Review

Phosphodiesterase Type 5 Inhibitors for the Treatment of Erectile Dysfunction: Pharmacology and Clinical Impact of the Sildenafil Citrate Orodispersible Tablet Formulation

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ABSTRACT

Purpose: The purpose of this review is to provide an overview of the pharmacology, tolerability, and efficacy of the different phosphodiesterase type 5 (PDE5) inhibitors available for the treatment of erectile dysfunction (ED), with a special focus on the sildenafil orodispersible tablet (ODT) formulation.

Methods: A literature search was performed in PubMed, EMBASE, and Cochrane Reviews using the terms *erectile dysfunction*, *patient preference*, *sildenafil*, and *PDE5 inhibitors* to identify articles published in English between May 1, 2006, and November 18, 2016. A total of 29 studies were included in this review.

Findings: There are substantial data in the literature on the use of PDE5 inhibitors for the treatment of ED. Oral PDE5 inhibitors have been found to be efficacious in the treatment of ED based on results from standard tools used to assess treatment outcomes, such as the Global Assessment Questionnaire 1. In addition, PDE5 inhibitors are defined as well tolerated because of the low occurrence of serious adverse effects or discomfort. Mild adverse reactions, compared with a placebo, include headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash. Both the film-coated tablet and ODT formulations of sildenafil with or without water have equivalent systemic exposure. However, use of a sildenafil ODT formulation offers a convenient alternative method of administration that would be advantageous for patients with ED.

Implications: According to the published literature, the PDE5 inhibitors are considered an effective and well-tolerated option for the treatment of ED as determined by data generated from standard instruments used in the assessment of treatment outcomes in ED and reported types and severity of adverse effects. The sildenafil ODT formulation, which disintegrates rapidly in the mouth, is an alternative to the solid film-coated tablet formulation that offers administration benefit with the potential to improve treatment adherence, thereby enhancing the sexual health and sense of psychological well-being of patients and their partners. (*Clin Ther*. 2017;39:370–377) © 2017 Published by Elsevier HS Journals, Inc.

Key words: erectile dysfunction, orodispersible tablet, PDE5 inhibitor, sildenafil citrate.

INTRODUCTION

Erectile dysfunction (ED) is defined as "the inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance and has been associated with both organic and psychogenic causes."[1] Damage to arteries, smooth muscle, and fibrous tissues that results in altered blood flow to and from the penis is thought to be the most common cause of ED.[2] Known psychogenic causes of ED include depression, anxiety, relationship problems, and

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schizophrenia.[3,4] The worldwide prevalence of ED is estimated to be approximately 322 million cases by 2025.[2] In the general population, 10% to 20% of men have experienced ED, with an overall incidence of 30% and 18.4% in the European Union and the United States, respectively.[5,6] In these 2 populations, the incidence of ED was reported to be the highest in the age group of ≥70 years (64% and 70.2%, respectively), followed by the age group of 60 to 69 years (38% and 43.8%, respectively) and 40 to 59 years (25% and 14.8%, respectively).[5,6]

ED has a significant impact on the quality of life of patients. Men with ED have been reported to have lower levels of physical activity, emotional satisfaction, and general happiness and have also been documented to exhibit role limitations because of the impact it has on their emotional well-being.[7] ED has an extensive impact on the self-perception and sexual being of men and influences their interactions with women or potential partners.[7] It also has a negative impact on their female partners, who report lower sexual satisfaction and sexual drive.[8] Because sexual satisfaction is considered to be a major predictor of life satisfaction, treatment of ED would likely improve the quality of life for these individuals and their partners.[9]

Several therapeutic options are available for the treatment of ED. One of these options is phosphodiesterase type 5 (PDE5) inhibitor–based pharmacotherapy. An overview of the pharmacology, tolerability, and efficacy of the different agents in the class, with an in-depth review of the pharmacologic and clinical aspects of the more recently available orodispersible tablet (ODT) formulation, is warranted for a better understanding of the overall impact of PDE5 inhibitors and the extent to which these agents address the clinical and psychosocial needs of patients with ED.

METHODS

A literature search was performed through PubMed, EMBASE, and Cochrane reviews using the search terms *PDE5/phosphodiesterase-5* AND *inhibitor* AND *erectile* AND *dysfunction* for articles published between May 1, 2006, and November 18, 2016. The search was restricted to articles published in the English language. Approximately 1200 articles were retrieved. An additional search was performed manually to find specific studies recommended for inclusion that did not appear in the original search results. Studies were considered eligible for inclusion if at least any one of the outcomes regarding the pharmacology, tolerability, efficacy, or convenience of sildenafil were reported. Study eligibility was independently determined by 2 authors (F.S. and S.D.). Any discrepancies were resolved by a third investigator (E.A.J.). A total of 29 eligible studies were identified (24 in the electronic search and 5 in the manual search) and included in this review.

Overview of PDE5 Inhibitors

PDE, an enzyme that breaks the phosphodiester bond in biological molecules, is present throughout the body and is categorized into 11 different families, 21 subfamilies, and 53 isoforms.[10,11] PDE types 2, 3, 4, and 5 are present in the penis, with PDE5 being the most predominant.[11] PDE5 is also found in platelets, skeletal muscles, and vascular and visceral muscles.[11]

The PDE5 inhibitors approved by the US Food and Drug Administration include sildenafil (approved in 1998), tadalafil, vardenafil (both approved in 2003), and avanafil (approved in 2012).[3,12] Despite the differences in the durations of action, absorption, elimination, the PDE5 inhibitors have been reported to have similar efficacy.[12,13]

Mechanism of Action

Penile erection is primarily mediated by the neurotransmitter nitric oxide through the cyclic guanosine monophosphate (cGMP) pathway. Sexual stimulation occurs in nonadrenergic and noncholinergic nerves in the pelvic parasympathetic plexus, which leads to the release of nitric oxide across the penile arteries' and cavernosal smooth muscles' neuromuscular junction. This increase in nitric oxide causes an increase in cGMP, which results in the relaxation of penile smooth muscle and several-fold increase in the blood flow. This relaxation subsequently results in the compression of veins, which prevent the backward flow of blood and lead to erection. This pathway is regulated by the hydrolysis of cGMP to GMP by the PDE5 enzyme during the flaccid stage.[3,11] The inhibitors of PDE5 impede the hydrolysis of cGMP to GMP. They amplify the normal erectile physiology, relying on intact libido, sexual stimulation, sensory pathways, and multiple other factors required for a normal erectile function.[3] PDE5 inhibitors act as competitive inhibitors of PDE5 enzyme. The structural similarity between PDE5 and the PDE5 inhibitors allows them to impede the breakdown of