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Real-world safety analysis of deutetrabenazine post-marketing: a disproportionality study leveraging the FDA Adverse Event Reporting System (FAERS) database

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Abstract

Background Deutetrabenazine, a selective vesicular monoamine transporter type 2 (VMAT2) inhibitor, has been demonstrated efficacy in treating refractory neurologic disorders such as Tardive Dyskinesia (TD) and Huntington's disease but have potential adverse events (AEs) that require detailed pharmacovigilance. This study aimed to comprehensively assess the safety profile of deutetrabenazine in real-world settings by analyzing AEs reported from the FDA Adverse Event Reporting System (FAERS) database.

Methods We conducted a retrospective pharmacovigilance study using FAERS data from Q3 2017 to Q3 2024, focusing on deutetrabenazine-related AEs. We applied four disproportionality analysis methods–Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN) and Multinomial Gamma Poisson Shrinkage (MGPS)--to identify potential safety signals. Furthermore, we utilized the Weibull distribution model to analyze the temporal risk of AEs.

Results Among the 10,571,578 reports obtained from the FAERS database, 4,337 AE reports were associated with deutetrabenazine. Using four independent computational methods at the preferred term (PT) level, we identified 1,131 PTs that indicated noteworthy adverse reactions. The drug's label-listed adverse reactions, including depression, somnolence, suicidal ideation, and fatigue, showed remarkable signals. Furthermore, we detected potential adverse reactions that were not specified on the label, such as drug ineffectiveness, dyskinesia, death, falls, and insomnia. The majority of these AEs were reported within the initial month of deutetrabenazine treatment, with a median time to onset of 40.5 days.

Conclusion This research has yielded initial safety insights into the practical use of deutetrabenazine, validating established adverse reactions and uncovering further possible risks. These findings present essential safety considerations for physicians when prescribing deutetrabenazine for the clinical treatment.

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Keywords Deutetrabenazine, Tardive dyskinesia, Adverse events, Pharmacovigilance, FAERS, Disproportionality analysis

Introduction

Tardive dyskinesia (TD) is characterized by involuntary movements which typically manifest as movements affecting the tongue, torso, or extremities [1]. These movements may be irreversible and linked to the use of dopamine receptor-blocking agents such as antipsychotic medications, leading to significant functional impairment and reduced quality of life [2]. However, conventional therapeutic approaches for TD have generally been associated with limited efficacy or a lack of consistent success [3, 4]. Although tetrabenazine, grounded in a modest dataset, has risen as a favored unconventional treatment for this disorder [5], its application has been constrained by potential dose-associated adverse events (AEs) like neuropsychiatric symptoms of sedation, anxiety, and depression, leading to low treatment initiation and high discontinuation rates [6, 7].

Deutetrabenazine, a novel and highly selective vesicular monoamine transporter type 2 (VMAT2) inhibitor containing deuterium [8], was approved by the US Food and Drug Administration (FDA) on August 30, 2017, for the treatment of adults with TD [9]. This approval marks it as the second pharmaceutical agent approved in the US for this indication, following valbenazine, which received approval in April 2017 [10]. In comparison to tetrabenazine, deuteration may extend the half-life of active metabolites, enabling more consistent systemic exposure with lower and less frequent doses, which could potentially reduce drug-related AEs [11]. Following the FDA's endorsement of deutetrabenazine, there is a heightened focus on monitoring AEs in real-world settings due to its extensive application. The FDA-approved prescribing information highlights several frequently occurring AEs, which include suicidal ideation, QTc interval prolongation, neuroleptic malignant syndrome, Parkinsonism, sedation, and somnolence. Subsequent safety trials have emphasized and validated the significance of the mentioned AEs [12]. However, existing studies into the adverse effects of deutetrabenazine are largely based on data from clinical trials, which are characterized by their stringent and selective enrollment criteria. A holistic understanding of deutetrabenazine's safety profile in broader, real-world contexts remains elusive. Although extensive researches have been performed to fully comprehend the AEs associated with deutetrabenazine within diverse patient populations in real-world settings, to the best of our knowledge, there is a remarkable absence of safety analyses based on large sample sizes that specifically focus on post-marketing AE signals related to deutetrabenazine use.

Given that the intricacies and potential underreporting of AEs in clinical trials, real-world data sources, such as the FDA's Adverse Event Reporting System (FAERS), are crucial for obtaining a comprehensive safety profile [13]. Acting as an open and voluntary reporting platform, FAERS captures AEs that emerge after a drug's widespread post-marketing adoption and the reliability and effectiveness of FAERS in monitoring drug-related AEs in real-world clinical settings were confirmed by substantial research [14]. The objective of our study is to utilize four different algorithms to detect the potential risks associated with deutetrabenazine, providing theoretical guidance for the clinical use of deutetrabenazine.

Methods

Data source and collection

We embarked on a retrospective pharmacovigilance assessment leveraging the FAERS database to examine AE reports associated with deutetrabenazine between Q3 2017 and Q3 2024, encompassing the period post-FDA approval in August 2017. The FAERS database aggregates information from multiple sources, including demographic and administrative details (DEMO), adverse drug reactions (REAC), patient outcomes (OUTC), specifics about drugs (DRUG), therapy timelines (THER), reporting entity details (RPSR), and indications for use (INDI) [15]. This information was employed to categorize AEs in relation to individual patient drug exposures. AEs were codified using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) codes, which are organized within a hierarchical framework that includes system organ class (SOC), high-level group term (HLGT), and high-level term (HLT) [16]. To ensure analytical precision, we removed duplicate reports by retaining the entry with the most recent FDA_DT for matching CASEID and FDA_DT within the DEMO Table [17]; in cases where no match was identified, we selected the record with the higher PRIMARYID [18]. We accessed a total of 10,571,578 AE reports from the FAERS database, identifying 4,337 of these reports deutetrabenazine as the primary suspect (PS) drug. A detailed flowchart depicting the methodology of our study is presented in Fig. 1.

Statistical analysis

We utilized descriptive statistical methods to delineate the characteristics of AE reports associated with deutetrabenazine. Disproportionality analysis, which evaluates the correlation strength between a specific drug and AEs, was conducted by comparing observed frequency ratios between drug-exposed and non-exposed groups using a

