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Authors

Abbasi, Behzad
Shaw, Nathan M
Lui, Jason L
et al.

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ORIGINAL ARTICLE

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Oral phosphodiesterase type 5 inhibitors and priapism: A VigiBase analysis

Behzad Abbasi[1] | Nathan M. Shaw[1,2,3] | Jason L. Lui[1] | Nizar Hakam[1] | Behnam Nabavizadeh[1] | Benjamin N. Breyer[1,4]

[1]Department of Urology, University of California San Francisco, San Francisco, California, USA

[2]Department of Urology, MedStar Georgetown University Hospital, Washington, District of Columbia, USA

[3]Department of Plastic and Reconstructive Surgery, MedStar Georgetown University Hospital, Washington, District of Columbia, USA

[4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

Correspondence
Benjamin N. Breyer, Department of Urology, University of California, 1001 Potrero Suite 3A, San Francisco, CA 94110, USA.
Email: benjamin.breyer@ucsf.edu

Abstract

Purpose: To explore the differences of priapism events among a diverse cohort taking erectogenic medicines (i.e., phosphodiesterase type 5 inhibitors [PDE5i] and intracavernousal drugs).

Methods: We queried the World Health Organization global database of individual case safety reports (VigiBase) for records of the adverse drug reactions (ADR) with sildenafil, tadalafil, avanafil, vardenafil, papaverine, and alprostadil. Disproportionality analyses (case/non-case approach) were performed to assess the reporting odds ratio (ROR) of priapism reporting in PDE5i consumers compared to intracavernousal drug recipients.

Results: From a total of 133 819 ADR events for erectogenic medications, 632 were priapism (PDE5is: $n = 550$, 0.41%; intracavernousal drugs: $n = 82$, 9.92%). Priapism disproportionality signals from intracavernousal drugs were 25 times stronger than PDE5is (ROR = 34.7; confidence interval [CI] 95%: 27.12–43.94 vs. ROR = 1.38; 95% CI: 1.24–1.54). For all PDE5i agents, the 12–17 years age group had the highest ROR (9.49, 95% CI: 3.76–19.93) followed by 2–11 years (4.31, 95% CI: 1.57–9.4). Disproportionality signals for consumers under 18 for both all PDE5is as a whole (ROR = 4.57, 95% CI: 2.48–7.73) and sildenafil (ROR = 4.89, 95% CI: 2.51–8.62) were stronger than individuals 18 or older (ROR = 1.06, 95% CI: 0.93–1.21 and ROR = 1.08, 95% CI: 0.91–1.26, respectively).

Conclusions: PDE5i use shows disproportionate priapism signals which are higher in young patients.

KEYWORDS

cialis, erectile dysfunction, phosphodiesterase 5 inhibitor, priapism, sildenafil, tadalafil, viagra

Key Points

- Priapism from phosphodiesterase type 5 inhibitors (PDE5is) is only reported by limited case reports. This study sought to investigate the disproportionality signals for priapism among PDE5i users in a large international dataset and to assess the differences between different PDE5i products in the development of priapism.
- We found a very small reporting odds of priapism with oral PDE5is compared with other adverse drug reactions.
- The use of PDE5is among young patients is associated with a stronger pharmacovigilance signal for priapism compared to adults, albeit low. Our analysis further confirms that priapism due to PDE5i use among older men is rarely reported and is not disproportionate.

Plain Language Summary

Priapism is an erection persisting for over 4 h and implicates emergent intervention to prevent the risk of erectile dysfunction in the future. Oral phosphodiesterase type 5 inhibitors (PDE5is) are used to treat erectile dysfunction and have rarely been reported to cause priapism. Looking at the largest international database of individual case safety reports for drugs (VigiBase), we aimed to explore the differences the disproportionality signals of priapism among PDE5is and identify available patient factors that may affect these signals. We identified reports of priapism corresponding to sildenafil, tadalafil, vardenafil, and avanafil in VigiBase from 1994 to 2021 and performed disproportionality analysis calculating the reporting odds ratio (ROR), which corresponds to the odds of an adverse reaction being reported for a specific drug versus all other drugs in a dataset, for priapism in PDE5is. We found a very small reporting odds of priapism with PDE5is compared with other drugs in our data. PDE5i use among young patients was associated with a stronger pharmacovigilance signal pharmacovigilance signal for priapism compared to adults, albeit low. Our analysis further confirmed that the reportings of priapism among older men is extremely rare. This warrants clinical studies looking at adult men who get priapism from PDE5i.

