JITSS (Journal of Innovation and Trend in Social Sciences)
Vol. 2, No. 2, 2025, pp. 87-100
ISSN 3064-1977 (Electronic)
https://doi.org/10.63203/jitss.v2i2.376

JITSS
Journal of Innovation and Trend in Social Sciences
https://journal.aapbk.org/index.php/jitss

Received: 03 October 2025 | *Revised: 28 December 2025* | *Accepted: 30 December 2025*

Original Article

Systemic Effects of Phosphodiesterase Type 5 Inhibitors Beyond Erectile Dysfunction: A Narrative Review

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Abstract. Phosphodiesterase type 5 inhibitors (PDE5Is) are widely prescribed for erectile dysfunction; however, growing evidence indicates that their pharmacological effects extend beyond urological indications and involve multiple organ systems. This narrative review aims to synthesize and critically evaluate current evidence on the systemic effects of PDE5 inhibitors across cardiovascular, renal, neurological, and urological domains, as well as emerging therapeutic indications. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science for studies published up to May 2024, including preclinical studies, clinical trials, observational studies, systematic reviews, and meta-analyses. The reviewed evidence demonstrates that PDE5 inhibitors are associated with reduced cardiovascular morbidity and mortality, improvements in cardiac and pulmonary hemodynamics, preservation of renal function in diabetic populations, potential neuroprotective effects against cognitive decline and ischemic stroke, and symptomatic improvement in benign prostatic hyperplasia and lower urinary tract symptoms. Additional benefits have been reported in conditions characterized by vascular dysfunction, such as angina pectoris and Raynaud's phenomenon. Overall, PDE5 inhibitors represent a pharmacologically versatile drug class with clinically relevant systemic effects beyond erectile dysfunction, supporting their potential role as adjunctive therapies in broader disease management, although further well-designed randomized controlled trials are needed to inform clinical guidelines.

Keywords: Phosphodiesterase Type 5 Inhibitors, Erectile Dysfunction, Cardiovascular Disease, Renal Function, Neuroprotection

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Introduction

Phosphodiesterase type 5 inhibitors (PDE5Is) are widely recognized for their role in the treatment of erectile dysfunction (ED); however, increasing evidence suggests that their pharmacological effects extend far beyond urological applications. Originally developed for cardiovascular indications, PDE5Is have attracted growing interest due to their systemic actions across multiple organ systems, including the cardiovascular, renal, neurological, and urological systems. This expanding therapeutic profile highlights the need for a comprehensive evaluation of their systemic effects and clinical relevance (Nemr et al., 2024; Paronetto & Crescioli, 2024).

Phosphodiesterases (PDEs) comprise a diverse superfamily of enzymes responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), thereby regulating intracellular signaling mediated by these second messengers. Through the modulation of cyclic nucleotide levels, PDEs exert tight control over a wide range of physiological processes, including vascular tone, cardiac contractility, inflammation, neurotransmission, and cellular proliferation (Maurice et al., 2014; Omori & Kotera, 2007).

The PDE enzyme family is encoded by 21 genes grouped into 11 families (PDE1–PDE11), which differ in substrate specificity, regulatory mechanisms, expression patterns, and sensitivity to inhibitors (Maurice et al., 2014; Omori & Kotera, 2007). While some PDE isoforms selectively hydrolyze either cAMP or cGMP, others act on both nucleotides. Structurally, PDEs share a conserved catalytic domain located at the C-terminal region and a variable N-terminal domain containing regulatory motifs such as GAF domains, calmodulin-binding regions, and phosphorylation sites. These features enable compartmentalized and highly specific regulation of cyclic nucleotide signaling within cells (Maurice et al., 2014).

Beyond their enzymatic activity, PDEs contribute to the formation of spatially restricted signaling microdomains, often referred to as "signalosomes," which ensure selective activation of downstream effectors including protein kinase A (PKA), protein kinase G (PKG), cyclic nucleotide-gated channels, and exchange proteins directly activated by cAMP (Epac) (Zhu et al., 2024). Dysregulation of PDE activity has been implicated in numerous pathological conditions, including cardiovascular disease, pulmonary hypertension, neurological disorders, and malignancies (Delhaye & Bardoni, 2021; Maurice et al., 2014). Consequently, PDEs have emerged as important pharmacological targets, with several isoform-selective inhibitors approved for clinical use (Nemr et al., 2024).

Among these isoforms, phosphodiesterase type 5 (PDE5) is a cGMP-specific hydrolase that plays a central role in nitric oxide (NO)-dependent signaling pathways. PDE5 is a homodimeric enzyme consisting of regulatory GAF domains at the N-terminal region and a conserved catalytic domain responsible for cGMP degradation (Maurice et al., 2014; Paronetto & Crescioli, 2024). Binding of cGMP to the GAF domains enhances catalytic activity, creating a feedback mechanism that tightly regulates intracellular cGMP levels. Through this mechanism, PDE5 influences smooth muscle relaxation and vascular tone in multiple tissues (Paronetto & Crescioli, 2024).