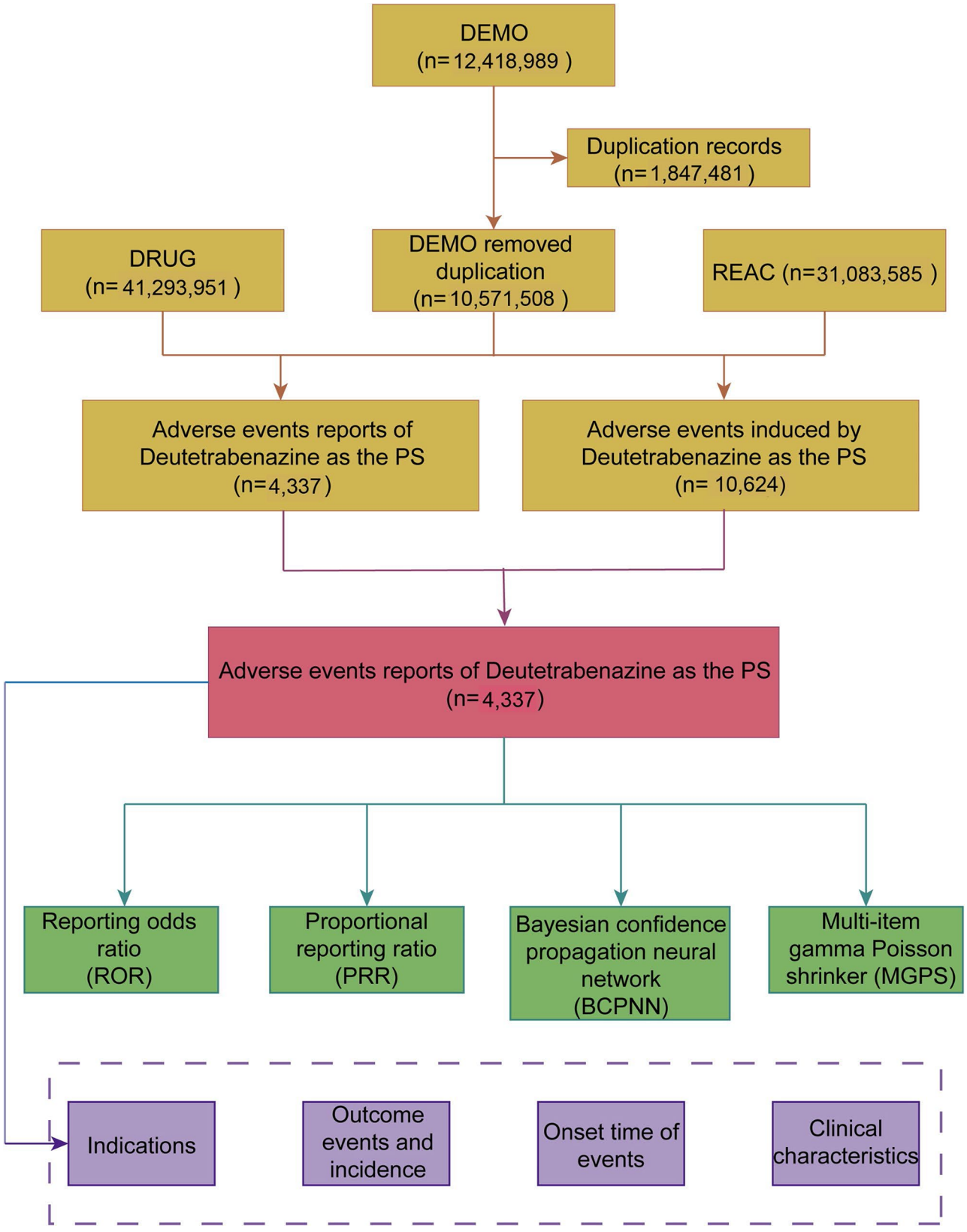

Fig. 1 Flowchart demonstrating the adverse event analysis process for deutetrabenazine using the FAERS database

four-cell table (Supplementary Table 1). Within the scope of our study, we performed disproportionality analysis to identify potential safety signals. A heightened risk of AEs associated with deutetrabenazine was confirmed by examining employed the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multinomial Gamma Poisson Shrinkage (MGPS). An AE is considered a potential adverse drug reaction if it exceeds the positivity threshold according to any of these methods [19]. A higher value indicates a stronger signal and a more significant link between the suspect medication and the AE. Supplementary Table 2 provides details on the methods and thresholds used for these disproportionality analyses. The R software, version 4.2.2, was used for all analytical processes.

Results

Descriptive analysis

From Q3 2017 to Q3 2024, our research extracted a total of 10,571,578 AE reports from the FAERS database. Within this dataset, deutetrabenazine was identified as the primary suspect drug in 4,337 of the reports, suggesting a potential link to the reported AEs. Between 2017 and 2021, there was a gradual increase in the number of AE reports associated with deutetrabenazine, followed by a decline in 2022 (Fig. 2). However, from 2022 to 2023, there was no significant increase or decrease in the number of AE reports. During the period up to the third quarter of 2024, an additional 916 reports were documented. It is expected that the number of reports will reach its peak throughout 2024.

Table 1 shows clinical characteristics of reports with deutetrabenazine from the FAERS Database. From this table, we found that the probability of experiencing AEs was higher in females (60.5%) compared to males (29.1%). Furthermore, there was a modest correlation between age and the prevalence of AEs, with a higher prevalence observed in the 18 to 65 age group (28.7%) and the 65 to 85 age group (22.2%), and a lower prevalence in individuals under the age of 18 (0.6%) and those over 85 years old (0.9%). The vast majority of the AE reports were derived from the United States, accounting for 99.3% of the total AEs. Reports from other countries collectively constituted less than 0.7% of the overall submissions. The primary indication reported is Tardive dyskinesia, which accounted for 40.3% of cases. Others are Huntington's disease (12.4%), Dykinesia (9.4%) and Chorea (1.1%). The

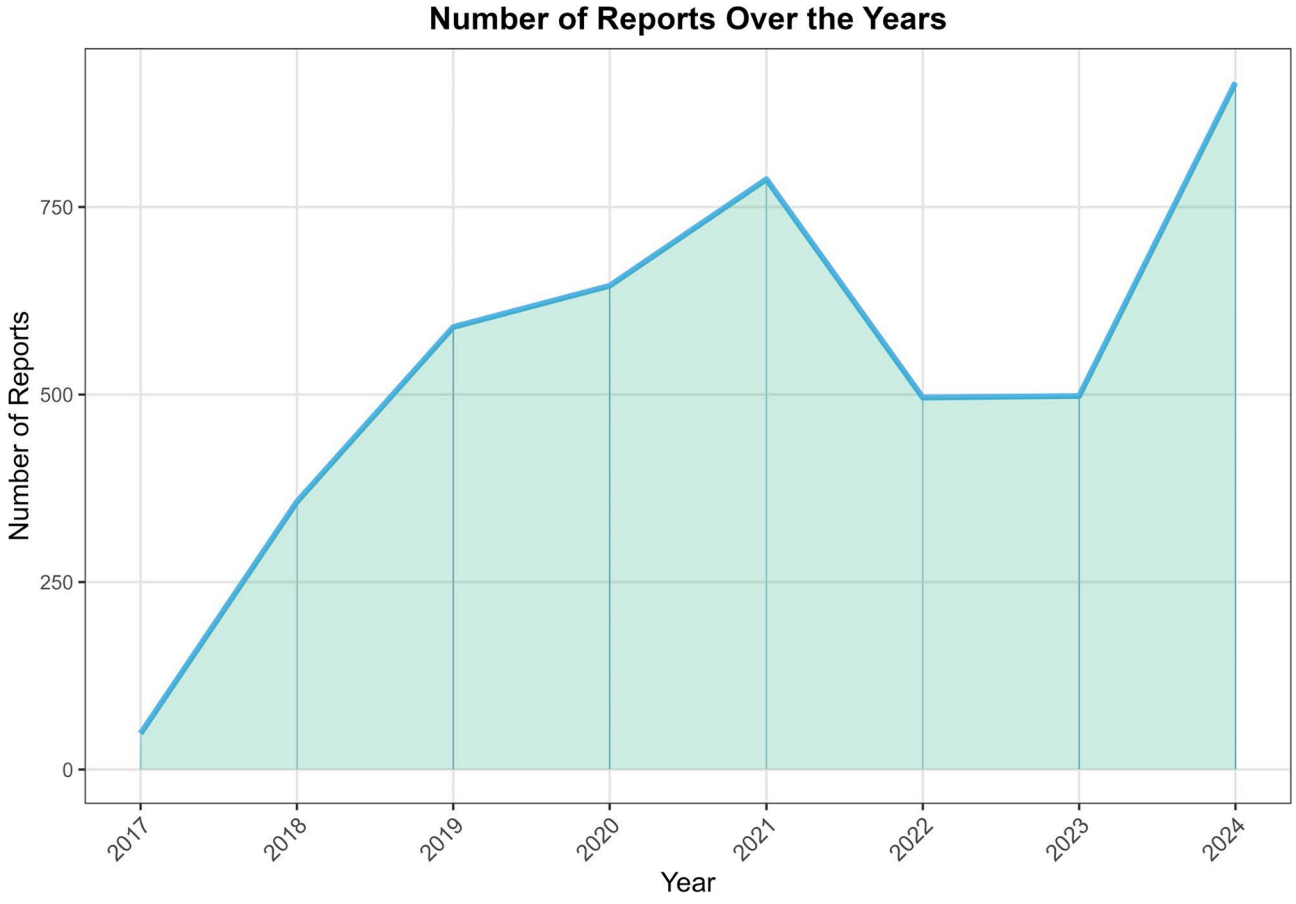

Fig. 2 Number of AEs reported annually since deutetrabenazine was introduced to the market

Table 1 Clinical characteristics of reports with deutetrabenazine from the FAERS database

Characteristics	Case number	Proportion (%)
Number of events	4337	
Gender (%)		
Female	2622	60.5
Male	1261	29.1
Not specified	454	10.5
Weight (kg)		
< 50	14	0.3
> 100	44	1.0
50∼100	222	5.1
Not specified	4057	93.5
Age(years)		
< 18	24	0.6
18∼65	1245	28.7
65∼85	963	22.2
>85	41	0.9
Not specified	2064	47.6
Reported Countries		
United States	4305	99.3
Israel	9	0.2
China	9	0.2
Brazil	3	0.1
Puerto Rico	3	0.1
Others	8	0.1
Reporter		
Consumer	2329	53.7
Health Professional	694	16.0
Pharmacist	535	12.3
Medical Doctor	391	9.0
Other health-professional	186	4.3
Not specified	202	4.7
Year of report		
2017	48	1.1
2018	357	8.2
2019	590	13.6
2020	645	14.9
2021	787	18.1
2022	496	11.5
2023	498	11.5
2024	916	21.1
Outcomes		
Other serious outcome	853	19.7
Hospitalization	473	10.9
Death	271	6.2
Disability	23	0.5
Required Intervention to Prevent Permanent Impairment	7	0.2
Life-Threatening	12	0.3
Cancer	2	0.1
Not specified	2696	62.1
Indications		
Tardive Dyskinesia	1749	40.3
Huntington's Disease	537	12.4
Dyskinesia	406	9.4
Chorea	49	1.1
Not specified	1596	46.8

indications for the cases reported in this database are consistent with FDA-approved indications (Table 1).

