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ORIGINAL ARTICLE

Adverse reactions of PDE5 inhibitors: An analysis of the World Health Organization pharmacovigilance database

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Abstract

Background: Despite their efficacy and general safety, rare but devastating adverse drug reactions have been associated with phosphodiesterase type 5 inhibitors.

Objectives: To determine the safety profile of oral phosphodiesterase type 5 inhibitors with a particular focus on priapism and malignant melanoma.

Materials and methods: In this case–non-case study, we queried the individual case safety reports for phosphodiesterase type 5 inhibitors within the World Health Organization global database of individual case safety reports (VigiBase) between 1983 and 2021. We included all individual case safety reports for sildenafil, tadalafil, vardenafil, and avanafil in men. For comparison, we also extracted the safety data from the Food and Drug Administration trials for these drugs. We assessed the safety profile of phosphodiesterase type 5 inhibitors by disproportionality analysis by measuring reporting odds ratio for their most commonly reported adverse drug reactions, once for all phosphodiesterase type 5 inhibitor reports and once for reports of oral phosphodiesterase type 5 inhibitor use in adult men (≥18 years old) with sexual dysfunction.

Results: A total of 94,713 individual case safety reports for phosphodiesterase type 5 inhibitors were extracted. A total of 31,827 individual case safety reports were identified relating to adult men taking oral sildenafil, tadalafil, vardenafil, or avanafil for sexual dysfunction. The most common adverse drug reactions included poor drug efficacy (42.5%), headache (10.4% vs. 8.5%–27.6% [Food and Drug Administration]), abnormal vision (8.4% vs. ≤4.6% [Food and Drug Administration]), flushing (5.2% vs. 5.1%–16.5% [Food and Drug Administration]), and dyspepsia (4.2% vs. 3.4%–11.1% [Food and Drug Administration]). Priapism showed significant signals for sildenafil (reporting odds ratio = 13.81, 95% confidence interval: 11.75–16.24), tadalafil (reporting odds ratio = 14.54, 95% confidence interval: 11.56–18.06), and vardenafil (reporting odds ratio = 14.12, 95% confidence interval: 8.36–22.35). Comparing with other medications in VigiBase, sildenafil (reporting odds ratio = 8.73, 95% confidence interval: 7.63–9.99) and tadalafil (reporting odds ratio = 4.25, 95% confidence interval: 3.19–5.55) had significantly higher reporting odds ratios for malignant melanoma.

Conclusion: Phosphodiesterase type 5 inhibitors show significant signals correlating with priapism among a large international cohort. Further clinical study is needed to elucidate whether this is from proper or inappropriate use or other confounding conditions, as analysis of pharmacovigilance data does not allow for quantifying the clinical risk. Also, there appears to be a relationship between phosphodiesterase type 5 inhibitor use and malignant melanoma, which warrants additional study to better understand causation.

KEYWORDS
erectile dysfunction, malignant melanoma, PDE5 inhibitor, priapism, sexual dysfunction, sildenafil

1 | INTRODUCTION

By estimation, 322 million men will be affected by erectile dysfunction (ED) worldwide by 2025.[1] The prevalence of ED increases with age, and national data show that as many as 70% of American men aged 70 years or older are affected.[2] Oral phosphodiesterase type 5 inhibitors (PDE5is) are the most commonly used treatment for ED and are established in the guidelines as the first-line therapy for patients with the disease.[3,4] PDE5is are generally considered efficient and safe. Although the rate of adherence in PDE5i users is relatively low (59.6%–70.2%), fear of side effects seems to play a minor role in their decision to discontinue the medication.[5]

Several severe, albeit rare, adverse drug reactions (ADRs) have been associated with oral PDE5is with limited understanding of prevalence: relationships between oral PDE5is and priapism and malignant melanoma have been explored recently.[6] Although both ADRs are difficult to characterize, they highlight the importance of early identification and treatment. Histopathologic studies have suggested that PDE5is promote malignant melanoma cell growth through two separate signaling pathways that increase tumor invasiveness and survival.[7,8] However, observational data fail to depict a causative association between PDE5is and malignant melanoma.[9]

Pharmacovigilance databases collect reports of suspected ADRs by patients, healthcare professionals, and post-authorization safety trials and offer a longitudinal perspective of a drug's safety and allow for the assessment of rare ADRs. VigiBase is the World Health Organization's (WHO) global Individual Case Safety Reports (ICSRs) database, which captures a large international multidecade cohort and is uniquely equipped to detect new, serious, and/or rare potential ADRs, particularly conditions resulting from long-term administration.[10] Given the infrequency of melanoma and priapism among men taking PDE5is, VigiBase represents a previously unused resource capable of assessing these adverse events.

We aimed to investigate the possible relationship between oral PDE5is and the risk of priapism and malignant melanoma across a global dataset. Our secondary aim is to characterize the most commonly reported ADRs in this drug class and compare them with frequencies reported by Food and Drug Administration (FDA) clinical trials.

2 | MATERIALS AND METHODS

2.1 | Database

We used VigiBase, the WHO's Programme for International Drug Monitoring database of ICSRs. VigiBase is currently the most extensive pharmacovigilance database worldwide launched in 1985, with over 27 million ICSRs as of October 2021. The Uppsala Monitoring Centre (UMC) is in charge of the development and maintenance of VigiBase, collecting ICSRs from 140 countries.[10] These safety reports are made by healthcare professionals, pharmaceutical companies, or patients (https://who-umc.org/vigibase). We queried ICSRs pertaining to PDE5is from October 1998 to October 2021 (data extracted on October 26, 2021).

