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Drug-associated porphyria: a pharmacovigilance study

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Abstract

Background The potentially fatal attacks experienced by porphyria carriers are triggered by various porphyrinogenic drugs. However, determining the safety of particular drugs is challenging.

Methods We retrospectively used the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) to identify drugs associated with porphyria as an adverse event (AE) extracted from data from January 2004 to March 2022. The associated search terms included "Porphyria," "Porphyria screen," "Porphyria non-acute," "Porphyria acute," "Acquired porphyria," and "Pseudoporphyria." Signal mining analysis was performed to identify the association between drugs and AEs by four algorithms, namely the reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and multi-item gamma Poisson shrinker.

Results FAERS reported 1470 cases of porphyria-related AEs, and 406 drugs were screened after combining trade and generic names. All four algorithms identified 52 drugs with signals. The characteristics of all the reports and signaling drugs were analyzed.

Conclusions This is the first report of drug-associated porphyria that provides critical information on drug porphyrogenicity, facilitating rational and evidence-based drug prescription and improving the accuracy of porphyrogenicity prediction based on model algorithms. Moreover, this study serves a reference for clinicians to ensure that porphyrinogenic drugs are not prescribed to carriers of porphyria genetic mutations.

Keywords Porphyria, Drug-induced porphyria, FAERS, Drug porphyrogenicity

Background

Porphyria is a group of rare metabolic diseases caused by inherited or acquired enzymatic deficiency in the metabolic pathway of heme biosynthesis [1]. Eukaryotic heme biosynthesis comprises eight enzymatic reactions; each type of porphyria is associated with a different defect. The first and rate-limiting step in the heme biosynthetic pathway involves the formation of δ-aminolevulinic acid (ALA) from the condensation of glycine and succinyl CoA by δ-aminolevulinic acid synthase (ALAS)1 in the liver and ALAS2 in the erythroblastic system [2]. Porphyria is classified as hepatic or erythroid, depending on whether the excess production of porphyrin precursors or porphyrins arises from and accumulates in

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the liver or developing erythrocytes, respectively. It is also classified clinically as acute or cutaneous based on the respective major clinical manifestations [3]. Acute hepatic porphyria (AHP) includes acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and δ-aminolevulinic acid dehydratase deficient porphyria (ADP). All four types of AHP present with acute abdominal and neuropsychiatric symptoms. For example, porphyria cutanea tarda (PCT) is a hepatocutaneous porphyria, as it presents with cutaneous lesions, but the primary site of porphyrin accumulation is the liver. Meanwhile, erythropoietic porphyria includes congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP), and X-linked protoporphyria (XLP), and presents with cutaneous photosensitivity [4]. AIP is clinically the most common type of acute porphyria, with a prevalence of 1 carrier per 2000 persons in Western populations [5]. However, acute attacks occur in less than 10% of the at-risk population [6]. HCP is markedly less prevalent than AIP, with HCP and ADP considered very rare with no reliable epidemiological data available. Acquired PCT is the most prevalent cutaneous porphyria, estimated to affect 5–10 persons per 100,000 population [7]. Porphyria diagnosis is made based on corresponding clinical manifestations and significantly elevated laboratory indexes, such as urinary heme precursors (PBG and ALA) and urinary, fecal, erythrocyte and plasma porphyrins. Enzyme activity measurement and genetic testing are recommended to confirm the type of porphyria and help identify asymptomatic carriers.

The potentially fatal attacks experienced by patients with AHP are triggered by various porphyrinogenic factors, including starvation, infection, alcohol consumption, menstruation, and certain commonly prescribed drugs, including cytochrome P450 (CYP450)-inducing agents [5]. Some drugs also precipitate PCT [6], including barbiturates, estrogen, griseofulvin, rifampicin, sulfonamides, and nitrofurantoin [7]. Porphyrinogenic drugs induce the hepatic expression of *ALAS1* or enhance utilization and depletion of hepatic regulatory heme, producing more neurotoxic porphyrin precursors, ALA, and porphobilinogen (PBG) [8]. It is, therefore, important for medical providers to accurately determine the safety of drugs for use in carriers of porphyria genetic mutations. Clinical case reports of drug side effects and analysis of drug structural and functional information [9], as well as experimental systems using animal or cell culture models, have been used to predict the porphyrogenicity of drugs. However, minute changes in the chemical structure of porphyrinogenic drugs may essentially modify their effect, and in vitro models differ greatly from human physiology, impeding the determination of a specific drug's safety. Hence, a resource compiling the drugs that induce porphyria in real-world practice will serve to not only verify the porphyrogenicity of drugs but also provide valuable information regarding safe drug use in porphyria.

