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ORIGINAL RESEARCH ARTICLE

Sexual Dysfunctions Associated with Proton Pump Inhibitors: Insights from VigiBase, the World Health Organization Pharmacovigilance Database

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Abstract

Background Over the years, several observational studies and case reports have been published hypothesizing a potential association between the use of proton pump inhibitors (PPIs) and sexual dysfunctions in both male and female patients.

Objectives We aimed to investigate the potential association between PPI use and sexual dysfunction onset using VigiBase, the World Health Organization international pharmacovigilance database.

Methods All individual case safety reports of sexual dysfunctions containing PPIs (i.e. omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole) as suspected or interacting drugs until 4 September, 2024 were selected from VigiBase using the Standardised MedDRA Query "Sexual dysfunction". A descriptive analysis of the selected individual case safety reports was carried out. Potentially new safety signals were identified through a disproportionality analysis and calculated as a reporting odds ratio (ROR) along with a 95% confidence interval (CI), which were adjusted via Bonferroni correction for multiple testing. To account for age-related effects on sexual functions, a subgroup analysis was carried out by restricting the study population only to patients aged from 18 to 64 years.

Results A total of 420,598 individual case safety reports concerning PPIs were collected in VigiBase during the study period. Of these, 841 containing at least one Preferred Term included in the "Sexual dysfunction" Standardised MedDRA Query reporting information on sex were retrieved. Overall, disproportionate reporting for omeprazole concerning erectile dysfunction (adjusted ROR, 1.76; 95% CI 1.54–2.01) was observed, while two statistically significant adjusted RORs for esomeprazole, i.e. genital discomfort (ROR, 3.66; 95% CI 1.34–10.04) and oestrogen deficiency (ROR, 3.80; 95% CI 1.03–13.99) in female patients were found. The subgroup analysis confirmed the statistically significant disproportionate reporting of erectile dysfunction for omeprazole (adjusted ROR: 1.80; 95% CI 1.49–2.16), and generated new potential safety signals including an omeprazole-induced libido decrease (adjusted ROR, 1.49; 95% CI 1.05–2.12) and esomeprazole-induced hypogonadism (adjusted ROR, 5.22; 95% CI 1.22–22.34) in male individuals, and omeprazole-induced genital discomfort (adjusted ROR, 3.55; 95% CI 1.13–11.09) in female individuals.

Conclusions Findings of this study suggest the presence of safety signals of PPI-induced sexual dysfunctions, such as erectile dysfunction, genital discomfort and oestrogen deficiency. However, further observational studies are required to validate and further characterise these potential safety signals.

Salvatore Crisafulli and Francesco Ciccimarra are equal contribution as first authors.

Extended author information available on the last page of the article

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Key Points

Findings of this study suggest a potential involvement of esomeprazole and omeprazole in triggering erectile dysfunction, genital discomfort and oestrogen deficiency.

In the absence of other identifiable causes, clinicians should consider the use of proton pump inhibitors as a possible contributor to sexual dysfunctions and should evaluate whether discontinuation is warranted.

1 Introduction

Proton pump inhibitors (PPIs) are among the most commonly prescribed drug classes worldwide for both the prevention of non-steroidal anti-inflammatory drug-induced ulcers and the treatment of acid-related disorders (e.g. gastroesophageal reflux disease and peptic ulcer disease). A large body of evidence documented an increased risk of severe adverse reactions, especially with long-term and inappropriate use of these drugs [1–3].

Specifically, PPIs can lead to serious adverse effects, such as an increased risk of fractures, susceptibility to severe infections as well as impaired absorption of nutrients as well as orally administered medicines, thus leading to their reduced effectiveness [4]. Given the widespread use of PPIs, these drugs have been associated with a large number of potential adverse outcomes. However, many of these associations are likely to be spurious and largely driven by confounding factors such as polypharmacy and underlying comorbidities.

Over the years, several published observational studies and case reports have hypothesised a potential association between the use of PPIs and the onset of sexual dysfunctions (SDs) in both male and female individuals [5–9]. Sexual dysfunctions are medical conditions that can affect any phase of the sexual response cycle and individuals of any age. The International Statistical Classification of Diseases and Related Health Problems, 11th Edition, in Chapter 17 (HA00–HA8Z) "Conditions related to sexual health", lists six major families of SDs: hypoactive sexual desire dysfunction (male and female), sexual arousal dysfunctions (encompassing symptoms related to erection and lubrication), orgasmic dysfunctions (male and female), ejaculatory dysfunctions (premature or delayed ejaculation), gender incongruence and sexual pain disorders [10].

An analysis of pharmacovigilance data conducted by the Netherlands Pharmacovigilance Centre Lareb showed a disproportionate reporting of PPI-related erectile dysfunction (ED). In detail, they received 17 reports of ED in association with omeprazole, and for eight of them, a positive dechallenge was observed [5].

Moreover, based on 66 reports of ED associated with esomeprazole retrieved from EudraVigilance, in October 2023, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) initiated a referral and warranted further investigation to evaluate the potential association of esomeprazole/omeprazole with ED and other SDs [11].

In this case, impaired sexuality or SD could be associated with a central dopaminergic derangement and/or directly associated with high prolactin levels in both men and women [12–18]. Proton pump inhibitor use has been linked to hyperprolactinemia, which may have a significant effect on the patient's quality of life and fertility, as well as genitourinary and gynaecological adverse reactions [19].

As such, exploring the potential association between PPIs and SDs is particularly important, as ED, retrograde ejaculation, pubertal failure and hyperprolactinemia are included in the important medical event (IME) terms list [20]. This list, developed by the EudraVigilance Expert Working Group, aims to facilitate the classification of suspected serious adverse drug reactions (ADRs) and includes life-threatening events, events resulting in death or requiring hospitalisation/prolongation of hospital stay or resulting in persistent or significant disability/incapacity, as well as congenital anomalies/birth defects [21].