1 | INTRODUCTION

Priapism is an erection persisting for over 4 h, often associated with pain. Most commonly, priapism is coupled with the absence or reduction in intracavernosal arterial flow, known as ischemic priapism, which implicates emergent intervention to prevent fibrosis of corpora cavernosa and the subsequent risk of long-term erectile dysfunction (ED). Priapism incidence ranges from 0.3 to 1.5 per 100 000 men, with approximately 30% drug-induced.[1–3] Pharmacological interventions for ED are known causes of priapism. While intracavernosal therapy's role in priapism is well-evidenced, priapism from PDE5i is only recorded in limited case reports.[4–9] Recently, a study demonstrated that priapism accounts for 0.7% of reported adverse drug reactions (ADR) for PDE5is, suggesting that extensive patient counseling regarding priapism when prescribing may be unnecessary.[10]

Our aim is to investigate the disproportionality signals of priapism among PDE5i users in a large international pharmacovigilance dataset. We focus on assessing the differences in disproportionality in reported priapism between different PDE5i products and common intracavernosal agents as a natural point of comparison. Further, we examine variations in disproportionality signals across different age groups.

2 | MATERIALS AND METHODS

2.1 | Data source

In this retrospective case-non-case study, we used VigiBase, the World Health Organization (WHO) global database of individual case safety reports developed and maintained by Uppsala Monitoring Centre.[11] VigiBase is the largest pharmacovigilance database globally, with over 30 million reports of ADR from 140 countries (https://who-umc.org/vigibase), and contains data on the region of origin, patient (age group and sex), ADR, onset/end date, seriousness, and outcome), and medication data (indication, start/end dates, dose, regimen, and route of administration). WHODrug and MedDRA were used to code the recorded drugs and the adverse effects in this study, respectively. We received institutional review board exempt due to public availability of the database.

2.2 | Study population

We queried ADR reports for a subset of a broad "men's health" data consisting of drugs as follows (according to WHODrug): phosphodiesterase inhibitors, PDE5i (sildenafil, tadalafil, vardenafil, avanafil), opium antispasmodics (papaverine), prostaglandin agonists (alprostadil), alpha-1 antagonists (phentolamine, tamsulosin, terazosin, alfuzosin, silodosin), anti-diuretic hormone analog (desmopressin), anticholinergics (oxybutynin, tolterodine darifenacin, solifenacin, trospium, festerodine), and beta-3 agonists (mirabegron, vibegron). We searched for the ADR reports for sildenafil, tadalafil, avanafil, vardenafil, papaverine, and alprostadil in men and extracted the ones before September 29th, 2021. Next, the reports with an uncommon or unknown route of administration for ED treatment purposes were excluded: all routes other than oral and intracavernousal for PDE5is and alprostadil/papaverine, respectively. Of note, we included all men taking these medications regardless of indication.

2.3 | Study endpoint

Our primary outcome was the pharmacovigilance signals for priapism. Descriptive statistics were reported as frequency (%) for categorical variables.

2.4 | Statistical analysis

We implemented a disproportionality analysis to evaluate the correlation between the queried drugs and the ADR of priapism. Reporting odds ratio (ROR) and the 95% confidence intervals (CI) were calculated according to methods described by Stricker and Tijssen.[12] ROR is a homolog to the odds ratio for case–control studies and corresponds to the ratio of reporting odds for individuals exposed to the drug of interest compared to those who were not exposed[13]: ROR = ad/bc; *a*: drug and ADR of interest, *b*: drug of interest with other ADRs, *c*: other drugs with ADR of interest, and *d*: other drugs and ADRs.[12]

For a drug of interest, cases (a) were considered the reports of "priapism" according to MedDRA, while non-cases (b) were all other ADR reports during the same period. The analysis was then stratified for the age groups of the consumers. A ROR was deemed significantly disproportionate if the ROR's lower bound of the 95% CI was ≥1, and the number of observed event combinations was ≥3.[14] A positive disproportionality signal for a specific drug-ADR relationship in a pharmacovigilance database potentially suggests a drug-ADR association and warrants further investigation via case–control or cohort studies to verify the relationships.[13] Statistical analysis was performed using Stata 13 (StataCorp, TX, USA). The design and reporting of the study followed the Council for International Organizations of Medical Sciences (CIOMS) guidelines for signal detection in pharmacovigilance (see Data S1).