The Food and Drug Association's Adverse Event Reporting System (FAERS) is a post-marketing surveillance program seeking voluntary input on adverse drug reactions (ADRs) to monitor drug safety; as such, it is the world's largest repository of reported hazardous drug events [10]. Although adverse events (AEs) are reported to the FDA by healthcare professionals, consumers, and manufacturers [11], research gaps exist in the study of drugs that induce porphyria in clinical practice using big data. Accordingly, in this study, we conducted a retrospective pharmacovigilance study using data from the FAERS database to perform signal mining analysis and extract drugs with AEs related to porphyria. We then presented the characteristics of drugs inducing porphyria in clinical practice using big data.

Methods

Data source collection

We used FAERS data covering the from January 2004 to March 2022. AEs were identified using the MedDRA terms "Porphyria (10036181)," "Porphyria screen (10050928)," "Porphyria non-acute (10036182)," "Porphyria acute (10036182)," "Acquired porphyria (10053147)," and "Pseudoporphyria (10037145)." Drugs in the FAERS database can be registered using different conventions. Report listings include the primary suspect (PS) or secondary suspect (SS) agent. Herein, we selected the PS of the porphyria drugs, and 1470 drugs were obtained.

Data mining

The whole process can be divided into the following four steps:

Step 1 In the FAERS database, we first used "adverse events" as a search condition and "Porphyria" as a search condition; we selected the PS of the porphyria drugs to obtain the corresponding 1470 drug names.

Step 2 Since generic names and trade names are both reported in the FAERS, we manually used www.drugbank.com to match the generic and trade names of each drug; ultimately, 406 unique drugs were identified.

Step 3 In the US FDA's spontaneous reporting database, drug-event combinations are disproportionately present; hence, screening algorithms and computer systems are used to effectively signal higher-than-expected combinations of drugs and events. Signaling drugs are associated with the occurrence of corresponding adverse events, as defined by the Adverse Reactions Database Reporting System.

Four screening algorithms, namely the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) [12–20], were used to identify the association between drugs and AEs. Additionally, these four algorithms were employed to calculate the corresponding values for each drug. The specific contents of the four algorithms are shown in Fig. 1.

Step 4: Drugs were classified as signaling/non-signaling according to whether the drug values were positive among all four algorithms. The flowchart is depicted in Fig. 2.

Signal detection

In contrast to clinical trials, where the incidence of adverse reaction is easily computed, counts of spontaneously reported drug-event combinations cannot be assessed as "large" or "small" without a comparison value. Therefore, we defined a drug with a positive result in all four algorithms as having "signals," defined in CIOMS VI as "a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance" [21]. By detecting signals, 52 signaling drugs were obtained; all were associated with porphyria and signal detection was positive among all four methods.

Production of the data analysis table

The anatomical therapeutic chemical (ATC) system is a global standard overseen by the World Health Organization (WHO) [22], that allocates each drug a unique code using the ATC classification system. This alpha-numeric code begins with a letter that represents a system of the human body. The ATC codes were applied to classify the 52 signaling drugs into nine categories, namely, J-general anti-infectives drugs, L-antineoplastics and immunomodulating agents drugs, A-alimentary tract and metabolism drugs, N-central nervous system drugs, C-cardiovascular drugs, G-genitourinary and sex hormones drugs, D-dermatological drugs, B-blood and blood-forming organ drugs, M-musculoskeletal drugs.

Results

Characteristics of the FAERS study population

Data characteristics

In total, 406 drugs from 1470 cases reported between January 2004 and March 2022 were included in the analysis for porphyria-related drugs from the FAERS. A clear relationship was observed between drug use and adverse drug reactions. The characteristics of the patients from the FAERS are presented in Table 1.

Reporting country distribution

The top three countries by number of reports for porphyria were the United States of America, France, and Spain (38.71%, 8.78%, and 5.31%, respectively).

Age and sex

The most common reporting age range was 18–44 years old (26.94%), followed by 45–64 years old (22.11%). More cases involved females than males (47.07% vs. 38.98%, respectively).

	Drug of interest	All other drugs in the database	Total
Adverse drug reaction of interest	a	b	a+b
All other adverse drug reaction	c	d	c+d
Total	a+c	b+d	a+b+c+d

Algorithms	Equation*	Criteria
ROR	$ROR=(a/b)/(c/d)$ $95\%CI=e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	95% CI>1, N≥2
PRR	$PRR=(a/(a+c))/(b/(b+d))$ $\chi^2=\Sigma((O-E)^2/E)$; (O=a, $E=(a+b)(a+c)/(a+b+c+d)$)	PRR≥2, $\chi^2\geq4$, N≥3
BCPNN	$IC=\log_2 a(a+b+c+d)/((a+c)(a+b))$ $IC025=e^{\ln(IC)-1.96(1/a+1/b+1/c+1/d)^{0.5}}$	IC025>0
MGPS	$EBGM=a(a+b+c+d)/((a+c)(a+b))$ $EB05=e^{\ln(EBGM)-1.64(1/a+1/b+1/c+1/d)^{0.5}}$	EB05≥2, N>0