To date, the potentially harmful effects of PPIs on male and female reproductive health have been little studied. In light of this evidence and also considering the widespread and often inappropriate use of PPIs, there is a need to further investigate the association of PPIs with SDs. Therefore, the aim of this study was to explore the relationship between PPIs and SDs by performing a disproportionality analysis on VigiBase.

2 Methods

2.1 VigiBase

VigiBase, the World Health Organization global database of individual case safety reports (ICSRs) of suspected ADRs, is the largest spontaneous reporting system (SRS) database in the world, currently containing over 34 million ICSRs on suspected ADRs submitted from around 150 member countries. It is maintained by the Uppsala Monitoring Centre in Sweden. Drugs recorded on the reports are coded according to the *World Health Organization Drug Global Dictionary*

and ADRs are classified according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.1 [22].

For data extraction, we used VigiLyze, a data warehousing system provided by the Uppsala Monitoring Centre. We used the de-duplicated dataset automatically calculated by VigiMatch, a probabilistic record matching method [23].

2.2 Study Drugs and Study Outcomes

We included in the analysis ICSRs concerning PPIs approved for use by the EMA and/or the US Food and Drug Administration (FDA), namely omeprazole (Anatomical Therapeutic Chemical [ATC]: A02BC01), pantoprazole (ATC: A02BC02), lansoprazole (ATC: A02BC03), rabeprazole (ATC: A02BC04), and esomeprazole (ATC: A02BC05), as suspected or interacting drugs. Individual case safety reports concerning SDs in which PPIs were reported as concomitant drugs were not included in the analysis. We extracted ICSRs recorded in VigiBase, from its inception to 4 September, 2024 (last data drawn). Reports including the study drugs and suspected ADRs related to SDs were defined as cases, while all other reports in the database were defined as non-cases. Reports with missing information on a patient's sex were not included in the analysis.

Suspected ADRs of interest were identified using the Standardized MedDRA Query (SMQ) "Sexual dysfunction". Furthermore, as hyperprolactinemia may be eventually an intermediate factor in the SD-PPI association, we also identified ICSRs concerning PPIs and reporting the Preferred Term (PT) "hyperprolactinemia". Standardized MedDRA Queries include different PTs covering a range of clinical conditions, including well-defined diseases and symptoms. Preferred terms included in the SMQ "Sexual dysfunctions" are listed in Table 1 of the ESM. As SMQs can be applied as either broad or narrow searches, we used the specific narrow scope search [24].

2.3 Data Analysis

For each report identified, the following variables were extracted: individual safety report identifier, date in which the ICSR was received, age, sex, country, drug name (normalised to generic name), ADR of interest and seriousness and related outcome. A descriptive frequency analysis of patients' age and sex, type of reporter (physician, pharmacist, other healthcare professional and patient/non-healthcare professional), ADR outcome and seriousness [25] was conducted. Continuous variables were reported as median with interquartile ranges. Categorical variables were summarised as frequencies and percentages.

Adverse drug reaction reporting disproportionality for potential signal detection was carried out by calculating the reporting odds ratio (ROR), along with 95% confidence intervals (CIs), using a case/non-case methodology [26]. This quantitative approach is based on the measurement of the frequency of drug-suspected adverse reaction pairs, as compared with distributions of all other ADRs (i.e. non-cases) from the whole database (excluding vaccines) reported in the same period [27]. To identify potential signals of disproportionate reporting, the statistical threshold was defined as the lower bound of the 95% CIs of the ROR >1 with three or more individual ICSRs, according to the guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system [28]. Reporting odds ratios were adjusted via Bonferroni correction for multiple testing.

In the primary analysis, RORs were individually calculated for each pair of single study drugs, the PT included in the narrow definition of the SMQ "sexual dysfunctions". As a secondary analysis, we also calculated the RORs for the PT "hyperprolactinemia". Because of differences between sexes, disproportionality analyses were carried out separately for male and female patients. Disproportionality analyses were conducted in accordance with READUS-PV recommendations [29, 30].

To account for age-related effects on sexual functions, a subgroup analysis was carried out by excluding patients aged from 12 to 17 years and those aged ≥ 65 years from the disproportionality analysis. In addition, for each PPI under investigation, the time to onset (TTO) of each PT included in the SMQ "sexual dysfunctions" as well as for hyperprolactinemia was calculated as the time between the beginning of the treatment with PPIs and the onset of the ADR. Time to onset was calculated only for PTs with a statistically significant ROR and for drugs with at least three ICSRs reporting the information needed to calculate the TTO (i.e. the date of PPI treatment beginning and the date of ADR onset). Box plots were used to graphically visualise the median TTO for each ADR, stratified by study drugs. A Chi-square test or Fisher's exact test was performed to compare categorical variables, while a Kruskal–Wallis test was performed to compare medians, as appropriate. A p value < 0.05 denoted statistical significance. All analyses were performed using R statistical software (version 4.3.1).

Last, the EMA and FDA summary of product characteristics (SmPCs) of the PPIs included in the study were screened to identify the notoriety of ADRs for those pairs PPI-PT with a significant ROR value. For the ICSRs that generated potential safety signals, data concerning dechallenge/rechallenge, and co-reported medications known to induce SDs were evaluated.

3 Results

3.1 Descriptive Analysis

Up to 4 September, 2024, 30,548,821 de-duplicated ICSRs (excluding vaccines) were collected in VigiBase, and 420,598 (1.4%) of them concerned the PPIs under study. Individual case safety reports related to the SMQ "sexual dysfunction", and the PT hyperprolactinemia accounted for 870 (0.2%) of the PPIs-related ICSRs. Of these, 841 ICSRs (96.7%) reporting information on patients' sex were included in the analyses, with omeprazole being the most frequently reported ($N = 432$; 51.4%), followed by esomeprazole ($N = 162$; 19.3%), pantoprazole ($N = 132$; 15.7%), lansoprazole ($N = 110$; 13.1%) and rabeprazole ($N = 40$; 4.7%) (Fig. 1).