2.5 | Sensitivity analysis

We conducted sensitivity analyses to investigate the disproportionality signals associated with PDE5is concerning headache and backpain, and comparing the RORs to that of priapism. Initially, we focused on headache as it represents a well-known ADR associated with all PDE5i products. We hypothesized that the disproportionality signals for headache would be positive for all PDE5is. Subsequently, we selected backpain for analysis due to the frequent user reports related to tadalafil, as this particular ADR has not been recorded for other PDE5i drugs. Our assumption was that the disproportionality signal for backpain would only be significant for tadalafil.

3 | RESULTS

A total of 132 993 and 826 reports of ADR were found for PDE5is and intracavernousal drugs (i.e., alprostadil and/or papaverine), respectively. Of these, 632 were priapism (PDE5is 550; 0.4%, and intracavernousal drugs 82; 9.9%). Among PDE5is, sildenafil had the highest number of priapism reports (360; 0.42%), followed by tadalafil (140; 0.4%), vardenafil (49; 0.5%), and avanafil (1; 0.1%).

Table 1 shows the differences in the RORs of PDE5i agents. We observed a 25-fold increase in odds of reporting priapism for intracavernousal remedies (ROR = 34.7; 95% CI: 27.1–43.9) in comparison with PDE5is (ROR = 1.4; 95% CI: 1.2–1.5). Priapism was most commonly reported in sildenafil among PDE5is.

TABLE 1 Results of disproportionality analysis for all the queried phosphodiesterase type 5 inhibitors divided by age groups, and each of the erectogens individually (all ages).

	All reports	Priapism cases (%)	
	n	*n* (%)	ROR (95% CI)
All PDE5is (all ages)	132 993	550 (0.4)	1.4 (1.2–1.5)
<18 years	931	14 (1.5)	4.6 (2.5–7.7)
0–27 days	55	0 (0)	-
28 days—23 months	228	1 (0.4)	1.3 (0.03–7.4)
2–11 years	421	6 (1.4)	4.3 (1.6–9.5)
12–17 years	227	7 (3.1)	9.5 (3.8–19.9)
≥18 years	79 821	281 (0.4)	1.1 (0.9–1.2)
18–44 years	10 131	106 (1.1)	3.3 (2.7–4.1)
45–64 years	40 452	136 (0.3)	1 (0.8–1.2)
65–74 years	19 902	28 (0.1)	0.4 (0.3–0.6)
≥75 years	9336	11 (0.1)	0.4 (0.2–0.6)
Unknown	52 241	255 (0.5)	1.6 (1.4–1.8)
Sildenafil	85 894	360 (0.4)	1.3 (1.2–1.5)
Tadalafil	35 341	140 (0.4)	1.2 (1–1.4)
Vardenafil	10 811	49 (0.5)	1.4 (1–1.8)
Intracavernousal drugs	826	82 (9.9)	34.7 (27.1–43.9)

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; PDE5i, phosphodiesterase type 5 inhibitor; ROR, reporting odds ratio.

For all PDE5i agents, the 12–17 years age group was associated with a higher reporting of priapism ($n = 7$; ROR = 9.5, 95% CI: 3.8–19.9) followed by 2–11 years ($n = 6$; ROR = 4.3, 95% CI: 1.6–9.4) and 18–44 years ($n = 106$; ROR = 3.3, 95% CI: 2.7–4.1; Figure 1).

The disproportionality signals for consumers under 18 years of age were nearly four times bigger than the ones 18 or older for both all PDE5is ($n = 14$; ROR = 4.6, 95% CI: 2.5–7.7 vs. $n = 281$; ROR = 1.1, 95% CI: 0.9–1.2) and sildenafil ($n = 12$; ROR = 4.9, 95% CI: 2.5–8.6 vs. $n = 174$; ROR = 1.1, 95% CI: 0.9–1.3). Tadalafil, vardenafil, avanafil, and intracavernousal drugs had no priapism reports under the age of 18.