Fig. 1 Specific contents of the four algorithms

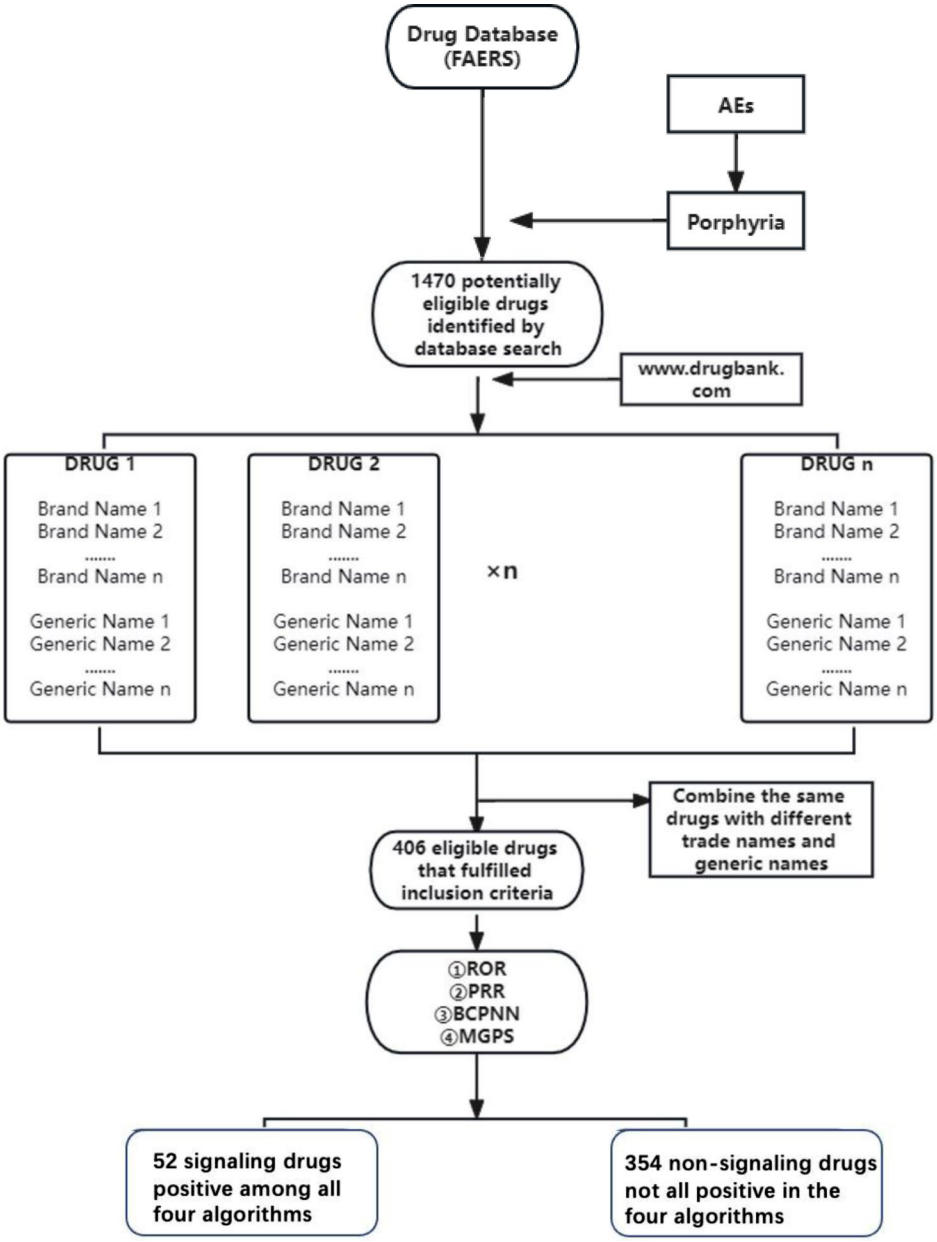

Fig. 2 Flowchart of drugs associated with porphyria obtained from the FAERS database

Distribution of reporters

The FARES database contains AEs submitted by healthcare professionals, such as doctors, nurses, and pharmacists, and consumers, who may include patients, family members, or lawyers. Of the 1470 cases, most were submitted by healthcare professionals (69.80%), followed by consumers (13.79%), while 13.88% of reporters did not include their identifying information.

Outcome events and incidence

Through the FAERS system, we obtained a total of seven adverse outcomes. We determined the associated prognosis of porphyria after using these drugs based on the outcomes: death (3.31%), disability (2.03%), hospitalization (31.01%), life-threatening condition (2.61%), need for further intervention to prevent permanent impairment/damage (0.17%), and other adverse events (59.88%).

Characteristics of signaling drugs

The corresponding 52 drugs were identified as signal-positive using the four methods through the four algorithms.