The main demographic and clinical characteristics of these ICSRs, stratified by sex and PPI, are presented in Table 1. Overall, those reports mainly concerned male patients (male/female ratio = 5.2), and those aged between 18 and 64 years. Reports of PPI-related SDs and hyperprolactinemia primarily originated from Europe ($N = 419$; 46.2%) and America ($N = 357$; 39.2%) and were mostly reported by physicians ($N = 289$; 31.9%) and consumers ($N = 218$; 24.0%).

A total of 186 (20.5%) serious ADRs, mainly concerning male patients (72.6%), were reported. However, for each PPI, the proportions of serious ADRs were higher among women than men (Table 1).

3.2 Disproportionality Analysis

With a total of 532 cases, ED was the most commonly reported PT, followed by hypoactive sexual desire [i.e. decrease ($N = 143$), and loss ($N = 31$) of libido], hyperprolactinemia ($N = 66$), sexual disfunction ($N = 52$) and vulvovaginal dryness ($N = 26$). Among the 42 PTs included in the narrow definition of the SMQ "sexual dysfunction" (Table 1 of the ESM), disproportionate reporting for at least one PPI was observed for three (7.1%) PTs. Of these, two (i.e. ED and genital discomfort) belong to the system organ class "Reproductive and Breast Disorders", and one (i.e. oestrogen deficiency) to the system organ class "Endocrine Disorders". Statistically significant adjusted RORs for PPI-induced SD are presented in Fig. 2.

A statistically significant adjusted ROR was observed for omeprazole concerning ED (adjusted ROR, 1.76; 95% CI 1.54–2.01), while two statistically significant adjusted RORs were found for esomeprazole, i.e. genital discomfort (adjusted ROR, 3.66; 95% CI 1.34–10.04) and oestrogen deficiency (adjusted ROR, 3.80; 95% CI 1.03–13.99) in female patients. Statistically significant RORs in relation to the number of cases for each PT, stratified by the individual PPI, are shown in Fig. 3. In the secondary analysis concerning PPI-induced hyperprolactinemia, we did not find

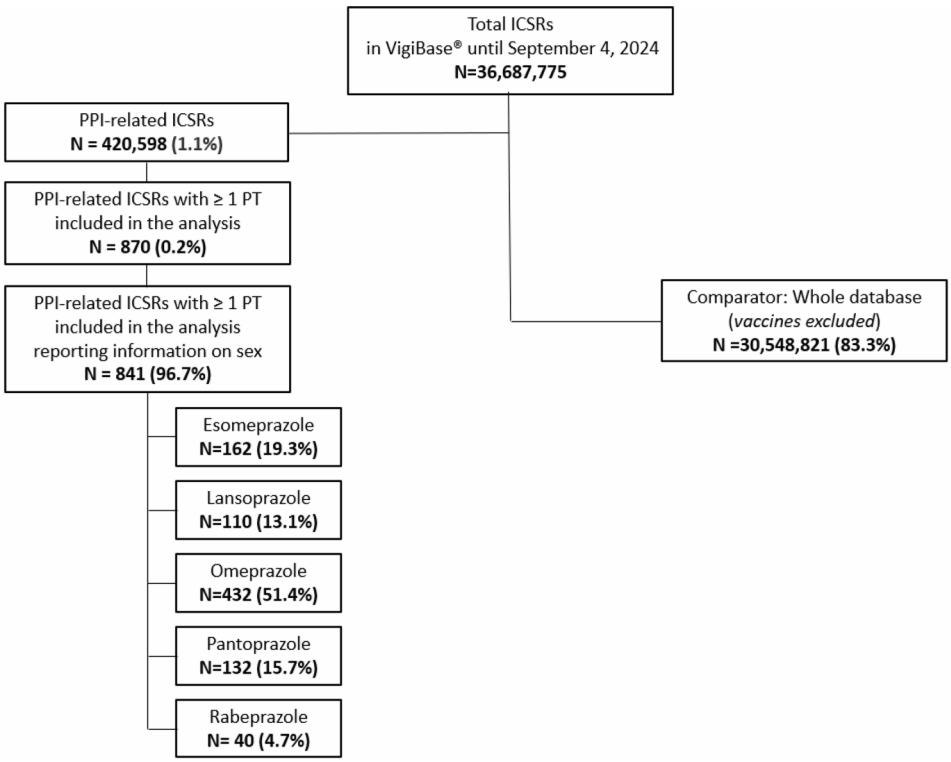

Fig. 1 Flow chart for individual case safety report of proton pump inhibitor (PPI)-related sexual dysfunction selection process in VigiBase. *ICSRs* individual case safety reports, *PT* Preferred Term

Table 1 Characteristics of ICSRs of proton pump inhibitors vs all other drug (excluding vaccine)-related sexual dysfunctions and hyperprolactinemia in VigiBase until 4 September, 2024