Table 2 presents the most common indications for oral PDE5i use stratified by different age groups.

The sensitivity analyses yielded strong disproportionality signals associated with headache for each PDE5i agent. In the case of back pain, only tadalafil demonstrated a disproportionate signal (ROR = 5.4, 95% CI: 5–5.8; see Data S2).

Finally, among all PDE5i consumers with priapism, 133 patients (24.18%) recovered without sequela, and the recovery rate was higher in the 18 or older age group than those under 18 (35.9% vs. 14.3%), although not statistically significant. The outcomes of priapism events due to PDE5is are listed in Table 3.

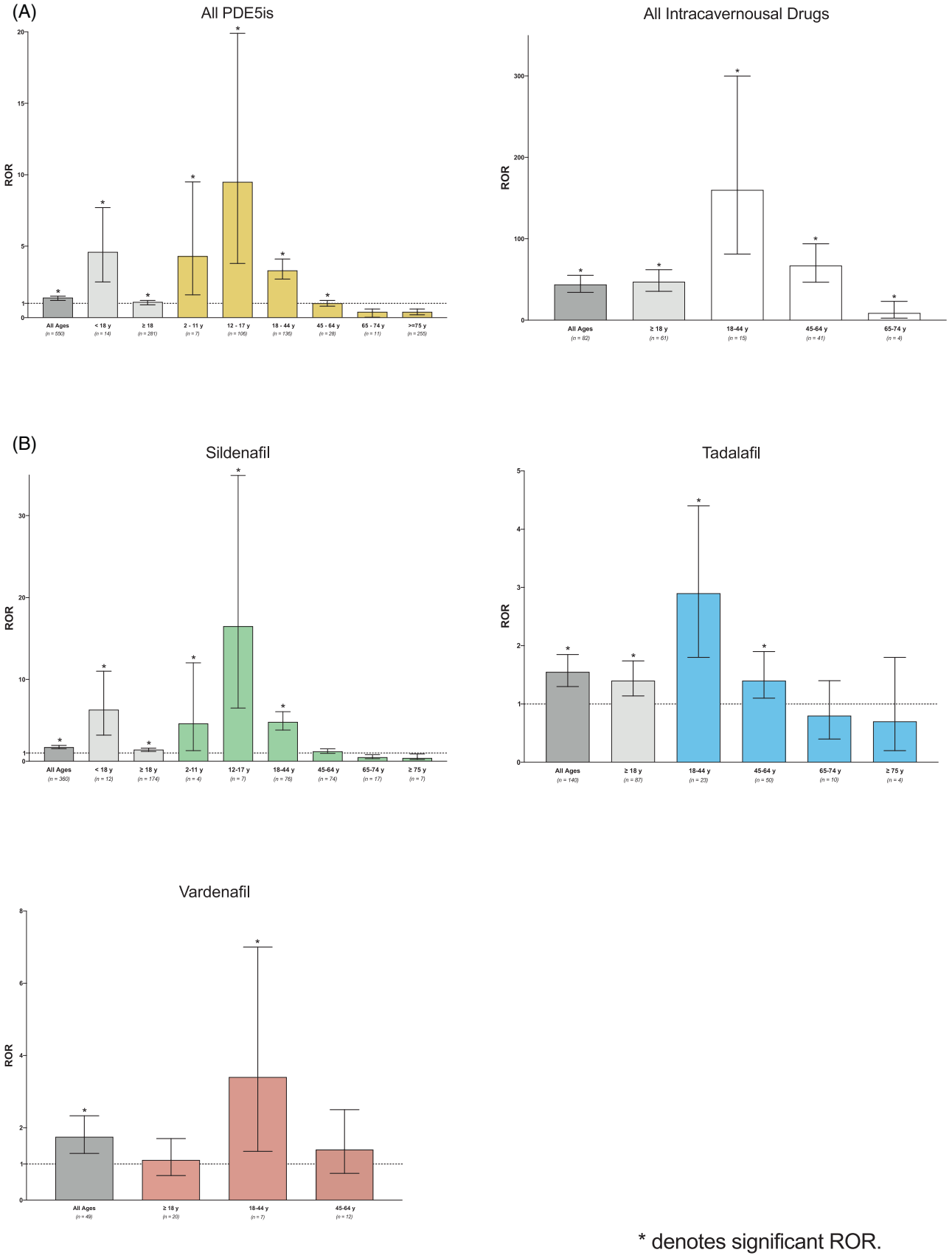

FIGURE 1 Difference between disproportionality signals (presented as reporting odds ratio and 95% confidence intervals) between age groups for (A) all phosphodiesterase type 5 inhibitors and intracavernousal drugs; and (B) different phosphodiesterase type 5 inhibitor agents.

