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CNS Drugs-induced Akathisia: A Disproportionality Analysis of ICSRs from the FAERS Database

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Abstract

Background

Akathisa is one of the most common and distressing neuroleptic-induced extrapyramidal side effects. It can be also caused by the other drugs such as antidepressants, antiemetics, and gastroprokinetic. This study aims to evaluate the occurrence of drug-induced akathisia using real-world data from the FDA Adverse Event Reporting System (FAERS) and identify drugs most closely associated with akathisia.

Methods

We retrieved individual case safety reports (ICSRs) of drug-induced akathisia from the FAERS database (open public access) and analyzed multiple aspects of drug-induced akathisia including reporting frequencies, gender distribution, age distribution, and reporting sources. We performed disproportionality analysis using the Reporting Odds Ratio (ROR) with a significance threshold of ROR ≥ 2 and the lower bound of the 95% confidence interval > 1, on 102 signals. A case-by-case analysis was performed to validate the signals.

Results

Various kinds of drugs are found to be associated with akathisia, including antiemetics, tipsychotics, and antidepressants. Consumers were the main reporting source, with the United States being the country contributing the most number of reports. Among the drugs, antipsychotics accounted for half of the top 30 drugs. The top signal was molinone with ROR = 661.79 (95% CI: 175.55, 2494.9). Importantly, some of the akathisia-associated drugs did not have a clear mention of akathisia risk on their labels. Among the drugs, antipsychotics accounted for half of the top 30 drugs

Conclusion

These results underscore the importance of drug-induced akathisia in clinical practice, especially under psychiatric medications. While the FAERS database provides valuable real-world data, as disproportionality analysis is a hypothesis-generating approach, caution is warranted in interpreting the results due to the spontaneous nature of reporting, which may introduce biases.

Keywords: Disproportionality Analysis, Drug-Induced Akathisia, FAERS Database, Pharmacovigilance, Pharmaceutical Research.

Background

Akathisa is one of the most common and distressing neuroleptic-induced extrapyramidal side effects [1]. It manifests as subjective sensations of inner restlessness or tension, coupled with irresistible impulses to move, resulting in repetitive movements of the limbs and trunk [2]. The debilitating impact of akathisia on patients' quality of life and daily functioning is profound. Notably, the incidence of akathisia during antipsychotic medication treatment approximates 20% [3]. While the broad conceptualization of akathisia encompasses the intrinsic agitation observed in conditions like idiopathic Parkinson's disease, post-encephalitic Parkinsonism syndrome, and restless leg syndrome, our focus lies solely on drug-induced akathisia in this study [4].

A multitude of pharmacological agents have been implicated in the onset of akathisia, including antipsychotic medications, antidepressants, and antiemetics, among others, correlating with the emergence of akathisia[5-9]. These pharmacotherapies exert their effects on the central dopaminergic system by disrupting neural signaling governing movement in the brain, thereby precipitating akathisia. Nonetheless, due to the subjective symptomatology of akathisia, it frequently eludes clinical detection [10-12].

In exploring drugs-induced akathisia, the FDA Adverse Event Reporting System (FAERS) stands as an indispensable repository of drug adverse reaction (AR) data[13]. Administered by the U.S. Food and Drug Administration (FDA), FAERS is a publicly accessible database with aggregating reports of adverse events (AEs) submitted by healthcare practitioners, pharmaceutical manufacturers, and patients[14]. Leveraging the extensive data reservoirs within FAERS, researchers can scrutinize the associations between diverse pharmaceuticals and Ars[15]. Through the analysis of voluminous real-world datasets, novel drug safety concerns can be identified, and the risk-benefit profiles of pharmaceuticals can be assessed, informing clinical decision-making and guiding therapeutic management strategies.

Spontaneous reporting systems such as FAERS, which collect individual case safety reports (ICSRs), are particularly suitable for detecting rare or under-recognized adverse events like akathisia that may be underreported in clinical trials due to their subjective nature. Disproportionality analysis, as a hypothesis-generating approach, is well-suited to identify unexpected drug-event associations from large-scale ICSR databases, thereby complementing existing clinical trial evidence and filling the knowledge gap regarding the real-world safety profiles of CNS drugs. Therefore, as part of routine pharmacovigilance to investigate the overall safety profile of CNS drugs, this study aims to comprehensively characterize the reporting patterns and signals of drug-induced akathisia in FAERS, and to assess whether akathisia is adequately labeled in the package inserts of these pharmaceuticals.

Methods

Data Source and Processing

The analysis of drugs associated with akathisia was conducted using the FAERS database, maintained by FDA, covering spontaneous adverse event reports from healthcare professionals, consumers, and manufacturers worldwide (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). This database serves the purpose of documenting post-marketing surveillance of ARs to pharmaceuticals and therapeutic biologics. We procured report files from the FAERS database spanning from the first quarter of 2004 to the fourth quarter of 2023, in the American Standard Code for Information Interchange (ASCII) format.

Data analysis was executed using R version 4.3.2. Initially, we purged redundant reports, retained solely the latest reports based on date for entries with identical case IDs in the DEMO table. Subsequently, we employed the Medex_UIMA_1.8.3 system to standardize drug nomenclature, and ultimately extracted reports of drugs suspected to be causally related to akathisia. These reports encompassed diverse variables, including report date, patient medication indication, demographic details such as age and gender, geographic region, and duration from drug administration to onset of AR.

Definition of Drug Adverse Reaction

AEs and drug-related AEs were delineated utilizing the Preferred Terms (PT) from the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0) encoded within the FAERS database. The PT hierarchy within MedDRA comprises four levels, with the PT being the most salient. We conducted a search within the PT column for "akathisia" (MedDRA code: 10001540) to identify drugs implicated in akathisia. Subsequently, all reports pertaining to akathisia were systematically retrieved. Generic drug names served as the unequivocal identifiers for statistical analysis, with conversions to generic names from brand names where applicable.

Data Analysis and Visualization

We conducted a comprehensive examination of age and gender distribution in akathisia occurrences utilizing standard descriptive statistical techniques and visualized the findings using the ggplot2 package. To identify the top 30 drugs associated with akathisia, we aggregated Individual Safety Reports (ISRs), where each ISR corresponded to a single AE report. Disproportionality analysis was employed to generate hypotheses regarding potential associations between drugs and akathisia. Four distinct methods for signal detection were utilized: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS) (DuMouchel)[16-18].