2.2 | Case selection

In VigiBase, ADRs are grouped according to the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA terminology is categorized into three hierarchical levels: System Organ Class, Preferred Terms (PT), and Lowest Level Terms.[10] We primarily queried VigiBase for ICSRs on single-ingredient PDE5i products as the suspecting and interacting drugs: sildenafil, tadalafil, vardenafil, and avanafil. We included ADR reports for male individuals consuming PDE5is for sexual dysfunction (see Supporting Information). Administration routes other than oral and age under 18 years were our exclusion criteria. For our analysis, we selected reports based on their PT categorization. We focused on the most commonly reported ADRs according to the FDA pre-marketing trials and VigiBase data. We included all malignant melanoma and priapism reports. Groupings of PTs used are shown in Supporting Information, and Figure 1 shows a summary of methods implemented for this study.

2.3 | Data analysis

2.3.1 | Frequencies

VigiBase inherently does not provide information for patients who did not experience any adverse reactions. Thus, frequencies are reported

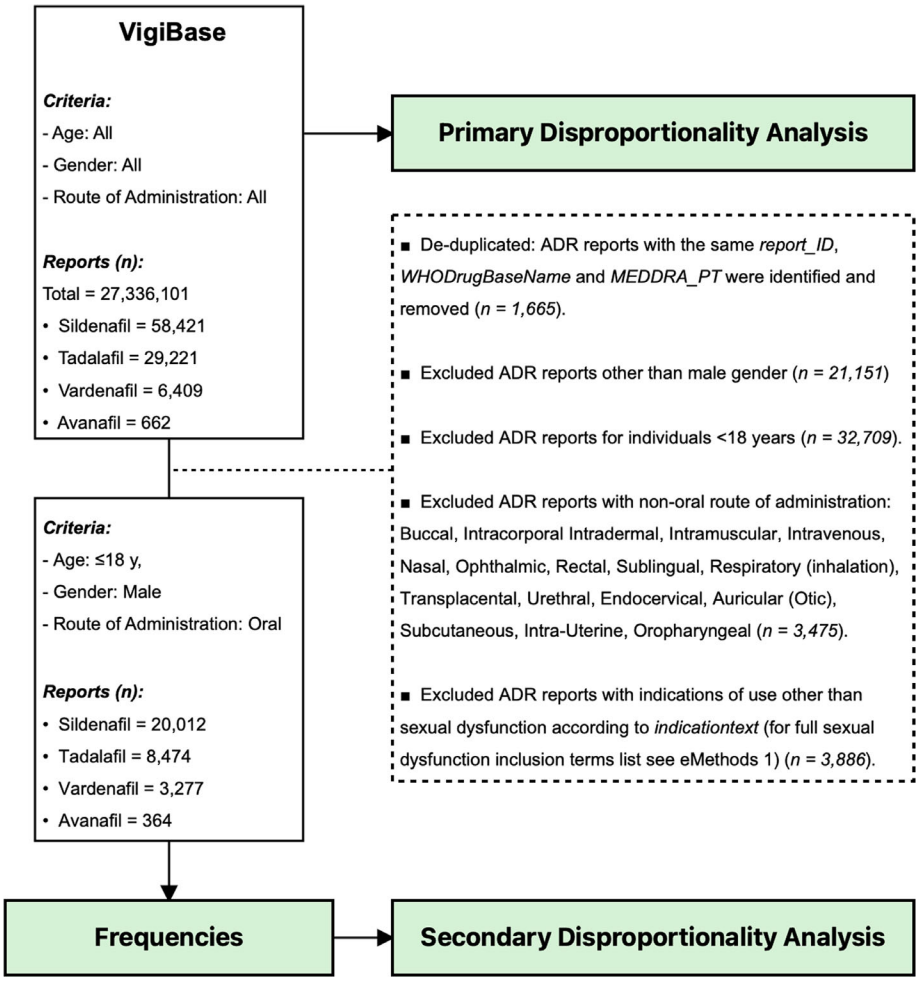


FIGURE 1 Summary of inclusion and exclusion criteria.

as the number of reports mentioning a specific ADR for a distinct PDE5i divided by the cumulated number of all reports of ADRs pertaining to that drug, presented as percentages.

ADR frequencies from FDA clinical trials for each corresponding PDE5i were included as a comparison for the reader to contextualize the calculated frequencies.[11–14] In these trials, the frequencies were presented as a percentage: for ADR_1, $FREQ_1 = 100 \times a_1/(a_1 + b_1)$, where a_1 denotes number of patients taking the drug of interest expressing ADR_1 and b_1 denotes number of patients taking the drug of interest not expressing ADR_1.[11–14] To match our results, we calculated the secondary frequencies based on the data extracted from trial data according to this formula:

$$FREQ'_1 = \frac{FREQ_1 \times (a_1 + b_1)}{(FREQ_1/100) \times (a_1 + b_1) + (FREQ_2/100) \times (a_2 + b_2) + (FREQ_3/100) \times a_3 + b_3) + \cdots}$$

The trials did not provide decimals and reported the frequencies lower than two as <2 or a combination of ≥1 and <2, or <1. This led us to report the intervals when the provision of exact relative frequencies was not feasible.

2.3.2 | Disproportionality analysis

After identification of the most frequently reported ADRs in our dataset and FDA trial data, we measured reporting odds ratio (ROR) and the 95% confidence intervals (CI) for each PDE5i–ADR combination in comparison with the all-other drugs/reports in VigiBase: primarily with the raw data including all genders, age groups, and indications for PDE5i use, and secondarily after excluding all genders except for males, age groups 18 years and under, all routes of administration except oral, and indications other than sexual dysfunction (see

Supporting Information for included terms for sexual dysfunction). ROR is an alternative for the odds ratio in case–control studies and corresponds to the exposure odds among cases of a specific ADR over the odds of exposure among non-cases (i.e., other queried drugs in a designated dataset)[15]:

$$\mathrm{ROR} = \frac{a \times c}{b \times d}$$

where a = drug of interest–ADR of interest; b = drug of interest–other ADRs; c = other drugs–ADR of interest; and d = other drugs–other ADRs.[15,16]

For single drug–ADR, we calculated RORs as follows[17]:

$$\mathrm{ROR} = \frac{Cxy_1 \times [Cy_1 - Cxy_1]}{[Cx - Cxy_1] \times [C - Cx - Cy_1 + Cxy_1]}$$

where Cxy_1 = number of reports for the drug x and the ADR y_1; Cx = number of reports for the drug x; Cy_1 = number of reports for the ADR y_1; C = total number of reports for all drug–ADRs in the database.