TABLE 2 Disproportionality signals for all the queried phosphodiesterase type 5 inhibitors grouped by indications.

Indications	All reports	Priapism	
All ages	*n* (%)	*n* (%)	ROR (95% CI)
Unknown/missing	70 384 (52.9)	389 (0.6)	2.4 (2.1–2.6)
Sexual dysfunction	51 685 (38.9)	136 (0.3)	1 (0.8–1.2)
PAH	7044 (5.3)	8 (0.1)	0.4 (0.2–0.9)
LUTS	1511 (1.1)	2 (0.1)	0.5 (0.1–1.8)
Chronic penile ulceration	208 (0.2)	4 (1.9)	7.5 (2–19.5)
<18			
Unknown/missing	433 (46.5)	9 (2.1)	8.1 (3.7–15.6)
PAH	414 (44.5)	3 (0.7)	2.8 (0.6–8.2)
Sexual dysfunction	49 (5.3)	1 (2)	7.3 (0.2–42.8)
Peripheral vasodilation	11 (1.8)	1 (9.1)	38.1 (0.9–268.4)
Accidental poisoning	5 (0.5)	0	-
≥18			
Unknown/missing	37 099 (46.5)	176 (0.5)	1.9 (1.6–2.2)
Sexual dysfunction	35 031 (43.9)	89 (0.3)	1 (0.8–1.2)
PAH	5028 (6.3)	1 (0)	0.1 (0–0.4)
LUTS	946 (1.2)	1 (0.1)	0.4 (0–2.3)
Chronic ulceration of penis	195 (0.2)	4 (2.1)	8 (2.2–20.8)
0–27 days			
Unknown/missing	30 (54.5)	0	-
PAH	25 (45.5)	0	-
28 days–23 months			
PAH	128 (56.1)	1 (0.8)	3 (0.1–17.1)
Unknown/missing	97 (42.5)	0	-
ESRD	2 (0.9)	0	-
Chronic penile ulceration	1 (0.4)	0	-
2–11 years			
Unknown/missing	227 (53.9)	4 (1.8)	6.8 (1.8–17.8)
PAH	180 (42.8)	1 (0.6)	2.1 (0.1–12.1)
Peripheral vascular disorder	7 (1.7)	1 (14.3)	63.6 (1.4–525.4)
Accidental poisoning	5 (1.2)	0	-
Complement system defects	1 (0.2)	0	-
12–17 years			
Unknown/missing	102 (44.9)	5 (4.9)	19.7 (6.2–47.6)
PAH	81 (35.7)	1 (1.2)	4.8 (0.1–27.3)
Sexual dysfunction	31 (13.7)	1 (3.2)	12.7 (0.3–76.6)
Peripheral vascular disorder	4 (1.8)	0	-
Eisenmenger's syndrome	2 (0.9)	0	-
18–44 years			
Unknown/missing	4806 (47.4)	70 (1.5)	5.8 (4.5–7.4)
Sexual dysfunction	4397 (43.4)	30 (0.7)	2.6 (1.8–3.8)
PAH	520 (5.1)	0	-
LUTS	63 (0.6)	0	-
Ejaculation disorder	51 (0.5)	1 (2)	7.6 (0.2–44.5)
45–64 years			
Sexual dysfunction	19 481 (48.2)	51 (0.3)	1 (0.7–1.3)
Unknown/missing	18 007 (44.5)	78 (0.4)	1.7 (1.3–2.1)
PAH	1670 (4.1)	0	-
LUTS	413 (1)	0	-
Chronic penile ulceration	100 (0.2)	2 (2)	7.8 (0.9–28.9)
65–74 years			
Unknown/missing	9786 (49.2)	21 (0.2)	0.8 (0.5–1.3)
Sexual dysfunction	8085 (40.6)	5 (0.1)	0.2 (0.1–0.5)
PAH	1384 (7)	1 (0.1)	0.3 (0–1.5)
LUTS	309 (1.6)	1 (0.3)	1.2 (0–7)
Chronic penile ulceration	60 (0.3)	0	-
≥75 years			
Unknown/missing	4500 (48.2)	7 (0.2)	0.6 (0.2–1.2)
Sexual dysfunction	3068 (32.9)	3 (0.1)	0.4 (0.1–1.1)
PAH	1454 (15.6)	0	-
LUTS	161 (1.7)	0	-
Chronic penile ulceration	12 (0.1)	1 (8.3)	34.7 (0.8–238.8)

