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

Faysal A. Yafi, MD, FRCSC, Ira D. Sharlip, MD, and Edgardo F. Becher, MD, PhD

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.

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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. The most commonly used class of medications for the treatment of ED is phosphodiesterase type 5 inhibitors (PDE5Is). PDE5Is were serendipitously discovered to induce penile erections while being investigated for hypertension and angina pectoris. 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. Since then, other PDE5Is have been investigated and similarly approved by the FDA for the management of ED. 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. Currently, PDE5Is are considered first-line therapy for the management of most etiologies of ED. Although most AEs related to PDE5Is are believed to be mild and self-limited,
they do unfortunately contribute to significant treatment dropout rates. 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 vaso-relaxation 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
More importantly, two prospective studies using a case-crossover design have identified a doubling of the risk of NAION occurrence within five half-lives of PDE5I use. In one of these studies, 43 definite cases of NAION were found. 40 In this study, the odds ratio for NAION after PDE5I use was 2.15 (95% CI = 1.06–4.34). This study estimated that weekly use of PDE5I added three cases of NAION annually per 100,000 men at least 50 years old to the baseline NAION incidence of 2.3 to 11.8 cases per 100,000 men of this age. 40 In the other prospective study, a similar case-crossover design was used. 41 Of 279 men with confirmed NAION, 22 had been exposed to a PDE5I intermittently within the 30 days before the onset of NAION. The Mantel-Haenszel rate ratio for risk of NAION associated with PDE5I exposure was 2.27 (95% CI = 0.99–5.20). These two studies suggest that the risk of NAION in men using PDE5Is is approximately twice the baseline risk. Because the baseline risk of NAION is very small, the increased risk of NAION with PDE5I is still small. From a clinician’s perspective, it appears that benefit-to-risk analysis of PDE5I use with respect to the risk of NAION strongly favors benefit.

Auditory Changes

Sudden hearing loss has been reported in small or single-case series of patients receiving PDE5Is, but it is not known whether these events are more frequent than the baseline of these events in men who do not use PDE5Is. Nevertheless, the FDA now requires a warning about the risk of hearing loss from PDE5I use. The first case was reported in 2007 in a 44-year-old man after a daily dose of 50 mg for 15 days. 42 Maddox et al 43 subsequently reported two cases of sudden sensorineural hearing loss and reviewed the FDA’s postmarketing data. They identified 25 patients, of whom 88% experienced hearing loss 24 hours after PDE5I ingestion. Only 20% had complete resolution and 12% had partial recovery. Another publication by Khan et al 44 identified 47 cases of sudden sensorineural hearing loss from publications and pharmacovigilance agencies. Skeith et al 45 found a synergistic adverse relation for auditory morbidity between sildenafil and furosemide and CYP3A4 inhibitors such as diltiazem, especially in cases of renal failure and high peak drug levels.

In a prospective study of 25 patients taking tadalafil (15 on 10 mg and 10 on 20 mg), audiometry showed a modest increase in hearing thresholds for higher frequencies in 3 of 10 patients on 20 mg. 46 In contrast, sildenafil showed a therapeutic effect on blast-induced tinnitus and hearing impairment. 47 Au et al 48 reported on a study of a strain of mice with high susceptibility to age-related hearing loss, and they were unable to find a statistically significant difference between treated and untreated mice with the highest tolerated dose of sildenafil evaluated by auditory brainstem responses. In summary, although there are some small case series reporting sudden sensorineural hearing loss, the etiology and pathophysiology remain uncertain. Clinicians should be aware of this reported side effect.

Cardiovascular Effects

Although PDE5Is were initially developed as antiangina drugs with expected cardioprotective effects, the most feared and highly publicized AEs, especially in the early days of sildenafil, were cardiovascular (CV) in nature. According to current guidelines and consensus, there are clear cautions and contraindications for PDE5Is in patients with unstable angina, severe congestive heart failure, or uncontrolled hypertension, those at high risk for arrhythmias, and those receiving nitrates or any other form of nitric oxide donors. 49 Some studies also have suggested that caution should be observed when contemplating the use of PDE5Is in patients with systolic heart failure and pulmonary hypertension. 50