Although PDE5 inhibitors were initially developed for cardiovascular indications, they are now widely prescribed for erectile dysfunction and pulmonary arterial hypertension. Importantly, emerging preclinical and clinical evidence suggests that PDE5Is exert pleiotropic systemic effects involving the heart, kidneys, central nervous system, and lower urinary tract (Nemr et al., 2024). However, existing literature remains fragmented, with findings dispersed across organ-specific studies and heterogeneous methodologies. Therefore, this narrative review aims to synthesize and critically evaluate current evidence regarding the systemic effects of PDE5 inhibitors beyond erectile dysfunction, with a focus on cardiovascular, renal, neurological, and urological outcomes, as well as emerging therapeutic indications.

Method

Study Design

This study was conducted as a systematic literature review with a PRISMA-guided approach (light PRISMA). The review aimed to systematically identify, screen, and synthesize available evidence regarding the systemic effects of phosphodiesterase type 5 inhibitors (PDE5Is) beyond their established use in erectile dysfunction. The review followed key elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including

structured searching, eligibility criteria, and transparent study selection, without performing a quantitative meta-analysis.

Literature Search Strategy

A comprehensive literature search was performed using PubMed, Scopus, and Web of Science databases. Articles published up to May 2024 were considered. The search strategy combined relevant keywords and Medical Subject Headings (MeSH) terms, including *"phosphodiesterase type 5 inhibitors," "PDE5 inhibitors," "erectile dysfunction drugs," "cardiovascular effects," "renal effects," "neurological effects," "benign prostatic hyperplasia," "lower urinary tract symptoms," "Alzheimer's disease," "stroke," "angina pectoris,"* and *"Raynaud's phenomenon."* Reference lists of relevant articles were also manually screened to identify additional studies.

Eligibility Criteria

Studies were included if they met the following criteria:
1. Published in peer-reviewed journals
2. Written in English
3. Investigated systemic or extra-urological effects of PDE5 inhibitors
4. Included human studies or relevant preclinical models
5. Reported cardiovascular, renal, neurological, urological, or vascular outcomes

Exclusion criteria were:
1 Conference abstracts without full text
2 Editorials, commentaries, or opinion papers
3 Case reports with insufficient outcome data
4 Studies focusing exclusively on erectile dysfunction without systemic outcomes

Study Selection Process

All identified records were initially screened based on titles and abstracts to remove duplicates and irrelevant articles. Full-text screening was then conducted to assess eligibility according to the predefined inclusion and exclusion criteria. The study selection process followed a PRISMA-consistent flow involving identification, screening, eligibility assessment, and final inclusion.

Data Extraction

Data from eligible studies were extracted using a standardized data extraction form, including:
1 Author and year of publication
2 Study design and population
3 Type and dosage of PDE5 inhibitor
4 Target organ system
5 Main outcomes and key findings

Data Synthesis

Data were synthesized using a qualitative thematic analysis. Findings were grouped into major domains reflecting systemic effects of PDE5 inhibitors:
1. Cardiovascular outcomes and mortality
2. Cardiac functional parameters

3. Renal outcomes in diabetic kidney disease
4. Neurocognitive function and stroke incidence
5. Benign prostatic hyperplasia and lower urinary tract symptoms
6. Angina pectoris and Raynaud's phenomenon

Results were interpreted descriptively, emphasizing trends, therapeutic implications, and research gaps. No statistical pooling or meta-analysis was conducted due to methodological heterogeneity across studies.