Time to event onset

From Q3 2017 and Q3 2024, our research compiled 372 reports that described the timing of AEs. The median time to AE onset was 40.5 days, with an interquartile range of 11 to 200 days. Figure 3 shows that the majority of AEs related to deutetrabenazine were documented within the first 30 days of treatment ($n = 164$, 44.1%), while a considerable number were reported after 360 days of treatment ($n = 56$, 15.1%). AEs within the 61–90 day timeframe following treatment were infrequently recorded ($n = 27$, 7.3%). The analysis of the Weibull Shape Parameter (Table 2) revealed an estimated shape parameter (β) of 0.59, with a 95% confidence interval (CI) ranging from 0.54 to 0.63. This β value indicated a decreasing trend in AE occurrence over time, suggesting a pattern often linked with early adverse reactions.

System organ class (SOC) level of AEs distribution

The AEs associated with deutetrabenazine affected 26 of the 27 system organ classes (SOCs). A detailed examination of significant signals within these SOCs is presented in Table 3. In parallel, Fig. 4 illustrates the distribution of AEs related to deutetrabenazine at the SOC level. Remarkable observations were recorded across various categories, including general disorders and administration site conditions ($n = 2167$, ROR 1.2 [1.14–1.26], PRR 1.16 [56.31], EBGM 1.16 [1.11], IC 0.21 [-1.46]), nervous system disorders ($n = 2081$, ROR 2.97 [2.83–3.12], PRR 2.59 [2187.04], EBGM 2.58 [2.48], IC 1.37 [-0.3]), psychiatric disorders ($n = 1937$, ROR 3.98 [3.79–4.18], PRR 3.44 [3535.18], EBGM 3.44 [3.3], IC 1.78 [0.11]), surgical and medical procedures ($n = 307$, ROR 2.04 [1.82–2.29], PRR 2.01 [158.35], EBGM 2.01 [1.83], IC 1.01 [-0.66]), and social circumstances ($n = 220$, ROR 4.5 [3.94–5.15], PRR 4.43 [586.21], EBGM 4.43 [3.96], IC 2.15 [0.48]). This analysis underscores the primary organ systems that are predominantly affected by AEs in the context of deutetrabenazine treatment. Although the number of AEs in the general disorders and administration site conditions system is the largest, due to the broadness of the scope

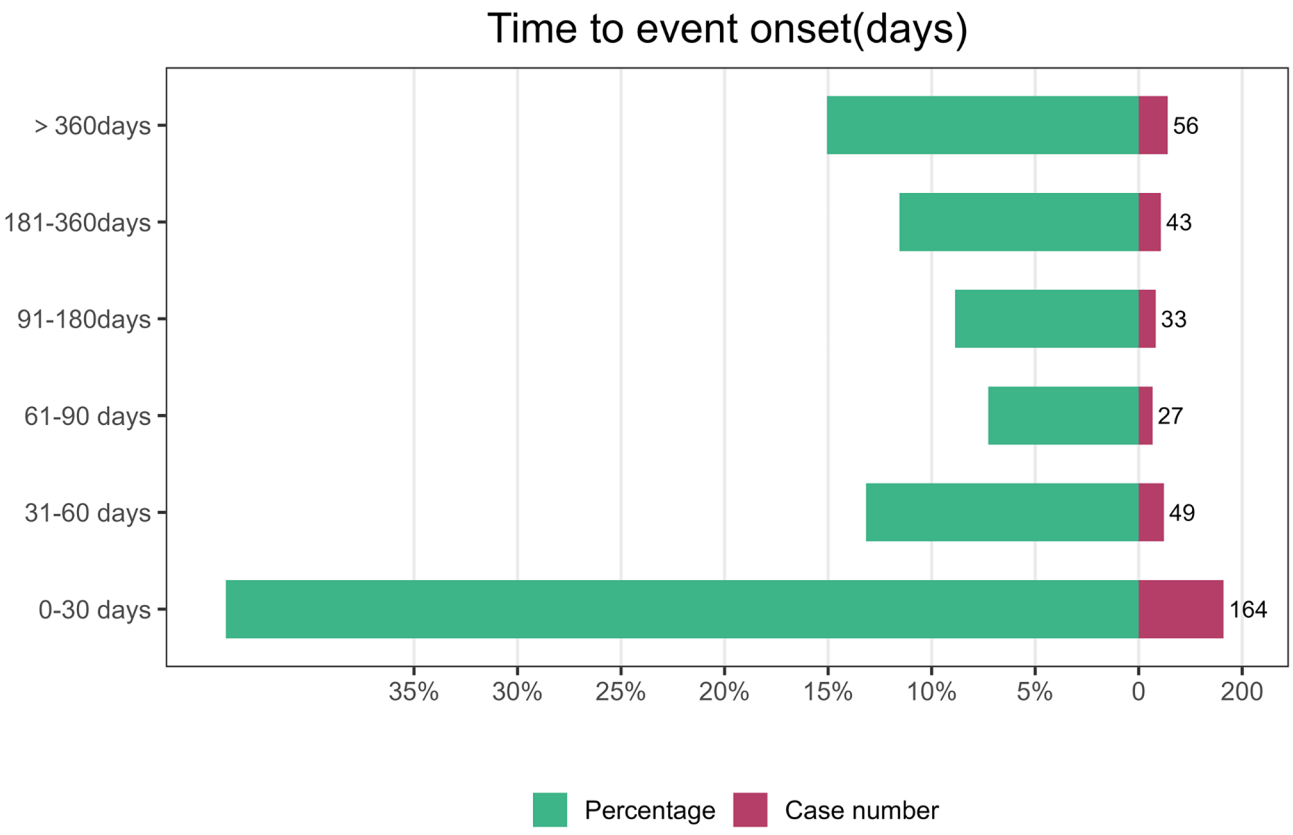

Fig. 3 Time to event onset

Table 2 Time to onset of Deutetrabenazine-associated adverse events and Weibull distribution analysis

Drug	Time to onset (days)		Weibull distribution		
	Case reports	Median (IQR)	Scale parameter: α (95% CI)	Shape parameter: β (95%CI)	Type
Deutetrabenazine	372	40.5 (11–200)	106.80 (87.20–126.41)	0.59 (0.54–0.63)	Early failure

Abbreviations: CI, confidence interval; IQR, interquartile range

of symptom manifestations it encompasses and the complexity of the potential causes of different symptoms, we are unable to conduct more in-depth and precise classification. Besides, we can observe that AEs in the neuropsychiatric system account for a substantial proportion. In fact, the combined proportion of nervous system disorders and psychiatric disorders is nearly 60% of the total number of AEs with positive signals at the SOC levels. It underscores the importance of more stringent surveillance and research to better understand and potentially mitigate these effects. Clinicians should be vigilant when prescribing this drug, especially for patients with pre-existing neuropsychiatric conditions.

Preferred term (PT) level distribution of AEs

In our analysis, we utilized four distinct computational methods at the Preferred Term (PT) level to evaluate adverse drug reactions and assess their conformity with predefined screening criteria, resulting in the identification of 1,131 PTs. Figure 5 illustrates that 167 PTs met the criteria set by all four computational approaches. Table 4 lists the top 30 most commonly reported PTs, ordered by the frequency of reports. Within this subset of the most frequently reported AEs, we detected positive signal reactions including the following: drug ineffective, dyskinesia, depression, death, tremor, somnolence, suicidal ideation, insomnia, fatigue, fall, anxiety, feeling abnormal, product use in unapproved indication, dizziness, product use issue, gait disturbance, confusional state, hospitalisation, restlessness, tardive dyskinesia, balance disorder, agitation, speech disorder, technique in product usage process and parkinsonism.