Adverse reaction onset-time

Generally, the most common time to onset of drug-associated porphyria was within 1 month (106; 39.70%)

Table 1 Demographic characteristics of patients from the FAERS

Characteristic	Value
Number of patients, n	1470
Age, years	
< 18 years old, *n* (%)	94 (6.39%)
18–44 years old, *n* (%)	396 (26.94%)
45–64 years old, *n* (%)	325 (22.11%)
> 64 years old, *n* (%)	227 (15.44%)
Unknown, *n* (%)	428 (29.12%)
Sex	
Male, *n* (%)	573 (38.98%)
Female, *n* (%)	692 (47.07%)
Unknown, *n* (%)	205 (13.95%)
Outcome events	
Death, *n* (%)	54 (3.31%)
Disability, *n* (%)	35 (2.03%)
Hospitalization, *n* (%)	535 (31.01%)
Life-threatening condition, *n* (%)	45 (2.61%)
Need for further intervention, *n* (%)	3 (0.17%)
Other adverse events, *n* (%)	1033 (59.88%)
Unknown, *n* (%)	20 (1.12%)
Distribution of reporters	
Health-care professionals, *n* (%)	964 (69.80%)
Consumers, *n* (%)	240 (16.32%)
Unknown, *n* (%)	204 (13.89%)

of medication prescription, the second was more than 1 year (65; 23.34%), followed by within 3 months to 1 year (49; 18.35%) and within 2–3 months (47; 17.60%).

Drug indication

The most common drug indication was against hepatitis C virus (HCV) infection (111; 8.43%), followed by porphyria acute (85; 6.46%) and human immunodeficiency virus (HIV) infection (72; 5.47%). Other common conditions included neoplastic diseases, infectious diseases, rheumatic immune system diseases, and psychoneurotic diseases.

Drug distribution

In the analysis table (Table 2), porphyria-associated drugs were most frequently reported for anti-infective drugs (211; 27.73%), followed by antitumor and immune drugs (120; 15.77%), digestive system drugs (111; 14.59%), nervous system drugs (89; 11.70%), and cardiovascular system drugs (69; 9.06%). The top ten drugs with the highest number of reports are shown in Fig. 3. The 52 drugs with signals are presented using the ATC code classification in Table 2.

Exploration of porphyrinogen in drugs

The Norwegian Porphyria Centre (NAPOS) has collaborated with the European Porphyria Network (Epnet) and many porphyria experts to create a database (https://www.drugs-porphyria.org/), providing drug safety information on acute porphyria for more than 1,000 drugs, classifying the risk of porphyria from non-porphyritic drugs (which can be used safely) to high-risk porphyritic drugs (which can be used only for emergency indications and under close clinical monitoring) into five levels. We searched the database and divided the signaling drugs into six categories: porphyrinogenic (P), probably porphyrinogenic (PRP), possibly porphyrinogenic (PSP), probably not porphyrinogenic (PNP), not porphyrinogenic (NP), and not yet classified (NC). Among the 52 signaling drugs, 16 were predicted to have a porphyrinogens and thus classified as P, PRP, or PSP, with strong clinical warnings. Twenty-eight drugs were predicted not to have porphyrinogens and were thus classified as NP (six) or PNP (22). The remaining eight drugs were NC (Table 2).

Discussion

In this study, we collected porphyria AEs from 1470 reporters on the FAERS using four algorithms "ROR", "PRR," "BCPNN," and "MGPS"; 406 drugs were obtained by combining different trade names and generic names representing the same drug, 52 drugs with signals were identified by all four algorithms. Anti-infective, antitumor and immune, digestive system, nervous system, cardiovascular system, urogenital system, dermatological system, hematological system, and musculoskeletal system drugs had high signals. Therefore, extreme caution must be taken to ensure that porphyrinogenic drugs are not prescribed to carriers of porphyria genetic mutations.

Porphyrinogenic drugs are potentially life-threatening to patients with hepatic porphyria and should thus be contraindicated. Early identification and removal of the offending drug, along with immediate treatment, are life-saving [23]. Development of photosensitivity or production of dark urine during drug therapy suggests the possibility of drug-induced PCT, which may respond to cessation of the offending drug [24]. However, these drugs are chemically unique and apparently structurally unrelated, making it difficult to pinpoint the culprit due to conflicting results published in the literature. Thunell et al. [9, 25]. developed a risk assessment model for individual patients receiving a drug, which formed the basis of the www.drugs-porphyria.org database where information on more than 1000 drugs is available for review. Although drug porphyrogenicity prediction can guide drug prescription and reduce drug risk, its accuracy requires verification in clinical practice. The FAERS collects ADR data from the United States and Europe through the MedWatch reporting system [26] and provides an opportunity to perform real-world studies on drug toxicity monitoring [27].