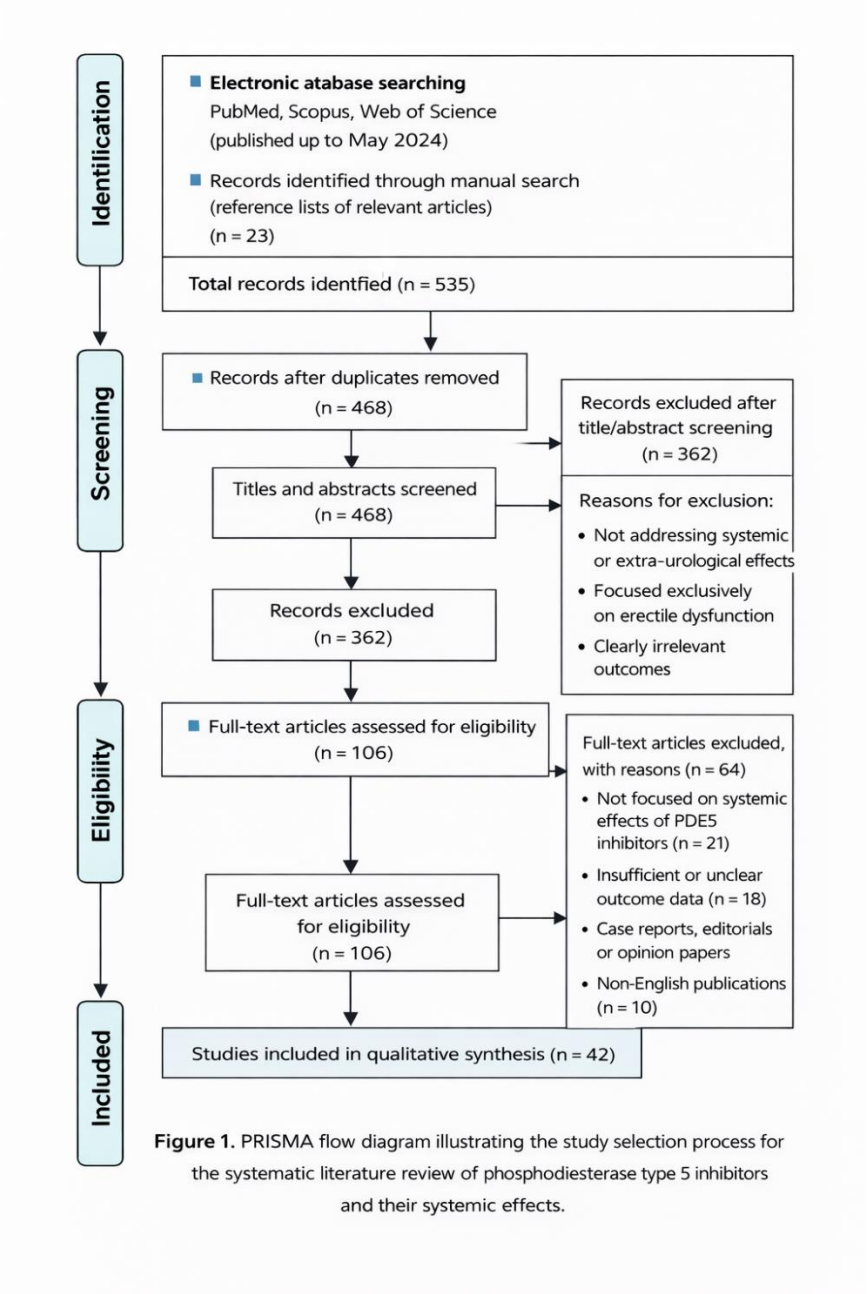

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic literature review of phosphodiesterase type 5 inhibitors and their systemic effects.

Results and Discussions

PDE5 among other PDE enzyme families and their function

Phosphodiesterases (PDEs) comprise a diverse superfamily of enzymes that catalyze the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), thereby regulating intracellular signalling mediated by these second messengers. Through the modulation of cyclic nucleotide levels, PDEs exert tight control over a multitude of physiological processes, including vascular tone, cardiac contractility, inflammation, neurotransmission, and cellular proliferation (Maurice et al., 2014; Nemr et al., 2024; Tian et al., 2020).

The PDE enzyme family is encoded by 21 genes grouped into 11 families (PDE1–PDE11), distinguished by their substrate specificity, regulatory mechanisms, expression profiles, and sensitivity to inhibitors (Omori & Kotera, 2007; Paronetto & Crescioli, 2024). While some PDEs exhibit substrate selectivity, targeting either cAMP or cGMP, others can hydrolyze both nucleotides. Moreover, the structural organization of PDEs is modular; they share a conserved catalytic core located at the C-terminal domain and a variable N-terminal region containing regulatory motifs, including GAF domains, calmodulin-binding sites, or phosphorylation sites. These regions determine subcellular localization and responsiveness to intracellular signals, enabling compartmentalized and highly specific modulation of cyclic nucleotide signalling pathways.

Beyond their enzymatic activity, PDEs play a crucial role in creating spatially restricted signalling domains within the cell, often referred to as “signalling microdomains” or “signalosomes” (Zhu et al., 2024). This compartmentalization is essential to ensure selective activation of downstream effectors, such as protein kinase A (PKA), protein kinase G (PKG), cyclic nucleotide-gated channels (CNG), and exchange proteins directly activated by cAMP (Epac). Dysregulation of PDE activity has been implicated in a broad spectrum of pathological conditions, including cardiovascular disorders, pulmonary hypertension, neurological diseases, and various forms of cancer (Delhaye & Bardoni, 2021; Nemr et al., 2024). Accordingly, PDEs have emerged as promising drug targets, and several isoform-selective inhibitors are already in clinical use.

