SEXUAL MEDICINE REVIEWS

Non-Sexual Implications of Phosphodiesterase Type 5 Inhibitors

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ABSTRACT

Introduction: Phosphodiesterase type 5 (PDE5) hydrolyses cyclic guanylate monophosphate specifically to 5′ guanylate monophosphate, promoting corporeal vascular relaxation and penile erection in response to sexual stimulation. Oral PDE5 inhibitors (PDE5-Is) have afforded effective and well-tolerated treatment for erectile dysfunction. In addition, PDE5-Is have stimulated academic and clinical interest for their potential benefits in diverse non-sexual applications.

Aim: To highlight possible potential non-sexual implications of PDE5-Is.

Methods: A systematic review was conducted until January 2016 based on a search of all relevant articles in Medline Medical Subject Heading, Scopus, Cochrane Library, EMBASE, and CINAHL databases without language restriction. Key words used to assess outcome and estimates for the relevant associations were *PDE5 inhibitors, sildenafil, tadalafil, vardenafil*, and *avanafil.*

Main Outcome Measures: Different non-sexual implications for PDE5-Is.

Results: PDE5-Is demonstrated beneficial effects in different medical applications with possible widespread implications for cardiovascular, pulmonary, cutaneous, gastrointestinal, urogenital, cellular, musculoskeletal, neurologic, and reproductive disorders. However, most applications were carried out experimentally in preclinical studies of off-label indications.

Conclusion: PDE5-Is are a conceptually attractive therapeutic class of agents with pleiotropic effects. Exploring PDE5-Is for their possible implications seems to be valuable in different medical disorders. However, well-designed clinical trials are needed before these agents can be recommended for selected applications.

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Key Words: Phosphodiesterase Type 5 Inhibitors; Sildenafil; Tadalafil; Vardenafil; Avanafil

INTRODUCTION

Phosphodiesterase type 5 isoenzyme inhibitors (PDE5-Is) are first-line therapy for erectile dysfunction (ED). Specifically, PDE5 hydrolyses cyclic guanylate monophosphate (cGMP) to 5′ GMP and, by blocking cGMP hydrolysis, potentiates the effects of cGMP, resulting in decreased intracellular calcium, penile smooth muscle relaxation, and vasodilatation with increased penile blood flow.[1,2] Four orally PDE5-Is have been approved by the Food and Drug Administration, namely sildenafil, vardenafil, tadalafil, and avanafil. Sildenafil was released in 1998, has a maximal plasma concentration (Tmax) at 60 minutes on an empty stomach, and acts for 4 to 6 hours. Vardenafil was approved in 2003, has a Tmax of 60 minutes on an empty stomach, and acts for up to 7 hours. Tadalafil was approved in 2003, has a Tmax of 120 minutes with or without an empty stomach, and acts up to 36 hours. Avanafil was approved in 2012 and has a Tmax of 30 to 45 minutes on an empty stomach and sexual attempts can begin as soon as 10 minutes after taking the drug.[3,4]

The high tolerability of PDE5-Is has made them an attractive tool to investigate physiologic functions beyond ED, with collateral benefits for a multitude of non-sexual implications[5,6] (Table 1).

This review aimed to highlight the possible potential non-sexual implications of using PDE5-Is.

PULMONARY IMPLICATIONS

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a chronic disabling condition characterized by increased pulmonary vascular resistance, increased mean pulmonary arterial pressure (PAP), decreased bioavailability of nitric oxide (NO), and downstream

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Table 1. Non-Sexual Implications of Phosphodiesterase Type 5 Inhibitors