For grouped ADRs (see Supporting Information for groupings), we calculated the cumulative RORs as follows:

$$\mathrm{ROR}_{cumulative} = \frac{(Cxy_1 + Cxy_2 + \cdots) \times [(Cy_1 + Cy_2 + \cdots) - (Cxy_1 + Cxy_2 + \cdots)]}{[Cx - (Cxy_1 + Cxy_2 + \cdots)] \times [C - Cx - (Cy_1 + Cy_2 + \cdots) + (Cxy_1 + Cxy_2 + \cdots)]}$$

An ADR is considered significantly disproportionate if the ROR's lower bound of the 95% CI and the number of observed event combinations were ≥1 and ≥3, respectively.[17] A positive disproportionality signal (ROR > 1) for a particular drug–ADR relationship in a pharmacovigilance database potentially indicates an association between the drug and the ADR and should prompt further investigation through case–control or cohort studies to confirm drug–ADR relationships.[15]

All statistical analyses were performed using Stata 17 (StataCorp, College Station, TX, USA), and all p-values were two-sided with a significance level set at <0.05. The design and reporting of the study followed the STROBE guidelines and checklist for observational studies.[18]

3 | RESULTS

A total of 94,713 ICSRs for PDE5is were received from VigiBase. After de-duplication and application of exclusion criteria, 31,827 ICRS remained pertaining to sildenafil (n = 20,012), tadalafil (n = 8474), vardenafil (n = 3277), and avanafil (n = 364) (Figure 1).

3.1 | Frequency

3.1.1 | Malignant melanoma

Our cohort's overall number of malignant melanoma cases was 278 (0.9%). For sildenafil, tadalafil, and vardenafil, malignant melanoma comprised 1.1%, 0.6%, and 0.03% of cases, respectively. Avanafil did not have any melanoma cases. In the comparator group, the FDA trials did not report malignant melanomas for the queried PDE5is (Table 1).

3.1.2 | Priapism

The total number of reports in the study cohort of priapism events was 258 (0.8%). Priapism comprised 0.8%, 1%, and 0.6% of ADR reports for sildenafil, tadalafil, and vardenafil, respectively (Table 1). No priapism events were recorded for adult men taking avanafil for ED. In data extracted from FDA trials, ≤44 (<3.5%) events for priapism were recorded for vardenafil. However, no case of priapism was reported for sildenafil, tadalafil, and avanafil in these trials.

3.1.3 | Common ADRs

Overall, poor drug efficacy (42.5%), headache (10.4% vs. 8.5%–27.6% [FDA trials]), abnormal vision (8.4 vs. ≤4.6 [FDA trials]), flushing (5.2% vs. 5.1%–16.5% [FDA trials]), and dyspepsia (4.2% vs. 3.4%–11.1% [FDA trials]) comprised the most frequently reported ADRs for all PDE5i drugs. Of the 20,012 sildenafil ADR reports, poor drug efficacy (43.4%), headache (9.8% vs. 7.6%–31% [FDA trials]), visual impairment (9.5% vs. 1.7%–6.8% [FDA trials]), flushing (5.2% vs. 5.4%–21.8% [FDA trials]), and dyspepsia (3.9% vs. 3.5%–14.4% [FDA trials]) were the most frequently noted. For tadalafil (n = 8474), poor drug efficacy (33.3%), headache (10.4% vs. 7.7%–26.2% [FDA trials]), hypertension (8% vs. 0.2%–0.5% [FDA trials]), asthenia (7.2%), and back pain (6.7% vs. 3.7%–12.6% [FDA trials]) were among the most common ADRs.

Poor drug efficacy (53.3%), headache (13.9% vs. 8.8%–26.8% [FDA trials]), abnormal vision (9.3% vs. <3.5% [FDA trials]), flushing (8.4% vs. 6.5%–19.6% [FDA trials]), and nasal congestion (4.7%) were the most commonly reported ADRs for vardenafil (n = 3277). Among 364 avanafil cases, poor drug efficacy (69.2%), flushing (8% vs. 7.5%–12.2% [FDA trials]), headache (7.1% vs. 14.4%–23.6% [FDA trials]), ED (5.5%), wrong technique in product use (5.2%), and dyspepsia (2.8% vs. 0.9%–2.9% [FDA trials]) were the most commonly reported ADRs (Table 1).