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; ESRD, end-stage renal disease; LUTS, lower urinary tract synptoms; PAH, pulmonary arterial hypertension; ROR, reporting odds ratio.

4 | DISCUSSION

The epidemiology of PDE5i-induced priapism is poorly understood, and the evidence is confined to primarily case reports.[1–3] To our knowledge, this is the largest study over the longest collection period on the association between PDE5i consumption and priapism. We also present the first pharmacovigilance reports of PDE5i-induced priapism among children and adolescents.

A recent study on the U.S. Food and Drug Administration (FDA) Adverse Reporting System Public Dashboard has found that priapism accounts for 0.7% of all ADRs recorded for PDE5i consumers not diagnosed with sickle cell disease (SCD), which is a known risk factor for priapism.[10] Similarly, we found priapism comprised 0.4% of ADRs for PDE5is with respect to the international population sampled by the VigiBase database. Further, we estimated the proportion to be lower given that we have not excluded SCD cases, which have a higher incidence of priapism at baseline. Additionally, as VigiBase

TABLE 3 The reported outcomes of priapism events with oral phosphodiesterase type 5 inhibitor as the interacting/suspected drug.

	12–17 years	≥18 years
Outcome	***n* (%)**	***n* (%)**
Recovered/resolving	1 (14.3)	101 (35.9)
Recovered with sequelae	0 (0)	9 (3.2)
Not recovered/not resolved	0 (0)	12 (4.3)
Fatal	0 (0)	1 (0.4)
Unknown	4 (57.1)	62 (22.1)
-	2 (28.6)	96 (34.2)
$p = 0.37$*		

*Fisher's exact test.

lacks many clinical parameters, it is not clear if the reported priapism events are ischemic and/or the interventions (and associated success/failure) carried out. This could further contribute to an even lower incidence for true ischemic priapism requiring intervention in our data.

Priapism can occur at any age, most frequently affecting men over 50.[2] However, in children and adolescents, priapism is rare, and data on its epidemiology is scarce and inconsistent, partly due to variation in priapism's definition.[15] SCD is the leading etiology behind childhood priapism compared to pharmacological agents in adults.[3,16] Nevertheless, the same drugs responsible for drug-induced priapism in adults are capable of causing priapism in children, and PDE5is at therapeutic doses are thought to induce priapism in 1% of cases.[15] Likewise, we found that priapism constituted 1.2% of all ADRs reported for PDE5is in consumers under 18 years old, which is three times higher than in older patients. PDE5is tendency to cause priapism decreases with age, possibly due to alterations in tissue characteristics of penile nerves, blood vessels, and corpus spongiosum, resulting in higher rates of ED and decreasing the response to PDE5i agents.[17,18]