Among these, phosphodiesterase type 5 (PDE5) is a cGMP-specific hydrolase that plays a central role in the fine-tuning of nitric oxide (NO)-dependent signalling pathways. Structurally, PDE5 is a dimer composed of regulatory GAF domains at the N-terminal, which bind cGMP allosterically, and a conserved catalytic domain responsible for the breakdown of cGMP to 5′-GMP (Nemr et al., 2024). The binding of cGMP to the GAF domains enhances catalytic activity, establishing a feedback mechanism that ensures tight spatial and temporal regulation of cGMP signalling (Maurice et al., 2014; Paronetto & Crescioli, 2024)

By this method, PDE5 regulates the relaxation of smooth muscles as well as the functions of larger physiological systems, such as the heart, kidneys, and central nervous system. Its ability to compartmentalize cyclic nucleotide signalling within subcellular microdomains underscores its value as a pharmacological target. PDE5 inhibitors were first created to treat cardiovascular diseases, but they are now widely used in medicine, particularly to treat pulmonary arterial hypertension and erectile dysfunction (Nemr et al., 2024; Paronetto & Crescioli, 2024)

Mortality among CVD Patients and Relation with PDE5I Intake

Phosphodiesterase type 5 inhibitors (PDE5Is), which were first created to treat erectile dysfunction (ED), have shown in recent years to have significant cardioprotective advantages, especially for patients with cardiovascular disease (CVD). Large-scale observational studies and

meta-analyses have consistently shown a significant reduction in both major adverse cardiovascular events (MACE) and all-cause mortality in patients exposed to PDE5Is, especially those with pre-existing cardiovascular risk factors (Kloner et al., 2023; Soulaidopoulos et al., 2024).

One pivotal retrospective cohort study involving over 70,000 men found that those prescribed PDE5Is experienced a 25% lower risk of overall mortality and a 39% lower risk of cardiovascular death compared to non-users (Kloner et al., 2023). Additionally, decreases were noted in a number of other cardiovascular outcomes, such as heart failure, unstable angina, and coronary revascularization. Interestingly, the cardioprotective effect appeared to be dose-dependent, with higher cumulative exposure to PDE5Is associated with greater reductions in risk. Patients who aggressively pursued ED treatment also had a decreased risk of myocardial infarction and heart failure, especially in the first three years after starting therapy, according to a parallel statewide Danish studyve (Vestergaard et al., 2017).

Although the exact processes underlying these surprising cardiovascular advantages are yet unknown, a number of theories have been put up. By preventing the breakdown of cyclic guanosine monophosphate (cGMP), PDE5Is improve endothelial function across the systemic vasculature, not just in the corpus cavernosum, and consequently boost nitric oxide (NO)-mediated vasodilation. This improved endothelial responsiveness may lead to better regulation of vascular tone, reduced arterial stiffness, and decreased inflammatory burden (Seidu et al., 2022; Soulaidopoulos et al., 2024). Additionally, preclinical and clinical investigations have shown that PDE5Is may have direct cardiac effects, such as increased contractility and decreased ischemia-reperfusion damage (Soulaidopoulos et al., 2024).

It is important to recognize a number of limitations in spite of these encouraging results. Despite thorough statistical corrections, residual confounding may still exist because many research conducted to far have been observational in nature. In addition to PDE5I exposure, patients who use PDE5Is may differ from non-users in significant behavioral or health-related aspects (e.g., greater medication adherence, more proactive healthcare participation), which may have an impact on outcomes. Additionally, there are very few and underpowered randomized controlled trials (RCTs) that directly evaluate cardiovascular outcomes in this cohort (Seidu et al., 2022).

The promise of PDE5Is as supplemental treatments in cardiovascular medicine is nevertheless highlighted by the steady direction and extent of effect shown in a variety of populations, including those with type 2 diabetes mellitus and established coronary artery disease. They are more appealing due to their good safety record and simplicity of oral administration. Crucially, the new information casts doubt on the conventional wisdom that PDE5Is are only urological agents and pave the way for more widespread uses in cardiology.

To sum up, PDE5Is seem to lower cardiovascular morbidity and mortality in individuals who have both ED and concomitant cardiovascular disease. Vascular, endothelial, and potentially cardiac systems work together to mediate this impact. Although these results suggest a viable treatment approach, more prospective RCTs are necessary to validate causation and improve clinical recommendations. In addition to redefining PDE5Is' function in preventing cardiovascular disease, future studies may identify novel molecular pathways that can be modulated by pharmaceuticals.

