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REVIEW

# Phosphodiesterase type 5 inhibitors as a treatment for erectile dysfunction: Current information and new horizons

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**KEYWORDS**

Erectile dysfunction;
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**ABBREVIATIONS**

ED, erectile dysfunction;
PDE5(i), phosphodies-

**Abstract** ***Introduction:*** Over the past 15 years, the discovery and development of oral medications that selectively inhibit the enzyme phosphodiesterase type 5 (PDE5) have revolutionised the treatment of erectile dysfunction (ED). Currently, three PDE5 inhibitors are widely available clinically, i.e., sildenafil, vardenafil and tadalafil. New PDE5 inhibitors, including avanafil and udenafil, are now in clinical use in a few countries, and other compounds are under development.

***Methods:*** We describe the current use and future direction of PDE5 inhibitors in the treatment of ED.

***Results and conclusion:*** Each PDE5 inhibitor has an excellent and comparable efficacy and tolerability. These drugs are highly effective for ED of various causes, and are effective in preventing ED after radical prostatectomy. However, whilst

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terase type 5 (inhibitors);
IIEF, International Index of Erectile Function;
SHIM, Sexual Health Inventory in Men;
NO, nitric oxide;
sGC, soluble guanylyl cyclase;
cGMP, cyclic guanosine monophosphate;
GTP, guanosine triphosphate;
FDA, USA Food and Drug Administration;
Cmax, maximum serum concentration;
Tmax, time to Cmax;
RCT, randomised controlled trial

being at least 60% effective, PDE5 inhibitors are still ineffective in at least 30% of patients, prompting current research into other pharmacological targets for ED.



## The epidemiology of erectile dysfunction (ED)

ED is defined as the recurrent inability to obtain and maintain an erection for sexual function [1]. Clinically, the diagnosis of ED is based mostly on the patient's report, which can be quantified using well-validated questionnaires including the International Index of Erectile Function (IIEF) and the shorter Sexual Health Inventory in Men (SHIM) [2,3]. In addition, laboratory and physiological studies can supplement the patient's history and physical examination, to aid the clinician in determining the cause and severity of ED. These include, but are not limited to, serum testosterone levels, penile Doppler ultrasonography, combined intracavernous injection and stimulation, and monitoring nocturnal penile tumescence. However, the use of these tests has declined significantly with the advent of medications that are effective for all causes of ED [4].

ED is a common problem worldwide, especially among ageing men. Using a meta-analysis of over 24 international studies, the prevalence of ED in men in their 40s was 2–9%. This increased to 20–40% in men in their 60s, and by the age of 80 years, 75% of men report ED [5]. In 1995 there were >152 million men worldwide who experienced ED, and this total is estimated to reach 322 million by 2025 [6]. In the USA the crude incidence rate of ED in white men is estimated at 26/1000 man-years. This rate increases with each decade (per 1000 man-years) to 12.4 for 40–49 years, 29.8 for 50–59 years and 46.4 for 60–69 years [7].

The age-adjusted risk (per 1000 man-years) of ED was higher for men with diabetes mellitus (50.7 cases), treated heart disease (58.3 cases), and treated hypertension (42.5 cases). Using these data and the known population of the USA, it was estimated that there are 617,715 new cases of ED per year in those aged 40–69 years [8]. Some authors predict that continuing public education about ED and phosphodiesterase type 5 inhibitors (PDE5i) will increase the patient-reported incidence of this disease [9].

In Middle Eastern countries there is comparatively little information about the overall disease burden of ED, and how it compares to western countries. However, one study using random questionnaires via the website Facebook™ showed that among younger Arab men (mean age 35 years) there is a high prevalence of mild ED, based on the SHIM score, and a low willingness to treat this with PDE5i due to a high distrust of these medications [10]. The authors of this study suggest that this distrust might be due to a mass media campaign focusing on the overestimated side-effects of these medications.

## The physiology and pathophysiology of ED

Erectile function depends on a complex interplay of psychological sexual stimulation, sensory feedback, peripheral neurotransmitter release, smooth muscle cell relaxation, and vascular engorgement of the corporal penile tissue, resulting in erection. After sexual stimulation, postsynaptic neurones and endothelial cells in the penis release various erectogenic substances, the most important of which is nitric oxide (NO). Despite its very short half-life, this gaseous molecule can diffuse quickly across the smooth muscle cell membrane to activate a signalling cascade that ultimately results in arteriolar smooth muscle relaxation, vascular engorgement, and erection. NO activates soluble