Consistent with the prescribing details for deutetrabenazine, numerous AE reports were linked to depression ($n = 288$, ROR 9.17 [8.16–10.31], PRR 8.95 [2034.27], EBGM 8.93 [8.09], IC 3.16 [1.49]), somnolence ($n = 199$, ROR 6.29 [5.47–7.24], PRR 6.19 [867.28], EBGM 6.18 [5.5], IC 2.63 [0.96]), suicidal ideation ($n = 197$, ROR 15.81 [13.73–18.21], PRR 15.53 [2667.91], EBGM 15.46 [13.73], IC 3.95 [2.28]), and fatigue($n = 176$, ROR 1.26

Table 3 The signal strength of AEs related to deutetrabenazine at the SOC level in the FAERS database was detected by four algorithms

System organ class (SOC)	Case reports	ROR (95% CI)	PRR (95% CI)	EBGM (EBGM05)	IC (IC025)
General Disorders And Administration Site Conditions*	2167	1.2 (1.14–1.26)	1.16 (56.31)	1.16 (1.11)	0.21 (-1.46)
Nervous System Disorders*	2081	2.97 (2.83–3.12)	2.59 (2187.04)	2.58 (2.48)	1.37 (-0.3)
Psychiatric Disorders*	1937	3.98 (3.79–4.18)	3.44 (3535.18)	3.44 (3.3)	1.78 (0.11)
Injury, Poisoning And Procedural Complications	1150	0.91 (0.86–0.97)	0.92 (8.64)	0.92 (0.88)	-0.12 (-1.78)
Gastrointestinal Disorders	673	0.77 (0.71–0.83)	0.78 (43.82)	0.78 (0.73)	-0.35 (-2.02)
Musculoskeletal And Connective Tissue Disorders	342	0.62 (0.56–0.69)	0.63 (77.99)	0.63 (0.58)	-0.67 (-2.33)
Investigations	309	0.49 (0.43–0.54)	0.5 (162.75)	0.5 (0.46)	-1 (-2.66)
Surgical And Medical Procedures*	307	2.04 (1.82–2.29)	2.01 (158.35)	2.01 (1.83)	1.01 (-0.66)
Respiratory, Thoracic And Mediastinal Disorders	301	0.61 (0.54–0.68)	0.62 (74.08)	0.62 (0.56)	-0.69 (-2.36)
Social Circumstances*	220	4.5 (3.94–5.15)	4.43 (586.21)	4.43 (3.96)	2.15 (0.48)
Infections And Infestations	185	0.3 (0.26–0.35)	0.32 (290.38)	0.32 (0.28)	-1.66 (-3.33)
Skin And Subcutaneous Tissue Disorders	176	0.27 (0.23–0.31)	0.28 (340.69)	0.28 (0.25)	-1.82 (-3.49)
Metabolism And Nutrition Disorders	138	0.65 (0.55–0.77)	0.66 (25.25)	0.66 (0.57)	-0.61 (-2.27)
Cardiac Disorders	133	0.61 (0.52–0.73)	0.62 (32.48)	0.62 (0.53)	-0.7 (-2.36)
Eye Disorders	122	0.58 (0.49–0.7)	0.59 (35.54)	0.59 (0.51)	-0.76 (-2.43)
Renal And Urinary Disorders	71	0.33 (0.26–0.41)	0.33 (97.69)	0.33 (0.27)	-1.59 (-3.26)
Vascular Disorders	68	0.34 (0.26–0.43)	0.34 (88.92)	0.34 (0.28)	-1.56 (-3.22)
Immune System Disorders	41	0.31 (0.23–0.42)	0.31 (62.67)	0.31 (0.24)	-1.68 (-3.34)
Product Issues	41	0.21 (0.15–0.28)	0.21 (122.82)	0.21 (0.16)	-2.24 (-3.91)
Ear And Labyrinth Disorders	39	0.87 (0.63–1.19)	0.87 (0.8)	0.87 (0.67)	-0.21 (-1.87)
Congenital, Familial And Genetic Disorders	34	1.17 (0.84–1.64)	1.17 (0.87)	1.17 (0.89)	0.23 (-1.44)
Hepatobiliary Disorders	26	0.29 (0.2–0.43)	0.29 (45.25)	0.29 (0.21)	-1.78 (-3.45)
Reproductive System And Breast Disorders	22	0.32 (0.21–0.48)	0.32 (32.11)	0.32 (0.23)	-1.65 (-3.31)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	18	0.05 (0.03–0.08)	0.05 (324.06)	0.05 (0.04)	-4.27 (-5.94)
Endocrine Disorders	7	0.25 (0.12–0.52)	0.25 (15.83)	0.25 (0.13)	-2 (-3.67)
Blood And Lymphatic System Disorders	6	0.03 (0.01–0.07)	0.03 (170.9)	0.03 (0.02)	-4.9 (-6.57)

Asterisks (*) indicate statistically significant signals. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; IC, information component; IC025, the lower limit of the 95% confidence interval of the IC

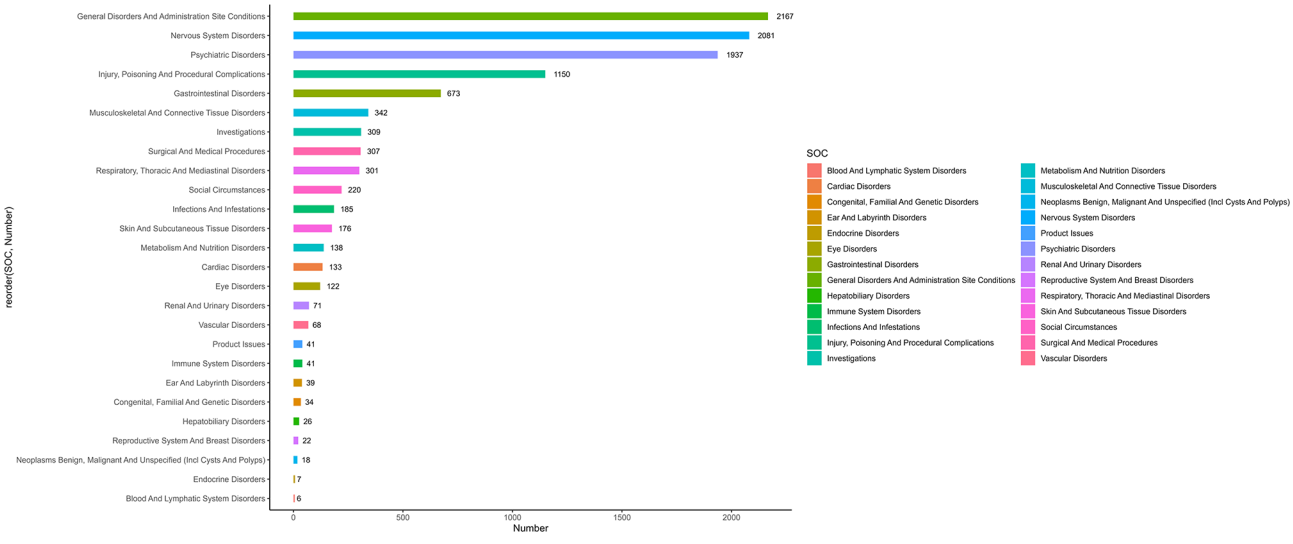

Fig. 4 The number of AEs related to deutetrabenazine at the SOC level in the FAERS database