Positive Effect of PDE5I on Cardiac Parameters

Initially created to treat pulmonary arterial hypertension and erectile dysfunction, phosphodiesterase type 5 inhibitors (PDE5Is) have drawn more and more attention for their cardioprotective benefits, especially in heart failure (HF) patients. Multiple positive effects on cardiac and pulmonary vascular function are attributed to PDE5Is, which enhance the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) pathway. With encouraging outcomes

across a number of cardiac measures, their therapeutic role is currently being investigated in heart failure with preserved ejection fraction (HFpEF) as well as heart failure with reduced ejection fraction (HFrEF).

A meta-analysis of randomized controlled trials confirmed that in HFrEF patients, PDE5Is significantly improve exercise capacity, left ventricular ejection fraction (LVEF), and pulmonary hemodynamics. Specifically, they were associated with increased peak VO_2, enhanced LVEF and reduced pulmonary vascular resistance (Hwang et al., 2017). Increased cGMP availability and downstream vasorelaxation in the pulmonary circulation are probably the causes of these benefits, which indicate an overall improvement in systolic performance and a decrease in right ventricular afterload.

PDE5 inhibition may be especially helpful for individuals with combined pre- and post-capillary pulmonary hypertension (Cpc-PH), according to certain research, despite the more variable findings in HFpEF populations. Reduced vascular resistance and pulmonary artery pressures in these phenotypes suggest that PDE5Is lessen the hemodynamic load of left-sided heart failure (Adhikari et al., 2022). This is especially notable given the paucity of effective treatments for HFpEF.

PDE5I treatment has demonstrated further potential in individuals using left ventricular assist devices (LVADs). Although there is a higher risk of gastrointestinal bleeding, a meta-analysis found that post-implant treatment of PDE5Is is linked to decreased all-cause mortality and a lower incidence of thrombotic events such ischemic stroke and pump thrombosis (Xanthopoulos et al., 2022). These findings suggest that PDE5Is may improve microcirculatory function and endothelial performance in a setting of mechanical cardiac support, potentially by enhancing right ventricular function and decreasing pulmonary resistance.

Additionally, PDE5Is show positive effects on pulmonary arterial pressures in a variety of cardiovascular disease types. Due to vasodilatory mechanisms aided by cGMP buildup, patients with mild to moderate hypertension treated with PDE5Is showed notable decreases in both systolic and diastolic blood pressure. Since right ventricular afterload is a key factor in determining clinical outcomes, such hemodynamic alterations are especially advantageous in HF patients with pulmonary hypertension.

When considered collectively, the available data indicates that PDE5 inhibitors enhance a variety of cardiac metrics, from pulmonary artery pressure to left ventricular ejection fraction, in various patient groups. Patients with increased baseline pulmonary pressures or Cpc-PH seem to be particularly affected. PDE5Is represent a promising supplementary therapy in the management of cardiovascular disease, especially for enhancing functional capacity, right ventricular load, and myocardial performance. However, bigger, well-powered trials are required to validate these findings in broader HF cohorts.

Impact of PDE5I on Renal Function of DM Patients

One of the main causes of end-stage renal disease (ESRD) and a significant contributor to morbidity and mortality in diabetic patients is diabetic kidney disease (DKD), a dangerous microvascular consequence of diabetes mellitus (DM). PDE5Is, or phosphodiesterase type 5 inhibitors, are among the medicinal substances that are attracting interest due to their renoprotective qualities. PDE5Is were first created to treat erectile dysfunction, but they have also shown promise in enhancing renal outcomes, especially for those with type 2 diabetic mellitus (T2DM).

In DKD, the decrease of the urinary albumin/creatinine ratio (UACR), a crucial indicator of glomerular damage and early renal failure, is one of the most frequently mentioned advantages of PDE5I treatment. Both tadalafil and pentoxifylline significantly decreased UACR in a randomized controlled experiment. Tadalafil achieved a 47.5% reduction in microalbuminuria, indicating a considerable attenuation in glomerular leakage (Hegazy et al.,

2024). According to experimental and clinical evidence, PDE5 inhibition increases the expression of nephrin and podocin in podocytes, which is mediated via intracellular cGMP signalling and restores the integrity of the glomerular filtration barrier (Swiecicka, 2023).

After PDE5I medication, the estimated glomerular filtration rate (eGFR), another crucial metric, frequently exhibits preservation or improvement. Despite some inconsistent findings, there is mounting proof that PDE5Is slow the progressive deterioration of renal function linked to diabetes. Both hemodynamic processes (such as enhanced renal perfusion through vasodilation) and anti-inflammatory properties are responsible for these benefits. As an illustration, PDE5 inhibition lowers oxidative stress, pro-inflammatory cytokine levels such as TNF-α, and fibrosis-inducing factor expression.(Hegazy et al., 2024; Swiecicka, 2023).

