SEXUAL MEDICINE REVIEWS

Update on the Safety of Phosphodiesterase Type 5 Inhibitors for the Treatment of Erectile Dysfunction

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ABSTRACT

Introduction: Phosphodiesterase type 5 inhibitors (PDE5Is) have demonstrated efficacy in the treatment of erectile dysfunction (ED). Although historically found to have limited drug-related adverse events, emerging data have suggested that PDE5Is might be associated with melanoma or recurrence of prostate cancer after radical prostatectomy.

Aim: To summarize the literature on the safety of PDE5Is.

Methods: A literature review was performed through PubMed from 1990 through 2016 regarding ED. Keywords used for the search were *erectile dysfunction, phosphodiesterase type 5 inhibitors, sildenafil, vardenafil, tadalafil, avanafil, safety, side effects,* and *adverse events,* among others.

Main Outcome Measures: Visual, auditory, cardiovascular, renal, hepatic, priapic, and oncologic outcomes associated with the intake of PDE5Is for the treatment of ED, in addition to drug interactions, abuse, overdose, and the phenomenon of counterfeit medications.

Results: PDE5Is are safe drugs for the management of ED. Although recent studies have shown an increased risk of non-arteritic ischemic optic neuropathy with PDE5Is, the magnitude of that risk is small. The possibility that PDE5Is cause sensorineural hearing loss remains uncertain. PDE5Is display a safe cardiovascular profile if used according to the Princeton III Consensus guidelines. There appears to be an association between PDE5I use and melanoma but the absence of a mechanism of causation raises doubt that the association is cause and effect. PDE5Is do not increase the risk of biochemical recurrence after prostate cancer management. PDE5I abuse and use of counterfeit medications present serious global health concerns.

Conclusion: Current data strongly support the efficacy, tolerability, and overall safety of PDE5Is for the treatment of ED. PDE5Is probably cause a small increase in the risk of non-arteritic ischemic optic neuropathy. Evidence on increased rates of melanoma and prostate cancer recurrence is weak and controversial. PDE5Is should still be considered first-line therapy for the treatment of most etiologies of ED. **Yafi FA, Sharlip ID, Becher EF. Update on the Safety of Phosphodiesterase Type 5 Inhibitors for the Treatment of Erectile Dysfunction. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Phosphodiesterase Type 5 Inhibitors; Erectile Dysfunction; Safety; Melanoma; Prostate Cancer

INTRODUCTION

Erectile dysfunction (ED) is the most commonly occurring male sexual dysfunction, with 152 million men worldwide with ED in 1995 and an estimated 320 million by 2025.[1,2] The most commonly used class of medications for the treatment of ED is phosphodiesterase type 5 inhibitors (PDE5Is).[3] PDE5Is were serendipitously discovered to induce penile erections while being investigated for hypertension and angina pectoris.[4] After a registration trial, the original PDE5I, sildenafil citrate (Viagra, Pfizer, New York, NY, USA), received approval from the Food and Drug Administration (FDA) in 1998 as the first oral drug for the treatment of ED.[5] Since then, other PDE5Is have been investigated and similarly approved by the FDA for the management of ED.[3]

Over time, PDE5Is have demonstrated excellent efficacy in randomized placebo-controlled trials, with limited drug-related adverse events (AEs), thus leading to wide adoption in clinical practice.[6,7] Currently, PDE5Is are considered first-line therapy for the management of most etiologies of ED.[3] Although most AEs related to PDE5Is are believed to be mild and self-limited,

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they do unfortunately contribute to significant treatment dropout rates.[8] Furthermore, although PDE5Is also have been possibly associated with more serious AEs such as hearing loss, visual disturbances, and priapism, among others, emerging data suggest additional possible associations with melanoma and prostate cancer recurrence after radical prostatectomy, among others.[9–11]

In light of these emerging concerns, we sought to provide a timely and comprehensive update on the safety of PDE5Is for the treatment of ED. For this purpose, an ED literature review spanning 1982 to 2016 was performed through PubMed. Keywords used for the search were *erectile dysfunction, impotence, phosphodiesterase type 5 inhibitors, sildenafil, vardenafil, tadalafil, avanafil, safety, side effects,* and *adverse events,* such as non-arteritic ischemic optic neuropathy (NAION), vision loss, hearing loss, priapism, infertility, prostate cancer recurrence, and melanoma.