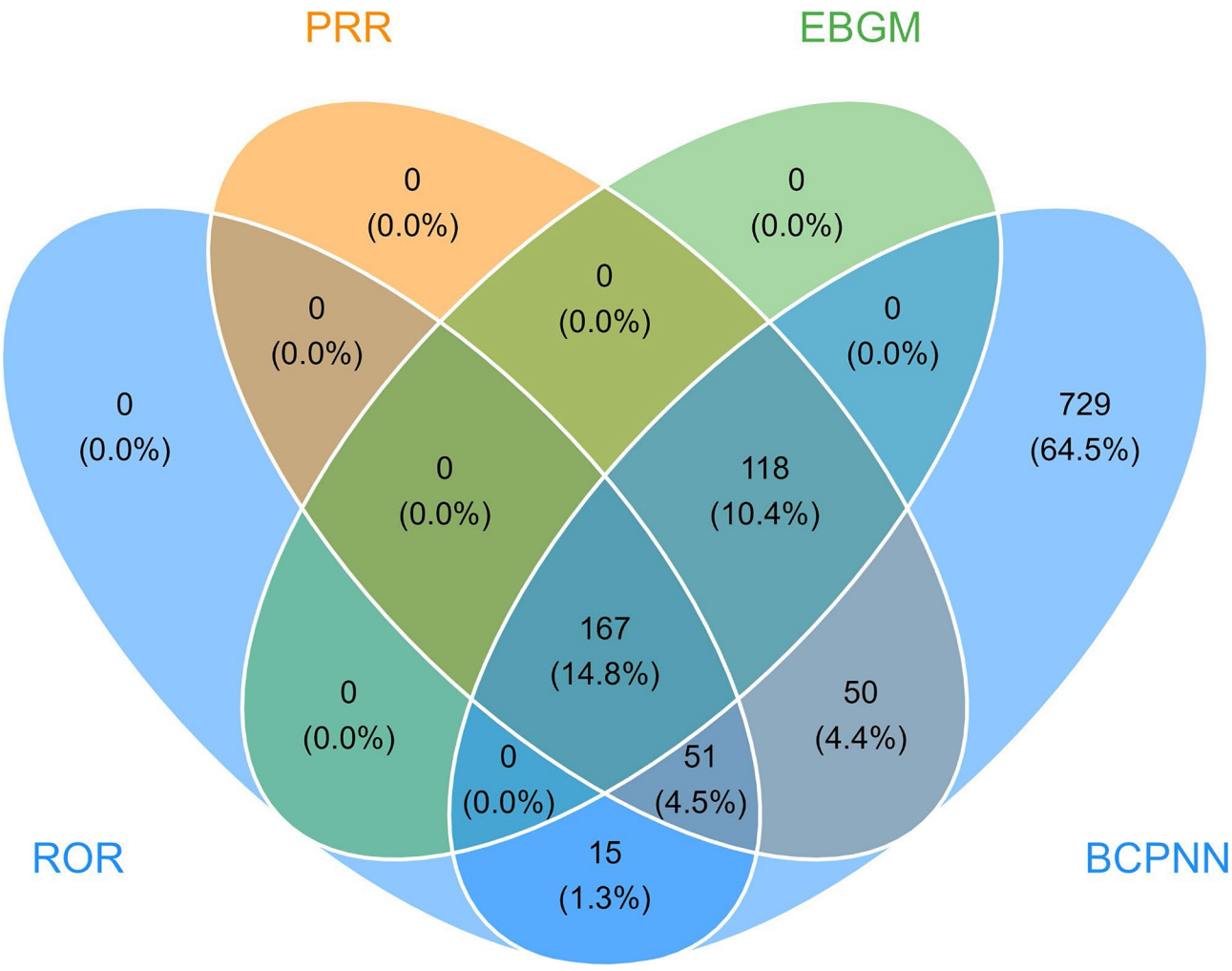

Fig. 5 Venn diagram for the screening of all PTs based on the results of the four algorithms

[1.09–1.47], PRR 1.26 [9.56], EBGM 1.26 [1.11], IC 0.33 [-1.33]). Beyond the adverse reactions listed in the drug's prescribing information, there was a remarkable frequency of reports for other issues, such as drug ineffectiveness ($n = 603$, ROR 2.5 [2.31–2.72], PRR 2.42 [513.66], EBGM 2.42 [2.26], IC 1.27 [-0.39]), dyskinesia ($n = 288$, ROR 50.24 [44.64–56.53], PRR 48.9 [13298.97], EBGM 48.11 [43.59], IC 5.59 [3.92]), death ($n = 243$, ROR 1.6 [1.41–1.82], PRR 1.59 [53.46], EBGM 1.59 [1.43], IC 0.67 [-1]), falls ($n = 155$, ROR 2.88 [2.46–3.38], PRR 2.85 [187.49], EBGM 2.85 [2.5], IC 1.51 [-0.15]), and insomnia ($n = 189$, ROR 4.78 [4.14–5.52], PRR 4.71 [553.92], EBGM 4.71 [4.17], IC 2.23 [0.57]), with drug ineffectiveness being the most commonly reported AE across all PTs and standing out as particularly prominent. To more clearly delineate the association between these AEs and their system organ class categorizations, Fig. 6 presents the leading 20 PTs along with their linked SOCs. Moreover, to offer a chronological view of the occurrence of these AEs, Fig. 7 tracks the cumulative incidence of the top 10 most frequently reported PTs during the study's observation period, underscoring the pattern and rate at which these AEs were documented.

Sensitivity analysis

Our examination of the FAERS database revealed that deutetrabenazine is often used in conjunction with various other pharmaceuticals, such as trazodone, vitamin D_3, atorvastatin, gabapentin, and seroquel (Table 5). After eliminating reports with the simultaneous use of other drugs, our study identified 1037 individual reports accounting for 3,891 unique AEs. The persistent adverse reactions potentially included drug ineffective, dyskinesia, death, depression, tremor, somnolence, suicidal ideation, insomnia, fall, anxiety, feeling abnormal, product use in unapproved indication, dizziness, product use issue, gait disturbance, hospitalization, confusional state, tardive dyskinesia, wrong technique in product usage process, restlessness, parkinsonism, therapeutic product

Table 4 The top 30 signal strength of adverse events of deutetrabenazine ranked by the number of case reports at the PTs level in FAERS database

Preferred terms (PTs)	Case reports	ROR (95% CI)	PRR (95% CI)	EBGM (EBGM05)	IC (IC025)
Drug Ineffective*	603	2.5 (2.31–2.72)	2.42 (513.66)	2.42 (2.26)	1.27 (-0.39)
Dyskinesia*	288	50.24 (44.64–56.53)	48.9 (13298.97)	48.11 (43.59)	5.59 (3.92)
Depression*	288	9.17 (8.16–10.31)	8.95 (2034.27)	8.93 (8.09)	3.16 (1.49)
Death*	243	1.6 (1.41–1.82)	1.59 (53.46)	1.59 (1.43)	0.67 (-1)
Tremor*	207	8.58 (7.48–9.85)	8.44 (1356.04)	8.41 (7.5)	3.07 (1.41)
Somnolence*	199	6.29 (5.47–7.24)	6.19 (867.28)	6.18 (5.5)	2.63 (0.96)
Suicidal Ideation*	197	15.81 (13.73–18.21)	15.53 (2667.91)	15.46 (13.73)	3.95 (2.28)
Insomnia*	189	4.78 (4.14–5.52)	4.71 (553.92)	4.71 (4.17)	2.23 (0.57)
Fatigue*	176	1.26 (1.09–1.47)	1.26 (9.56)	1.26 (1.11)	0.33 (-1.33)
Fall*	155	2.88 (2.46–3.38)	2.85 (187.49)	2.85 (2.5)	1.51 (-0.15)
Off Label Use	140	0.71 (0.61–0.84)	0.72 (15.7)	0.72 (0.63)	-0.48 (-2.14)
Anxiety*	127	2.78 (2.34–3.32)	2.76 (143.17)	2.76 (2.38)	1.46 (-0.2)
Feeling Abnormal*	122	3.21 (2.69–3.84)	3.19 (183.37)	3.18 (2.74)	1.67 (0)
Product Use In Unapproved Indication*	121	1.9 (1.59–2.28)	1.89 (51.12)	1.89 (1.63)	0.92 (-0.75)
Dizziness*	121	1.57 (1.31–1.88)	1.56 (24.69)	1.56 (1.34)	0.64 (-1.02)
Product Use Issue*	102	2.97 (2.44–3.61)	2.95 (131.65)	2.95 (2.5)	1.56 (-0.11)
Gait Disturbance*	99	3.16 (2.59–3.85)	3.14 (144.71)	3.14 (2.66)	1.65 (-0.02)
Diarrhoea	90	0.78 (0.63–0.96)	0.78 (5.66)	0.78 (0.66)	-0.36 (-2.02)
Nausea	90	0.71 (0.58–0.88)	0.72 (10.2)	0.72 (0.6)	-0.48 (-2.15)
Confusional State*	89	3.66 (2.97–4.51)	3.64 (170.36)	3.63 (3.05)	1.86 (0.2)
Hospitalisation*	82	2.67 (2.15–3.32)	2.66 (85.23)	2.66 (2.22)	1.41 (-0.25)
Headache	79	0.76 (0.61–0.95)	0.77 (5.67)	0.77 (0.64)	-0.38 (-2.05)
Restlessness*	77	14.08 (11.25–17.63)	13.99 (924.52)	13.92 (11.54)	3.8 (2.13)
Tardive Dyskinesia*	76	41.13 (32.77–51.63)	40.85 (2913.99)	40.3 (33.32)	5.33 (3.67)
Balance Disorder*	75	5.52 (4.4–6.93)	5.49 (275.38)	5.48 (4.53)	2.46 (0.79)
Agitation*	73	7.74 (6.15–9.75)	7.7 (424.52)	7.68 (6.33)	2.94 (1.27)
Speech Disorder*	72	9.11 (7.22–11.49)	9.06 (514.88)	9.03 (7.44)	3.18 (1.51)
Product Dose Omission Issue	72	1.07 (0.85–1.35)	1.07 (0.34)	1.07 (0.88)	0.1 (-1.57)
Wrong Technique In Product Usage Process*	70	1.4 (1.11–1.78)	1.4 (8.09)	1.4 (1.15)	0.49 (-1.18)
Parkinsonism*	68	47.18 (37.1–60)	46.88 (3005.86)	46.16 (37.75)	5.53 (3.86)

Asterisks (*) indicate statistically significant signals. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; IC, information component; IC025, the lower limit of the 95% confidence interval of the IC

effect incomplete, speech disorder and balance disorder (Table 6).