The ROR is calculated as the ratio of a given AE in a population not exposed to a particular drug. The ROR value of 1 indicates the absence of signal, i.e. the ADR is equally reported among the drug of interest and the other drugs[19]. In contrast, a ROR greater than 1 reports the existence of a signal indicating more frequently reported cases of ADR with the drug of interest relative to the others.

The calculation formulas of ROR, PRR, BCPNN, and MGPS are shown in Table 1, along with their thresholds[20].

Table 1: Formulas of ROR, PRR, BCPNN, and EBGM

Method	Formula	Threshold
ROR	ROR=(a / c)/(b / d)	a ≥ 3; ROR ≥ 3 95%CI (lower limit) > 1
	SE(lnROR)=√(1/a+1/b+1/c+1/d)	
	95%CI= $e^{\wedge \ln(ROR) \pm 1.96se}$	
PRR	PRR=(a / (a+b))/(c / (c+d))	a ≥ 3; PRR ≥ 2 95%CI (lower limit) > 1
	SE(lnPRR)=√(1/a-1/(a+b)+1/c-1/(c+d))	
	95%CI= $e^{\wedge \ln(PRR) \pm 1.96se}$	
BCPNN	$IC = \log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025>0
	$E(IC) = \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(ln2)^2}[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)} + \frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)} + \frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}]$	
	γ=γ11 ((a+b+c+d+α)(a+b+c+d+β))/((a+b+α1)(a+c+β1))	
	IC-2SD=E(IC)-2 √(V(IC))	
EBGM	EBGM=(a(a+b+c+d))/((a+c)(a+b))	EBGM05>2
	SE(lnEBGM)=√(1/a+1/b+1/c+1/d)	
	95%CI= $e^{\wedge \ln(EBGM) \pm 1.96se}$	

Notes: ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; BCPNN, Bayesian Confidence Propagation Neural Network; EBGM, Empirical Bayes Geometric Mean.

The interpretation of the variables (a, b, c, d) and of their combinations (a + b, a + c, b + d, c +d, a + b + d + d) in these formulas are shown in Table 2.

Table 2: The Interpretation of the Variables and Various Combinations of Them

	Drug-related ADEs	Non-drug-related ADEs	Total
Drug	a	b	a + b
Non-drug	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

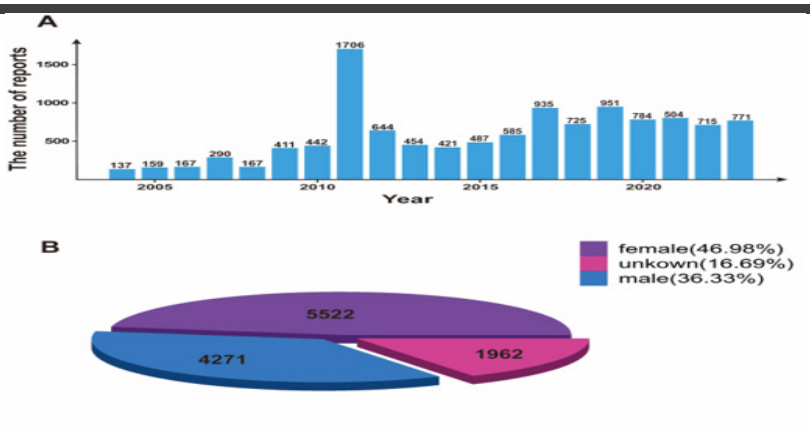
This study employed a disproportionality analysis design using individual case safety reports (ICSRs) from FAERS. The primary analysis applied four signal detection measures (ROR, PRR, BCPNN, MGPS) with predefined thresholds. Active ingredients (generic names) were used as the analytical unit; trade names were converted to generics. No subgroup stratification, or case-by-case review was performed.

To evaluate the potential influence of missing sex information on the temporal trend analysis, we performed a sensitivity analysis by excluding reports with unknown sex. In this analysis, only reports with clearly recorded sex were retained, and the annual number and proportion of reports were recalculated. The annual trend figure was then redrawn based on this complete-case dataset. The sensitivity analysis showed that the overall temporal pattern remained generally consistent with the primary analysis, suggesting that missing sex information did not materially affect the main findings regarding annual reporting trends.

Results

The gender distribution and annual changes of akathisia reports .From 2004 Q1 to 2023 Q4, the FAERS database contained 17,383,038 AE cases. Of which, 11,755 (0.07%) were akathisia.

As shown in Fig. 1A, reports increased annually from 2004, reaching a distinct peak of 1,708 cases in 2011. This sharp spike likely corresponds to the introduction of several new antipsychotic agents into clinical practice during that period[21].



The Time and Age of Akathisia onset, and Consequences

As shown in Fig. 2A, 52.35% of reports did not specify the time from drug administration to AR onset. Among the remaining reporters (47.65%), 24.45% (n=1,139) occurred within 7 days, 7.17% (n=334) occurred within 7–28 days, 4.06% (n=189) occurred within 28–60 days, and 11.98% (n=558) occurred after 60 days (including 60 days). For onset age (Fig. 2B), 4,429 cases (47.05%) lacked age data and were therefore not further analyzed. Of the remaining cases, 22.88% occurred at 19–41 years, 18.75% at 42–65 years, 6.07% after 65 years, and 5.27% before 19 years. Moreover, we utilized a Waffle pie chart to visualize the outcomes of ARs, each square representing 100 cases. Among the seven types of outcomes, 48.80% of cases did not report a specific healthy condition. Of the reported conditions, 0.1% had cognitive anomaly, 0.94% showed body damage, 28.11% were hospitalization, 14.77% suffered disabilities, 4.11% reported life threatening, 3.17% were death cases (Fig. 2C).