3.2 | Disproportionality analysis

3.2.1 | Primary

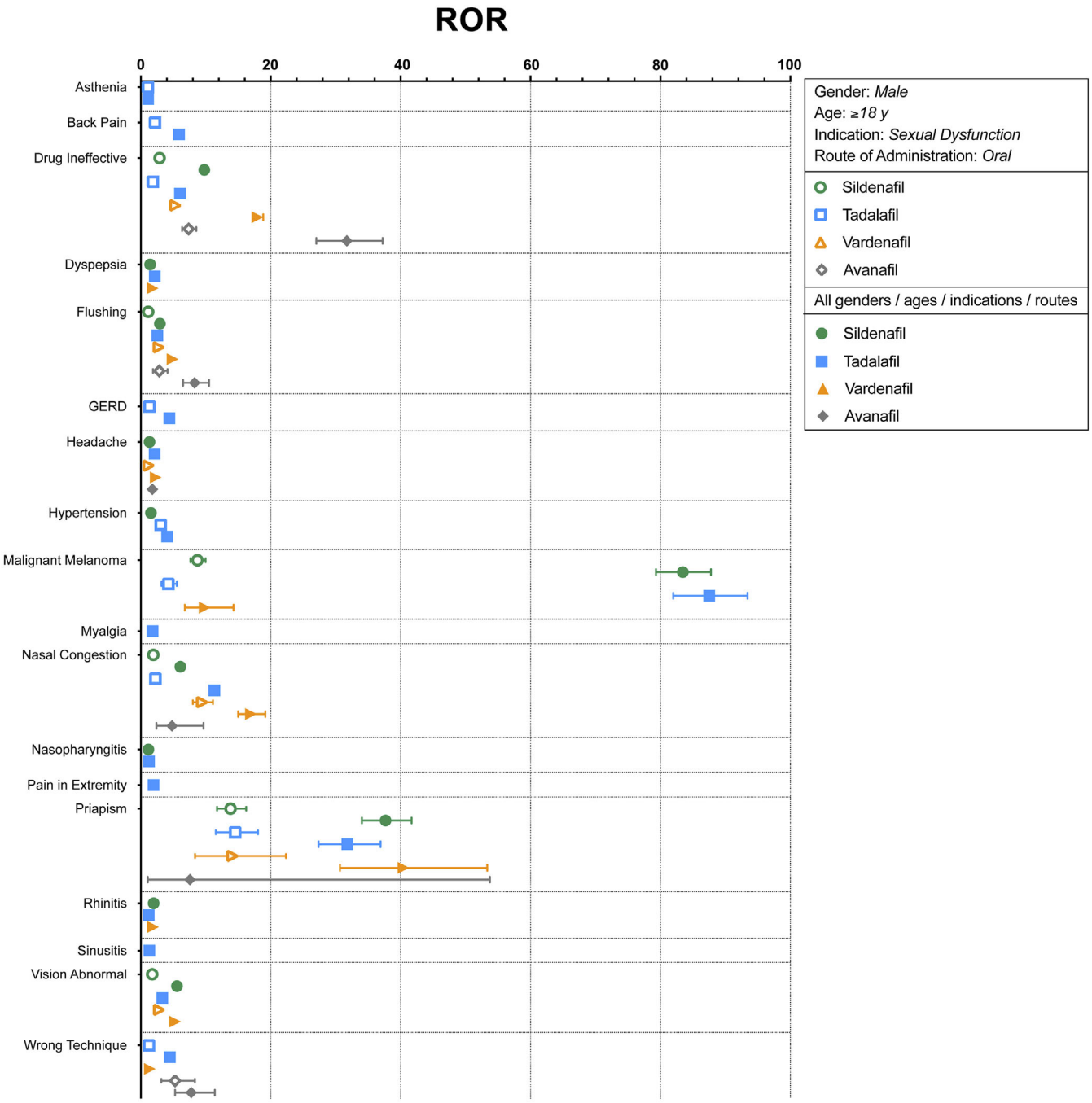
For PDE5is used by subjects regardless of age, gender, the indication of use, and route of administration, we found positive

TABLE 1 Relative adverse drug reaction (ADR) frequencies of the study population compared with the pooled data from the Food and Drug Administration (FDA) trials.

