. Visual abnormalities have been rarely reported with tadalafil. Sildenafil and vardenafil have a half-life of approximately 4 hours, and the half-life of tadalafil is about 17.5 hours. With regard to onset and duration of activity, sildenafil has an onset of about 45 minutes with 4-hour duration of effect. Tadalafil onset is about 45 minutes with 24- to 36-hour duration of effect and vardenafil has an onset of about 25 minutes with 4-hour duration of action<sup>20</sup>. All the currently available PDE5 inhibitors are remarkably similar with respect to efficacy. Novel PDE5 inhibitors with unique pharmacokinetic characteristics may offer increased dosing flexibility and less complicated planning of sexual activity and highly selective pharmacodynamic features may produce fewer systemic adverse effects.

## **2. PULMONARY ARTERY HYPERTENSION (PAH)**

Pulmonary arterial hypertension (PAH) is characterized by variable presence of vasoconstriction leading to increased pulmonary vascular resistance and right heart failure. PAH can present in an idiopathic form, usually called primary pulmonary hypertension (PPH), but it is also associated with a spectrum of other diseases such as scleroderma, HIV infection, portal hypertension with or without cirrhosis, and anorectic drug ingestion<sup>21</sup>. The pathogenesis of endothelial dysfunction are believed to result from a persistent imbalance between endogenous vasoconstrictors (e.g., endothelin-1) and vasodilators (e.g., nitric oxide [NO], prostacyclin). This is thought to lead to chronic vascular constriction which predisposes to thrombosis and progressive remodeling of the pulmonary arteries. Patients with PAH often present with signs and symptoms of right heart failure. The right-sided heart failure often leads to death within 2–3 years before the emergence of vasodilator therapy. Calcium channel blockers were the first drugs shown to benefit patients with idiopathic PAH<sup>22</sup>. PAH remains

a terrible disease with majority of available therapies being not only expensive but offer minimum benefits. Thus, there is a strong rationale to consider a number of novel therapies related to pathogenic mechanisms. PDE-5 is essentially situated within the smooth muscles of the arteries of the lungs and penis, sildenafil acts particularly in both these areas. Current PAH-specific therapies target one of three major pathways involved in the development and progression of PAH: 1) the endothelin pathway targeted by the endothelin receptor antagonists; 2) the prostacyclin pathway targeted by prostacyclin analogues; and 3) the nitric oxide (NO) pathway targeted by the phosphodiesterase type-5 inhibitors<sup>23</sup>. In this context, sildenafil has emerged as an effective first-line oral therapeutic agent for symptomatic PAH patients who are not suitable for intravenous prostacyclin therapy. The US FDA originally approved Revatio, a brand of sildenafil in 2005 for use in the treatment of WHO Group I pulmonary hypertension. The United States Food and Drug Administration (FDA) also approved Adcirca® (Tadalafil) tablets for oral administration in PAH in May of 2009. This is the first once-a-day PDE5 inhibitor for the treatment of WHO Group I Pulmonary arterial hypertension<sup>24</sup>. Chronic daily treatment with PDE5-inhibitors specifically Sildenafil (Revatio) and Tadalafil (Adcirca) has been established as safe and effective treatment in pulmonary arterial hypertension. PDE5 inhibitors are known to cause pulmonary artery vasodilation and inhibit vascular remodeling, thus lowering pulmonary vascular resistance, which in turn reduces the load of the right ventricle of the heart and improves symptoms of right-sided heart failure.

## **3. LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERTROPHY WITH OR WITHOUT ED**

Benign Prostatic Hypertrophy (BPH) and ED are common disorders among elderly males. The presence of lower urinary tract symptoms (LUTS) related to BPH is defined as an independent risk factor for the development of ED. In BPH, lower urinary tract symptoms develop partly as a result of a fast growing prostate and the resultant

bladder outlet obstruction (static component), and partly due to bladder decompensation and hyperfunction (dynamic component)<sup>25</sup>. Several studies have demonstrated that treatment of ED with PDE5 inhibitors such as sildenafil not only alleviates ED symptoms, but also improve LUTS<sup>26</sup>. The highest level of PDE5 expression after the corpus cavernosum is in the bladder and prostate. ED and BPH coexist in elderly males with a high frequency and seriously interfere with the sexual function and decrease the quality of life (QOL) in aging men. Meta-analysis of the available cross-sectional data suggests that PDE5-Inhibitors can significantly improve LUTS and ED in men with BPH<sup>27</sup>. PDE5-Inhibitors alone or in combination with  $\alpha$ 1-adrenergic blockers in patients with lower urinary tract symptoms (LUTS) / benign prostatic hyperplasia (BPH) seem to be a promising treatment option for patients with LUTS secondary to BPH with or without ED.

#### **POTENTIAL USES OF PDE5-INHIBITORS IN CLINICAL MEDICINE:**

##### **1. HIGH-ALTITUDE PULMONARY EDEMA**

High altitude pulmonary edema (HAPE) is a life-threatening form of non-cardiogenic pulmonary edema that occurs in otherwise healthy mountaineers at altitudes typically above 2,500 meters (8,200 ft.). Sildenafil and Tadalafil have been shown to be useful for the prevention and treatment of high-altitude pulmonary edema associated with altitude sickness<sup>27</sup>. It may be helpful by dilation of pulmonary vessels and reducing pressure and leakage of fluid into lungs<sup>28</sup>. It is not the first choice treatment but of late its use in this area is becoming increasingly favored by many physicians.