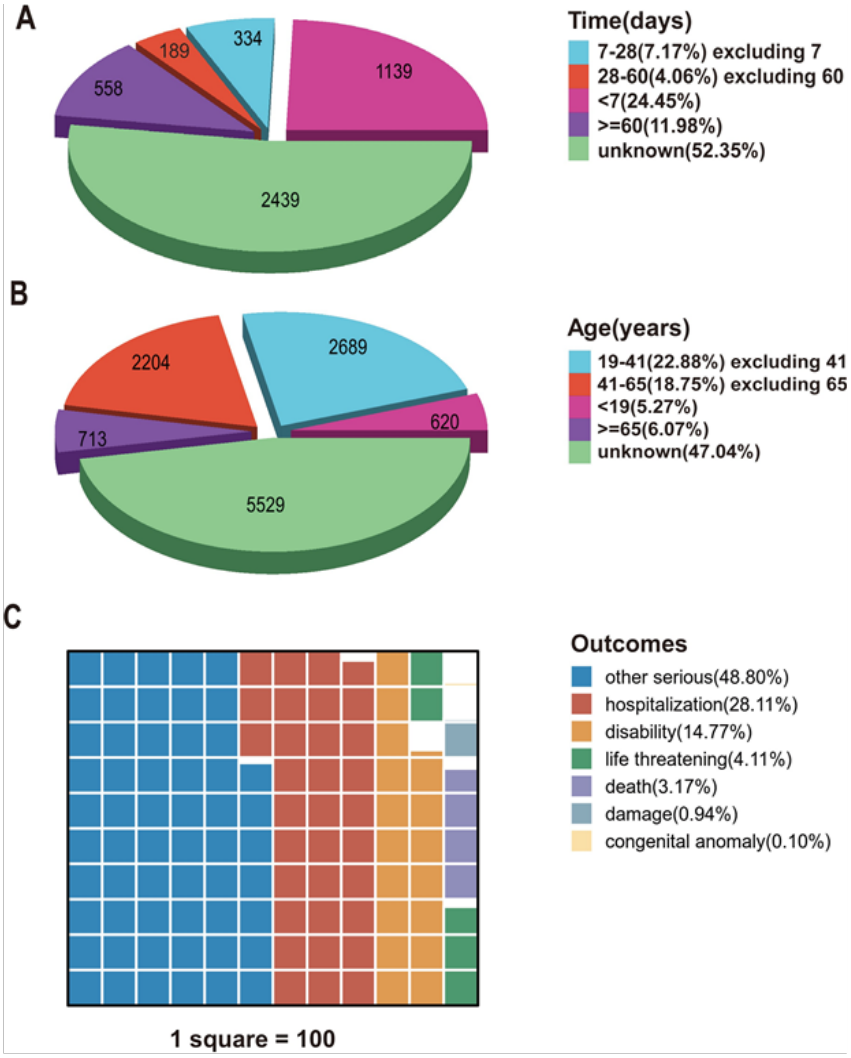


Figure 2: The time and age of akathisia onset, and consequences. A. The time of akathisia onset. B. The age of akathisia onset. C. The outcomes of the drug-induced akathisia.

Demographic and Geographic Characteristics of Akathisia Reports

From 2004 Q1 to 2023 Q4, of all the FAERS1 reporters, consumers contributed the most cases (3,774, 32.11%), followed by physicians (2,806, 23.87%), other health professionals (1,713, 14.57%), pharmacists (1,421, 12.09%), and lawyers (1,719, 14.62%); only 2 cases (0.02%) were reported by registered nurses, with 320 (2.72%) unknown. For geographic distribution, 4,563 cases (38.79%) were categorized as "Others" (non-identified sources/rare cases). Among identified countries, reports predominantly came from developed nations. The United States contributed the highest number of identified cases (4,124, 35.08%), followed by the United Kingdom (568, 4.83%), Canada (524, 4.46%), and other developed countries (Sweden, Japan, Germany, etc.) having more than 100 cases (Table 3).

Table 3:Demographic and Geographic Characteristics of Akathisia Reports

Category	Subcategory	Number of Cases	Percentage (%)
Reporter Type	Consumer	3,774	32.11
	Physician	2,806	23.87
	Other health-professional	1,713	14.57
	Pharmacist	1,421	12.09
	Lawyer	1,719	14.62
	Unknown	320	2.72
	Registered nurse	2	0.02
Country	United States	4,124	35.08
	United Kingdom	568	4.83
	Canada	524	4.46
	Sweden	458	3.89
	Japan	319	2.71
	Germany	270	2.3
	Italy	171	1.45
	France	156	1.33
	Australia	133	1.13
	Spain	113	0.96
	Netherlands	111	0.94
	Others	4,563	38.79

The Top Twenty Drugs Most Frequently Reported with Akathisia

Last but least, we listed the top twenty drugs most frequently reported with akathisia as shown in Fig. 3. Among them, aripiprazole (1,995 cases) was the most commonly reported drug, followed by metoclopramide (1,817 cases), risperidone (680 cases), brexpiprazole (615 cases), paliperidone palmitate (568 cases), olanzapine (562 cases), quetiapine (441 cases), lurasidone (424 cases), escitalopram (302 cases), and fluoxetine (252 cases). Among these 20 drugs, 13 are antipsychotics, 5 are antidepressants, and the remaining 2 are antiemetics.

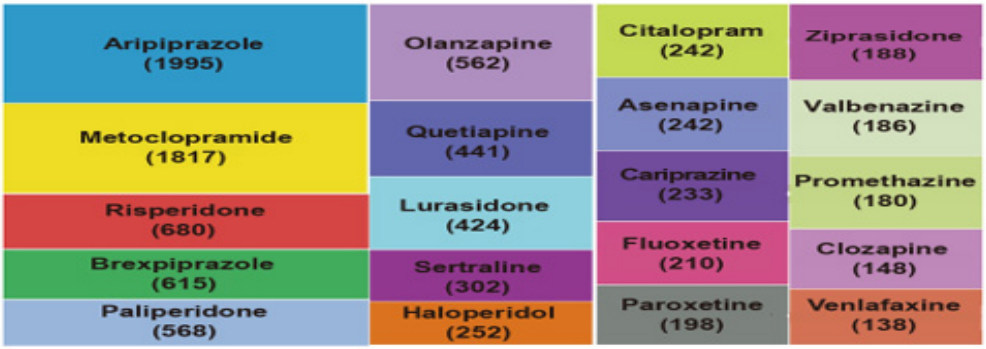


Figure.3: The First Twenty Drugs that Cause Akathisia

Regarding drug classes, antipsychotics dominated the list, accounting for 13 of the top 20 drugs. This is consistent with the mechanism of akathisia, which is strongly linked to dopaminergic blockade in the nigrostriatal pathway. Notably, five antidepressants (Sertraline, Citalopram, Fluoxetine, Paroxetine, Venlafaxine) also appeared in the top 20, suggesting that serotonergic agents, particularly SSRIs, can also induce akathisia, albeit less frequently than antipsychotics. The remaining two drugs were antiemetics (Metoclopramide and Promethazine), further emphasizing that any drug affecting dopamine receptors carries a potential risk.

These findings underscore the importance of monitoring for akathisia, particularly when initiating or titrating antipsychotics and antidepressants. Clinicians should be vigilant for early signs of restlessness, especially with high-risk agents like aripiprazole and risperidone. Detailed information on the top 20 drugs, including generic names, brand names, report counts, and drug classes, is provided in Supplementary Table 1.