ADR	Reported events for each ADR, no. (%)							
	Sildenafil		Tadalafil		Vardenafil		Avanafil	
Total events (VigiBase) = 69,618	VigiBase (*n* = 20,012)	FDA trials (*n*: 1342–5468)	VigiBase (*n* = 8474)	FDA trials (*n*: 776–2644)	VigiBase (*n* = 3277)	FDA trials (*n*: 1233–3745)	VigiBase (*n* = 364)	FDA trials (*n*: 622–1019)
Abdominal pain	222 (1.1)	≤41 (<3)	67 (0.8)	7 (0.3–0.9)	37 (1.1)	≤44 (<3.4)	6 (1.7)	NR
Accidental injury	NR	≤41 (<3)	NR	NR	NR	66 (1.8–5.4)	NR	NR
Asthenia	171 (0.9)	≤41 (<3)	613 (7.2)	NR	17 (0.5)	≤44 (<3.5)	5 (1.4)	NR
Back pain	139 (0.7)	65 (1.2–4.8)	566 (6.7)	98 (3.7–12.6)	41 (1.3)	44 (1.2–3.6)	4 (1.1)	30–37 (2.8–5.6)
CK increased	27 (0.1)	NR	12 (0.1)	NR	5 (0.2)	44 (1.12–3.6)	NR	NR
Cough	75 (0.4)	≤41 (<3)	23 (0.3)	14 (0.5–1.8)	8 (0.2)	NR	NR	≤7 (<1.1)
Diarrhea	194 (1)	NR	109 (1.3)	16 (0.6–2.1)	48 (1.5)	NR	5 (1.4)	7–14 (0.7–2.2)
Dizziness	716 (3.6)	60 (1.1–4.5)	263 (3.1)	6 (0.2–0.8)	140 (4.3)	44 (1.2–3.6)	8 (2.2)	10–17 (1–2.7)
Drug ineffective	8691 (43.4)	NR	2824 (33.3)	NR	1746 (53.3)	NR	252 (69.2)	NR
Dyspepsia	785 (3.9)	193 (3.5–14.4)	401 (4.7)	143 (5.4–18.4)	135 (4.1)	88 (2.4–7.1)	10 (2.8)	9–18 (0.9–2.9)
ECG abnormal	52 (0.3)	≤41 (<3)	7 (0.1)	NR	7 (0.2)	NR	0 (0)	4 (0.4–0.6)
Flu syndrome	73 (0.4)	NR	33 (0.4)	NR	8 (0.2)	66 (1.8–5.4)	1 (0.3)	16–33 (1.6–5)
Flushing	1030 (5.2)	293 (5.4–21.8)	308 (3.6)	45 (1.7–5.8)	274 (8.4)	242 (6.5–19.6)	29 (8)	76 (7.5–12.2)
Gastroenteritis	7 (0.03)	≤41 (<3)	1 (0.01)	8 (0.3–1)	NR	≤44 (<3.5)	NR	3 (0.3–0.5)
GERD	54 (0.3)	NR	96 (1.1)	12 (0.5–1.5)	8 (0.2)	≤44 (<3.5)	NR	≤7 (<1.12)
Headache	1960 (9.8)	416 (7.6–31)	877 (10.4)	203 (7.7–26.2)	456 (13.9)	330 (8.8–26.8)	26 (7.1)	147 (14.4–23.6)
Hypertension	271 (1.4)	NR	680 (8)	4 (0.2–0.5)	20 (0.6)	≤44 (<3.5)	1 (0.3)	16–33 (1.6–5)
Malignant melanoma	223 (1.1)	NR	54 (0.6)	NR	1 (0.03)	NR	NR	NR
Myalgia	104 (0.5)	37 (0.7–2.7)	472 (5.6)	58 (2.2–7.5)	22 (0.7)	≤44 (<3.5)	3 (0.8)	≤7 (<1.1)
Nasal congestion	286 (1.4)	108 (2–8)	164 (1.9)	48 (1.8–6.2)	153 (4.7)	NR	3 (0.8)	47 (4.6–7.6)
Nasopharyngitis	96 (0.5)	NR	20 (0.2)	41 (1.5–5.3)	4 (0.1)	NR	0 (0)	55 (5.4–8.9)
Nausea	370 (1.9)	37 (0.7–2.7)	153 (1.8)	≤49 (<6)	88 (2.7)	44 (1.2–3.6)	6 (1.7)	9–18 (0.9–2.9)
Pain in extremity	96 (0.5)	NR	288 (3.4)	49 (1.8–6.3)	21 (0.6)	NR	1 (0.3)	≤7 (<1.1)
Priapism	157 (0.8)	NR	83 (1)	NR	18 (0.6)	≤44 (<3.5)	NR	NR
Rash	149 (0.8)	43 (0.8–3.2)	86 (1)	≤49 (<6)	35 (1.1)	≤44 (<3.5)	5 (1.4)	9–18 (0.9–2.9)
Rhinitis	254 (1.3)	NR	36 (0.4)	NR	34 (1)	198 (5.3–16.1)	1 (0.3)	NR
Sinusitis	23 (0.1)	≤41 (<3)	8 (0.1)	NR	2 (0.1)	66 (1.8–5.4)	0 (0)	16–33 (1.6–5)
URTI	17 (0.1)	22 (0.8–2.8)	7 (0.1)	NR	1 (0.03)	NR	0 (0)	21–38 (<5.7)
UTI	22 (0.1)	NR	12 (0.1)	4 (0.2–0.5)	4 (0.1)	NR	NR	≤7 (<1.1)
Vision abnormal	1725 (8.6)	91 (1.7–6.8)	471 (5.6)	≤49 (<6)	303 (9.3)	≤44 (<3.5)	7 (1.9)	NR
Wrong technique	39 (0.2)	NR	200 (2.4)	NR	31 (1)	NR	19 (5.2)	NR

Note: ADRs in this table were selected based on the relative frequency of each being >2 for at least one drug at any dosage in either VigiBase or FDA trials data.

Abbreviations: CK, creatine kinase; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; NR, not reported; URTI, upper respiratory tract infection; UTI, urinary tract infection.



[a] ADRs in this table were selected based on the relative frequency of each being >2 for at least one drug at any dosage in either VigiBase or FDA trials data.
[b] Criteria: i) primary analysis: age ≥18y, male gender, indicated for sexual dysfunction, and oral route of administration, ; ii) secondary analysis: all ages / genders / indications / routes of administration.
ROR: Reporting odds ratio; GERD: Gastroesophageal reflux disease.

FIGURE 2 Comparison between primary and secondary disproportionality analyses. Adverse drug reactions (ADRs) were selected based on the relative frequency of each being >2 for at least one drug at any dosage in either VigiBase or Food and Drug Administration (FDA) trials data. Criteria: (i) primary analysis—age ≥18 years, male gender, indicated for sexual dysfunction, and oral route of administration. (ii) Secondary analysis—all ages/gender/indications/routes of administration. GERD, gastroesophageal reflux disease; ROR, reporting odds ratio.

disproportionality signals for malignant melanoma pertaining to sildenafil (ROR = 83.45; 95% CI: 79.33–87.79), tadalafil (ROR = 87.52; 95% CI: 81.98–93.43), and vardenafil (ROR = 9.85; 95% CI: 6.79–14.28). Likewise, sildenafil (ROR = 37.68; 95% CI: 34.05–41.7), tadalafil (ROR = 31.8; 95% CI: 27.38–36.92), and vardenafil (ROR = 40.44; 95% CI: 30.66–53.34) showed significant RORs for priapism. However, avanafil exhibited disproportionate signals for neither malignant melanoma nor priapism (ROR < 1). The results of primary disproportionality analysis are depicted in Figure 2.

TABLE 2 Results of disproportionality analysis (reporting odds ratio [ROR]) for the most common adverse drug reactions (ADRs) for sildenafil, tadalafil, vardenafil, and avanafil.