From our analysis, 1470 cases were reported with porphyria AEs in the FAERS, and 406 drugs were obtained by

Table 2 Signaling drugs associated with porphyria from the FAERS

Drug	Porphyrogenicity*	ATC** code	*n*	ROR (95% two-sided ci)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Anti-infective drugs (*n* = 211)							
Antiviral drugs (*n* = 113)							
Ribavirin	PNP	J05AP01	59	31.51 (24.28, 40.9)	31.42 (1668.45)	4.92 (3.79)	30.21 (24.28)
Efavirenz	PRP	J05AG03	11	8.31 (4.59, 15.04)	8.3 (70.12)	3.04 (1.68)	8.25 (5.02)
Nevirapine	PRP	J05AG01	9	14.79 (7.68, 28.5)	14.77 (114.85)	3.88 (2.01)	14.69 (8.48)
Ritonavir	P	J05AE03	9	4.2 (2.18, 8.09)	4.2 (21.8)	2.06 (1.07)	4.18 (2.41)
Harvoni	NC	/	7	4.18 (1.99, 8.79)	4.18 (16.87)	2.06 (0.98)	4.17 (2.24)
Truvada	PNP	J05AR03	6	4.19 (1.88, 9.34)	4.19 (14.49)	2.06 (0.92)	4.17 (2.13)
Kaletra	NC	/	5	10.78 (4.48, 25.95)	10.77 (44.18)	3.42 (1.42)	10.74 (5.15)
Dolutegravir	PNP	J05AJ03	4	4.75 (1.78, 12.67)	4.75 (11.8)	2.24 (0.84)	4.74 (2.08)
Atazanavir	PRP	J05AE08	3	7.21 (2.32, 22.4)	7.21 (16.01)	2.85 (0.92)	7.2 (2.79)
Antibacterial drugs (*n* = 49)							
Ciprofloxacin	PNP	J01MA02	18	5.69 (3.57, 9.06)	5.69 (68.68)	2.49 (1.57)	5.63 (3.82)
Doxycycline	PNP	J01AA02	13	10.24 (5.93, 17.69)	10.24 (107.39)	3.34 (1.94)	10.15 (6.43)
Nitrofurantoin	P	J01XE01	9	24.38 (12.65, 46.98)	24.32 (200.05)	4.6 (2.38)	24.18 (13.96)
Imeth	NC	/	6	6.35 (2.85, 14.17)	6.35 (26.94)	2.66 (1.19)	6.33 (3.23)
Cephalexin	PNP	/	3	10.18 (3.28, 31.62)	10.17 (24.77)	3.34 (1.08)	10.15 (3.93)
Antifungal drugs (*n* = 33)							
Voriconazole	PRP	J02AC03	33	33.84 (23.95, 47.81)	33.73 (1024.83)	5.04 (3.57)	33 (24.71)
Antiparasitic drug (*n* = 10)							
Hydroxychloroquine	PSP	P01BA02	10	7.65 (4.11, 14.25)	7.65 (57.38)	2.93 (1.57)	7.6 (4.52)
Antituberculosis drugs (*n* = 6)							
Rifampicin	P	J04AB02	6	15.54 (6.96, 34.66)	15.51 (81.15)	3.95 (1.77)	15.45 (7.9)
Antitumor and immune drugs (*n* = 120)							
Imatinib	PNP	L01EA01	50	10.69 (8.06, 14.17)	10.68 (423.68)	3.37 (2.54)	10.35 (8.17)
Peginterferon-alpha-2 A	PNP	L03AB11	21	7.93 (5.15, 12.2)	7.93 (125.28)	2.97 (1.93)	7.83 (5.46)
Docetaxel	PNP	L01CD02	15	3.33 (2, 5.54)	3.33 (24.24)	1.73 (1.04)	3.31 (2.16)
Interferon Alfa	PNP/PSP	/	13	21.69 (12.56, 37.46)	21.64 (253.74)	4.42 (2.56)	21.46 (13.58)
Leflunomide	PNP	L04AA03	12	8.54 (4.84, 15.08)	8.54 (79.2)	3.08 (1.75)	8.48 (5.27)
Betaferon	PNP	L03AB08	6	15.63 (7, 34.86)	15.6 (81.68)	3.96 (1.77)	15.54 (7.94)
Busulfan	PSP	L01AB01	3	6.02 (1.94, 18.68)	6.01 (12.51)	2.59 (0.83)	6 (2.33)
Digestive system drugs (*n* = 111)							
Givosiran	NP	A16AX16	96	5139.78 (4011.33, 6585.66)	3506.26 (314573.85)	11.68 (9.11)	3278.43 (2664.32)
Nitisinone	NC	A16AX04	15	196.81 (117.78, 328.85)	193.18 (2838.88)	7.58 (4.54)	191.22 (124.45)
Nervous system drugs (*n* = 89)							
Tramadol	PNP	N02AX02	24	9.15 (6.11, 13.69)	9.14 (171.18)	3.17 (2.12)	9.01 (6.43)
Levetiracetam	PNP	N03AX14	16	3.92 (2.39, 6.41)	3.91 (34.35)	1.96 (1.2)	3.88 (2.57)
Phenytoin	P	N03AB02	13	9 (5.21, 15.55)	9 (91.61)	3.16 (1.83)	8.93 (5.65)
Valproic Acid	P	N03AG01	9	4.6 (2.39, 8.87)	4.6 (25.23)	2.2 (1.14)	4.58 (2.65)
Carbamazepine	P	N03AF01	8	4.36 (2.18, 8.74)	4.36 (20.61)	2.12 (1.06)	4.34 (2.43)
Diazepam	PNP	N05BA01	7	4.93 (2.34, 10.35)	4.92 (21.79)	2.29 (1.09)	4.91 (2.63)
Mirtazapine	PNP	N06AX11	6	4.16 (1.87, 9.29)	4.16 (14.36)	2.05 (0.92)	4.15 (2.12)
Haloperidol	PNP	N05AD01	6	5.96 (2.67, 13.3)	5.96 (24.67)	2.57 (1.15)	5.94 (3.04)
Cardiovascular system drugs (*n* = 69)							
Furosemide	PNP	C03CA01	35	19.96 (14.27, 27.92)	19.92 (614.19)	4.28 (3.06)	19.47 (14.71)
Torsemide	NC	/	9	145.9 (75.42, 282.26)	143.89 (1269.43)	7.16 (3.7)	143.02 (82.34)
Hydralazine	P	C02DB02	7	27.29 (12.98, 57.41)	27.22 (176)	4.76 (2.26)	27.1 (14.55)
Propafenone	PSP	C01BC03	7	37.87 (18, 79.69)	37.74 (249.17)	5.23 (2.49)	37.56 (20.16)
Nife	NC	/	6	19.02 (8.53, 42.45)	18.99 (101.86)	4.24 (1.9)	18.92 (9.67)
Nifedipine	PNP	C08CA05	5	11.09 (4.61, 26.7)	11.08 (45.71)	3.47 (1.44)	11.05 (5.3)
Urogenital system drugs (*n* = 66)							
Estradiol	PSP	G03CA03	25	6.47 (4.36, 9.61)	6.47 (113.55)	2.67 (1.8)	6.37 (4.58)