Low and Costabile 51 analyzed 10 years of AEs reported to the FDA for PDE5Is. CV AEs represented 16.2% of the total reported events and deaths were approximately 5% after reviewing all published clinical trials on the first three PDE5Is. These data are supported by recent data from the International Society for Sexual Medicine on conservative ED treatment did not find a statistically significant difference between active and placebo groups in myocardial infarctions or CV-related deaths. 52 Notably, in a recent Swedish study of 43,145 patients hospitalized for a first-time myocardial infarction, men who received medical treatment for ED had a 33% lower mortality and a 40% lower risk of hospitalization for heart failure compared with those who did not receive such treatment. 53 In a recent review, Ventimiglia et al 9 did not find any difference in CV safety when comparing all seven available PDE5Is. In contrast, after several published reports on the cardioprotective role of PDE5Is, a recent meta-analysis showed that these drugs actually have anti-remodeling properties, improve cardiac inotropism, and have a good safety profile. 54 Accordingly, the investigators concluded that PDE5Is could be offered to patients with heart failure and left ventricular hypertrophy.

Renal Function

PDE5Is undergo extensive tubular reabsorption in the kidney, thus leading to minimal renal clearance and excretion. As such, oral doses of PDE5I are mostly excreted as metabolites in the stool, rather than in urine. 55 Data collated from 67 sildenafil double-blinded placebo-controlled trials and a postmarketing safety database demonstrated similar efficacy, safety profile, and discontinuation rates in patients with ED with vs without moderate renal insufficiency. 56 In men with chronic renal insufficiency (creatinine clearance < 30 mL/min), it is recommended to initiate PDE5I therapy at a lower dose and titrate up as tolerated because of decreased drug clearance. 3

Furthermore, ED occurs frequently in patients with end-stage renal disease, in patients undergoing peritoneal dialysis, and in patients after kidney transplantation, with prevalence rates as...
high as 71% to 80% in patients on dialysis.\textsuperscript{57--62} In a review of double-blinded placebo-controlled trials of patients undergoing dialysis or after renal transplantation, PDE5I demonstrated significant improvements in International Index of Erectile Function scores, with no increase in AE or AE-related discontinuation rates compared with placebo.\textsuperscript{63}

Hepatic Function

PDE5Is undergo rapid metabolism and excretion in the liver primarily through the CYP3A pathway, but also through the CYP2C9, CYP2C19, and CYP2D6 pathways.\textsuperscript{64} Studies have demonstrated that mild and moderate hepatic impairment significantly decrease oral clearance and increase maximum concentration, area under the curve, and drug half-life for sildenafil and vardenafil, but not for tadalafil.\textsuperscript{65} As such, current manufacturer labeling recommends initiating therapy with sildenafil and vardenafil at lower doses and titrating up as tolerated.\textsuperscript{66,67} However, this does not seem necessary with tadalafil. To date, severe hepatic insufficiency has not been studied for any of the PDE5Is and, as such, their use remains contraindicated in this population.\textsuperscript{56}

Priapism

Although often advertised as a major concern with PDE5I therapy, reported treatment-induced priapism rates are very low.\textsuperscript{5,56} In a sildenafil double-blinded placebo-controlled study, priapism occurred in 0.1% of participants, with mostly mild episodes not requiring intervention, and in 2.5% to 2.7% of patients in the postmarketing surveillance analysis.\textsuperscript{56} Of note, 27% of men with an incidence of priapism in the latter analysis had been using concomitant medications that might have contributed to the priapic episodes.\textsuperscript{56} Few other individual case reports of PDE5I-induced priapism have been published, some of which were confounded by the concomitant use of opiates and intracavernosal injections.\textsuperscript{56--70} Recently, emerging data have even suggested a potential role for daily PDE5I therapy for the suppression of priapic episodes in men with stuttering priapism, a condition in which PDE5 dysregulation is believed to be contributory.\textsuperscript{71}

Fertility

Preliminary animal studies have suggested that tadalafil can cause alterations in the seminiferous tubules with ensuing decreased spermatogenesis in dogs.\textsuperscript{72} However, these results have not translated to humans. In two studies of 421 healthy men or men with mild ED who were at least 45 years and were randomized to 6 months of treatment with placebo or daily tadalafil, Hellstrom et al\textsuperscript{72} reported no drug-related AEs on spermatogenesis or on reproductive hormones. Similar findings were noted in a double-blinded, placebo-controlled, non-inferiority study of men who were randomized to receive tadalafil 20 mg or placebo for 9 months followed by a 6-month washout period.\textsuperscript{73}

Cancer

Melanoma

Li et al\textsuperscript{10} reported an association between the use of sildenafil and an increased risk of melanoma. This study was performed on participants enrolled in the Health Professional’s Follow-up Study, in which sildenafil users showed an increased risk of developing subsequent melanoma but no other malignant skin lesions, with a multivariate-adjusted hazard ratio of 2.24 (95% CI = 1.05--4.78). The rationale behind this investigation was that low levels of PDE5, by BRAF gene activation or sildenafil use, might increase melanoma’s invasiveness through the mitogen-activated protein kinase and extracellular signal-regulated kinase pathway.