Rank	Generic name	Brand name	Number of reports	Drug class
1	Aripiprazole	Abilify	1,995	Antipsychotic (Partial Dopamine Agonist)
2	Metoclopramide	Reglan / Maxolon	1,817	Antiemetic (Dopamine Antagonist)
3	Risperidone	Risperdal	680	Antipsychotic (Typical/Atypical)
4	Brexpiprazole	Rexulti	615	Antipsychotic
5	Paliperidone	Invega	568	Antipsychotic
6	Olanzapine	Zyprexa	562	Antipsychotic
7	Quetiapine	Seroquel	441	Antipsychotic
8	Lurasidone	Latuda	424	Antipsychotic
9	Sertraline	Zoloft	302	Antidepressant (SSRI)
10	Haloperidol	Haldol	252	Antipsychotic (typical)
11	Citalopram	Celexa	242	Antidepressant (SSRI)
12	Asenapine	Saphris	242	Antipsychotic
13	Cariprazine	Vraylar	233	Antipsychotic
14	Fluoxetine	Prozac	210	Antidepressant (SSRI)
15	Paroxetine	Paxil	198	Antidepressant (SSRI)
16	Ziprasidone	Geodon	188	Antipsychotic
17	Valbenazine	Ingrezza	186	Antipsychotic (VMAT2 Inhibitor)
18	Promethazine	Phenergan	180	Antihistamine/Antiemetic
19	Clozapine	Clozaril	48	Antipsychotic (Atypical)
20	Venlafaxine	Effexor	38	Antidepressant (SNRI)

Supplementary Table 1: Detailed information on the top 20 drugs, including generic names, brand names, report counts, and drug classes

Recognizing the critical importance of sensitivity analyses in pharmacovigilance research and the well-known susceptibility of spontaneous reporting data to reporting biases and sociodemographic variation, the demographic and clinical characteristics of reports, including age, sex, reporter type, time to onset, indication, are provided in the Table 4.

Table 4:Descriptive Characterization of the Case Population

Variable	Category	Total
Sex		
	Female	3227 (54.25)
	Male	2721 (45.75)
Age (years)		
	Median (IQR)	40.00 (27.00, 54.00)
Age category (years)		
	<19	587 (9.87)
	19–41	2584 (43.44)

	41–65	2097 (35.26)
	≥65	680 (11.43)
Weight (kg)		
	Median (IQR)	70.00 (58.97, 85.00)
Reporter		
	Consumer	2013 (33.84)
	Physician	1745 (29.34)
	Other health-professional	1175 (19.75)
	Pharmacist	941 (15.82)
	Lawyer	73 (1.23)
	Registered Nurse	1 (0.02)
Reported countries		
	Other	1972 (33.15)
	United States	1859 (31.25)
	United Kingdom	432 (7.26)
	Sweden	360 (6.05)
	Canada	351 (5.90)
	Japan	230 (3.87)
	Germany	220 (3.70)
	Italy	132 (2.22)
	France	127 (2.14)
	Australia	92 (1.55)
	Netherlands	87 (1.46)
	Spain	86 (1.45)
Administration routes		
	Oral	2684 (45.12)
	Other	2642 (44.42)
	Intramuscular	408 (6.86)
	Intravenous	81 (1.36)
	Sublingual	78 (1.31)
	Subcutaneous	23 (0.39)
	Intravenous Drip	18 (0.30)
	Transdermal	14 (0.24)
Outcomes		
	Other serious	3070 (46.87)
	Hospitalization	2228 (34.73)
	Disability	514 (8.01)
	Life-threatening	385 (6.00)
	Death	187 (2.92)
	Required intervention	84 (1.31)
	Congenital anomaly	10 (0.16)
Time to onset (days)		
	Median (IQR)	6.00 (0.00, 61.00)
Time-to-onset category (days)		
	<7	929 (29.47)
	7–28	277 (8.79)

	28–60	154 (4.89)
	≥60	447 (14.18)
	Unknown	1345 (42.67)
Indications		
	Abnormal behaviour	15 (0.22)
	Acute psychosis	11 (0.16)
	Adjuvant therapy	26 (0.38)
	Adverse drug reaction	13 (0.19)
	Affective disorder	40 (0.59)
	Aggression	17 (0.25)
	Agitation	42 (0.62)
	Akathisia	33 (0.49)
	Anxiety	230 (3.40)
	Anxiety disorder	15 (0.22)
	Asthma	13 (0.19)
	Attention deficit hyperactivity disorder	14 (0.21)
	Attention deficit/hyperactivity disorder	53 (0.78)
	Autism spectrum disorder	13 (0.19)
	Bipolar disorder	476 (7.03)
	Bipolar i disorder	104 (1.54)
	Bipolar ii disorder	45 (0.66)
	Blood cholesterol increased	12 (0.18)
	Delusion	11 (0.16)
	Delusional disorder, unspecified type	16 (0.24)
	Dementia	13 (0.19)
	Dementia alzheimer's type	11 (0.16)
	Depressed mood	16 (0.24)
	Depression	564 (8.33)
	Depressive symptom	25 (0.37)
	Diabetes mellitus	11 (0.16)
	Diabetic neuropathy	16 (0.24)
	Drug use for unknown indication	63 (0.93)
	Emotional distress	23 (0.34)
	Epilepsy	11 (0.16)
	Gastrooesophageal reflux disease	30 (0.44)
	Generalised anxiety disorder	28 (0.41)
	Hallucination	11 (0.16)
	Hypertension	47 (0.69)
	Ill-defined disorder	19 (0.28)
	Impaired gastric emptying	10 (0.15)
	Insomnia	84 (1.24)
	Major depression	217 (3.21)
	Mania	45 (0.66)
	Mental disorder	50 (0.74)
	Migraine	26 (0.38)

	Multiple sclerosis	10 (0.15)
	Nausea	58 (0.86)
	Neuralgia	18 (0.27)
	Obsessive-compulsive disorder	40 (0.59)
	Others	835 (12.33)
	Pain	44 (0.65)
	Panic attack	12 (0.18)
	Panic disorder	14 (0.21)
	Paranoia	10 (0.15)
	Parkinson's disease	31 (0.46)
	Post-traumatic stress disorder	21 (0.31)
	Product used for unknown indication	1199 (17.71)
	Psychotic disorder	212 (3.13)
	Psychotic symptom	29 (0.43)
	Restless legs syndrome	11 (0.16)
	Restlessness	16 (0.24)
	Schizoaffective disorder	154 (2.27)
	Schizoaffective disorder bipolar type	19 (0.28)
	Schizoaffective disorder depressive type	10 (0.15)
	Schizophrenia	759 (11.21)
	Schizophrenia, paranoid type	68 (1.00)
	Seizure	14 (0.21)
	Sleep disorder	23 (0.34)
	Spinal anaesthesia	10 (0.15)
	Stress	14 (0.21)
	Tardive dyskinesia	41 (0.61)
	Tourette's disorder	14 (0.21)
	Unknown	550 (8.12)
	Vomiting	15 (0.22)

Note: Data are presented as n (%) or median (IQR). Percentages may use different denominators because some fields contain missing values or multiple responses.

