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Phosphodiesterase Type 5 Inhibitors and Priapism: A VigiBase Analysis.

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Abstract

Purpose: To explore the differences among erectile aids (i.e., phosphodiesterase type 5 inhibitors [PDE5i] and intracavernousal drugs) of the relative risk of priapism and identify age groups at risk. **Methods:** We queried the World Health Organization global database of individual case safety reports (VigiBase) for records of the ADR with sildenafil, tadalafil, avanafil, vardenafil, papaverine, and alprostadil. Disproportionality analyses (case/non-case approach) were performed to assess the relative risk 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%). We observed a strong signal for priapism induction for intracavernousal drugs than PDE5is (reporting odds ratio [ROR]=34.7; confidence interval [CI] 95%: 27.12 - 43.94 *vs.* ROR= 1.38; CI 95%: 1.24 - 1.54). For all PDE5i agents, the 12-17 years age group had the highest highest ROR (ROR=9.49, CI 95%: 3.76 - 19.93) followed by 2-11 years (ROR=4.31, CI 95%: 1.57 - 9.4). Disproportionality signals for consumers under eighteen for both all PDE5is as a whole (ROR=4.57, CI 95%: 2.48 - 7.73) and sildenafil (ROR=4.89, CI 95%: 2.51 - 8.62) were significantly stronger than individuals eighteen or older (ROR=1.06, CI 95%: 0.93 - 1.21 and ROR=1.08, CI 95%: 0.91 - 1.26, respectively). **Conclusions:** While the overall risk of priapism following the oral administration of PDE5is is extremely low compared with intracavernousal remedies, adolescents are at a higher risk of priapism than older men.

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Running Title:

Phosphodiesterase Type 5 Inhibitors and Priapism

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Abstract

Purpose: To explore the differences among erectile aids (i.e., phosphodiesterase type 5 inhibitors [PDE5i] and intracavernousal drugs) of the relative risk of priapism and identify age groups at risk.

Methods: We queried the World Health Organization global database of individual case safety reports (VigiBase) for records of the ADR with sildenafil, tadalafil, avanafil, vardenafil, papaverine, and alprostadil. Disproportionality analyses (case/non-case approach) were performed to assess the relative risk 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%). We observed a strong signal for priapism induction for intracavernousal drugs than PDE5is (reporting odds ratio [ROR]=34.7; confidence interval [CI] 95%: 27.12 - 43.94*vs.* ROR= 1.38; CI 95%: 1.24 - 1.54). For all PDE5i agents, the 12-17 years age group had the highest highest ROR (ROR=9.49, CI 95%: 3.76 - 19.93) followed by 2-11 years (ROR=4.31, CI 95%: 1.57 - 9.4). Disproportionality signals for consumers under eighteen for both all PDE5is as a whole (ROR=4.57, CI 95%: 2.48 - 7.73) and sildenafil (ROR=4.89, CI 95%: 2.51 - 8.62) were significantly stronger than individuals eighteen or older (ROR=1.06, CI 95%: 0.93 - 1.21 and ROR=1.08, CI 95%: 0.91 - 1.26, respectively).

Conclusions: While the overall risk of priapism following the oral administration of PDE5is is extremely low compared with intracavernousal remedies, adolescents are at a higher risk of priapism than older men.

Keywords

priapism; erectile dysfunction; phosphodiesterase 5 inhibitor; sildenafil; Cialis; Viagra; tadalafil.

Key Points

- Priapism from phosphodiesterase type 5 inhibitors (PDE5is) is only recorded by limited case reports. This study sought to verify the low incidence of 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 risk of priapism with PDE5is compared with other adverse drug reactions.
- The use of PDE5is among young patients is associated with a higher risk of priapism compared to adults, albeit low. Our analysis further confirms that the risk of priapism amongst older men with erectile dysfunction is extremely rare.