In another study using Swedish databases, Loeb et al\textsuperscript{74} correlated the number of PDE5I prescriptions with the risk of melanoma. They found that, of patients with melanoma, 11% had PDE5I prescriptions vs 8% of controls. Surprisingly, the highest melanoma risk was for men with a single prescription and the most significant difference was found for patients with a stage 0 melanoma. In a recent editorial, Loeb and Stattin\textsuperscript{75} raised the question of whether this association might be causal or non-causal.

Prostate Cancer Recurrence

In a retrospective study from a high-volume radical prostatectomy center in Germany, Michl et al\textsuperscript{11} reported an increased risk of biochemical recurrence (BCR) in patients taking PDE5Is. The cohort was composed of 4,752 consecutive patients with a 5-year BCR-free survival rate of 84.7% for those who received a PDE5I postoperatively \((n = 1,110)\) vs 89.2% for those who did not \((n = 3,642); P = .0006\). They concluded that the use of a PDE5I was an independent risk factor for BCR \((\text{hazard ratio} = 1.38)\).

Gallina et al,\textsuperscript{78} using data from a high-volume center in Italy, published a study on 2,579 patients after nerve-sparing radical prostatectomy and did not find a significant difference in BCR with regard to PDE5I use, type of administration schedule (on demand, daily rehabilitation schedule), or number of pills used.

In another study using the National Prostate Cancer Register from Sweden linked with the Prescribed Drug Register,
Table 1. Select studies examining the effects of PDE5I use on melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects</th>
<th>Study type</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Li et al(^{10})</td>
<td>2014</td>
<td>25,848 men enrolled in Health Professionals' Follow-up Study</td>
<td>Prospective Sildenafil users showed increased risk of developing subsequent melanoma but no other malignant skin lesions (multivariate-adjusted HR = 2.24, 95% CI = 1.05–4.78)</td>
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<tr>
<td>Loeb et al(^{74})</td>
<td>2015</td>
<td>4,065 melanoma cases diagnosed from 2006 through 2012 and 5 randomly selected controls per case with matching year of birth</td>
<td>Nationwide, population-based, nested case-control study in Swedish Prescribed Drug Register, Swedish Melanoma Register, and other health care registers and demographic databases in Sweden</td>
<td>435 men (11%) had filled prescriptions for PDE5Is, as did 1,713 of 20,325 controls (8%); PDE5Is were significantly associated with melanoma stage 0 (OR = 1.49, 95% CI = 1.22–1.83; 13% for cases vs 8% for controls) and stage I (OR = 1.21, 95% CI = 1.02–1.43; 12% for cases vs 10% for controls), but not stages II–IV (OR = 0.83, 95% CI = 0.63–1.09; 6% for cases vs 7% for controls); PDE5I use also was associated with increased risk of basal cell carcinoma (OR = 1.19, 95% CI = 1.14–1.25; 9% for cases vs 8% for controls); men taking PDE5Is had higher educational level and annual income, factors that also were significantly associated with melanoma risk.</td>
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<td>Lian et al(^{76})</td>
<td>2016</td>
<td>142,983 patients, of whom 440 were newly diagnosed with melanoma during follow-up</td>
<td>Retrospective UK Clinical Practice Research Datalink cohort of men newly diagnosed with ED from 1998 to 2014 and followed until 2015</td>
<td>PDE5I use was not associated with overall increased risk of melanoma (66.7 vs 54.1 per 100,000 person-years; HR = 1.18, 95% CI = 0.95–1.47); risk was significantly increased in those who had received ≥7 prescriptions (HR = 1.30, 95% CI = 1.01–1.69) and ≥25 pills (HR = 1.34, 95% CI = 1.04–1.72); there was no overall association with basal and squamous cell carcinoma.</td>
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<tr>
<td>Matthews et al(^{77})</td>
<td>2016</td>
<td>145,104 men with ≥1 PDE5I prescription, and 560,933 unexposed matched controls</td>
<td>Matched cohort study using data from UK Clinical Practice Research Datalink of men initiating a PDE5I and with no prior cancer diagnosis and matched by age, diabetes status, and general practice vs up to 4 unexposed controls</td>
<td>There was a small positive association between PDE5I use and melanoma risk (HR = 1.14, 95% CI 1.01–1.29, P = .04); there was increased risk for basal cell carcinoma (HR = 1.15, 95% CI 1.11–1.19, P &lt; .001) and solar keratosis (HR = 1.21, 95% CI 1.17–1.25, P &lt; .001); there was no evidence that risk increased with number of prescriptions received (P for trend = .83); solar keratosis was associated with future PDE5I use (OR = 1.28, 95% CI 1.23–1.34, P &lt; .001).</td>
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ED = erectile dysfunction; HR = hazard ratio; OR = odds ratio; PDE5I = phosphodiesterase type 5 inhibitor.
Loeb et al\textsuperscript{79} did not find a relation between PDE5I use and BCR after radical prostatectomy or radiation therapy. Moreover, the incidence of BCR was lower in those patients exposed to a larger number of pills.