Disproportionality Analysis

We identified 102 signals associated with drug-induced akathisia by performing signal analysis of the drugs. Table 5 presents the top 30 drugs ranked by the Reporting Odds Ratio (ROR). These drugs met the pre-set thresholds (ROR $\geq$ 3, PRR $\geq$ 2) to highlight the drugs with the strongest disproportionality signals (high-risk signals). Notably, akathisia is not mentioned as an AE in the package inserts or literature relevant to 8 drugs in this table. In contrast, Fig. 4 displays the top 20 drugs ranked by case numbers to visualize the most commonly reported drugs (common drugs). The top 5 drugs ranked by ROR were molindone, metoclopramide, brimipridazole/epipiprazole, carbipramine, and promethazine.

Sensitivity Analysis

In the primary analysis, a total of 11,755 reports were included, comprising 5,522 female reports (46.98%), 4,271 male reports (36.33%), and 1,962 reports with unknown sex (16.69%). To assess the potential influence of missing sex information on the annual reporting trend, we further conducted a sensitivity analysis after excluding reports with unknown sex. After exclusion, 9,793 reports with clearly recorded sex were retained, including 5,522 female reports (56.39%) and 4,271 male reports (43.61%). Compared with the primary analysis, the total number of reports decreased by 1,962, whereas the absolute numbers of female and male reports remained unchanged; therefore, the increased proportions of female and male reports were mainly attributable to the change in denominator. Regarding temporal trends, the overall annual distribution after excluding reports with unknown sex remained broadly consistent with that observed in the primary analysis, although the number of reports decreased in several years. The most prominent annual peak in the primary analysis was 1,706 reports, which decreased to 1,282 reports after exclusion of unknown-sex reports (Fig. 4). These findings suggest that reports with unknown sex contributed to the magnitude of some annual peaks but did not materially alter the overall temporal reporting pattern.

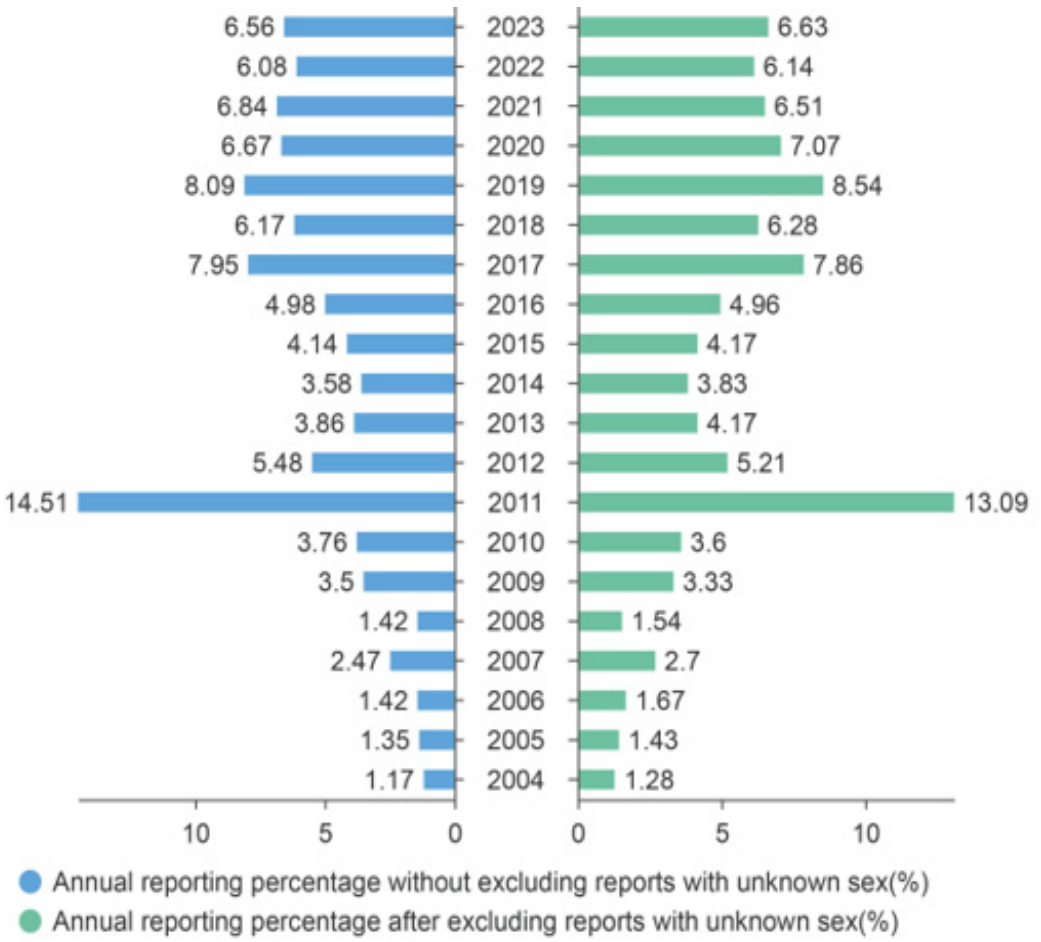


Figure 4: Sensitivity analysis after excluding reports with unknown sex from a total of 11,755 reports. Left, annual reported cases; Right, percentage (%) of the.

Discussion

Akathisia is a common AE associated with antipsychotic drug therapy. It may manifest as subjective and objective restlessness, including persistent, repetitive movements, an inability to sit still, and restlessness while seated, with an incidence ranging from 5% to 50% depending on treatment duration and the drug used[3]. Previous studies have found certain correlations between akathisia and suicidal tendencies in males, agitation in patients previously unexposed to antipsychotic drugs, as well as depression in patients exposed to antipsychotic drugs before admission. We have delineated the clinical characteristics of these AEs and identified the drugs most closely associated with the drug-induced akathisia in this study[22].