##### **2. CHRONIC HEART FAILURE (CHF)**

PDE5 inhibition is an emerging therapy proposed for CHF treatment<sup>29</sup>. Defective NO release is one of the major factors involved in vasoconstriction a pathophysiological hallmark of CHF. It involves systemic and the pulmonary circulation, and results in increased impedance to both left and the right ventricular ejection. Among strategies that involve enhancement of NO-based mechanisms, PDE5 inhibitors have attracted interest as potential therapeutic tools in CHF.

PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure<sup>30</sup>. Sildenafil can cause significant improvements in pulmonary hemodynamics, right ventricular contractility and chamber dimensions in pulmonary hypertension with chronic heart failure. These effects were paralleled by an improvement in quality of life and clinical status. Thus, the favorable effects on cardiac remodeling, lung function, secondary pulmonary hypertension, RV function, lung diffusion capacity and systemic blood flow distribution support the possibility that PDE5 inhibition may be beneficial adjunctive therapy for patients with CHF<sup>30</sup>.

##### **3. TYPE2 DIABETES MELLITUS CARDIOMYOPATHY**

Type 2 Diabetes Mellitus (T2DM) illustrates a model of endothelial dysfunction with nitric oxide (NO) deprivation leading to a loss of vascular endothelium-relaxant function and an increase of insulin levels promotes cardiotoxicity by increasing the expression of ventricular angiotensin II type 1 receptor (AT1). All these mechanisms lead to cardiovascular remodeling associated with diabetic cardiomyopathy that is characterized by an impairment of heart diastolic performance with a ventricular hypertrophy/dilatation and an increase of heart torsion<sup>31</sup>. PDE5 inhibitors improve endothelial dysfunction by preventing the breakdown of cyclic guanosine monophosphate (cGMP), resulting in its increased cellular content and consequent relaxation of smooth muscle cells of all systemic arteries and veins<sup>32, 33</sup>. PDE5 inhibitors therefore have the potential to impact cardiovascular performance by acting through all these mechanisms.

##### **3. MUSCULAR DYSTROPHY**

Duchenne muscular dystrophy (DMD) is a recessive X-linked form of muscular dystrophy, affecting around 1 in 3,600 boys, which results in muscle degeneration and eventual death. DMD is caused by mutations in the dystrophin gene at locus Xp21. Loss of dystrophin initiates a progressive decline in skeletal muscle integrity and contractile

capacity which weakens respiratory muscles including the diaphragm. It culminates in respiratory failure, the leading cause of morbidity and mortality in DMD patients<sup>34</sup>. In a study done at The Montreal Heart Institute mice with muscular dystrophy were assigned to either a placebo or sildenafil. The mice received the drug or placebo once a day for six weeks. At the end of the six week period imaging tests showed that the mice that had received sildenafil had significantly improved heart performance compared to those that received placebo<sup>35</sup>. In Duchenne muscular dystrophy, the lack of dystrophin causes a decrease in nitric oxide (NO) that may cause "ischemia," or damage due to a lack of oxygen. By blocking the enzyme PDE5, sildenafil may be able to compensate for the loss of NO at the muscle membrane by up regulating cGMP directly and protecting the muscles of those with Duchenne muscle dystrophy during exercise. Sildenafil was found to improve muscle blood flow in a mouse model of muscular dystrophy, but their benefit to boys with DMD is unknown and is being evaluated in clinical trials<sup>36</sup>.

#### **4. RAYNAUD'S PHENOMENON**

Raynaud's phenomenon (RP) is characterized by temperature-induced vasospasms that lead to pale and cyanotic skin mostly limited to the digits. It occurs in about 3% to 5% of the general population. A secondary form of the condition occurring in connective tissue disease such as systemic sclerosis (SSc) presents as a more severe form with potentially disabling ulceration or tissue necrosis. An important clinical manifestation of the SSc-related vasculopathy is ischemic digital ulcer (DU) which is associated with significant morbidity. Use of PDE5 inhibitors in SSc-related RP and DU has been explored in randomized studies<sup>37</sup>. The effects of sildenafil in SSc-RP as measured by the microcirculatory blood flow, production of endothelial progenitor cells, and serum levels of vascular endothelium growth factor are being evaluated in ongoing in clinical trials. PDE5 inhibitors are well tolerated and have become one of the favored options for treatment of SSc-RP and SSc-DUs among rheumatologists<sup>38</sup>. Administration of 50 mg sildenafil twice daily

during 4 week period in randomized clinical studies increased mean capillary blood cell velocity significantly in patients with secondary Raynaud's phenomenon<sup>39</sup>. The occurrence and duration of symptoms of Raynaud's phenomenon decreased considerably, thus leading to significantly better well-being of the patients. These clinical studies have also demonstrated that sildenafil significantly improves microcirculation in patients with Raynaud's phenomenon resistant to therapy with vasodilators. PDE-5 inhibition appears to be a promising new approach in patients with microcirculatory disorders<sup>40</sup>. Due to lack of robust randomized clinical trials of PDE5 inhibitors in SSc-RP/DUs, the PDE-5 inhibitors have not yet been approved by the US-FDA for these particular indications.