Table 2 (continued)

Drug	Porphyrogenicity*	ATC** code	*n*	ROR (95% two-sided ci)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Tamioxifen	NC	/	21	49.52 (32.16, 76.26)	49.29 (979.51)	5.6 (3.64)	48.6 (33.87)
Progesterone	PRP	G03DA04	9	14.92 (7.75, 28.75)	14.9 (116.03)	3.89 (2.02)	14.82 (8.56)
Oxybutynin	PNP	G04BD04	7	7.78 (3.7, 16.36)	7.78 (41.16)	2.95 (1.41)	7.75 (4.16)
Tolterodine	PNP	G04BD07	4	7.9 (2.96, 21.08)	7.89 (24.02)	2.98 (1.12)	7.88 (3.46)
Dermatological drugs ($n=55$)							
Diclofenac	PNP	D11AX18	39	6.96 (5.06, 9.56)	6.95 (193.57)	2.76 (2.01)	6.8 (5.21)
Fluconazole	NC	D01AC15	16	21.08 (12.87, 34.51)	21.04 (302.06)	4.38 (2.67)	20.82 (13.78)
Hematological systemic drugs ($n=32$)							
Hemin	NP	B06AB01	15	697.64 (412.59, 1179.62)	653.91 (9680.37)	9.34 (5.52)	647.28 (417.09)
Erythropoietin	NP	B03XA01	12	10.66 (6.04, 18.82)	10.65 (104.08)	3.4 (1.93)	10.57 (6.57)
Iron sucrose	NP	/	5	11.01 (4.57, 26.5)	11 (45.29)	3.45 (1.44)	10.96 (5.26)
Musculoskeletal system drugs ($n=8$)							
Rocuronium	NP	M03AC09	5	22.51 (9.35, 54.22)	22.46 (102.2)	4.48 (1.86)	22.39 (10.73)
Pamidronic acid	NP	M05BA03	3	7.93 (2.55, 24.63)	7.93 (18.12)	2.98 (0.96)	7.91 (3.07)

*Predicted porphyrogenicity of drugs by https://www.drugs-porphyria.org/

**The international drug Anatomical Therapeutic Chemical (ATC) codes were used to classify drugs

Abbreviations p Porphyrinogenic, *PRP* probably porphyrinogenic, *PSP* possibly porphyrinogenic, *PNP* probably not porphyrinogenic, *NP* not porphyrinogenic, *NC* not yet classified