	Esomeprazole ($N = 162$)			Lansoprazole ($N = 110$)			Omeprazole ($N = 432$)			Pantoprazole ($N = 132$)			Rabeprazole ($N = 40$)			SD-related ICSR reporting other drugs (excluding vaccines)		
	Male $N = 120$ (%)	Female N= 42 (%)	*p* value	Male $N = 93$ (%)	Female $N = 17$ (%)	*p* value	Male $N = 385$ (%)	Female $N = 47$ (%)	*p* value	Male $N = 102$ (%)	Female $N = 30$ (%)	*p* value	Male $N = 34$ (%)	Female $N = 6$ (%)	*p* value	Male $N =$ 69,373 (%)	Female $N =$ 30,108 (%)	*p* value
Age groups (years), *n* (%)																		
12–17	1 (0.8)	1 (2.4)	0.452	–	7 (41.2)	<0.001	–	–	–	–	2 (6.7)	0.050	–	–	–	390 (0.6)	310 (1.0)	<0.001
18–44	28 (23.3)	7 (16.7)	0.493	28 (30.1)	3 (17.6)	0.449	93 (24.2)	16 (34.0)	0.195	19 (18.6)	8 (26.7)	0.483	9 (26.5)	3 (50.0)	0.499	16,926 (24.4)	14,660 (48.7)	<0.001
45–64	52 (43.3)	16 (38.1)	0.682	40 (43.0)	3 (17.6)	0.089	160 (41.6)	16 (34.0)	0.405	41 (40.2)	6 (20.0)	0.070	13 (38.2)	2 (33.3)	1.000	21,838 (31.5)	4851 (16.1)	<0.001
65–74	9 (7.5)	5 (11.9)	0.579	12 (12.9)	1 (5.9)	0.677	47 (12.2)	5 (10.6)	0.940	14 (13.7)	4 (13.3)	1.000	2 (5.9)	–	1.000	6518 (9.4)	830 (2.8)	<0.001
≥75	4 (3.3)	1 (2.4)	1.000	2 (2.2)	–	1.000	10 (2.6)	2 (11.8)	0.855	3 (2.9)	1 (3.3)	1.000	1 (2.9)	–	1.000	2014 (2.9)	354 (1.2)	<0.001
Unknown	26 (21.7)	12 (28.6)	0.486	11 (11.8)	3 (17.6)	0.790	75 (19.5)	8 (17.0)	0.835	25 (24.5)	9 (30.0)	–	9 (26.5)	1 (16.7)	1.000	21,573 (31.1)	9049 (30.1)	0.001
Continents, *n* (%)																		
Africa	–	–	–	3 (3.2)	–	1.000	3 (0.8)	1 (2.1)	0.370	–	–	–	3 (8.8)	–	1.000	1156 (1.7)	265 (0.9)	<0.001
Americas	62 (51.7)	27 (64.3)	0.217	18 (19.4)	7 (41.2)	0.097	161 (41.8)	28 (59.6)	0.031	31 (30.4)	14 (46.7)	0.152	7 (20.6)	2 (33.3)	0.874	35,204 (50.7)	14,819 (49.2)	<0.001
Asia	15 (12.5)	4 (9.5)	0.812	4 (4.3)	–	1.000	6 (1.6)	2 (4.3)	0.471	5 (4.9)	6 (20.0)	0.024	10 (29.4)	1 (16.7)	0.882	5665 (8.2)	761 (2.5)	<0.001
Europe	41 (34.2)	11 (26.2)	0.447	63 (67.7)	10 (58.8)	0.663	193 (50.1)	16 (34.0)	0.054	60 (58.8)	9 (30.0)	0.010	13 (38.2)	3 (50.0)	0.928	25,233 (36.4)	13,704 (45.5)	<0.001
Oceania	2 (0.1)	–	1.000	5 (5.4)	–	0.730	22 (5.7)	–	0.183	6 (5.9)	1 (3.3)	0.933	1 (2.9)	–	1.000	2115 (3.0)	559 (1.9)	<0.001
Reporter qualification, *n* (%)[a]																		
Consumers[c]	49 (40.8)	15 (35.7)	0.689	18 (19.4)	1 (5.9)	0.316	61 (15.8)	14 (29.8)	0.029	38 (37.3)	12 (40.0)	–	9 (26.5)	1 (16.7)	1.000	26,976 (38.9)	17,498 (58.1)	<0.001
Lawyer	–	1 (2.4)	0.259	–	1 (5.9)	–	–	0 (0.0)	–	–	2 (6.7)	0.050		0 (0.0)	–	883 (1.3)	317 (1.1)	0.003
Other healthcare professional[b]	11 (9.2)	3 (7.1)	0.934	3 (3.2)	8 (47.1)	<0.001	25 (6.5)	3 (6.4)	1.000	4 (3.9)	2 (6.7)	0.618	0 (0.0)	0 (0.0)	–	4584 (6.6)	2271 (7.5)	<0.001
Pharmacist	12 (10.0)	2 (4.8)	0.471	7 (7.5)	0 (0.0)	0.530	17 (4.4)	1 (2.1)	0.723	8 (7.8)	3 (10.0)	1.000	3 (8.8)	0 (0.0)	1.000	3586 (5.2)	1020 (3.4)	<0.001
Physician	31 (25.8)	8 (19)	0.499	29 (31.2)	5 (29.4)	1.000	130 (33.8)	14 (29.8)	0.702	39 (38.2)	15 (50.0)	0.347	14 (41.2)	4 (66.7)	0.476	20,724 (29.9)	5245 (17.4)	<0.001
Serious, *n* (%)																		
No	78 (65)	28 (66.7)	0.994	25 (26.9)	4 (23.5)	1.000	103 (26.8)	14 (29.8)	0.789	49 (48.0)	13 (43.3)	0.806	17 (50.0)	3 (50.0)	1.000	32,433 (46.8)	15,999 (53.1)	<0.001
Yes	32 (26.7)	13 (31.0)	0.739	13 (14.0)	8 (47.1)	0.004	60 (15.6)	15 (31.9)	0.009	25 (24.5)	14 (46.7)	0.035	5 (14.7)	1 (16.7)	1.000	17,675 (25.5)	9421 (31.3)	<0.001

Table 1 (continued)