Pulmonary implications	12. Brain hypoxia	11. Anal fissure
1. Pulmonary arterial hypertension	13. Multiple sclerosis	12. Acalculous cholecystitis
2. Persistent pulmonary hypertension of newborn	14. Withdrawal signs	13. Hepatic regeneration
3. High altitude illness	15. Blast-induced tinnitus	14. Sphincter of Oddi dysfunction
4. Eisenmenger syndrome	16. Neurogenesis	15. Paracetamol hepatic toxicity
5. Cystic fibrosis	17. Locomotor activity	16. Crohn disease
6. Chronic obstructive pulmonary disease	18. Schizophrenia	17. Intra-abdominal surgery
7. Bronchopulmonary dysplasia	19. Vertebrobasilar insufficiency	Reproductive implications
8. Hypoxia	20. Sympathetic activity	1. Recurrent abortion
9. Hyperoxia	21. Spinal cord I/R	2. Pre-eclampsia
10. Fontan operation	22. Cold complex regional pain	3. Fetal growth restriction
11. Idiopathic pulmonary fibrosis	Urogenital implications	4. Ovarian I/R
12. Lung transplantation	1. LUTS and BPH	5. Poor ovarian response
13. Tuberculosis	2. Urinary stones	6. Endometrial thickness
14. Primary ciliary dyskinesia	3. Testicular I/R injury	7. Uterine blood flow
15. Exercise oscillatory breathing	4. Renal I/R injury	8. Uterine contractility
16. Obstructive sleep apnea	5. Nephrogenic diabetes insipidus	9. Primary dysmenorrheal
17. Acute lung injury	6. Contrast-induced nephropathy	10. Sperm parameters
18. Decompression sickness	7. Overactive bladder	11. Androgen binding protein
19. Complex pulmonary atresia	8. Obstructed bladder	12. Leydig cell function
20. Interstitial pneumonia	9. Interstitial cystitis	13. Temporary ejaculation failure
21. Pulmonary sarcoidosis	10. Chronic prostatitis	Cutaneous implications
22. Thromboembolic pulmonary hypertension	11. After vasectomy	1. Raynaud phenomenon
23. Pulmonary Langerhans cell histiocytosis	12. Renal transplantation	2. Systemic sclerosis
Cardiovascular implications	13.Gentamicin-induced nephrotoxicity	3. Flap viability
1. Cardioprotection	14. Urethral continence	4. Wound repair
2. Congenital heart disease	15. Shock wave lithotripsy	5. Fat grafting
3. Heart failure	16. Diabetic nephropathy	6. Palmar-plantar erythrodysesthesia
4. Valvular surgery	Cellular implications	7. Pressure ulcers
5. Hypertension	1. Oxidative stress	8. Skin perfusion
6. Atherosclerosis	2. Endothelial dysfunction	9. Skin hypopigmentation
7. Myocardial dysfunction	3. Metabolic effects	10. Antiphospholipid syndrome
8. Myocardial I/R injury	4. Obesity	11. Pansclerotic morphea
9. Cardiac hypertrophy	5. H_2S pathway	12. Cellulite
10. Angiogenesis	6. Anti-inflammatory effects	Oncology implications
11. Cardiac contractility	7. Heme oxygenase induction	1. Cancer cells
12. Heart transplantation	8. Antiapoptotic effects	2. Chemotherapeutics efficacy
13. Cardiomyopathy	9. Mitochondrial biogenesis	3. Multidrug resistance
14. Ischemia	10. Xanthine oxidase inhibition	Endocrinal implications
15. Cardiac fibrosis	11. Endothelial progenitor cells	1. Diabetes mellitus
16. Intermittent claudication	12. Lymphocytic malformation	2. Hypogonadism
17. Vascular anastomosis	13. Androgen receptor	Musculoskeletal implications
18. Cardiac stem cells	14. Carbonic anhydrase activator	1. Blood perfusion
19. Coronary dysfunction	15. Sickle cell disease	2. Muscle function
20. Cardiopulmonary resuscitation	16. Stem cells	3. Fracture healing
Neurologic implications	17. Oxygen release	4. Arthritis
1. Alzheimer disease	Gastrointestinal implications	5. Sport performance
2. Spinal cord injury	1. Congenital diaphragmatic hernia	6. Skeletal I/R
3. Subarachnoid hemorrhage	2. Gastrointestinal I/R injury	7. Muscle wasting
4. Antinociceptive effects	3. Hepatic fibrosis	Infectious implications
5. Peripheral neuropathy	4. Gastroprotection	1. Malaria
6. Nerve regeneration	5. Hepatic encephalopathy	2. Anti-infective
7. Cognitive functions	6. Distal esophageal spasm	3. Sepsis

(continued)