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Review article

# Evolution of phosphodiesterase type 5 inhibitors in treatment of erectile dysfunction in Taiwan☆

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ABSTRACT

Erectile dysfunction (ED) is a prevalent form of male sexual dysfunction. Phosphodiesterase type 5 (PDE5) inhibitor is the first-line treatment for ED. Numerous well-designed and -conducted clinical trials and postmarketing studies have established the safety and efficacy of PDE5 inhibitors for the treatment of ED. Ever since the first approval of sildenafil in 1998, PDE5 inhibitors have had several advances in their clinical use. More new agents with different pharmacokinetic profiles and new formulations were marketed. Conventional on-demand administration expanded to daily dosing. These advances provide more flexibility in clinical treatment of ED for patients and physicians. Moreover, clinical indications of PDE5 inhibitors extend from treatment of ED to pulmonary arterial hypertension and signs and symptoms of benign prostatic hyperplasia because of the distribution of PDE5 enzyme in human organs and tissues. The evolution of PDE5 inhibitors heralds a remarkable medical history from bench to clinical practice.



## 1. Introduction

The phosphodiesterase (PDE) system had been identified for many years but was not initially considered to play a significant physiological role in humans. The system includes 11 families with > 50 isoforms and is widely distributed in human organs and tissues.[1] PDEs catalyze breakdown of cyclic GMP or cyclic AMP, so-called second messengers, which in turn are converted to biologically inactive monophosphates, resulting in termination of their physiological functions. PDE type 5 was first discovered by Francis and Corbin[2] in 1980 and is enriched in the corpus cavernosum compared with other PDE enzymes. PDE5 enzyme is a homodimer containing two identical subunits that each consists of regulatory and catalytic domains (Figure 1). The catalytic domain is the direct target of PDE5 inhibitors. The regulatory domain contains allosteric cGMP-binding sites and a phosphorylation site for negative feedback regulation of the enzyme.[3]

## 2. Serendipity: From angina to erectile dysfunction

The discovery of PDE5 inhibitors for treatment of erectile dysfunction (ED) is a remarkable case of serendipity. Before the advent of PDE5 inhibitors, treatment choices for ED were limited to penile implant and intracavernosal injection. The invasive nature and fear of injection prevented them from widespread acceptance by patients and physicians. Only a small portion of ED patients ever benefited from such treatments. In 1989, compound UK-92,480, now better known as sildenafil citrate, was first synthesized and tested in Pfizer's laboratories.[4] Preliminary data showed that inhibiting PDE5 might produce beneficial effects of decreased vascular resistance and reduced platelet aggregation. Clinical studies on sildenafil citrate 50 mg, three times daily, as an anti-angina agent began in 1991 in England but the clinical effects were mild. The untoward side effect of penile erection hinted to scientists that PDE5 and cGMP might play a role in penile erection and the potential of sildenafil as a treatment for ED. Occupation of the catalytic domain by PDE5 inhibitor, a competitive inhibitor, blocks the access of cGMP and its breakdown, which increases the concentration of cGMP in tissues. The Ignarro group reported that penile erection was mediated through elevation of NO-induced cGMP in corpus cavernosum smooth muscle of rabbits in 1990.[5] Subsequent research provided insights into the biological and

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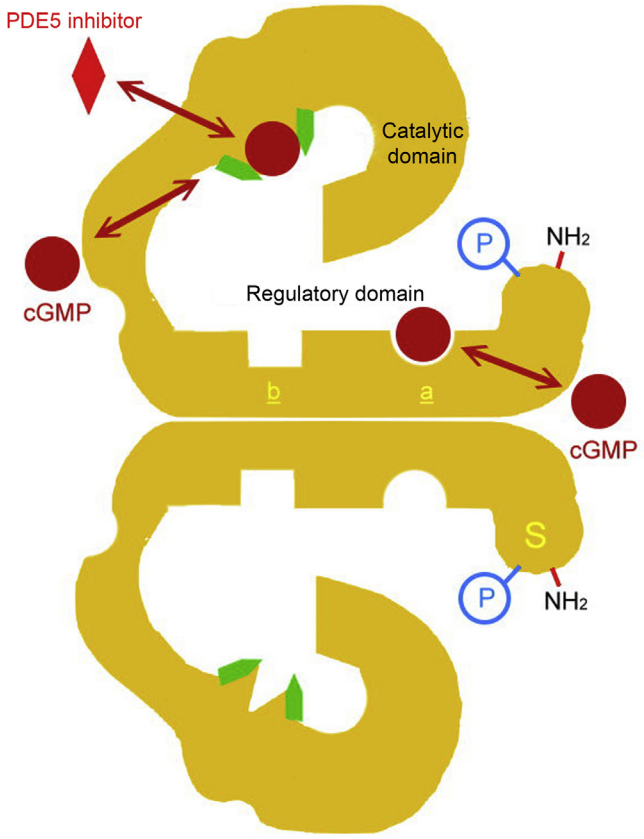


**Figure 1.** Structure of PDE5 enzyme shows two identical submits and each contains a catalytic and a regulatory domain. PDE5 inhibitors target the catalytic domain. The regular domain in the amino-terminal protein contains a phosphorylation site and two allosteric cGMP-binding sites (a and b). PDE5 = phosphodiesterase type 5; cGMP = cyclic guanosine manuscript; p = phosphate; S = serine-102.

pharmacological roles of NO, cGMP, and PDE5 in the regulation of vascular smooth muscle relaxation and vasodilation, and penile erection. Accumulation of cGMP in smooth muscle cells of the penile corpus cavernosum after taking a PDE5 inhibitor results in improvement of erectile rigidity and helps management in men with erectile impairment.