Additionally, it has been demonstrated that PDE5Is improve insulin sensitivity and glucose metabolism. Tadalafil and sildenafil may improve insulin signaling via NO–cGMP pathways, boost GLUT4 expression, and improve glucose absorption in skeletal muscle cells, according to experimental research and modest clinical trials (Swiecicka, 2023). In some preclinical models, chronic PDE5I treatment has led to improved fasting glucose and insulin levels, as well as attenuation of hepatic inflammation associated with insulin resistance.

Remarkably, PDE5Is also seem to reverse glomerular hyperfiltration, one of the early signs of DKD, by lowering intraglomerular pressure and reestablishing equilibrium in NO bioavailability. This effect helps to stop further proteinuria and glomerular damage. Furthermore, by modifying the Bcl-2/Bax axis, these substances exhibit antioxidant and anti-apoptotic qualities, hence promoting the survival and functionality of renal cells (Swiecicka, 2023).

In conclusion, PDE5 inhibitors provide diabetic patients with a multifaceted protective effect on renal function. They may have a beneficial effect on glucose metabolism, maintain or enhance glomerular filtration, and lower albuminuria. Given the shortcomings of the available DKD therapies, such as ACE inhibitors and ARBs, which frequently fall short of completely stopping the disease's progression, these advantages are especially pertinent. Because of their pleiotropic properties, PDE5Is have the potential to be useful supplemental treatments for diabetic nephropathy. Larger randomized controlled trials, however, are required to validate these advantages and provide precise clinical recommendations.

Impact of PDE5I on Neurocognitivity and Stroke Incidents

The potential benefits of phosphodiesterase type 5 inhibitors (PDE5Is) for neurological health have recently attracted attention, especially in relation to ischemic stroke, Alzheimer's disease (AD), and cognitive decline. Despite not being the original focus of treatment, there is growing evidence that PDE5Is may have neuroprotective effects in both vascular and degenerative brain diseases by modulating cGMP and NO signalling.

PDE5Is may considerably lower the risk of Alzheimer's disease, according to several studies. PDE5I users had a 47% lower risk of AD, according to a 2024 comprehensive review and meta-analysis involving over 8 million participants. Sildenafil had the strongest protective impact (HR: 0.46, $p < 0.001$) (Abouelmagd et al., 2024). Similarly, large-scale pharmacoepidemiologic analyses in the U.S. confirmed a 69% reduced incidence of AD among sildenafil users compared to matched controls (Cheng et al., 2021). These results lend credence to the idea that the observed cognitive benefits may be due to greater neurovascular coupling and improved cerebral perfusion, both of which are mediated by cGMP-related vasodilation.

Mechanistically, PDE5 inhibition increases CREB phosphorylation, a transcription factor essential for memory and learning, which in turn improves synaptic plasticity and memory consolidation. PDE5Is have been demonstrated to repair deficiencies in both spatial and associative memory and restore long-term potentiation (LTP) in experimental models of AD (Arancio et al., 2022). Additionally, tadalafil has been shown to improve working memory

in both young and old rats by lowering oxidative stress in the hippocampus, which may indicate an antioxidant component to its cognitive effects (Al-Amin et al., 2014).

But even with these encouraging results, there are still some unknowns and inconsistent evidence quality. For instance, vardenafil and tadalafil have less conclusive data, possibly because of varying CNS penetration or pharmacokinetic variations, but sildenafil has continuously demonstrated protective links with decreased AD risk (Abouelmagd et al., 2024). Additionally, there aren't many large, randomized clinical trials, which are desperately needed, and the majority of the information currently available comes from observational or preclinical investigations.

PDE5Is may be beneficial in the treatment and prevention of ischemic stroke. Through cGMP-NO pathway regulation, they enhance endothelial function, lessen neuroinflammation, and promote cerebral perfusion. Tadalafil and sildenafil enhance cerebral blood flow and lower thrombotic events, which may lessen the immediate severity and long-term consequences of ischemic stroke, according to a 2024 review (AlRuwaili et al., 2024). Furthermore, clinical evidence indicates that sildenafil use is linked to a lower frequency of ischemic events in patients with pulmonary hypertension, a group at higher risk for stroke (Chang et al., 2022).

However, not all results are categorically favourable. Despite detectable cerebrovascular effects, other trials, like the OxHARP research, did not show a substantial improvement in cognitive function in patients with small artery disease after short-term sildenafil treatment. This implies that although PDE5Is may enhance hemodynamics, their effect on cognitive outcomes may vary depending on the patient's unique characteristics, treatment duration, and illness stage.