Subgroup analysis

In our research, remarkable demographic heterogeneity was detected, especially in the gender distribution. To reduce the possible confounding impacts of demographic traits on the outcomes, we carried out a subgroup analysis classified by gender. In both the male and female subgroups, "Drug Ineffective" turned out to be the most frequently reported AEs. Among the 30 most prevalent AEs that met the positive signal criteria, specific events were solely seen in males. These included somnolence, restlessness, agitation, speech disorder, incorrect technique in the product usage process, aggression, and hallucination (as presented in Supplementary Table 3). Conversely, confusional state, dry mouth, tardive dyskinesia, loss of personal independence in daily activities, and weight gain were unique to females (Supplementary Table 4). Significantly, although "fatigue" was among the top 30 reported AEs in terms of the number of cases, it only fulfilled the positive signal criteria in the female subgroup. Similarly, the "dyspnoea" met the positive signal criteria solely within the male subgroup.

Discussion

This investigation broadly assessed the AEs associated with deutetrabenazine since its approval in 2017. The review of FAERS data confirmed the adverse responses previously documented on the deutetrabenazine label, including depression, somnolence, suicidal ideation, and fatigue. Furthermore, the study uncovered supplementary AEs absent from the label, including general disorders and administration site conditions (e.g., drug ineffectiveness, mortality), nervous system disorders (e.g., tremor), psychiatric disorders (e.g., insomnia), and

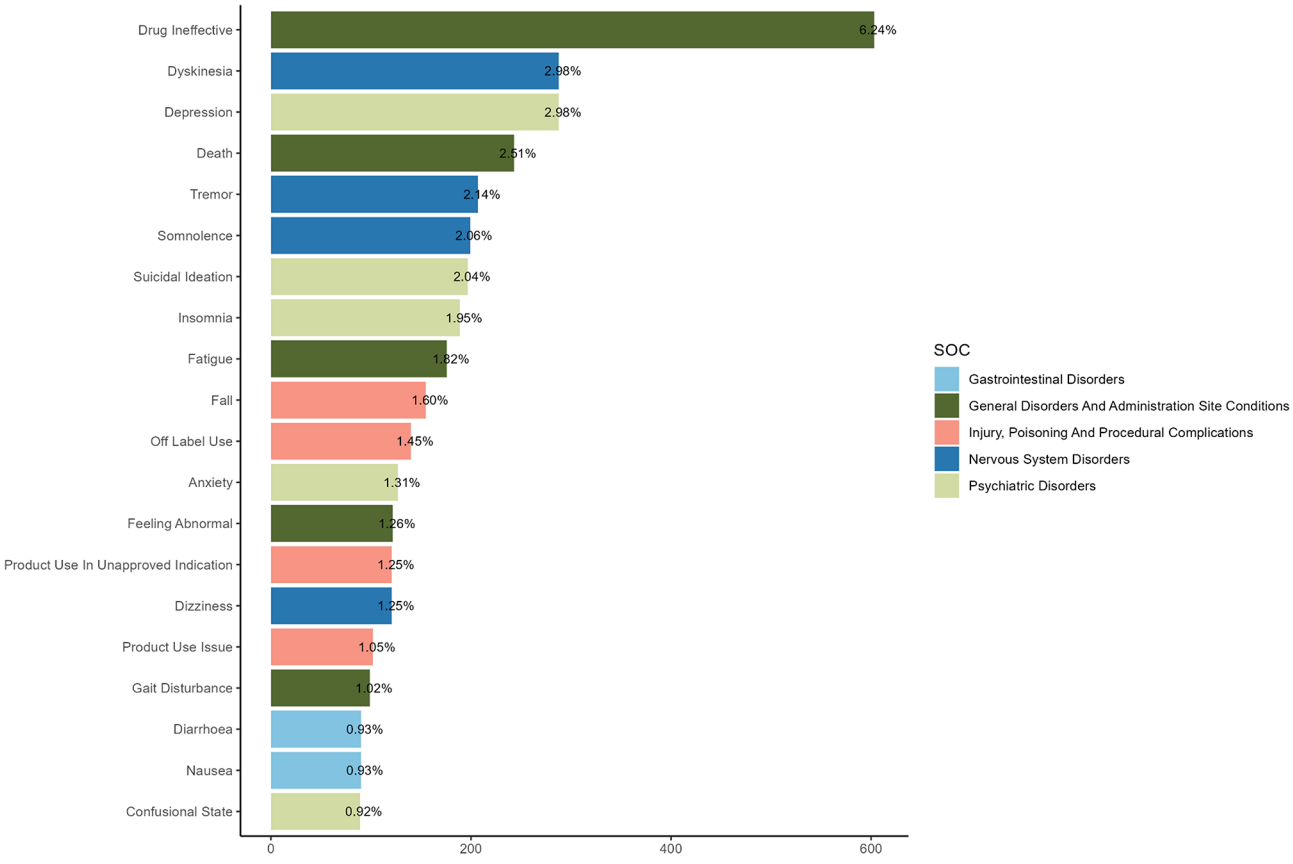

Fig. 6 Signal Strength of top 20 AEs of deutetrabenazine at the PT Level in FAERS Database

injury, poisoning and procedural complications (e.g., falls). The findings highlight the need for diligent medication monitoring, particularly in the first month after treatment commencement, to effectively manage and reduce the risk of side effects.

Previous safety and efficacy trials of deutetrabenazine for the treatment of TD have yielded somewhat varying results, particularly in terms of mood disorders and suicidality, but one consistent finding is the relatively high incidence of somnolence as an AE. For example, in a 3-year, open-label extension study with a mean treatment duration of 106.5 weeks and a total exposure time of 688 patient-years, the most frequently reported AEs were anxiety, depression, somnolence, weight loss, and urinary tract infections [20]. Throughout the study, there were eight fatalities; however, the investigators did not consider any of these deaths to be related to the study drug. In a randomized, double-blind, multicenter trial conducted by Hubert H. Fernandez and colleagues, a total of 117 patients with moderate to severe TD were randomly allocated to receive deutetrabenazine or placebo [21]. The top five AEs in terms of frequency were somnolence, fatigue, insomnia, headache, and diarrhea. It is noteworthy that the incidence of depression/dysphoria and suicidal ideation in the deutetrabenazine group was comparable to or lower than that in the placebo group. Deutetrabenazine has also proven effective for chorea in Huntington's disease [22, 23], and deserves a comprehensive assessment of its safety in this specific group of patients. In a randomized clinical trial involving 123 patients with Huntington's chorea, AEs to deutetrabenazine predominantly manifested as psychiatric and neurological disorders, mostly of mild to moderate intensity [24]. The majority of participants did not necessitate a reduction or cessation of the drug because of these adverse reactions (only 3 patients in each cohort, which is 6.7%, required a dosage decrease). Somnolence was the most frequently observed AE, typically ameliorating without dosage adjustment, while depression with the lowest incidence rates in all AEs. Our results closely align with prior studies, with the frequency of somnolence cases being relatively high among all AEs at the PT level. This emphasizes the importance of vigilant surveillance and proactive management of this adverse reaction when prescribing deutetrabenazine for the treatment of TD.