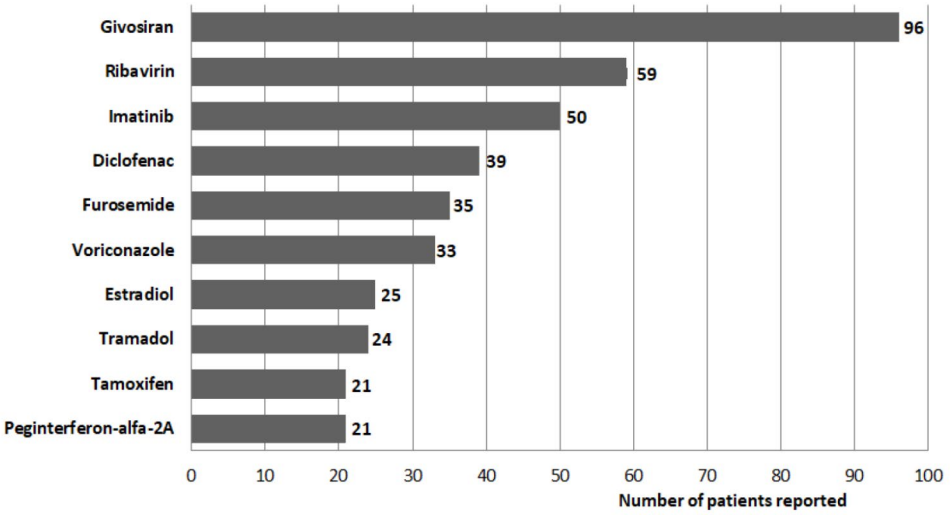

Fig. 3 Top ten signaling drugs with the most reports

combining the trade names and generic names. The most common patient age was 18–44 years, with more cases involving females than males. Porphyria typically occurs in women between 20 and 30 years of age and 2–4 days prior to menstruation, as ovarian hormones, particularly progesterone, are potent inducers on ALAS1 [28, 29]. Young women are also at high risk for drug-induced porphyria, as shown in this study. Regarding elderly patients, porphyria AEs were frequently reported due to the higher number of drugs prescribed for multiple comorbidities, increasing the risk of encountering porphyrinogenic drugs. Approximately 90% of acute attacks related to AIP occur in women [30]. However, in this study, only 47.07% of cases were reported to have occurred in women. This may be explained in part by male patients carrying porphyria genetic mutations seldomly receiving early diagnosis or drug prescription.

The interval between drug initiation and onset of porphyria as an AE varies greatly, with 1 month (106; 39.70%) as the most common duration. Various drugs have been implicated in exacerbating acute attacks [31], i.e., porphyrinogenic drugs [32]. These drugs deplete the heme pool by inducing or inhibiting cytochrome enzymes (CYP), or abnormally degrading heme [12, 33]. In this study, antiviral drugs were the most common signaling drugs. In a previous study, the association between HIV and HCV infection with PCT was well established [34]. The high dosage of ribavirin could increase hepatic

iron levels via hemolysis. The excess of iron in the cytosol of hepatocytes can reduce the action of uroporphyrinogen decarboxylase (UROD) and cause accumulation of its precursor [35]. Moreover, certain antiretroviral drugs also precipitate acute porphyria, such as atazanavir and ritonavir, which inhibit CYP-3A4, leading to heme depletion in hepatocytes, leading to compensatory activation of heme synthesis and toxic accumulation of ALA and PBG precursors in patients who are carriers of acute porphyria genetic mutations [36]. Appropriate antiretroviral regimens should be prescribed with vigilance to these patients. When patients who have been prescribed antiretroviral drugs experience unexplained abdominal pain or skin-photosensitivity symptoms, physicians must consider and closely monitor drug-induced porphyria.

The anti-tuberculosis drug rifampin and anti-fungal drug voriconazole induce or inhibit CYP-450 and provoke a porphyria attack [37]. In 2017, Zaman Babar et al [38]. reported pure motor axonal neuropathy, the peripheral neuropathy of AIP, triggered by anti-tuberculous therapy in an undiagnosed case of acute intermittent porphyria. Most first-line anti-tuberculous drugs are associated with acute attacks of porphyria, its mechanism of action includes: (1) activation of ALAS1 transcription and translation by inducing CYP expression; (2) irreversible inhibition of CYP and compensative activation of heme synthesis; (3) ALAS1 expression induction. Therefore, to prevent the acute onset of latent porphyria, anti-tuberculosis drugs should be used with caution.

Many people develop phototoxicity after using voriconazole [28, 39]. Voriconazole intake is subject to hepatic metabolism by CYP-450 enzymes. Voriconazole serum concentrations maintained between 1.5 and 4 μg/mL are generally safe; however, the possibility of hepatotoxicity cannot be excluded [40], with carriers of porphyria genes being at a greater risk.

Many psychotropic drugs have been implicated in exacerbating acute attacks [41, 42]. However, antipsychotics are often used in acute attacks of porphyria as agents for neuropathic abdominal pain.