#### **6. ASSISTED REPRODUCTIVE TECHNOLOGIES IN MALE INFERTILITY**

PDE5 is expressed in Leydig cells and peritubular cells of the testes, both in prepubertal and in adult rats. This observation tends to support the idea that in the mammalian testis cGMP-mediated processes might influence not only testicular vessel dilatation but also the testosterone synthesis by Leydig cells and the transfer of spermatozoa mediated by the relaxation of peritubular lamina propria cells. It has been demonstrated that oral administration of PDE5 inhibitors on a daily basis enhances the secretory function of the prostate and subsequently increases the qualitative and quantitative motility of spermatozoa<sup>41, 42</sup>. Both vardenafil and sildenafil enhance Leydig cell secretory function (LCSF) in oligoasthenospermic infertile men. If no contraindications exist, sildenafil for temporary erectile dysfunction during ART seems to be a simple and cost-effective method of assisting these men to produce spermatozoa on demand. This saves the need for surgical procedures in most cases. There are some case reports supporting the use of sildenafil after failed trials of >1 hour to produce spermatozoa, or planning the use of sildenafil in advance for men with such a history. This may prevent stress and frustration for the couple and a delay in the insemination, which may compromise the

IVF/IUI results. In the future, use of PDE5 inhibitors may lead to the improvement of the outcomes of assisted reproductive technology (ART) programs<sup>42</sup>.

### **7. PREMATURE EJACULATION**

Premature ejaculation (PE) is the most common type of sexual dysfunction in men younger than 40 years. PE can be operationally defined as an intravaginal ejaculation latency time of less than 1 minute in more than 90% of episodes of sexual intercourse, independent of age and duration of the relationship<sup>43</sup>. It is also defined as the occurrence of ejaculation prior to the wishes of both sexual partners or within two minutes of penetration. At least 30% of men with PE have concomitant ED. There are numerous studies which have shown that selective serotonin reuptake inhibitors (SSRIs) are safe and effective to treat this condition, and many physicians use these agents off label for this purpose. SSRIs have been the most successful agents in delaying the too-rapid response in men who experience premature ejaculation. Some recent studies have demonstrated that PDE5 inhibitors in combination with SSRIs provide better results when used to treat premature ejaculation than the use of SSRIs alone<sup>44</sup>. The effect may be partly due to an improved erection (firmness, duration, or both) that results from the PDE5 inhibitor-induced delay of ejaculation through down-regulation of receptors involved in somatosensory latency times. A reduction in performance anxiety may also exist at a subconscious level. PDE5 inhibitors have been found to be safe and effective as an adjunct to treating premature ejaculation in men if no contraindication exists. Sildenafil increased confidence, perception of ejaculatory control, and overall sexual satisfaction, and decreased the refractory time to achieve a second erection after ejaculation in men with PE<sup>45</sup>. A study comparing the effectiveness of sildenafil with the squeeze technique and on-demand use of two different SSRIs (paroxetine and sertraline) and clomipramine in PE patients was performed in a double-blind, prospective,

cross-over design<sup>45, 46</sup>. All medications were used 3–5 hours prior to sexual intercourse. The study demonstrated a 15- fold increase in intravaginal ejaculatory latency for the sildenafil group whereas SSRIs, clomipramine and the squeeze technique only resulted in a 2–4-fold increase in latency. Sildenafil was found to be very effective and safe to treat PE, and had a much higher efficacy than paroxetine (SSRI) and squeeze technique (in some prospective clinical study<sup>46</sup>). Surprisingly however, no studies have demonstrated superiority of PDE5 inhibitors over placebo in the treatment of premature ejaculation. PDE5 inhibitors are used off-label for the treatment of premature ejaculation as of now.

### **CONCLUSION**

PDE5 enzymes control the duration and localization of intracellular cyclic nucleotide cGMP signaling molecule which mediate interactions with various signaling cascades including the MAP kinase and Ca<sup>2+</sup> pathways. Inhibition of the hydrolysis of the cyclic nucleotide cGMP leads to elevation of its levels with consequent effects on cellular proliferation, smooth muscle relaxation and inhibition of inflammatory cells. Several cardiovascular effects and pleiotropic actions of PDE5 inhibitors have emerged and are being actively pursued for possible clinical application. Inhibition of PDE5 is currently the most tested strategy in various clinical conditions such as chronic heart failure, high altitude pulmonary edema and Raynaud's disease. As our understanding of the roles of PDE5 isoforms and other members of the PDE superfamily grows, these problems may be overcome by using isoform-specific inhibitors as well as dual specificity inhibitors. The strong safety profile of the three PDE5 inhibitors namely sildenafil, tadalafil and vardenafil that are currently marketed in most of the world has encouraged clinical investigators to test the efficacy of these drugs in treatment of a number of ailments.

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