Plain Language Summary

Priapism is an erection persisting for over four hours and implicates emergent intervention to prevent the risk of erectile dysfunction in 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 among PDE5is of the relative risk of priapism and identify age groups at risk. 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) [i.e., odds of an adverse reaction being reported for a drug in a dataset] for priapism in PDE5is. We found a very small risk of priapism with PDE5is compared with other adverse drug reactions. PDE5i use among young patients was associated with a higher risk of priapism compared to adults, albeit low. Our analysis further confirmed that the risk of priapism amongst older men with erectile dysfunction is extremely rare. This implies that although patient counseling when prescribing PDE5is for adults seems unneeded, providers should be aware of the higher risk of priapism in under-age patients.

Statements and Declarations

Competing Interests: None

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

Funding statement: No fundings were received for the conduction of this project.

Ethics of approval statement: This investigation received an exemption from the University of California San Francisco institutional review board as VigiBase data was deidentified.

Patient consent statement: Not applicable

Permission to reproduce material from other sources: Not applicable

Clinical trial registration: Exempted as our study is not a clinical trial by design.

Author contributions: BNB & NMS conceptualized; AS, CS, & JLL identified online forums; AS, CS, JLL, & BA extracted data from forum posts; AS & BA performed statistical analysis; AS & BA drafted the manuscript; UG, LAH, NMS, & BNB revised the manuscript.

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Information in this study does not represent the opinion of the UMC or the World Health Organization.

Introduction

Priapism is an erection persisting for over four hours, 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. Priapism incidence ranges from 0.3 to 1.5 per 100,000 men, with approximately 30% drug-induced. Pharmacological interventions for erectile dysfunction, including intracavernosal injection of erectogenic agents (e.g., papaverine and alprostadil) as well as oral intake of phosphodiesterase-5 inhibitors (PDE5i), are known causes of priapism. While intracavernosal therapy's role in priapism is well-evidenced, priapism from PDE5i is only recorded by limited case reports. 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.

We aim to verify the low incidence of priapism among PDE5i users in a large international dataset. Further, we aim to assess the differences between different PDE5i products and common intracavernosal agents in the development of priapism. We identify age groups at risk to help practitioners better counsel their patients.

Materials and Methods

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. 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.

Study Population

We queried ADR reports for a subset of a broad "men's health" data consisting of drugs as follows (according to WHODrug): Phospho Diesterase Inhibitors, PDE5i (Sildenafil, Tadalafil, Vardenafil, Avanafil), Prostaglandin Agonist: Alprostadil, Alpha-1 Antagonists (Phentolamine, Tamsulosin, Terazosin, Alfuzosin, Silodosin), Anti Diuretic Hormone analog (Desmopressin), Anti-Cholinergics (Oxybutynin, Tolterodine Darifenacin, Solifenacin, Trospium, Festerodine), Beta-3 Agonist (Mirabegron, Vibegron). We searched for the ADR reports for sildenafil, tadalafil, avanafil, vardenafil, papaverine, and alprostadil in men and extracted the ones in which the corresponding drug was listed as "suspect" or "interacting" before September 29$^{\text{th}}$, 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.

Study Endpoint

Our primary outcome was the frequency of PDE5i-related priapism events.

Statistical Analysis

Descriptive statistics were reported as frequency (%) for categorical variables. 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 Stricker and Tijssen. ROR is a homolog to the odds ratio for case-control studies and corresponds to the exposure odds among cases of priapism over the odds of exposure among non-cases: ROR = (a/b) × (c/d); 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.

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. An ROR was considered significant if the number of drug-ADR combinations was three or more. Statistical analysis was performed using Stata 13 (StataCorp, TX, USA). The design and reporting of the study followed the STROBE guidelines and checklist for observational studies (see appendix).

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; 0.41%, and intracavernousal drugs: 82; 9.92%). Among PDE5is, sildenafil had the highest number of priapism reports (360; 0.42%), followed by tadalafil (140; 0.4%), vardenafil (49; 0.45%), and avanafil (1; 0.11%) (table 1).

The most frequently reported indication for the use of PDE5is for patients eighteen or older was erectile dysfunction (n=34,608; 43.36%) (table 2). In individuals under eighteen, almost half the indications for PDE5i use were left blank in the dataset (n=405; 43.5%) and the second most common indication was pulmonary hypertention (n=354; 38.02%) followed by erectile dysfunction (n=34; 3.65%).