This study suggests that immunomodulating agent drugs, like Leflunomide, are associated with porphyria attacks. System lupus erythematosus (SLE) has been associated with porphyria since 1952 [43]. Hydroxychloroquine (HCQ) is often prescribed to patients with SLE to reduce flares; chloroquine and hydroxychloroquine may induce AIP in these patients. Moreover, the use of medium–high doses (250–500 mg/d chloroquine and 200–400 mg/d HCQ) may cause liver toxicity in patients with PCT [44]. However, the mechanism by which immunomodulatory drugs induce porphyria attacks is not well understood. In clinical practice, clinicians should monitor for acute attacks of porphyria when patients using immunomodulators have severe abdominal pain and neuropsychiatric manifestations [24].

Previous studies have reported on the relationship between antitumor drugs and porphyria. Imatinib mesylate is a tyrosine kinase inhibitor [45] that is primarily used to treat chronic myelogenous leukemia (CML). Cutaneous adverse events associated with imatinib are common, while the pathogenesis of pseudoporphyria is unclear. Mahon et al. [45]. speculated that the mechanism of imatinib may be associated with the modulation of c-Kit pathways, disrupting normal melanocyte biology and impairing photoprotective mechanisms. A possible relationship between chemotherapeutic agents and the occurrence of PCT has been discussed in case reports on varying drugs [44]. Manzione et al. speculate that certain chemotherapeutics may induce ALAS1 expression by inhibiting CYP450, which increases heme and porphyrin precursors [46].

Small interfering RNA (givosiran) [47] and hemin are agents without porphyrinogens that are used to stop acute porphyria attacks. Meanwhile, patients who receive givosiran or hemin are at increased risk of disease exacerbation. Consequently, these drugs have been designated as causative agents due to this indication bias when in fact they may not be. Indication of prescription drugs as an error reported as an AE may also occur in this self-reporting system [48]. Interferon (IFN)-α was frequently reported, likely due to its combination with porphyrinogenic antiviral drugs. Such drugs without porphyrinogens must be manually removed from the signaling drugs. Regarding other signal drugs that were predicted as NP, PNP, or NC in the porphyria network drug database, more information is needed to redefine their porphyrinogen status and classification.

This study has certain limitations. First, the FAERS technology does not address all challenges regarding the detection and analysis of adverse drug reaction signs. Hence, the signals from FAERS were used only for qualitative research. Second, false reporting, incomplete reporting, underreporting, and arbitrariness are also included in the data. Third, patients who develop an acute attack may have been simultaneously exposed to multiple drugs and infection or stress, rendering the attribution of blame uncertain. Further research is needed to address these limitations of FAERS.

Conclusions

Patients who experience drug-induced porphyria generally have bad outcomes. Hence, considerable care must be taken to ensure that carriers of acute porphyria genetic mutations are not prescribed porphyrinogenic drugs. The analysis of FAERS reports provides critical information on drug porphyrogenicity, allowing rational and evidence-based drug prescription and improving

the accuracy of predicted porphyrogenicity by model algorithms.

Abbreviations

ADP	Acid dehydratase deficient porphyria
ADR	Adverse drug reaction
AE	Adverse event
RAHP	Acute hepatic porphyria
AIP	Acute intermittent porphyria
ALA	Aminolevulinic acid
ALAS	Aminolevulinic acid synthase
ATC	Anatomical therapeutic chemical
BCPNN	Bayesian confidence propagation neural network
CEP	Congenital erythropoietic porphyria
CML	Chronic myelogenous leukemia
CYP450	Cytochrome P450
EPP	Erythropoietic protoporphyria
FAERS	FDA's Adverse Event Reporting System
HCP	Hereditary coproporphyria
HCV	Hepatitis C virus
HCQ	Hydroxychloroquine
HIV	Human immunodeficiency virus
IFN	Interferon
MGPS	Multi-item gamma Poisson shrinker
NAPOS	Norwegian Porphyria Centre
NC	Not yet classified
NP	Not porphyrinogenic
P	Porphyrinogenic
PBG	Porphobilinogen
PCT	Porphyria cutanea tarda
PNP	Probably not porphyrinogenic
PRR	Proportional reporting ratio
PRP	Probably porphyrinogenic
PSP	Possibly porphyrinogenic
ROR	Reporting odds ratio
UROD	Uroporphyrinogen decarboxylase
VP	Variegate porphyria
XLP	X-linked protoporphyria

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Author contributions
QW and MC were responsible for the initial plan and study design. BZ were for responsible data collection. QW and MC performed data analyses and data interpretation. WQ drafted the manuscript. MC and BZ participated in data interpretation. JLZ and BH participated in proofreading. QW and MC are guarantors and had full access to all the data, including statistical reports and tables, and take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis, as well as independent of the funders. All authors contributed to the article and approved the submitted version.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Peking Union Medical College Hospital.

Consent for publication
All authors approved the submitted version and agreed to publish it.

Competing interests
The authors declare no conflict of interest.

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