	Sildenafil		Tadalafil		Vardenafil		Avanafil	
ADR	ROR (95% CI)	*p*-Value	ROR (95% CI)	*p*-Value	ROR (95% CI)	*p*-Value	ROR (95% CI)	*p*-Value
Abdominal pain	0.15 (0.13–0.18)	<0.001	0.09 (0.07–0.12)	<0.001	0.23 (0.17–0.32)	<0.001	0.37 (0.13–0.81)	0.011
Accidental injury	–	–	–	–	–	–	–	–
Asthenia	0.15 (0.13–0.18)	<0.001	1.1 (1.02–1.2)	0.015	0.14 (0.08–0.22)	<0.001	0.4 (0.13–0.93)	0.033
Back pain	0.26 (0.22–0.31)	<0.001	2.17 (1.99–2.36)	<0.001	0.7 (0.5–0.95)	0.023	0.67 (0.18–1.71)	0.414
CK increased	0.32 (0.21–0.46)	<0.001	0.29 (0.15–0.5)	<0.001	0.54 (0.17–1.25)	0.157	–	–
Cough	0.08 (0.06–0.1)	<0.001	0.05 (0.03–0.08)	<0.001	0.08 (0.03–0.16)	<0.001	–	–
Diarrhea	0.11 (0.09–0.12)	<0.001	0.12 (0.1–0.14)	<0.001	0.24 (0.18–0.32)	<0.001	0.24 (0.08–0.57)	<0.001
Dizziness	0.3 (0.28–0.32)	<0.001	0.22 (0.19–0.25)	<0.001	0.53 (0.45–0.63)	<0.001	0.3 (0.13–0.59)	<0.001
Drug ineffective	2.89 (2.83–2.96)	<0.001	1.87 (1.8–1.94)	<0.001	5.33 (5.06–5.63)	<0.001	7.37 (6.36–8.55)	<0.001
Dyspepsia	0.39 (0.37–0.42)	<0.001	0.38 (0.34–0.42)	<0.001	0.72 (0.61–0.86)	<0.001	0.61 (0.29–1.13)	0.118
ECG abnormal	0.47 (0.35–0.62)	<0.001	0.13 (0.05–0.26)	<0.001	0.58 (0.23–1.2)	0.146	–	–
Flu syndrome	0.12 (0.1–0.15)	<0.001	0.11 (0.08–0.15)	<0.001	0.12 (0.05–0.24)	<0.001	0.15 (0–0.82)	0.027
Flushing	1.14 (1.07–1.22)	<0.001	0.68 (0.61–0.77)	<0.001	2.77 (2.45–3.13)	<0.001	2.84 (1.89–4.12)	<0.001
Gastroenteritis	0.12 (0.05–0.24)	<0.001	0.03 (0–0.18)	<0.001	0 (0–0.6)	0.012	–	–
GERD	0.38 (0.28–0.49)	<0.001	1.35 (1.09–1.65)	0.004	0.51 (0.22–1.01)	0.053	–	–
Headache	0.57 (0.55–0.6)	<0.001	0.51 (0.48–0.55)	<0.001	1.21 (1.1–1.33)	<0.001	0.67 (0.43–0.99)	0.042
Hypertension	0.61 (0.54–0.69)	<0.001	3.07 (2.84–3.31)	<0.001	0.43 (0.26–0.66)	<0.001	0.2 (0.01–1.12)	0.075
Malignant melanoma	8.73 (7.63–9.99)	<0.001	4.25 (3.19–5.55)	<0.001	0.35 (0.01–1.95)	0.273	–	–
Myalgia	0.08 (0.06–0.1)	<0.001	0.71 (0.65–0.78)	<0.001	0.15 (0.09–0.23)	<0.001	0.2 (0.04–0.59)	0.002
Nasal congestion	1.93 (1.72–2.17)	<0.001	2.25 (1.92–2.63)	<0.001	9.44 (8.01–11.12)	<0.001	1.79 (0.37–5.26)	0.307
Nasopharyngitis	0.29 (0.24–0.36)	<0.001	0.12 (0.07–0.19)	<0.001	0.11 (0.03–0.29)	<0.001	–	–
Nausea	0.1 (0.09–0.11)	<0.001	0.08 (0.07–0.1)	<0.001	0.21 (0.17–0.26)	<0.001	0.14 (0.05–0.31)	<0.001
Pain in extremity	0.1 (0.08–0.12)	<0.001	0.59 (0.52–0.66)	<0.001	0.2 (0.12–0.3)	<0.001	0.09 (0–0.51)	0.003
Priapism	13.81 (11.75–16.24)	<0.001	14.54 (11.56–18.06)	<0.001	14.12 (8.36–22.35)	<0.001	–	–
Rash	0.03 (0.03–0.04)	<0.001	0.04 (0.03–0.05)	<0.001	0.07 (0.05–0.1)	<0.001	0.1 (0.03–0.24)	<0.001
Rhinitis	1.09 (0.96–1.23)	0.176	0.31 (0.22–0.43)	<0.001	1.33 (0.92–1.86)	0.094	0.38 (0.01–2.13)	0.315
Sinusitis	0.15 (0.09–0.22)	<0.001	0.1 (0.04–0.2)	<0.001	0.12 (0.01–0.43)	<0.001	–	–
URTI	0.18 (0.1–0.29)	<0.001	0.15 (0.06–0.3)	<0.001	0.1 (0–0.54)	0.004	–	–
UTI	0.09 (0.06–0.14)	<0.001	0.1 (0.05–0.17)	<0.001	0.15 (0.04–0.38)	<0.001	–	–
Vision abnormal	1.76 (1.68–1.85)	<0.001	0.96 (0.88–1.05)	0.387	2.82 (2.51–3.17)	<0.001	0.63 (0.25–1.31)	0.22
Wrong technique	0.13 (0.09–0.17)	<0.001	1.27 (1.1–1.46)	0.001	0.93 (0.63–1.32)	0.671	5.29 (3.17–8.33)	<0.001

Note: ADRs in this table were selected based on the relative frequency of each being >2 for at least one drug at any dosage in either VigiBase or Food and Drug Administration (FDA) trials data. Criteria: age ≥18 years, male gender, the oral route of administration, and indicated for sexual dysfunction.
Abbreviations: CI, confidence interval; CK, creatine kinase; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; URTI, upper respiratory tract infection; UTI, urinary tract infection.