Table 1 shows the difference in the RORs of PDE5i agents. We observed a 25-fold dominance in odds of reporting priapism for intracavernousal remedies (ROR=34.7; CI 95%: 27.12 - 43.94; p<0.001) in comparison with PDE5is (ROR= 1.38; CI 95%: 1.24 - 1.54; p<0.001). Priapism was most commonly reported in sildenafil among PDE5is.

For all PDE5i agents, the 12-17 years age group was associated with a significantly higher reporting of

priapism (n=7; ROR=9.49; CI 95%: 3.76 - 19.93; p<0.001) followed by 2-11 years (n=6; ROR=4.31, CI 95%: 1.57 - 9.4, p<0.001) and 18-44 years (n=106; ROR=3.32, CI 95%: 2.69 - 4.06, p<0.001) (Fig. 1).

The disproportionality signals for consumers under eighteen years of age were nearly four times bigger that the ones eighteen or older for both all PDE5is (n=14; ROR=4.57, CI 95%: 2.48 - 7.73, p<0.001*vs.* n=281; ROR=1.06, CI 95%: 0.93 - 1.21, p=0.372) and sildenafil (n=12; ROR=4.89, CI 95%: 2.51 - 8.62 p<0.001*vs.* n=174; ROR=1.08, CI 95%: 0.91 - 1.26, p=0.371). Tadalafil, vardenafil, avanafil, and intracavernousal drugs had no priapism reports under the age of eighteen.

Finally, among all PDE5i consumers with priapism, 133 patients (24.18%) recovered without sequela, and the recovery rate was higher in the eighteen or older age group than those under eighteen (21.43% vs. 35.94%), although not statistically significant. The outcomes of priapism events due to PDE5is are listed in table 3.

Discussion

The epidemiology of PDE5i-induced priapism is poorly understood, and the evidence is confined to primarily case reports.[1–3] We have performed an extensive study on the association between PDE5i consumption and the risk of priapism, with relatively high number of cases. We also present the first epidemiologic 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. We found a similar global incidence (0.4%) with respect to the international population sampled by the VigiBase database. Further, we estimate the proportion to be lower given that we have not excluded SCD cases, which have a higher incidence of priapism at baseline. Additionally, in VigiBase, it is not clear if the reported priapism events are ischemic or are solely selected based on the time length of a prolonged erection. This could further contribute to an even lower incidence for true ischemic priapism in our data.

Priapism can occur at any age, most frequently affecting men over fifty. 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. SCD is the leading etiology behind childhood priapism compared to pharmacological agents in adults. 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. Likewise, we found the incidence of priapism among all reported ADRs to be 1.16% in consumers under eighteen 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.

PDE5is, specifically sildenafil and tadalafil, have been widely used to treat pulmonary arterial hypertension (PAH) in children and adolescents. Likewise, our data showed that the majority of male individuals under eighteen consume PDE5is for pulmonary hypertension. Although ED in teenagers is a relatively established entity, its incidence is not well-studied. Most cases are thought to be due to psychogenic and vasculogenic etiologies and are routinely referred for related work up. As of today, no PDE5i is approved for the treatment of ED in adolescents; nevertheless, its recreational use has been reported by some studies. In a survey of forty-three teenage males who self-identified as "lifetime sildenafil citrate users", it was shown that as many as nine percent had started abusing the product since the age of fourteen and that curiosity and peer pressure were the two most frequent contributory factor for the initial use. In our study, ED was also among the top indications for using PDE5i in the twelve to eighteen age group. Although PDE5is are prescription drugs in the US, they are available over the counter in other parts of the world and 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 young age potentially has everlasting impacts on sexual health.[25]

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. 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. 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. Accordingly, certain causal drug-ADR associations cannot be drawn.

Conclusions

We found a very small risk of priapism with PDE5i compared with other ADRs. The use of PDE5i among young patients is associated with a higher risk of priapism compared to adults, albeit low. Our analysis further confirms that the risk of priapism amongst older men with ED is extremely rare. This implies that although patient counseling when prescribing PDE5is for adults seems unneeded, providers should be made aware of the higher risk of priapism in under-age patients, and regulations may be useful to reduce their access to products containing PDE5is.