	Esomeprazole ($N = 162$)			Lansoprazole ($N = 110$)			Omeprazole ($N = 432$)			Pantoprazole ($N = 132$)			Rabeprazole ($N = 40$)			SD-related ICSR reporting other drugs (excluding vaccines)		
	Male $N = 120$ (%)	Female N= 42 (%)	*p* value	Male $N = 93$ (%)	Female $N = 17$ (%)	*p* value	Male $N = 385$ (%)	Female $N = 47$ (%)	*p* value	Male $N = 102$ (%)	Female $N = 30$ (%)	*p* value	Male $N = 34$ (%)	Female $N = 6$ (%)	*p* value	Male $N =$ 69,373 (%)	Female $N =$ 30,108 (%)	*p* value
Seriousness criteria, *n* (%)[d]																		
Caused/prolonged hospitalisation	7 (5.8)	3 (7.1)	1.000	2 (2.2)	1 (5.9)	0.399	12 (3.1)	3 (6.4)	0.464	3 (2.9)	3 (10.0)	0.130	–	–	–	3315 (4.8)	1748 (5.8)	<0.001
Congenital anomaly/birth defect	–	–	–	1 (1.1)	–	1.000	1 (0.3)	–	1.000	–	–	–	–	–	–	41 (0.1)	22 (0.1)	0.504
Death	1 (0.8)	–	1.000	2 (2.2)	–	1.000	3 (0.8)	1 (2.1)	0.370	–	–	–	–	–	–	353 (0.5)	58 (0.2)	<0.001
Disabling/incapacitating	7 (5.8)	3 (7.1)	1.000	2 (2.2)	2 (11.8)	0.112	9 (2.3)	2 (4.3)	0.766	3 (2.9)	1 (3.3)	1.000	–	–	–	3568 (5.1)	1279 (4.2)	<0.001
Life threatening	–	–	–	2 (2.2)	1 (5.9)	0.399	5 (1.3)	1 (2.1)	1.000	–	1 (3.3)	0.227	–	–	–	545 (0.8)	349 (1.2)	<0.001
Other medically important conditions	25 (20.8)	11 (26.2)	0.615	13 (14)	5 (29.4)	0.220	53 (13.8)	14 (29.8)	0.008	23 (22.5)	13 (43.3)	0.044	5 (14.7)	1 (16.7)	1.000	13,746 (19.8)	7,809 (25.9)	<0.001

ICSR individual case safety report, *SD* sexual dysfunctions

[a]Not all report formats include this information and the same report can also be reported with more than one reporter

[b]Non-healthcare professional, pharmaceutical companies

[c]Hospital doctors, general practitioners, family paediatricians, specialists

[d]Not all report formats include this information and the same report can also be reported with more than one seriousness criteria

[#]Uncoded drugs were removed

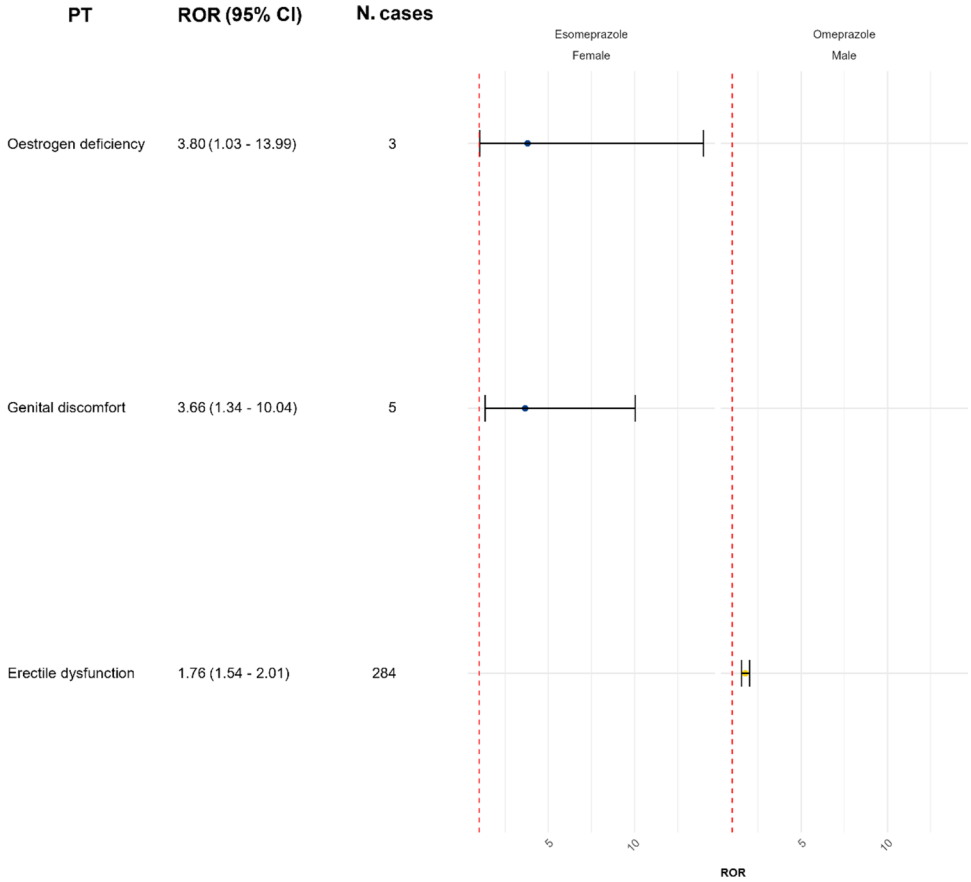

Fig. 2 Forest plot of a disproportionality analysis, at the Preferred Term (PT) level, of sexual dysfunctions and hyperprolactinemia related to proton pump inhibitors as reported in VigiBase, stratified by sex and proton pump inhibitors. Only PTs with statistically significant adjusted reporting odds ratios (RORs) are shown. *CI* confidence interval

disproportionate reporting for any of the PPIs included in the analysis.

As compared with the primary analysis, the subgroup analysis restricting the study population only to patients aged between 18 and 64 years led to an increased number of potential safety signals with statistically significant RORs (i.e. from 3 to 4). Specifically, only the statistically significant disproportionate reporting of ED for omeprazole was confirmed (adjusted ROR, 1.80; 1.49–2.16). New potential safety signals included an omeprazole-induced libido decrease (adjusted ROR, 1.49; 95% CI 1.05–2.12) and esomeprazole-induced hypogonadism (adjusted ROR, 5.22; 95% CI 1.22–22.34) in male individuals, and omeprazole-induced genital discomfort (adjusted ROR, 3.55; 95% CI 1.13–11.09) in female individuals (Table 2). Of the 876 SD-related ICSRs reporting PPIs, 292 (33.3%) contained the information necessary to calculate the TTO, but, concerning potential safety signals, TTO could only be calculated for omeprazole-induced ED (19 days [interquartile range 4–180]).