Consistent with prior literature, akathisia was expectedly associated with typical and atypical antipsychotics. However, several drugs not previously recognized as high-risk for akathisia, including aripiprazole and risperidone, emerged as disproportionality signals in this analysis, warranting further investigation. Some of these drugs lack akathisia labeling on their packaging, indicating that their akathisia risk had not been fully recognized. Untreated akathisia may increase the risk of suicide, aggression, and violence and result in poor medication adherence. Hence, identifying drugs that may cause akathisia is essential in clinical practice, particularly in psychiatric practice, as it enables clinicians to monitor at-risk patients, adjust treatment regimens proactively, and improve medication adherence[23,24].

To the best of our knowledge, this study represents the first and largest evaluation of drug-induced akathisia based on real-world data analyzed from the FAERS pharmacovigilance database. The reports of akathisia increased during 2005-2020, with a peak in 2011. This trend is in line with the history of antipsychotic use. In the United States, medical counselling data show that counselling involving prescriptions for antipsychotics almost tripled between 1995 and 2006 as newer antipsychotics entered the market, with most of the increase occurring after 2001[25].

As medical care and health awareness increased over the past few decades, the public concern about the side effects of these medications has enhanced. Following the peak in 2011, akathisia reports fluctuated at relatively high levels of 700-800 cases per year. The sustained high levels of reports during the last decade may be associated with the increasing applications of many new medicines in treating patients with mental disorders during 2011-2020, along with new ways of drug administration. On the other hand, the high levels of the reports reflect the increased knowledge and awareness of consumers and health professions about akathisia. Thereafter people became more familiar with akathisia thus being able to deal with it and keeping it unreported.

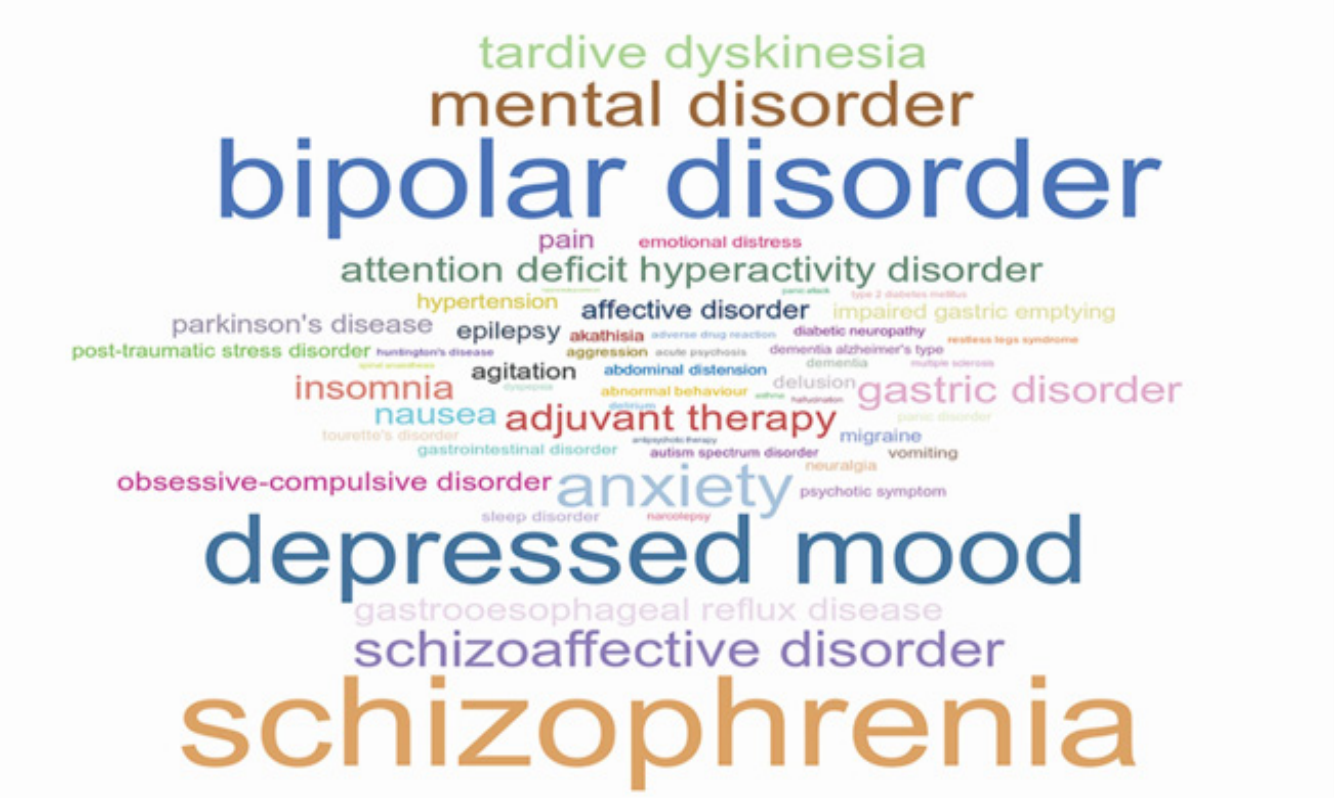
Of all akathisia cases, 46.98 % are females which is higher than that of males, although 16.69% of reporters had no gender label. This gender difference may be due to different tolerances of male and female to the drug-induced akathisia. This is not unexpected as significant differences exist between men and women in the efficacy and tolerability of antipsychotic drugs. In a comprehensive overview, Brand et al., summarized that slower drug absorption, metabolism and excretion in women, plus that women reach higher dopamine receptor occupancy compared to men at similar serum levels because oestrogens increase dopamine sensitivity.

All these factors can lead to higher plasma levels of antipsychotics used in women thus increasing the risk for side-effects of antipsychotics in this population[26]. In the same line, sex differences in pharmacokinetics predict adverse drug reactions in women, as reported in another meta-analysis in which elevated blood concentrations and longer elimination times were manifested by women, and these pharmacokinetics wvere strongly linked to sex differences in ADRs [27, 28].

We also noticed different proportions of akathisia cases in different age groups. Specifically, the cases in the age group between 19-41 years present the highest proportion of 22.88%, followed by those between 41-65 years with a proportion of 18.75%, while the cases in other age groups were much lower. Certainly, this age-dependent differences in reported cases reflect the fact that the populations in the foregoing age groups are the main afflicted people of the two major mental disorders schizophrenia and depression, as indicated by an estimated 70.8% of schizophrenia cases occurred in the 25-54 years age group, and most of depression patients occurred in the 20-75 age groups [29,30].