3.2.2 | Secondary

Table 2 presents the secondary RORs (for oral PDE5i male consumers 18 years or older aiming to treat sexual dysfunction) for the most frequently reported ADRs for PDE5is according to VigiBase and FDA trials. Comparing with all other medications in VigiBase, sildenafil (ROR = 8.73, 95% CI: 7.63–9.99) and tadalafil (ROR = 4.25, 95% CI: 3.19–5.55) had significantly higher RORs for malignant melanoma. Also, sildenafil (ROR = 13.81, 95% CI: 11.75–16.24), tadalafil (ROR = 14.54, 95% CI: 11.56–18.06), and vardenafil (ROR = 14.12, 95% CI: 8.36–22.35) showed significant disproportionality signals for priapism. Similar to the primary analysis, we found no significant RORs for avanafil for malignant melanoma or priapism.

4 | DISCUSSION

In our cohort of men taking oral PDE5is for sexual dysfunction, less than 1% of ADR reports were for malignant melanoma. Despite the low incidence, we found a significant disproportionality signal for metastatic melanoma, indicating a strong association between melanoma and sildenafil and tadalafil. Similarly, we found that 0.8% of ICSRs for sildenafil, tadalafil, and vardenafil consisted of priapism reports with positive pharmacovigilance signals. These data suggest a significant link between PDE5is and these rare events. Specifically, among patients taking PDE5is, there is a substantially increased, although still small absolute, risk of malignant melanoma.

PDE5i use has been suggested to affect several molecular pathways related to malignant melanoma proliferation, invasiveness, and survival.[7,8,19] However, the biological plausibility of this association is questioned.[20] A prior retrospective cohort by Li et al.[21] found that the association between malignant melanoma and sildenafil use persisted even after controlling for family history, sun exposure, and ultraviolet index of patients' state of residence. Contrarily, in a recent study of the Surveillance, Epidemiology, and End Results (SEER) database, it was found that after the introduction of PDE5is in 1998, the trend for the rate of malignant melanoma diagnosis did not change significantly.[22] However, by design, the SEER did not allow for controlling for the intensity of sun exposure, which could potentially confound their results.[22] In our study, reports of malignant melanoma were frequent and disproportionately positive for adults' use of sildenafil and tadalafil for sexual dysfunction. Further, when not controlling for gender, age, indication, and route of administration, we observed 40-fold greater RORs for sildenafil and tadalafil for malignant melanoma. This further supports our initial hypothesis and the findings of other investigators on this association and indicates that chronicity or beginning at an earlier age (e.g., in patients with pulmonary hypertension) may increase the PDE5i-mediated effects of melanoma development and/or progression. Nonetheless, our study was unable to control metabolic and lifestyle factors (e.g., sun exposure) that are associated with melanoma and may be associated with PDE5i use.[23] While further study is needed to assess causal relationships between PDE5is and melanoma, our findings add to the growing literature on the association between PDE5is and malignant melanoma from the lens of a multidecade, international cohort.

While priapism is a feared side effect of PDE5i use, its prevalence is poorly defined.[24] While many ADRs are detected in clinical trials, the small sample sizes and short testing periods of these clinical trials prevent the identification of all ADRs, particularly those that are rare.[25] Priapism from PDE5is is recorded by a limited number of case reports. In the majority of these cases, priapism occurred in the setting of sildenafil administration at common dosages, whether for therapeutic or recreational purposes, and co-existence of precipitating factors, namely, sickle cell disease, metastatic malignancy, or use of cytochrome P450 inhibiting substances (e.g., pomegranate juice). Additionally, two studies reported cases of sildenafil-related priapism in a healthy adult and a toddler without concomitant risk factors, which happened at irregular dosages (200 and 300 mg, respectively). This suggests that normally, PDE5is do not tend to induce priapism if prescribed in therapeutic dosages and under medical control. Harmoniously, a recent pharmacovigilance analysis of the FDA Adverse Event Reporting System database (2015–2020) showed a significant signal for tadalafil regarding priapism while indicating none for sildenafil.[26] Further, by sub-analyzing the characteristics of priapism cases related to PDE5i, they showed that the majority of these cases were associated with excessive dosage ingestion, unusual indications, and/or concomitant medication/recreational drug use and concluded that PDE5i consumption could not cause priapism without the presentation of precipitating factors. Using VigiBase, we monitored for ADRs associated with PDE5is from the introduction of these products in 1998–2021, which resulted in significant disproportionality signals for priapism in sildenafil, tadalafil, and vardenafil for all-comers. We similarly observed significant disproportionality signals for the same drugs when narrowing down our analysis to adult men taking oral PDE5i for sexual dysfunction (i.e., typical PDE5i users). Although we were unable to control for dosing because of database shortcomings, sub-analysis of typical PDE5i users enabled us to screen for PDE5i-related priapism in potentially more standardized dosages and exclude recreational use by the underaged.