Additionally, we found a noteworthy finding that, while emotional issues such as depression and suicidal ideation have been highlighted as significant adverse reaction warnings in the deutetrabenazine drug labeling, these have not constituted a large proportion of AEs

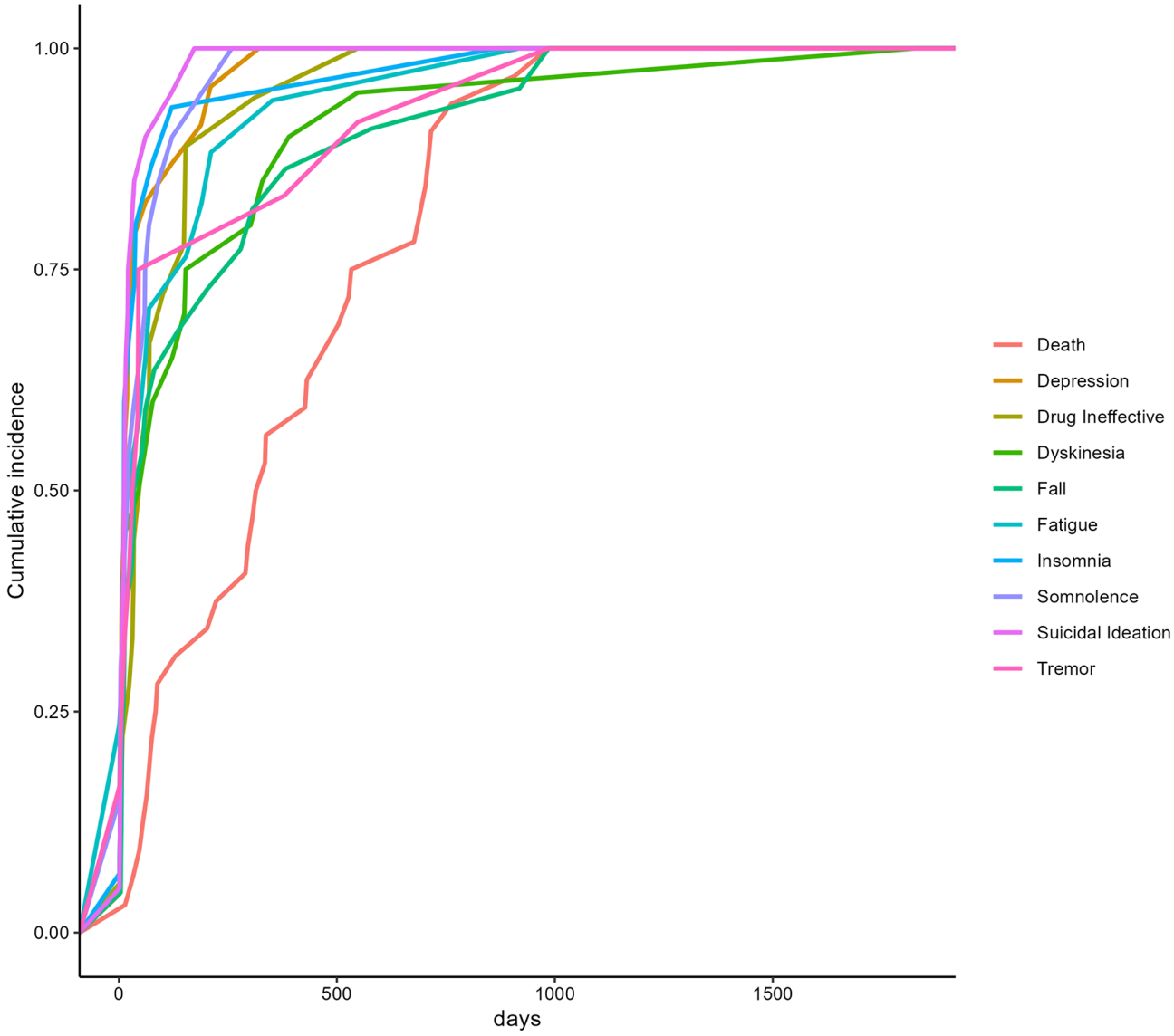

Fig. 7 The progression of cumulative incidence for the 10 most frequently reported PTs

Table 5 The top five drugs most frequently co-administered with deutetrabenazine in the FAERS database

Drug	Case number
Gabapentin	109
Trazodone	76
Vitamin D3	70
Seroquel	64
Atorvastatin	61

in some previous studies [10]. Some studies have even emphasized that deutetrabenazine does not increase the risk of depression or suicidal ideation [25, 26]. However, our findings agree with the perspective of the drug label that depression and suicidal ideation are among the most common AEs associated with deutetrazine, ranking third and seventh, respectively. Moreover, the number of reports for these events is comparable to that of somnolence, which is frequently cited as a high-incidence AE in most studies. This suggests that there is a need for heightened awareness and closer monitoring of the psychological and behavioral AEs associated with deutetrabenazine treatment [27]. It also underscores the importance of further research to elucidate the relationship between deutetrabenazine and these specific AEs, in order to guide clinical practice and improve patient safety.

Another noteworthy observation is that our research has uncovered several AEs not currently listed on the drug label. In our study, the two most frequently reported AEs associated with deutetrabenazine were Ineffectiveness and Dyskinesia, which were not listed on the drug's label. We speculate that the reason for this outcome may be significantly related to the nature and progression of

Table 6 Top 30 most frequent adverse events for deutetrabenazine excluding common medication co-usage at the PT level from FAERS data

Preferred terms (PTs)	Case reports	ROR (95% CI)	PRR (95% CI)	EBGM (EBGM05)	IC (IC025)
Drug Ineffective*	573	2.81 (2.58–3.06)	2.7 (625.68)	2.69 (2.51)	1.43 (-0.24)
Dyskinesia*	240	48.94 (43.01–55.68)	47.67 (10820.89)	47.03 (42.21)	5.56 (3.89)
Death*	229	1.77 (1.56–2.02)	1.75 (75.24)	1.75 (1.57)	0.81 (-0.86)
Depression*	223	8.3 (7.27–9.49)	8.12 (1394.17)	8.11 (7.25)	3.02 (1.35)
Tremor*	178	8.66 (7.46–10.04)	8.51 (1178.69)	8.49 (7.49)	3.09 (1.42)
Somnolence*	174	6.45 (5.55–7.5)	6.35 (785.14)	6.34 (5.59)	2.66 (1)
Suicidal Ideation*	169	15.9 (13.65–18.52)	15.62 (2304.7)	15.55 (13.69)	3.96 (2.29)
Insomnia*	147	4.35 (3.7–5.12)	4.3 (372.86)	4.29 (3.75)	2.1 (0.44)
Fatigue	141	1.19 (1–1.4)	1.18 (4.08)	1.18 (1.03)	0.24 (-1.42)
Fall*	134	2.92 (2.46–3.47)	2.89 (166.8)	2.89 (2.51)	1.53 (-0.13)
Off Label Use	127	0.76 (0.64–0.91)	0.76 (9.37)	0.76 (0.66)	-0.39 (-2.05)
Anxiety*	107	2.75 (2.27–3.33)	2.73 (117.58)	2.73 (2.32)	1.45 (-0.22)
Feeling Abnormal*	107	3.3 (2.73–4)	3.28 (169.68)	3.27 (2.79)	1.71 (0.04)
Product Use In Unapproved Indication*	105	1.94 (1.6–2.35)	1.93 (46.94)	1.92 (1.64)	0.94 (-0.72)
Dizziness*	103	1.57 (1.29–1.9)	1.56 (20.86)	1.56 (1.33)	0.64 (-1.02)
Product Use Issue*	94	3.21 (2.62–3.93)	3.19 (141.41)	3.19 (2.69)	1.67 (0.01)
Gait Disturbance*	85	3.18 (2.57–3.94)	3.16 (125.93)	3.16 (2.64)	1.66 (-0.01)
Diarrhoea	75	0.76 (0.61–0.95)	0.76 (5.63)	0.76 (0.63)	-0.39 (-2.06)
Hospitalisation*	75	2.87 (2.29–3.6)	2.86 (90.6)	2.85 (2.36)	1.51 (-0.15)
Nausea	74	0.69 (0.55–0.87)	0.69 (10.33)	0.69 (0.57)	-0.53 (-2.2)
Confusional State*	69	3.32 (2.62–4.21)	3.31 (111.17)	3.3 (2.71)	1.72 (0.06)
Headache	68	0.77 (0.61–0.98)	0.77 (4.53)	0.77 (0.63)	-0.37 (-2.04)
Tardive Dyskinesia*	65	41.18 (32.22–52.64)	40.89 (2500.29)	40.42 (32.92)	5.34 (3.67)
Wrong Technique In Product Usage Process*	64	1.51 (1.18–1.93)	1.5 (10.83)	1.5 (1.22)	0.59 (-1.08)
Restlessness*	62	13.28 (10.34–17.06)	13.2 (696.6)	13.15 (10.67)	3.72 (2.05)
Parkinsonism*	62	50.41 (39.2–64.83)	50.07 (2939.11)	49.36 (39.99)	5.63 (3.96)
Therapeutic Product Effect Incomplete*	62	3.6 (2.8–4.62)	3.58 (115.55)	3.58 (2.9)	1.84 (0.17)
Speech Disorder*	60	8.9 (6.9–11.48)	8.85 (416.94)	8.83 (7.14)	3.14 (1.48)
Product Dose Omission Issue	59	1.03 (0.8–1.33)	1.03 (0.05)	1.03 (0.83)	0.04 (-1.63)
Balance Disorder*	58	5.01 (3.87–6.48)	4.98 (184.42)	4.97 (4.01)	2.31 (0.65)