The analysis of the EMA and FDA SmPCs to evaluate the expectedness of SDs and hyperprolactinemia induced by PPIs revealed that oestrogen deficiency and genital discomfort were not listed in either the EMA or FDA SmPCs of the PPIs for which a statistically significant ROR was calculated. Erectile dysfunction is listed as a potential ADR in the FDA SmPCs of all PPIs, while it is not reported in their EMA SmPCs.

Finally, the information needed to perform a clinical assessment of SD cases was scarce. In particular, out of the 292 ICSRs generating potential safety signals in the primary analysis, 211 (71.5%) did not report concomitant drugs associated with an increased risk of SDs, and data on dechallenge/rechallenge were available only for 84 ICSRs (28.8%). For 61 (72.6%) of these, a positive dechallenge was reported (Tables 2 and 3 of the ESM).

4 Discussion

To the best of our knowledge, this is the first pharmacovigilance study using VigiBase to investigate the potential role of PPIs in inducing SDs in both male and female patients. We found potential safety signals for omeprazole-induced ED in male patients, and esomeprazole-induced genital discomfort and oestrogen deficiency in female patients. Findings for the subgroup analysis restricting the study population to patients aged from 18 to 64 years also showed additional potential safety signals concerning an omeprazole-induced libido decrease and esomeprazole-induced hypogonadism in male

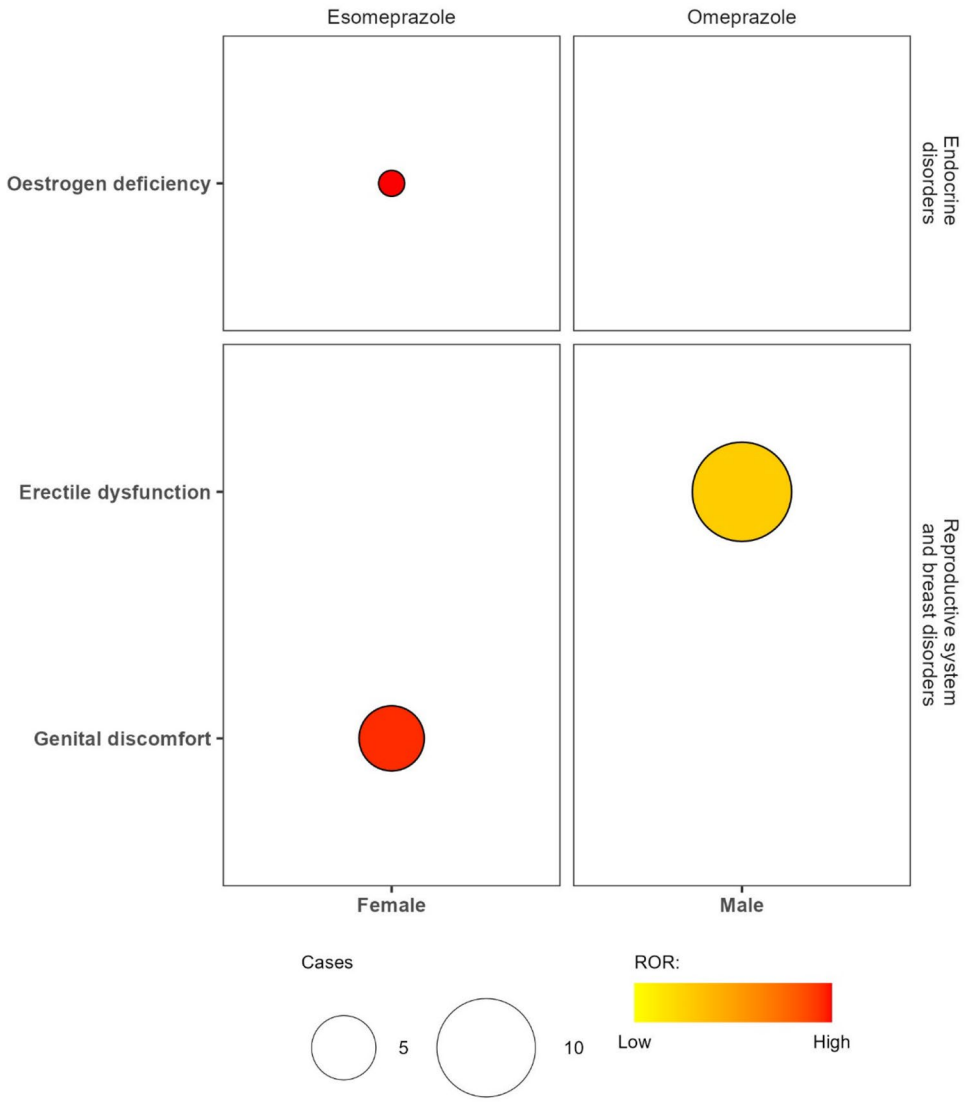

Fig. 3 Heat map of a disproportionality analysis for Preferred Terms with statistically significant reporting odds ratios (RORs). The size of the circles is proportional to the number of cases

individuals, as well as omeprazole-induced genital discomfort in female individuals. Although spontaneous reporting systems do not allow for the estimation of incidence rates of ADRs, the relative frequency of reports may still provide an approximate indication of the potential magnitude of the problem. In this regard, the finding that only 0.2% of ICSRs involving PPIs referred to SDs does not reflect the true incidence of these events, but it may nevertheless suggest that such reactions represent a relatively uncommon or unknown, yet clinically relevant, safety concern.

It has been estimated that about 25% of all cases of ED are caused by medications, especially antidepressants, antipsychotic drugss, antihypertensive medications, antineoplastic medications, antihistamines, drugs with anticholinergic activity and anti-hormones [31, 32]. The prevalence of iatrogenic ED could be even higher considering that several non-communicable chronic diseases share the ability to produce SDs through the same proinflammatory mechanism of action, but are, at the same time, treated with a number of the above-mentioned erectolytic drugs [33].