Another recent pharmacovigilance study on the FDA Adverse Reporting System Public Dashboard has shown that 0.7% of all recorded ADRs for PDE5i use in patients not diagnosed with sickle cell disease are attributable to priapism.[27] We similarly found that priapism accounted for less than 1% of ADR reports (disproportionately positive across sildenafil, tadalafil, and sildenafil). Accordingly, while there is a risk associated with priapism in oral PDE5i users, urologic association guidelines do not provide any recommendation on patient counseling about this ADR.[3,4]

In our study, poor drug efficacy was disproportionately positive in all PDE5is for oral use by adult men for sexual dysfunction and comprised almost half the ADR reports. Evidence shows that 30%—35% of men do not respond to initial PDE5i treatment.[28] Unique to PDE5is is their on-demand dosing and the ability for patients to self-assess drug efficacy, as effects occur in real time shortly after oral administration. Many drugs in the VigiBase dataset do not allow patients to perform a similar self-assessment and therefore have comparably lower ADRs related to poor drug efficacy. This is compounded in the dataset by missing dosing data and the lack of comparator lifestyle drugs that allow patients to self-assess efficacy. However, we acknowledge that adequate drug response is a valid concern for patients and providers considering PDE5is for ED. In contrast to poor drug efficacy which was unanimously disproportionate in all the PDE5i agents, some ADRs showed positive signals for specific products, such as visual impairment for sildenafil and vardenafil. While all currently available PDE5is are highly selective for PDE5, unique drug-specific ADR relationships exist because of each agent's pharmacodynamic profile (Figure 3). For instance, sildenafil and vardenafil have phosphodiesterase class 6 activity, which is expressed in the retina leading to visual complaints (e.g., blurred vision or color changes). Our findings reinforce these biochemical differences between each oral PDE5i.Treatment-specific side

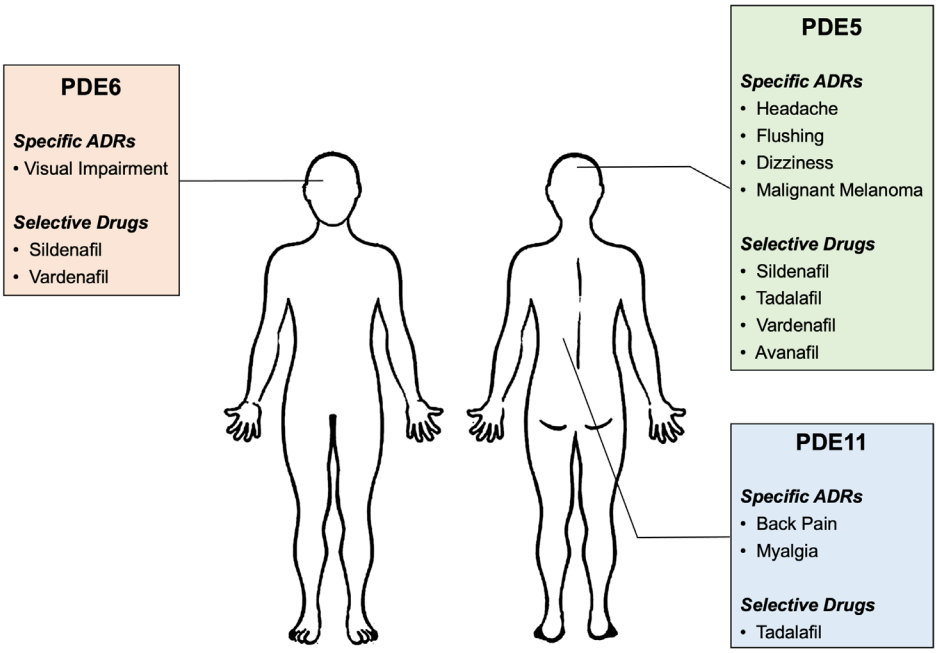


FIGURE 3 Phosphodiesterase (PDE)-specific adverse drug reactions (ADRs).

effects are essential for providers and patients to know and consider when choosing ED medication.

4.1 | Limitations

A complete list of limitations related to the VigiBase dataset can be found on the UMC website.[29] We highlight several important limitations here. First, analysis of pharmacovigilance data does not allow for the quantification of the clinical risk, and clinical studies are instead more suitable for this purpose.[15] Data in VigiBase are subjected to reporting bias, duplicated reports, confounding issues, and heterogeneity over time and across regions. Second, under-/over-reporting is common because ADR reports cannot be treated as a random sample from a population of patients. The total number of treated patients and those with a particular reaction is unknown. Third, ROR is a reporting rate, which is not the same as a risk estimate. Fourth, other known limitations include missing data, lack of fatal outcome information, and incomplete dosing data. Finally, comorbidity data are missing, and causal drug–ADR associations cannot be drawn. Similar ADRs were grouped by clinical reasoning for this study's analysis. Similar inclusion terms and PTs, such as flushing, feeling hot, and hot flush, were categorized into one grouping (Supporting Information). While multiple authors confirmed this list of similar terms, there is a possibility of a small number of missed ADRs.

5 | CONCLUSIONS

Although priapism is extremely rare among men taking phosphodiesterase type 5 inhibitors for sexual dysfunction, phosphodiesterase type 5 inhibitor still show signals correlating with the adverse drug reaction of priapism among a large international cohort. Whether this is from inappropriate use or other confounding conditions requires further clinical study as there is limited and poor-quality evidence available regarding the risk of side effects when the use of these medications happens out of medical control or for different indications. Furthermore, there appears to be a relationship between phosphodiesterase type 5 inhibitor use and malignant melanoma, which warrants additional study to better understand causation.

AUTHOR CONTRIBUTIONS

Benjamin N. Breyer and Nathan M. Shaw conceptualized the study. Jason L. Lui performed literature search. Behzad Abbasi and Jason L. Lui performed statistical analysis. Jason L. Lui drafted the manuscript. Nathan M. Shaw, Benjamin N. Breyer, Nizar Hakam, and Behzad Abbasi revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Uppsala Monitoring Centre. Restrictions apply to the availability of these data, which were used under license for this study. Data are available

from https://who-umc.org/ with the permission of Uppsala Monitoring Centre.

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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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