The first five kinds of case reporters are consumer, physician, lawyer, other health professional, and pharmacist. Of them, patients are sufferers who directly experience akathisia and its consequences in time, and physicians are among the first people being told akathisia and able to treat it. Interestingly, same amounts of akathisia cases were reported by lawyers and other health-professionals. When a lawyer is informed of an AE, the case is likely to involve legal issues due to potential serious consequences. On the other hand, when a case occurs in a hospital, whether outpatient or inpatient, other health professionals are more likely to witness or need to handle the case. Pharmacist is another professional having responsibility to tell AEs to patients and being told AEs by patients. As such, pharmacists are in the top rank of case reporters.

The word cloud of diseases associated with drug-induced akathisia shows the first three mental disorders of schizophrenia, bipolar disorder, and depression. In consistent with this result, the majority of the first 30 drugs associated with akathisia belong to antipsychotics and antidepressants, except metoclopramide and ingrezza (valbenazine) (Supplemental Figure 1). Notably, cariprazine, despite evidence from Leucht et al.'s network meta-analysis (NMA) indicating a higher relative risk of akathisia compared to aripiprazole, did not emerge as a top signal in our disproportionality analysis [31] .



Supplemental Figure 1: The mental disorders/physical diseases associated with akathisia. Annotation: Larger words represent a larger number of cases.

This finding underscores the distinction between relative risk derived from randomized controlled trials (RCTs) and reporting frequency observed in spontaneous reporting systems (SRS). This suggests that while cariprazine may carry a higher intrinsic risk, its usage patterns or reporting dynamics in the FAERS database differ from those of the top-ranked drugs. Several factors explain this divergence. First, the shorter market exposure of cariprazine is a primary factor. Cariprazine (Vraylar) was approved by the FDA in 2015, considerably later than aripiprazole (2002) and risperidone (1993).

The shorter post-marketing period likely resulted in a smaller total number of reports in FAERS, thereby limiting its ranking in reporting frequency. Second, there is an inherent reporting bias in FAERS. As a spontaneous reporting system, FAERS is subject to stimulated reporting and underreporting. Drugs with higher media attention or more established safety profiles (e.g., aripiprazole) tend to accumulate disproportionately more reports, which may not fully reflect the true relative risk. Third, differences in prescribing patterns in clinical practice play a significant role. Aripiprazole is one of the most widely prescribed antipsychotics globally, whereas cariprazine, despite its favorable efficacy profile, remains a relatively newer and less frequently prescribed agent. This difference in real-world usage naturally translates into fewer adverse event reports for cariprazine in FAERS. Finally, it is important to note that NMA vs. FAERS measure different things. The NMA by Leucht et al. derives relative risk estimates from controlled clinical trial data, whereas our analysis is based on spontaneous post-marketing reports. These two data sources capture different dimensions of drug safety and are not directly comparable in magnitude.

Like antipsychotics, metoclopramide is also a dopamine receptor antagonist[32]. Additionally, it acts as a 5HT3 receptor antagonist and 5HT4 receptor agonist thus has been used as an antiemetic and gastroprokinetic. In the both cases, the risk of tardive dyskinesia from metoclopramide is very low, in the range of 0.1% per 1000 patient years as a provisional medication[33]. However, chronic administration of this drug (average duration of exposure prior to onset of movement disorders was 12 months) was reported to cause akathisia too [34].

Ingrezza is a novel compound that selectively inhibits the vesicular monoamine transporter 2 (VMAT2) through an active metabolite. It has been developed for the treatment of tardive dyskinesia. Although available data on the side effects of ingrezza is limited, FDA issued drug trials snapshots for ingrezza on August 20, 2020, reporting an ingrezza-induced akathisia incidence of 2.7% compared to that of 0.5% in placebo group (Drug Trials Snapshots: INGREZZA | FDA), reminding us to be careful when using this medication.

Most of the akathisia case reports originated from high-income countries, including the United States, the United Kingdom, Canada, Sweden, Japan, Germany, Italy, France, Australia, Spain, and the Netherlands. This distribution is largely attributable to the nature of the FAERS database, which is maintained by the FDA and primarily captures adverse events reported within the United States. Consequently, the high volume of reports from the U.S. reflects the database's origin rather than a unique epidemiological phenomenon. More broadly, the predominance of reports from developed nations can be attributed to several factors. First, populations in these regions generally have better access to medical services, often at low cost or for free, leading to higher treatment coverage for mental disorders compared to developing countries.

In support of this, the Lancet data indicates that treatment coverage for mental health services ranges from 33% in high-income areas to only 8% in low- and lower-middle-income countries[35]. Furthermore, WHO data highlights that approximately 70% of people with mental illness receive treatment in high-income countries, compared to only 12% in low-income countries. Additionally, developed countries possess mature healthcare systems and efficient pharmacovigilance mechanisms. These systems facilitate adverse event reporting by consumers, physicians, lawyers, and other health professionals [36]. Therefore, the geographic distribution observed in this study mirrors the global disparity in healthcare access and the structural bias inherent in pharmacovigilance databases sourced from specific regulatory bodies.

However, the findings of this study may not be directly generalizable to populations in low- and middle-income countries where underreporting is substantial. It should be acknowledged that disproportionality analysis is a hypothesis-generating approach and cannot establish causation or quantify the true incidence of akathisia for any drug (READUS-PV guidelines)[37]. With this caveat in mind, several study-specific limitations deserve mention. Firstly, the total number of reported cases for each drug is unknown, as such, it is impossible to calculate and compare the true incidence of akathisia for each drug. Secondly, considering that FAERS is a spontaneous reporting system, a large amount of consumer self-reports may lead to issues such as underreporting, incomplete reporting, and misreporting, thus resulting in biased conclusions.

Thirdly, mental disorders are complex, and patients may suffer from multiple medical comorbidities, therefore requiring the use of multiple medications, which makes it difficult to confirm whether akathisia is caused by a single drug or multiple drugs. Last but not least, the top 20 drugs associated with akathisia do not necessarily mean that these drugs have high incidence of akathisia than the other unlisted drugs, given that these are most widely used drugs in clinical practice for patients with mental disorders as discussed above. Moreover, due to the absence of denominator data in FAERS, the disproportionality measures (e.g., ROR, IC) used in this study reflect reporting odds rather than true relative risk, which may be inflated by reporting bias. Future studies employing cohort or case-control designs using electronic health records are warranted to validate these disproportionality signals, estimate the true incidence of drug-induced akathisia, and adjust for confounders such as polypharmacy and comorbidities [38].