The first pivotal study of sildenafil for ED treatment consisted of a two-phase crossover study.[6] In the first phase, patients were randomized to sildenafil 10 mg, 25 mg, or 50 mg or placebo, and in the second phase, patients were randomized to sildenafil 25 mg or placebo for 7 days. Compared with placebo, taking sildenafil with sexual stimulation significantly improved penile erection in men with ED as monitored by nocturnal penile erection device.[6] A pivotal Phase III study of sildenafil was published in 1998,[7] in which the efficacy was assessed by a validated 15-item self-reported questionnaire, the International Index of Erectile Function (IIEF).[8]

Sildenafil (Viagra; Pfizer, New York, NY, USA) was the first PDE5 inhibitor approved for treatment of ED in the US in 1998 and Taiwan in 1999. Tadalafil (Cialis; Lilly ICOS, Indiana, IN, USA) and vardenafil (Levitra; Bayer AG, Leverkusen, Germany) were approved in Taiwan in 2003. Pharmacotherapy with PDE5 inhibitors has the advantages of easy administration and good effectiveness with minimal side effects, which brought a revolutionary change in the treatment of ED.[9]

## 3. Safety and efficacy of PDE5 inhibitors

PDE5 inhibitors are probably the best studied in well-designed clinical trials on the planet.[10] Most currently available evidence for efficacy and safety of PDE5 inhibitors for the treatment of ED are attributed to sildenafil, tadalafil, and vardenafil. Numerous well-conducted randomized placebo-control trials and postmarketing studies have established their safety and efficacy in the treatment of ED.[9,11,12] Oral PDE5 inhibitors are generally recommended for first-line therapy unless they have contraindications for clinical use. A tremendous growth of utilization data of PDE5 inhibitors in global and Taiwan markets was reported from 1999 to 2011.[13] The success of oral pharmacotherapy for ED culminated in the introduction of more agents, advent of new formulations and routes of administration, and new clinical indications for PDE5 inhibitors in the past decade (Table 1).

PDE5 inhibitors can be administered orally at concentrations sufficient to inhibit PDE5 with minimal serious side effects related to inhibition of other PDEs or non-PDE targets. The most commonly reported treatment-emergent adverse events include headache, flushing, and gastrointestinal upset that are related to the distribution of PDE enzyme, and are transient and mild in severity.[9] However, rare serious toxicity has been reported in association with PDE5 inhibitor use, including hearing loss, nonarteritic anterior ischemic optic neuropathy, and priapism.[14] A critical analysis and review of the literature demonstrates no conclusive evidence to indicate a direct cause–effect relationship between PDE5 inhibitor use and vision-threatening ocular events.[15] Likewise, no causal link could be established between sildenafil and cardiovascular events or any new safety risk relating to cardiovascular events and those rare toxicities.[10]

## 4. New PDE5 inhibitors

The success of the first generation of PDE5 inhibitors has stimulated the development and marketing of more new PDE5 inhibitors (Table 1) that provide greater flexibility for physicians and patients in clinical use. Udenafil[16] (Zydena; Dong-A Pharmaceutical Co., Seoul, Korea) has a relatively rapid onset [time to maximum concentration ($T_{max}$) = 1–1.5 hours] and a long duration of action ($T_{1/2}$ = 11–13 hours; Table 2), and can be used on demand or once daily.[17] To date, udenafil is approved only in Korea, Russia, and the Philippines. Avanafil (Stendra or Spedra; Vivus, Mountain View, CA, USA) has the advantage of rapid onset ($T_{max}$ 35 minutes) and a short half-life (< 1.5 hours)[18] compared with other PDE5 inhibitors. Avanafil was approved by the United States Federal Drug Administration (FDA) in 2012 and by the European Medicines Agency in 2013. Mirodenafil (SK Chemicals Life Science, Seoul, South Korea) is characterized by its selectivity toward PDE5 being 10-fold higher than that of sildenafil, whereas its inhibitory effects on other PDEs were much lower than those of sildenafil in preclinical studies.[19] Mirodenafil was approved in Korea in 2007.[20]

## 5. New formulation

The oral route of administration is the most convenient and popular for most therapeutic agents. Conventional PDE5 inhibitors are produced as solid film-coated tablets and have to be swallowed with water. Oral dispersible tablets (ODTs) provide a novel and an attractive formulation, dissolving or disintegrating rapidly in the oral cavity. Compared to conventional film-coated tablets, ODT formulation has several advantages, including rapid onset, easier administration (without water), bypassing the gastrointestinal tract and hepatic portal systems, and better patient compliance.[21] ODTs have a palatable flavor because of oral dissolving, avoiding a bitter taste and a connection with taking a pill for sex.

Levitra ODT (10 mg) was the first PDE5 inhibitor introduced in ODT formulation with a minty taste in 2011. A pharmacokinetic study demonstrated that taking vardenafil ODT without water can