Based on the data provided from these three studies, no changes in ED management after definitive prostate cancer treatment should be applied, including on-demand and rehabilitation schemes\textsuperscript{80} (Table 2).

### DRUG ABUSE AND OVERDOSE

The mode of action of PDE5Is is peripheral rather than central in nature and, as such, there is little to no evidence of men developing physical dependence or tolerance to these medications.\textsuperscript{81}

Reports, mostly emanating from the United Kingdom, have suggested significant rates of misuse, abuse, AEs, and even overdose from recreational use of PDE5I, particularly by young men without a formal diagnosis of ED.\textsuperscript{82–89} The overwhelming majority of pills was obtained without prescription and was used concomitantly with alcohol and illicit drugs, particularly marijuana and amphetamines.\textsuperscript{90} Case reports of seizures and myocardial infarction have been reported in these men, likely potentiated by the vasodilatory, pro-convulsant, and cytochrome P450 inhibitory properties of these illicit drugs.\textsuperscript{91–94} This recreational use also represents a public health concern because it has been associated with a higher incidence of sexually transmitted infections, including HIV, particularly when associated with illicit drug use.\textsuperscript{95,96}

Overdose from intentionally or inadvertently exceeding the maximal allowable dose of PDE5Is is rare.\textsuperscript{96} Clinical studies of sildenafil using higher concentrations and/or more frequent administration demonstrated a similar safety profile as standard dosing, but with higher frequency and severity of drug-related AEs.\textsuperscript{56} Similar findings were noted in a single-dose sildenafil volunteer study of doses up to 800 mg.\textsuperscript{95} The highest first total daily dose reported was in a 33-year-old man who consumed 24 tablets of sildenafil 100 mg, with significant visual complications, most of which resolved except for visual field defect and annular scotoma.\textsuperscript{56} However, there are a few case reports of suspected PDE5I-related overdoses, including two with a fatal outcome, one from an omental varix rupture in a man with advanced alcoholic cirrhosis and another from sudden cardiac death in a man with pre-existing risk factors for coronary artery disease.\textsuperscript{97–104}

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**Table 2. Select studies examining the effects of PDE5I on prostate cancer biochemical recurrence**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects</th>
<th>Study type</th>
<th>Findings</th>
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<tr>
<td>Michl et al\textsuperscript{11}</td>
<td>2015</td>
<td>4,752 consecutive patients treated with bilateral nerve-sparing RP from January 2000 to December 2010</td>
<td>Retrospective</td>
<td>5-y BCR-free survival estimates in PDE5I vs non-PDE5I group were 84.7% (95% CI = 82.1–87.0) and 89.2% (95% CI = 88.1–90.3), respectively (P = .0006); multivariate regression analysis showed that PDE5I use was an independent risk factor for BCR (HR = 1.38, 95% CI = 1.11–1.70, P = .0035)</td>
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<tr>
<td>Gallina et al\textsuperscript{78}</td>
<td>2015</td>
<td>2,579 patients treated with bilateral nerve-sparing RP from 2004 to 2013</td>
<td>Retrospective</td>
<td>PDE5I use, type of administration schedule, and number of PDE5I pills were not significantly associated with higher risk of BCR (P ≥ .2 for all comparisons) after accounting for multiple confounders including time from RP to PDE5I use</td>
</tr>
<tr>
<td>Loeb et al\textsuperscript{79}</td>
<td>2016</td>
<td>men with localized prostate cancer who underwent primary RP or RT during 2006–2007 with 5-y follow-up</td>
<td>Nested case-control study using National Prostate Cancer Register of Sweden linked to Prescribed Drug Register</td>
<td>PDE5I use was not associated with BCR after RP (OR = 0.78, 95% CI = 0.59–1.03) or RT (OR = 0.98, 95% CI = 0.49–1.97) after adjusting for marital status, education, income, prostate-specific antigen, clinical stage, Gleason score, and proportion of positive biopsy results; results were similar after additional adjustment for surgical pathology (OR = 0.86, 95% CI = 0.64–1.16)</td>
</tr>
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BCR = biochemical recurrence; HR = hazard ratio; OR = odds ratio; PDE5I = phosphodiesterase type 5 inhibitor; RP = radical prostatectomy; RT = radiation therapy.
COUNTERFEIT MEDICATIONS