Conclusion

An update comprehensive analysis of the akathisia case reports in the FAERS database revealed multitude of drugs associated with akathisia, including antiemetics, antipsychotics, and antidepressants. Consumers are the main reporters, with the United States being the country reporting a largest proporion of reports. Antipsychotics accounted for half of the top 30 drugs, while some of akathisia-associated drugs in the database did not have a clear mention of akathisia risk on their labels. These results underscore the importance of drug-induced akathisia in clinical practice, especially under psychiatric medications.

Ethics Approval

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

The dataset supporting the conclusions of this article is available via the public FDA Adverse Event Reporting System database found at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

The 'FAERS Public Dashboard' option was then selected prompting to its home page. The 'Search' tab was then selected. Additionally, our dataset comes from the public database, which can be found at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The rest of the information can be found within the Methods section of the manuscript. If readers require further information regarding the data analysis, they can email the corresponding authors or the first author for inquiries.

Competing Interests

The authors do not have conflicts of interest to declare.

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Authors' contributions

Y.L. prepared the first draft. Y.L. and L.J. conducted literature search at the same time. Y.Z. was involved in revising the manuscript. H.X. revised the manuscript.

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Supplementary Table 2: The READUS-PV checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
	1a	If disproportionality analyses are a prominent component of the published study, the study should be identified as a "disproportionality analysis". The type of data and name of the database(s) should be specified.	Page 1, Line 1-2
	1b	Report the name of adverse event(s) and/or drug(s) under study, when applicable.	Page 1, Line 1-2
Introduction			
Background	2a	Describe the drug(s) and its utilization, the nature of the adverse event(s) under study and its frequency, and the existing knowledge on the drug-event combination.	Page 3, Line 55-63
	2b	Specify the rationale for performing the analysis, e.g., as part of routine pharmacovigilance, to investigate an overall safety profile, or to assess a pre-specified hypothesis.	Page 4, Line 88-91
	2c	Explain why ICSR databases and disproportionality analysis are suitable to fill the knowledge gap.	Page 3, Line 82-87
Objectives	3	State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.	No applicable
Methods			
Study design	4a	Identify the study (i.e., "disproportionality analysis") and the type of data used (e.g., "individual case safety reports").	Page 4-5, Line 95,132-136
	4b	Provide an outline of the entire study design, including primary and sensitivity analyses performed, and other designs such as case-by-case analysis or literature review.	Page 5, Line 137-143
Data description, access, and pre-processing	5a	Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of drugs included within the database and the thesaurus, taxonomies, or ontologies used for coding drugs and events.	Page 4, Line 96-98
	5b	Specify the extraction dates and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.	Page 4, Line 99-105
Variables definition	6a	Describe the study population, including any restriction.	Page 4, Line 103-105
	6b	Describe the nature and the meaning of key variables assessed in the work.	Page 4, Line 105-107
	6c	Specify and justify any grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.	Page 4-5, Line 115-116,134-136
	6d	Describe any additional data source used, the type of data, and how they interact with ICSRs.	Page 5, Line 123-134

Statistical methods	7a	Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.	Page 4, Line 119-121
	7b	Describe the measure(s) selected for the disproportionality analysis including any threshold used to identify signals of disproportionate reporting. Explain the reason for this choice if applicable.	Page 5, Line 129-134
	7c	Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.	Page 5, Line 132-136
	7d	Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality, if performed.	Page 5, Line 132-136
	7e	Specify any statistical methods used for other data sources.	No applicable
Results			
Participants	8a	Specify the number of individual case safety reports included at each stage, including reasons for exclusion.	No applicable
	8b	Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.	Page 5-7, Line 146-188
Disproportionality analysis	9	Present all results including confidence intervals. Present also results of sensitivity analyses, if performed.	Refer to Table 4 and Additional file 4
Case-by-case analysis	10	Present the case-by-case analysis of key variables. Present the causality assessment, if applicable.	No applicable
Discussion			
Key results	11	Discuss key results with reference to study objectives and contextualize them within the current literature and other consulted sources. Clearly discriminate between expected reactions and emerging safety signals.	Page 9, Line 258-265
External validity	12a	Discuss the external validity of the results to the general population.	Page 13, Line 375-383
	12b	Discuss the potential relevance of results in clinical practice	Page 9-10, Line 274-279
	12c	Propose further study designs if applicable	Page 13, Line 381-383
Limitations	13	Present general limitations, making clear that disproportionality analysis alone cannot prove causation or measure incidence, and specific limitations, including confounding and reporting bias and efforts to mitigate them.	Page 12-13, Line 368-380
Declarations			
	14a	Provide the source of funding/sponsorship and the role of the funders/sponsors for the present study and for any original study on which the present article is based.	Page 14, Line 419-421
	14b	Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any drug/event investigated, whether financial, legal action, or software used).	Page 14, Line 417-418
	14c	Declare any institutional approval needed or granted in the investigation.	Not applicable
	14d	Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.	Page 14, Line 407-416

READUS-PV REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigi lance

Table 2: The READUS-PV Checklist for Abstracts for Standalone Studies

Section and topic	Item #	Checklist item	Location where item is reported
Background	1a	State the aim/rationale for performing the study.	Page 1, Line 23-25
	1b	Specify the adverse event(s) and/or the drug(s) under study, when applicable.	No applicable
	1c	Specify the specific population or setting, when applicable.	No applicable
Methods	2a	Identify the study as a "disproportionality analysis" and specify the type of data used.	Page 1, Line 26-29
	2b	Specify the name of the database(s) used and the type of access.	Page 1, Line 27
	2c	Specify the timeframe and geographical region, when applicable.	No applicable
	2d	Specify the disproportionality measure(s) used and their statistical significance threshold(s).	Page 1, Line 30
	2e	Specify if a case-by-case analysis is performed.	Page 1, Line 31
Results	3	Report main findings including their precision (e.g., 95% confidence intervals), together with a short summary of the case-by-case analysis.	Page 2, Line 35-36
Conclusion	4a	Clearly report key conclusions.	Page 2, Line 38-39
	4b	Acknowledge that the disproportionality analysis is a hypothesis generating or refinement approach.	Page 2, Line 40-41
	4c	State the implications and clinical relevance of the findings.	Page 2, Line 38-39

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