Asterisks (*) indicate statistically significant signals. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; IC, information component; IC025, the lower limit of the 95% confidence interval of the IC

the indications in the patient population treated with this medication. Deutetrabenazine is primarily indicated for the treatment of TD, a serious neurological condition characterized by hyperkinetic movements that can arise from the use of antipsychotic medications [28, 29]. This disorder poses challenges in management and is often resistant to reversal. In a research investigation focusing on the reversibility of tardive syndromes after discontinuation of the causative agent, only 13% of 108 patients experienced a complete resolution of their movement disorder [30]. Furthermore, patients with psychiatric disorders require stable dosing for long-term maintenance therapy, and complete discontinuation of medication is quite rare [31, 32]. This makes the progression and exacerbation of TD more challenging to manage. Although research indicates that deutetrabenazine is generally effective, safe, and well-tolerated in patients with TD compared to other traditional medications such as tetrabenazine and valbenazine [33], due to the irreversible nature of the disease and its poor prognosis, Ineffectiveness and Dyskinesia emerged as the most frequently occurring AEs at the PT level in our study results. Therefore, clinicians should weigh the disease prognosis and long-term clinical benefits when utilizing this deutetrabenazine.

Besides, another AE not listed on the drug label that warrants attention is mortality, which ranked third among the AEs at the PT level in our study. However, the majority of previous studies support the notion that cases of death attributed to deutetrabenazine are rare [34], and neither the investigators nor the sponsors generally consider death to be related to the study drug [25], which vary from our findings. We speculate that the reason for this outcome is that although the mortality rate directly attributed to deutetrabenazine itself may not be high, it can lead to emotional issues in patients, resulting

in negative ideations and suicidal behaviors. These extreme actions could contribute to an increased mortality rate. The occurrence of two additional AEs, insomnia and fall, which are also not listed on the drug label, prompted us to delve deeper into the pharmacological mechanisms of deutetrabenazine to explore the causes of these outcomes. Neuronal communication depends on the transfer of neurotransmitters across the synaptic cleft from the presynaptic to the postsynaptic neuron [35]. This process involves the action of vesicular monoamine transporters (VMATs), which facilitate the uptake of neurotransmitters into presynaptic vesicles. VMAT1 and VMAT2 are two such transporters, with VMAT1 being expressed in both the central and peripheral nervous systems, and VMAT2 being largely restricted to the CNS [36]. VMAT2, prominently localized in neurons, is crucial for the vesicular storage of monoamines such as dopamine, serotonin, norepinephrine, and histamine [37, 38]. The inhibition of VMAT2 can lead to a diminished release of these neurotransmitters [39, 40], consequently reducing the availability of dopamine for interaction with postsynaptic receptors [22]. Hence, agents that inhibit VMAT2 are utilized in the therapeutic management of hyperkinetic movement disorders [41, 42]. Decreased levels of dopamine and other neurotransmitters in the central nervous system can often lead to manifestations such as unsteady gait, bradykinesia, tremors, and rigidity, which in turn frequently result in mobility system impairments like falls [43, 44]. Additionally, DA is essential for maintaining arousal, which can lead to AEs such as somnolence and fatigue when its levels decrease [45]. Our research supports earlier studies, showing that deutetrabenazine frequently causes these effects. Insomnia remains a frequently reported AE in our study, which may be challenging to explain solely based on the mechanism of action of the drug. However, the majority of patients exhibiting symptoms of TD often have a history of long-term antipsychotic use, and these medications are typically associated with akathisia, restlessness, and insomnia rather than sedative effects during the initial phases of treatment [46, 47]. We speculate that patients on deutetrabenazine may also be taking antipsychotic medications, which could account for the emergence of insomnia.

By conducting a sensitivity analysis, we detected a consistent potential adverse reaction, termed 'Condition Aggravated', linked to the exclusive use of deutetrabenazine. This AE, while not fatal, can significantly influence patient compliance with treatment, thereby potentially diminishing the therapeutic effectiveness. In light of these results, close monitoring of such specific AEs is essential for maximizing treatment benefits and augmenting the efficacy of the medication. The results of the subgroup analysis underscored that, in addition to typical somatic ailments, the agitated emotional states in male patients, such as restlessness, agitation, and aggression, still merit special consideration. In contrast, female patients should be closely monitored for changes in somatic conditions, such as dry mouth, weight gain, and fatigue. Notably, somnolence is present in male patients, while confusion is present in female patients, and both of these AEs occur in relatively high numbers in their respective subgroups. This indicates that when using this drug, interdisciplinary collaboration is needed. We should frequently cooperate with psychiatrists and neurologists for joint diagnosis and treatment to effectively assess the disease progression and drug side-effects of patients [48]. Moreover, in male patients, nurses should also pay attention to timely assessment of the risk of danger and violence [49].

In addition to the primary analysis, our study incorporated a temporal evaluation of AEs, utilizing the Weibull distribution model to forecast the occurrence of these events. This approach aids in setting up efficient surveillance time frames for adverse reactions associated with drug therapy. The findings highlight the necessity for stringent oversight, especially within the initial month of commencing deutetrabenazine therapy. Focusing on this early detection phase is essential for promptly identifying and addressing possible AEs, ultimately aiming to enhance patient safety and therapeutic success.

Since this period encompasses the outbreak time of COVID-19, its impact on the efficacy of deutetrabenazine in treating diseases such as TD should be carefully considered. Although due to database limitations we are unable to conduct further analysis, the COVID-19 pandemic led to disruptions in healthcare services, which likely affected the regular monitoring of TD patients receiving deutetrabenazine treatment [50]. Delays in follow-up appointments might have hindered optimal dosing adjustments. Moreover, the psychological and physiological stress related to the pandemic could potentially have an impact on TD symptoms, possibly complicating the effectiveness of deutetrabenazine treatment [51, 52]. However, further research is needed to fully understand this relationship.

While this study offers an in-depth look at the safety profile of deutetrabenazine, certain limitations must be recognized. Firstly, the FAERS database, relying on voluntary reporting, is prone to biases such as underreporting and over-reporting. Reports from consumers may lack the reliability and completeness of data provided by healthcare professionals. Additionally, factors like drug interactions, pre-existing conditions, and polypharmacy, which could affect AE outcomes, were not uniformly accounted for in our analysis. Moreover, the analytical approaches we employed, including ROR, PRR, EBGM, and BCPNN, suggest statistical correlations but do not establish direct causality between the medication

and AEs. Thus, further investigative studies are required to confirm causal relationships. Nonetheless, the broad global data analyzed in this study strengthens its capacity to assess potential risks associated with deutetrabenazine. It is important to note, however, that the true risk of these AEs can only be determined through future prospective studies. Despite these limitations, our findings serve as a valuable resource for clinicians to monitor patients closely and detect possible AEs related to deutetrabenazine treatment.

Conclusion

In summary, we conducted an exhaustive appraisal of the safety profile of deutetrabenazine within a clinical context. By scrutinizing data from the FAERS database, we were able to assess the frequency of AEs and their respective timing of onset. Our examination reaffirmed previously recognized AEs and unveiled additional potential reactions not explicitly stated on the product label, including therapy failure, abnormal involuntary movements, mortality, incidents of falling, and sleep disturbances. These unprecedented insights stress the imperative for intensified vigilance in safety surveillance to alleviate the likelihood of experiencing AEs and to safeguard patient well-being, thereby informing upcoming studies and shaping clinical strategies.

Abbreviations

FAERS	The Food and Drug Administration Adverse Event Reporting System
ADRs	Adverse drug reactions
PT	Preferred Terms
SOC	System Organ Classes
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio
BCPNN	Bayesian Confidence Propagation Neural Network
MGPS	Multi-Item Gamma Poisson Shrinker
IC	Information component

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00872-9.

Supplementary Material 1

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Author contributions

GQ: designed and performed the research, collected and analyzed the data, wrote the paper. SY collected and analyzed the data. BW and YY: checked the data and revised the article.

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Data availability

Publicly available databases were used for all data analyses in this study. The original contributions presented in the study are included in the website: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Declarations

Ethics approval and consent to participate

Not applicable. This project was submitted for review through Advocate Health and was waived as this study was deemed non-human subject related research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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