MECHANISM OF ACTION OF PDE5 INHIBITORS

PDE5Is work by blocking the breakdown of 3′,5′-cyclic guanosine monophosphate, a signaling molecule generated by the nitric oxide–dependent soluble guanylate cyclase. In turn, cyclic guanosine monophosphate activates cyclic guanosine monophosphate–dependent protein kinase G, which leads to vascular tone modulation and vasorelaxation in the vascular smooth muscle of the penis.[12] These drugs require the presence of sexual arousal and nitric oxide production. Their effect also requires the presence of adequate and efficient smooth muscle cells in the corpora cavernosa.[3] Although all these drugs are similar in mechanism of action, their pharmacokinetics differ. Of commercially available PDE5Is, avanafil is associated with the shortest time to initiation of erection (maximum time = 0.75 hour) and tadalafil is associated with the longest duration of action (half-life = 17.5 hours), thus allowing physicians to cater treatment according to a patient's needs and preferences.[13–20] Furthermore, different PDE5Is have different affinities for PDE5 and different bioselectivities for the 11 available PDE isoenzymes, thus leading to divergent side effect profiles.[3] For example, sildenafil and vardenafil cross-react with PDE6, which is predominantly located in the retina, and tadalafil cross-reacts with PDE11.[12]

COMMON SIDE EFFECTS OF PDE5 INHIBITORS

In a meta-analysis of 119 PDE5I trials (31,195 individuals), the most commonly reported drug-related AEs were flushing, headache, dyspepsia, back pain, myalgia, dizziness, and rhinitis.[8] There were no differences in the side effect profiles among different PDE5Is, except tadalafil, which caused a higher incidence of myalgia than sildenafil (rate ratio = 4.69, 95% CI = 1.39–14.21), possibly due to tadalafil's cross-reactivity with PDE11. These AEs are mostly considered self-limited with minimal to no long-term deleterious consequences.[3,12] Accordingly, reported discontinuation rates owing to side effects are generally very low (<3–5%).[15,21–37]

MAIN CONCERNS WITH PDE5 INHIBITORS

Beyond the common side effects associated with PDE5Is, there are possibly some more serious drug-related AEs that require further scrutiny to establish causation. They are summarized in the following sections.

Visual Changes

As mentioned earlier, PDE5Is also inhibit non-PDE5s including PDE6. The affinity of sildenafil for PDE6 is approximately one tenth of its affinity for PDE5.[38] Other PDE5Is demonstrate similar or less inhibition of PDE6. Because PDE6 is highly concentrated in the rod and cone cells of the retina, PDE5 inhibition can result in PDE6 inhibition in the retina and cause brief and temporary ophthalmologic side effects. The most common of these AEs are mild and consist of transient blue color tinge to vision, increased sensitivity to light, and blurring of vision. Different ophthalmologic tests such as electroretinography, pupillometry, tests of central vision, photo stress tests, intraocular pressure measurements, tests of contrast sensitivity, and others have not shown evidence for structural or functional changes to the retina or significant changes in ocular circulation with therapeutic doses of PDE5Is.[38]

NAION has been reported to be a complication of PDE5I therapy. NAION is the most common acute optic neuropathy in adults at least 50 years of age. The typical symptoms of NAION are sudden and painless decrease in vision in one or rarely both eyes. Often, patients awake from sleep with loss of vision. The loss of vision with NAION is usually transient but can be permanent. NAION commonly occurs in persons who have vascular risk factors.[38] NAION is a rare condition with an estimated annual incidence of 2.3 to 10.2 cases per 100,000 men and women at least 50 years old.[39] This condition is believed to result from vascular insufficiency to the optic nerve, but the exact cause of NAION is not known. Because the condition is rare and occurs in men with pre-existing vascular risk factors who coincidentally might be using a PDE5I for treatment of ED, controversy exists as to whether PDE5Is cause NAION. Adding to this controversy is the poor understanding of the pathophysiology of NAION and the lack of an explanation for how PDE5Is might cause NAION. Moreover, multiple studies have supported or denied that PDE5Is cause NAION.

Several recent publications have addressed this controversy. A pharmacoepidemiologic nested case-control study using a large retrospective health claims database listed 1,109 cases of NAION during an 11-year period in 934,283 individuals compared with 1,237,290 age-matched controls.[39] The adjusted rate ratio for any use of PDE5Is in the year before the diagnosis of NAION was 1.01 (95% CI = 0.79–1.28). Use of a PDE5I in men 30 days before NAION had an adjusted rate ratio of 0.96