While blockers of the type 2 histamine receptor, used for the treatment of gastric hyperacidity, are well known to produce SDs through an anti-histaminergic effect [6], the current medical literature evaluating the association between PPI use and ED onset is limited. One of the first studies exploring the potential association between ED and omeprazole was a pharmacovigilance study conducted by the Uppsala Monitoring Center, dating back to 1992 [7]. This study described 15 cases of ED potentially associated with omeprazole use, including two cases involving men under the age of 40 years [7]. More recently, in 2015, pharmacovigilance reports published by Lareb suggested a potential association between ED and omeprazole or lansoprazole, with a latency period that ranges from 1 day to 6 months [5]. Such evidence is in line with our findings, as we observed a median TTO for potential omeprazole-induced ED of 19 days with an

Table 2 Disproportionate reporting analysis of reported sexual dysfunctions for the subgroup of patients aged 18–64 years with a statistically significant ROR value, stratified by sex and proton pump inhibitor at the Preferred Term level of Standardized MedDRA Query sexual dysfunction in VigiBase, until 4 September, 2024

Male sexual dysfunctions			
		Esomeprazole ($N = 83$)	Omeprazole ($N = 248$)
Erectile dysfunction	No. of cases (%)		187 (75.4)
	Crude ROR [95% CI]		1.80 [1.55–2.07]
	Adjusted[a] ROR [95% CI]		1.80 [1.49–2.16]
Libido decreased	No. of cases (%)		51 (20.6)
	Crude ROR [95% CI]		1.49 [1.13–1.96]
	Adjusted[a] ROR [95% CI]		1.49 [1.05–2.12]
Hypogonadism	No. of cases (%)	3 (3.6)	
	Crude ROR [95% CI]	5.22 [1.6 –16.34]	
	Adjusted[a] ROR [95% CI]	5.22 [1.22–22.34]	
Female sexual dysfunctions			
			Omeprazole ($N = 20$)
Genital discomfort	No. of cases (%)		3 (15.0)
	Crude ROR [95% CI]		3.55 [1.13–11.09]
	Adjusted[a] ROR [95% CI]		3.55 [1.13–11.09]

CI confidence interval, *ROR* reporting odds ratio

[a]Adjusted via Bonferroni correction for multiple testing

interquartile range from 4 to 180 days. The latency period observed between PPI initiation and the occurrence of SDs appears consistent with a plausible causality, as SDs may emerge relatively early during therapy. This pattern contrasts with other adverse events potentially associated with long-term PPI use, such as nutritional deficiencies or bone fractures, which typically require prolonged exposure before becoming clinically evident. Supporting such evidence, a case report published in 2021 documented the sudden onset of severe ED in a healthy young man shortly after starting over-the-counter omeprazole therapy. The patient's erectile function rapidly returned to normal following the discontinuation of the drug [8].

In recent years, regulatory agencies including the EMA [11], the FDA [34], and the Malaysian National Pharmaceutical Regulatory Agency [35] have issued safety notifications regarding the potentially increased risk of ED in patients receiving PPIs.

Following an analysis of the FDA Adverse Events Reporting System in 2022, the FDA acknowledged ED as a potential safety signal associated with PPIs [36]. As a result, in 2023, this regulatory agency determined that the SmPCs for all PPI-containing products, including combination products and combination packs, must include information about the risk of ED onset [37]. However, to date, the risk of ED is not mentioned in the EMA SmPCs of PPIs. Additionally, the esomeprazole periodic safety update report single assessment (PSUSA/00001269/202403) issued by the EMA Pharmacovigilance Risk Assessment Committee at the end of March 2025 did not mention any association between esomeprazole and ED [37].

Concerning the aetiopathology of PPI-induced ED, several mechanisms have been suggested in the literature. One of these is the induction of the cytochrome P450 3A4 enzyme by PPIs, which may reduce testosterone levels in some patients, thus leading to low desire and subsequent ED. Another pathological pathway may involve the ability of PPIs to impair endothelial nitric oxide production, which plays a role in in cavernous smooth muscle relaxation and finally in erectile function, thereby leading to ED [38, 39].

After testosterone, prolactin is considered one of the most important hormones affecting male sexual function [40]. Prolactin acts negatively on erectile function through central and peripheral mechanisms not fully understood [12]. In fact, dopamine is regarded as a major factor in triggering sexual motivation [13], implying that an enhanced dopamine level in the brain regions related to reward would lead to increased sexual drive [14]. At the same time, dopamine controls and reduces the lactotroph activity [15]. In this regard, peripheral high levels of prolactin reflect a central reduction of the dopaminergic pathway [12]. This has not been yet demonstrated as a possible mechanism of action of PPI-induced hyperprolactinemia. This lack of evidence jeopardises a clear-cut explanation of the sexual symptoms found in patients treated with PPIs long term. In fact, direct effects of prolactin on the sexual behavior have been demonstrated

only in the above-mentioned peripheral inhibition of the nitric oxide synthase activity, while the anti-sexual effects of hyperprolactinemic drugs have been consistently referred to their antidopaminergic activity, as happens with antipsychotic drugs [16]. Hence, if PPIs do not directly reduce dopamine central activity, prolactin may do it [17], partially explaining the sexual dysfunctions here discussed. However, the circularity of these loops remains to be fully elucidated.

Although the findings of our study did not show statistically significant disproportionality for PPI-induced hyperprolactinemia, safety signals generated by our analyses concerning oestrogen deficiency, libido decrease and hypogonadism might be explained by increased prolactin levels due to PPIs. In particular, two cross-sectional studies investigated the role of prolactin in the onset of PPI-related SDs in male and female patients, respectively. The first study involved 65 male patients consistently receiving PPIs for at least 3 months and showed significant variations for decreased libido, ED, and decreased semen volume between normal and hyperprolactinemic PPI users [18]. In another cross-sectional study of 101 patients receiving PPIs for at least 3 months, significant hormonal changes were observed in those who reported sexual complaints. These patients had significantly different levels of prolactin, oestrogen and progesterone compared with those without such problems. This study also found a statistically significant increase in the incidence of amenorrhea, menstrual irregularities, breast enlargement and breast tenderness in patients with elevated prolactin levels [41].