In 2009, the World Health Organization defined a “counterfeit medicine” as one “which is deliberately and fraudulently mislabeled with respect to identity and/or source” and more recently as “Substandard, Spurious, Falsely labeled, Falsified, and Counterfeit (SSFFC).” Alarming the global market for counterfeit medications, and notably PDE5Is, has increased exponentially in recent years, with reports estimating the proportion of falsified PDE5Is to be as high as 60% in some developing countries. Reasons for this surge and for targeting PDE5Is include an aging population with more ED, increased cost of original drugs, high profit margins, soft anti-counterfeit regulations, patient embarrassment, and ease of purchase through online “pharmacies.” However, cost concerns might be alleviated because patients taking PDE5Is will be expiring soon, potentially leading to significant decreases in pricing.

Unlike the original pills, counterfeit pills are unregulated and, as such, can present significant health hazards to patients ingesting them. In a 2009 raid and seize of 2,383 counterfeit Viagra pills in the United Kingdom, the concentration of active sildenafil ranged from 0% to 200% of indicated strength, and only 10% of samples contained an active ingredient within 10% of packaging. Similar findings were reported across the globe, notably in Italy, Austria, Canada, and Indonesia. Furthermore, an analysis of internet-ordered Viagra showed that 77% of pills were counterfeit, 5% were illegal, and only 18% were authentic. In addition, these pills can frequently contain non-reported contaminants such as gypsum, non-purified talc, amphetamine, commercial grade paints, paracetamol, metronidazole, and glyburide that can be toxic independently or through cross-reaction with other drugs. Notably, in 2008, 150 patients without diabetes but with severe hypoglycemia were admitted to the five public hospitals in Singapore. Glyburide was detected in blood or urine samples obtained from 127 of these patients (85%), of which 45 (30%) admitted ingesting illegal sexual-enhancement drugs before the onset of hypoglycemia. Seven patients remained comatose and four subsequently died, further highlighting the potentially lethal risks of drug contamination. Potentially harmful elevated microbial loads have been detected in counterfeit drugs, likely owing to non-sterile processing conditions. It is incumbent on sexual health care specialists to facilitate patient access to PDE5Is, educate patients on the risks of counterfeit drugs, remind them to purchase only from certified pharmacies, and report any illegal counterfeit practices.

PDE5Is should continue to be considered first-line therapy for the treatment of most etiologies of ED, but prescribers are strongly encouraged to discuss and counsel patients about all potential contraindications, drug interactions, and risks associated with PDE5I use.

Corresponding Author: Faysal A. Yafi, MD, FRCSC, Department of Urology, University of California—Irvine, 333 City Drive West, Suite 2170, Orange, CA 92868, USA. Tel: 714-456-5378; Fax: 888-378-4358; E-mail: faysalyafi@gmail.com

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STATEMENT OF AUTHORSHIP

Category 1
(a) Conception and Design
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher
(b) Acquisition of Data
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher
(c) Analysis and Interpretation of Data
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher

Category 2
(a) Drafting the Article
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher
(b) Revising It for Intellectual Content
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher

Category 3
(a) Final Approval of the Completed Article
Faysal A. Yafi; Ira D. Sharlip; Edgardo F. Becher

REFERENCES

CONCLUSIONS

Current data strongly support the efficacy, tolerability, and overall safety of PDE5Is for the treatment of ED. Evidence regarding increased rates of melanoma and prostate cancer recurrence is weak and controversial. Further robust prospective studies are needed before any definite conclusions can be made.