In conclusion, there is growing experimental and epidemiological evidence supporting PDE5 inhibitors' neurological potential, especially in the areas of dementia prevention and cerebrovascular protection. They make a strong case for more research because of their capacity to alter neurovascular signalling, penetrate the blood, brain barrier, and enhance synaptic function. Thorough randomized controlled trials must, however, test these relationships and elucidate the best dosage, treatment windows, and patient selection criteria in order to thoroughly validate their usage in clinical neurology.

PDE5I Impact on Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms

A considerable percentage of older men suffer from benign prostatic hyperplasia (BPH) and related lower urinary tract symptoms (LUTS); over 60% of men over 60 exhibit clinical symptoms (Li et al., 2024). Both static (such as mechanical urethral compression from prostatic enlargement) and dynamic (such as increased smooth muscle tone and neuronal dysregulation) factors contribute to the complex pathophysiology of LUTS in BPH (Stamatiou et al., 2024). Alpha-adrenergic blockers and 5-alpha-reductase inhibitors have historically dominated the pharmacological treatment of BPH; however, due to their limited effectiveness and unfavorable side effects, phosphodiesterase type 5 inhibitors (PDE5Is) are now being researched as alternative or supplemental treatments.

PDE5Is, like sildenafil and tadalafil, have been demonstrated to enhance LUTS via a number of hypothesized pathways. They primarily promote smooth muscle relaxation in the prostate, urethra, and bladder neck by improving the nitric oxide–cyclic guanosine monophosphate (NO–cGMP) pathway (Stamatiou et al., 2024). Additionally, PDE5Is have anti-fibrotic and anti-proliferative actions on prostatic stromal fibroblasts. According to a recent study, tadalafil mitigated stromal fibrosis, a defining feature of progressive BPH, by dramatically inhibiting stromal cell proliferation and reducing myofibroblast trans-differentiation through modulation of the TGF-β1/miR-3126-3p/FGF9 axis (Li et al., 2024).

The therapeutic effectiveness of PDE5Is in reducing LUTS associated with BPH is supported by clinical trials. Tadalafil and sildenafil both markedly enhanced post-void residual

volume (PVR), International Prostate Symptom Score (IPSS), and quality of life ratings (IPSS-QoL), according to a self-controlled trial comparing the two medications. Remarkably, sildenafil outperformed tadalafil in terms of lowering PVR and improving quality of life, especially in younger patients (Zahir et al., 2023). There has also been research in the potential synergy between PDE5Is and alpha-blockers. According to a review of combination medications, co-administration of PDE5Is and alpha-1-blockers reduces IPSS and PVR more than monotherapy, however there may be a higher chance of side effects including hypotension (Li et al., 2024; Stamatiou et al., 2024).

Although the results are encouraging, it is important to remember that patient response variability and the precise molecular processes through which PDE5Is affect LUTS are still unknown. However, PDE5Is, especially tadalafil 5 mg daily, are a strong pharmacological choice for men with coexisting BPH and sexual dysfunction due to the fact that they can both treat erectile dysfunction and improve LUTS.

PDE5 Inhibitors as a Treatment for Angina Pectoris and Raynaud's Phenomenon

PDE5Is have demonstrated promising off-label use in the management of cardiovascular and vascular disorders, including stable angina pectoris and Raynaud's phenomenon (RP). Because they increase cyclic guanosine monophosphate (cGMP) levels and promote smooth muscle relaxation, these drugs have vasodilatory effects that are particularly relevant in conditions characterized by ischemia and vascular dysfunction.

Myocardial ischemia manifests as chronic stable angina, which is typically treated with calcium channel blockers, nitrates, and β-blockers. PDE5Is, however, have become a viable alternative or supplementary treatment, especially for patients with concomitant erectile dysfunction or refractory symptoms. By dilating epicardial arteries and lowering left ventricular end-diastolic pressure, PDE5Is increase coronary perfusion and lower pulmonary vascular resistance through their nitric oxide–cGMP–mediated route. This improves oxygen supply to the ischemic myocardium (Kones, 2010).

Their capacity to enhance endothelial function and reduce pulmonary pressures offers a potential and, in certain studies, actual advantage in lowering anginal attacks, even though they are not regarded as first-line therapy. Patients who are suffering severe side effects or who do not react to traditional treatments should pay particular attention to this. Additionally, in certain people with chronic ischemia symptoms, PDE5Is may improve quality of life and increase exercise tolerance (Kones, 2010).