Proton pump inhibitor-induced SDs may also stem from other indirect mechanisms. Proton pump inhibitors have been found to disrupt the absorption of vitamin B_{12} and magnesium [42, 43], deficiency of which are suspected to be contributing causes of SDs and infertility in both men and women [42, 44, 45]. Last, findings from the notoriety analysis highlighted a considerable heterogeneity among EMA and FDA SmPC for the study drugs, confirming the results of previous comparisons [46, 47].

One of the main strengths of this study is that, to the best our knowledge, this is the first to provide an overview of potentially PPI-induced SDs using a spontaneous reporting database. Pharmacovigilance assessments represent an essential and reliable opportunity to monitor drug safety [48]. Spontaneous reporting systems are solid tools to detect and characterise ADRs under real-world conditions, not only for early detection of safety concerns with new drugs, but also for continuous monitoring of old medications [49], thus, supporting the emerging role of pharmacovigilance for risk-benefit assessments [50]. The analyses conducted in VigiBase were supplemented with a thorough review of both EMA and FDA SmPCs of PPIs with statistically significant disproportionate reporting of specific SDs for a notoriety assessment.

However, there are some limitations to acknowledge. First, spontaneous reporting data are generally subject to several biases, including under-reporting, selective reporting and the lack of a denominator (total number of drug users), all of which prevent measuring the absolute risk of suspected ADRs [51]. Second, disproportionality analyses reflect reporting imbalances and are not suitable to evaluate ADR incidence, risk or causality. Third, the absence of causality assessments and the significant lack of relevant clinical information, particularly for ICSRs that generated potential safety signals, represent two major limitations of our analysis. Moreover, the possibility of residual confounding due to factors not fully captured in spontaneous reporting systems cannot be completely ruled out. Fourth, as it was not possible to exclude other drugs known to induce SDs (e.g. antipsychotic drugs, testosterone-5-alpha reductase inhibitors and antidepressants) from the scrutiny, results of a disproportionate analysis may be affected by co-prescription bias (or confounding by association). In fact, it should be considered when evaluating our data that PPIs are not only used to cure gastric and oesophageal symptoms and diseases but also used frequently in association with other drugs known for their ability to attack the gastric mucosa, such as corticosteroid and non-steroid anti-inflammatory drug treatments. These treatments are typically, but not exclusively, used in the elderly. In these cases, polytherapy and the climaterium [52] should be also considered as a further possible risk factors in PPI-induced SD. Nevertheless, it should be considered that only ICSRs reporting PPIs as suspected or interacting drugs were included in the analysis. Fifth, through the descriptive analysis of these ICSRs, we identified potentially differential source patterns for geographical locations and reporters. As an example, while SD- and hyperprolactinemia-related ICSRs were more frequently reported in America than in Europe, ICSRs of lansoprazole-induced SDs, for both male and female patients, were mostly reported in Europe rather than America. As reported by Mestres et al. in 2024 [53], differential source patterns in signal detection could predispose certain drugs to be disproportionally associated with adverse events. Sixth, we conducted disproportionality analyses using both crude and Bonferroni-adjusted RORs. Other disproportionality methods (e.g. proportional reporting ratio, Bayesian Confidence Propagation Neural Network and empirical Bayes geometric mean), which might have contributed to identifying additional PPI-related SD signals, were not applied in this study. Finally, disproportionality analyses do not allow the quantification of the true risk of suspected ADRs, and potential signals detected through the analysis of SRS databases should be validated further. As such, the analysis of SRS is mainly aimed to generate hypotheses, and a causal association between the drugs and the studied

ADRs can only be confirmed with patient case reports. Notably, only 0.2% of PPI-related ICSRs in VigiBase were associated with SDs. This finding may suggest that the incidence of SDs related to PPI use is substantially lower compared with other, more commonly reported ADRs.

5 Conclusions

Findings from this analysis of VigiBase suggest the presence of potential safety signals of PPI-induced SDs, including ED, which is a clinically relevant condition reported in the IME terms list. Further observational studies based on more robust clinical data are required to assess and validate these potential safety signals. Healthcare professionals should consider also PPIs as a possible cause of SDs, particularly when no other causes are identified, and discontinuation of the drug should be evaluated.

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Declarations

Conflict of interest Gianluca Trifirò has served, over the last 3 years, on advisory boards/seminars funded by Sanofi, MSD, Eli Lilly, Sobi, Celgene, Daiichi Sankyo, Novo Nordisk, Gilead and Amgen on topics not related to content of this paper; he is also the scientific coordinator of the academic spin-off "INSPIRE srl", which has received funding from several pharmaceutical companies (Kiowa Kirin, Shionogi, Shire, Novo Nordisk and Daiichi Sankyo) for conducting observational studies and additional consultancy services on topics not related to content of this paper. Additionally, he is currently a consultant for Viatris in a legal case concerning a topic not related to the content of this paper. Emmanuele A. Jannini is or has been a consultant and/or paid speaker for Bayer, Ibsa, Kanna, Menarini, Mia, Otsuka, Pfizer, Recordati, Shionogi and Viatris. Gianluca Trifirò and Marco Tuccori are Editorial Board members of *Drug Safety*, but were not involved in the selection of peer reviewers for the manuscript nor in any of the subsequent editorial decisions. Salvatore Crisafulli, Francesco Ciccimarra, Fabio Scapini, Luca L'Abbate, Maria Cristina De Martino, Elisa Giannetta and Jordi Mestres have no conflicts of interest that are directly relevant to the content of this article.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data that support the findings of this study are available on request from the corresponding author. Access to the data is restricted based on the conditions for access within the World Health Organization Programme for International Drug Monitoring.

Code availability The code used in the extraction and analysis of data is available upon reasonable request.

Author contributions GT supervised the study and conceived the concept. SC and FC wrote the first draft of the manuscript. FS, FC, SC and LL conducted the analyses. EAJ, MCDM, EG, JM and MT critically revised the manuscript and have made important intellectual contributions. The corresponding author (GT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final version.

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