Authors' Contribution

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

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: The authors have no relevant financial or non-financial interests to disclose.

Research involving Human Participants and/or Animals: This study does not contain any human participants and/or animals.

Informed consent: Our study does not contain human subjects.

Funding

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References

Figures and Tables

Fig. 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. [**No need for use of color in print**]

Hosted file

`image1.emf` available at https://authorea.com/users/596652/articles/630044-phosphodiesterase-type-5-inhibitors-and-priapism-a-vigibase-analysis

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

	Total ADR Events	**Priapism Cases (%)**	**ROR (95% CI)**	**p-value**

	Total ADR Events	**Priapism Cases (%)**	**ROR (95% CI)**	**p-value**
All PDE5is	132,993	550 (0.41)	1.38 (1.24 - 1.54)	**< 0.001**
Under 18	931	14 (1.5)	4.57 (2.48 - 7.73)	**< 0.001**
0 - 27 days	55	0 (0)	-	-
28 days - 23 months	228	1 (0.44)	1.31 (0.03 - 7.39)	0.788
2 - 11 years	421	6 (1.43)	4.31 (1.57 - 9.48)	**< 0.001**
12 - 17 years	227	7 (3.08)	9.49 (3.76 - 19.93)	**< 0.001**
Over 18	79,821	281 (0.35)	1.06 (0.93 - 1.21)	0.372
18 - 44 years	10,131	106 (1.05)	3.32 (2.69 - 4.06)	**< 0.001**
45 - 64 years	40,452	136 (0.34)	1 (0.84 - 1.2)	0.983
65 - 74 years	19,902	28 (0.14)	0.41 (0.27 - 0.59)	**< 0.001**
>=75 years	9,336	11 (0.12)	0.35 (0.17 - 0.62)	**< 0.001**
Unknown	52,241	255 (0.49)	1.56 (1.36 - 1.79)	**< 0.001**
Sildenafil	85,894	360 (0.42)	1.34 (1.18 - 1.51)	**< 0.001**
Tadalafil	35,341	140 (0.4)	1.2 (1 - 1.44)	**0.04**
Vardenafil	10,811	49 (0.45)	1.36 (1 - 1.82)	**0.03**
Intracavernousal Drugs	826	82 (9.93)	34.7 (27.12 - 43.94)	**< 0.001**

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

Table 2 : Ten most frequently reported indications for the oral use of phosphodiesterase type 5 inhibitors.

12 − 17 y	**12 − 17 y**	**[?] 18 y**	**[?] 18 y**
Indication	**n (%)**	**Indication**	**n (%)**
Pulmonary hypertension	116 (37.18)	Erectile dysfunction	34,608 (43.36)
Blank	100 (32.05)	Blank	34,523 (43.25)
Unknown indication	47 (15.06)	Pulmonary hypertension	4,711 (5.9)
Erectile dysfunction	22 (7.05)	Unknown indication	2,576 (3.23)
Increased libido	5 (1.6)	LUTS	946 (1.19)
Vasodilatation	4 (1.28)	Chronic ulceration of penis	195 (0.24)
Intentional overdose	3 (0.96)	Hypertension	165 (0.21)
Eisenmenger's syndrome	2 (0.64)	Decreased libido	149 (0.19)
Malformation venous	2 (0.64)	Lung disorder	139 (0.17)
Morphea	2 (0.64)	Ejaculation disorder	118 (0.15)
% Cumulative	*97.12*	*% Cumulative*	*97.88*

LUTS, lower urinary tract symptoms.

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

Outcome	**12 - 17 y**	**[?] 18 y**
	n (%)	n (%)
Recovered / resolving	1 (14.29)	101 (35.94)
Recovered with sequelae	0 (0)	9 (3.2)

Outcome	**12 - 17 y**	**[?] 18 y**
Not recovered/not resolved	0 (0)	12 (4.27)
Fatal	0 (0)	1 (0.36)
Unknown	4 (57.14)	62 (22.06)
-	2 (28.57)	96 (34.16)
*p-value=0.37**		

* Fisher's exact test.