The severity of ischemia symptoms and risk of digital ulcers make Raynaud's phenomenon, especially in its tertiary form linked to connective tissue illnesses such systemic sclerosis, extremely challenging to treat. PDE5Is, such as vardenafil, tadalafil, and sildenafil, have demonstrated notable effectiveness in this regard in lowering the frequency, length, and intensity of vasospastic episodes. PDE5Is considerably beat placebo in all three outcome categories, attack frequency, intensity, and duration, though there was a modest increase in adverse events, according to a strong meta-analysis of randomized studies (Khouri et al., 2019).

Mechanistically, PDE5Is improve digital perfusion and endothelial-dependent vasodilation to restore blood flow, which makes them an essential choice, particularly in cases where first-line calcium channel blockers are ineffective. There is growing support for their early initiation in secondary RP, especially in cases including scleroderma where digital ischemia might progress to gangrene. Although findings on the long-term structural vascular improvement are still conflicting, several studies also show a decrease in the development of new ulcers (Haque & Hughes, 2020; Hinze & Wigley, 2018). Notably, PDE5Is like as vardenafil have shown promise even when used as a monotherapy for RP, exhibiting notable improvements in digital blood flow and patient-reported symptoms (Caglayan et al., 2012). These advantages

offer a strong case for wider use in vascular spasm disorders, as do their advantageous pharmacokinetics and daily oral dosage.

Discussion

PDE5 inhibitors' growing therapeutic range is a result of their crucial function in regulating cyclic nucleotide signalling, especially through the NO–cGMP axis. PDE5Is have shown notable biological effects with clinically significant results across several organ systems. Regarding cardiovascular disease, PDE5Is are consistently linked to lower cardiovascular and all-cause mortality, especially in patients who already have heart disease and erectile dysfunction. Enhancements in pulmonary hemodynamic, myocardial contractility, vascular compliance, and endothelial function highlight their usefulness as supplemental treatments for angina pectoris and heart failure. Although these results are encouraging, large-scale, randomized trials are still necessary to confirm them because the majority of observational research restrict the ability to draw conclusions about causality.

PDE5Is seem to have nephroprotective effects on diabetic renal disease patients' kidneys. Their potential to supplement current treatment regimens, especially in early-stage disease, is suggested by their reduction of albuminuria, preservation of eGFR, and anti-inflammatory signalling. Nonetheless, more consistent trial procedures are required due to the diversity of study groups and results.

In the CNS, evidence is mounting for a potential protective effect of PDE5Is against cognitive decline and cerebrovascular events. Reductions in Alzheimer’s disease risk and improvements in cerebral perfusion have been documented, especially with sildenafil. Yet, inconsistencies in results across drug types and the paucity of prospective trials limit immediate clinical translation. Additionally, the optimal dosing and patient subgroups most likely to benefit remain poorly defined.

There is growing evidence that PDE5Is may have a protective effect in the central nervous system against cerebrovascular events and cognitive impairment. Improvements in cerebral perfusion and a decreased risk of Alzheimer's disease have been reported, particularly with sildenafil. However, rapid clinical translation is limited by inconsistent outcomes across medication types and a lack of prospective trials. Furthermore, it is yet unclear which patient subgroups may benefit and what dosage is best.

Finally, its application in refractory angina and Raynaud's phenomenon highlights their vasodilatory potential beyond traditional indications. PDE5Is have been demonstrated to reduce the frequency and severity of symptoms in both disorders, especially in cases that are resistant to treatment. Even with these many advantages, there are still a few drawbacks. Most supporting evidence for off-label indications comes from animal models, retrospective cohorts, or short studies. More research is necessary to address issues with medication interactions, long-term safety, and the differences in effectiveness amongst PDE5Is (such as sildenafil and tadalafil). Furthermore, in practical clinical implementation, patient adherence, accessibility, and customized response must be taken into account.

To sum up, PDE5 inhibitors are a distinct family of pharmaceuticals with wide therapeutic applications in various organ systems. Although not yet shown for all suggested conditions, their pleiotropic benefits, which span the cardiovascular, renal, neurological, and urological domains are appealing. Redefining the use of PDE5I medication in contemporary medicine will require further research conducted through thorough, regulated clinical trials.

Conclusions

PDE5Is represent a versatile pharmacological class with therapeutic potential beyond erectile dysfunction. While evidence is promising, further large-scale randomized controlled trials are warranted to confirm efficacy and establish guidelines. Future research should prioritize large-scale, well-designed randomized controlled trials to establish the causal effects of phosphodiesterase type 5 inhibitors beyond erectile dysfunction, particularly in cardiovascular, renal, and neurological conditions. Emphasis should be placed on comparative effectiveness among different PDE5 inhibitors, long-term safety, optimal dosing strategies, and identification of patient subgroups most likely to benefit. Additionally, mechanistic studies exploring NO–cGMP signaling and related pathways are essential to support clinical translation and inform the development of evidence-based guidelines for systemic use of PDE5 inhibitors..

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