Our findings revealed a disproportionate pharmacovigilance signal for priapism in the oral use of PDE5is. However, this signal was 25 times stronger for intracavernousal medications. It is worth mentioning that while intracavernousal drugs are exclusively used to treat ED, oral PDE5is serve a broader range of indications. PDE5is, specifically sildenafil and tadalafil, have been widely used to treat pulmonary arterial hypertension (PAH) in children and adolescents.[19] Evidence shows that this treatment is accompanied by ADRs in 30% of the cases.[20] The most common ADRs following the administration of PDE5is for pediatric PAH include skin flushing, headache, nasal congestion, joint/muscle pain, and nausea.[21] Likewise, our data showed that the majority of male individuals under 18 consume PDE5is for PAH. Although ED in teenagers is a relatively established entity, its incidence is not well-studied. Most cases are thought to be due to psychogenic or vasculogenic etiologies and are routinely referred for related workup.[22] As of today, no PDE5i is approved for the treatment of ED in adolescents; nevertheless, its recreational use has been reported by some studies.[23–26] In a survey of 43 teenage males who self-identified as "lifetime sildenafil citrate users," it was shown that as many as 9% had started abusing the product since the age of 14 and that curiosity and peer pressure were the two most frequent contributory factors for the initial use.[24] In our study, sexual dysfunction was also among the top indications for using PDE5i in the 12–18 age group. Although PDE5is are prescription drugs in the United States, they are available over the counter in some other parts of the world. A recent cross-sectional study of community pharmacies in Ethiopia showed that 66.2% of oral PDE5i use is for recreational purposes.[23] It is unclear if the drug was obtained under the treatment of a physician or not in our set of cases. However, our results favor the highly selected use of these products for the enhancement of erection in adolescents, given that priapism at a young age potentially has everlasting impacts on sexual health.[24]

Our analysis indicates that the pharmacovigilance signal for priapism in patients using oral PDE5is for sex-related purposes was not positive. However, for other common indications of use (i.e., PAH, unknown/missing, and others), the signal was disproportionate. Although dosing data could not be reliably ascertained, this observation suggests a potential dose-dependent relationship between priapism and oral PDE5i consumption, possibly attributed to higher doses used by PAH patients compared to those with ED (common daily dose of 80 vs. 50 mg, respectively). Moreover, considering the substantial prevalence of recreational use of oral PDE5is, instances categorized as unknown/missing and others in our dataset could potentially encompass cases of drug recreational use, wherein individuals may ingest doses exceeding those prescribed for medical purposes.[23] This may also reflect on the potential dose-effect relationship between such products and priapism.

5 | LIMITATIONS

It is noteworthy that VigiBase collects data on individual case safety reports and does not contain information on PDE5i consumers who have not exhibited any adverse events (i.e., controls). Thus, the case-non-case approach does not estimate the risk of occurrence of a specific ADR, unlike case–control studies, and alternatively investigates the risk of ADR reporting through ROR.[13] Data in VigiBase are heterogeneous and gathered from various sources, including healthcare professionals, pharmaceutical companies, and patients. Consequently, data is subjected to reporting bias, and the probability that the suspected adverse event is drug-related is not the same in all cases.[27] Additionally, incomplete and unreliable dosing data imposes a significant limitation on our study, preventing us from performing a dose–response analysis and investigating whether the occurrence of an ADR in a particular subpopulation is a consequence of over-dose. Lastly, VigiBase, by nature, does not provide any information on patients' comorbidity, which may predispose one to a specific ADR. For instance, the notable clinical covariates (i.e., SCD, and concurrent use of non-captured erectogenic medication like trazodone), are not consistently recorded in VigiBase. Consequently, the calculated ROR may be biased toward an inflated estimation of priapism with PDE5i.

Moreover, the omission of other unrecorded covariates, like hypertension and diabetes, and their associated co-medications (e.g., antihypertensives), might potentially lower priapism risk and alter the ROR. Accordingly, certain causal drug-ADR associations cannot be drawn.

6 | CONCLUSIONS

In a large international data, we found disproportionate pharmacovigilance signals of priapism from PDE5i. The use of PDE5i among young patients is associated with a higher disproportionality signal of priapism compared to adults, albeit low. Studies looking specifically at adult men who get priapism from PDE5i may be warranted.

AUTHOR CONTRIBUTIONS

Benjamin N. Breyer, Nathan M. Shaw, Behzad Abbasi: Conceptualization. **Nathan M. Shaw, Behzad Abbasi:** Methodology. **Behzad Abbasi:** Formal analysis and investigation. **Behzad Abbasi:** Writing—original draft preparation. **Behzad Abbasi, Nathan M. Shaw, Jason L. Lui, Nizar Hakam, Behnam Nabavizadeh, Benjamin N. Breyer:** Writing—review and editing. **Benjamin N. Breyer:** Supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Uppsala Monitoring Centre.

ETHICS STATEMENT

This investigation received an exemption from the University of California San Francisco institutional review board as VigiBase data was deidentified. This study does not contain any human participants and/or animals.

ORCID

Behzad Abbasi https://orcid.org/0000-0002-7175-9984

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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