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Safety assessment of asenapine in the FAERS database: real adverse event analysis and discussion on neurological and psychiatric side effects

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Abstract

Purpose This study aims to comprehensively assess the safety of Asenapine by conducting an comprehensive statistical analysis of adverse event reports in the FAERS database, with a particular focus on potential adverse reactions related to its use in the treatment of psychiatric disorders.

Methods Event reports from the first quarter of 2009 to the third quarter of 2023 were collected and analyzed. Detailed examinations of gender, age, reporter identity, and other aspects were conducted to reveal the fundamental characteristics of Asenapine-related adverse events. Signal mining techniques were employed to systematically evaluate various adverse reactions associated with Asenapine.

Results The study found that adverse event reports involving Asenapine were more common among female patients, with the age group mainly distributed between 18 and 45 years. Physicians were the primary reporters of adverse events, and psychiatric disorders, neurological disorders, and gastrointestinal disorders were the most common areas affected by adverse reactions. In addition to known adverse reactions, potential risks not mentioned in the drug label were identified, such as anosognosia, attentional drift, and psychogenic compensation disorder.

Conclusion Asenapine carries the risk of various adverse reactions alongside its therapeutic effects. In clinical practice, physicians should closely monitor the occurrence of neurological disorders, psychiatric disorders, and gastrointestinal system disorders.

Keywords Asenapine, Schizophrenia, Bipolar disorder, FAERS database, Side effects

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Introduction

Schizophrenia and Bipolar Disorder are severe mental illnesses, with schizophrenia typically onset during adolescence or early adulthood, characterized by symptoms such as hallucinations, delusions, and thought disorders. The global incidence of schizophrenia is approximately 1% [1]. Bipolar Disorder features episodes of depression and mania, with a lifetime prevalence in the general population ranging from 2 to 4% [2].

Asenapine is a novel antipsychotic medication that demonstrates high-affinity binding and antagonistic activity across a wide range of dopamine, serotonin, norepinephrine, and histamine receptors. It is used to treat acute manic or mixed episodes associated with bipolar I disorder and schizophrenia [3]. After hepatic metabolism, asenapine is almost completely metabolized and is primarily available in sublingual and transdermal formulations [4]. The sublingual asenapine tablets are absorbed through the oral mucosa, reaching peak concentration within 30 to 90 min. The terminal half-life is approximately 24 h. Asenapine produces various inactive metabolites through direct glucuronidation (mainly via UGT1A4), demethylation, and oxidative metabolism (primarily via CYP1A2) [5]. Both hepatic and renal pathways contribute similarly to the elimination of asenapine and its metabolites [6]. A meta-analysis conducted by Snigdha Dutta and her team on asenapine treatment for schizophrenia included six studies and found that asenapine can alleviate patients' negative symptoms with fewer adverse reactions [7]. Ronald Landbloom and colleagues compared olanzapine and asenapine in the treatment of acute schizophrenia patients and found that asenapine was not superior to olanzapine in therapeutic effect but was associated with less weight gain than olanzapine. However, the incidence of oral hypoesthesia and taste disturbances (combined) was significantly higher with asenapine than with olanzapine [8]. Similar conclusions were drawn by Vasudev and colleagues [9].

The Food and Drug Administration Adverse Event Reporting System (FAERS) database compiles adverse event reports globally related to drug treatments, providing valuable real-world data to deepen our understanding of potential adverse events patients may experience during medication, enabling a more comprehensive assessment of safety and risk profiles [10]. Therefore, this study aims to utilize the FAERS database to identify adverse reactions reported during the post-marketing use of asenapine and to conduct a disproportionality analysis of these adverse reactions. First, we extracted adverse reaction reports related to asenapine from the FAERS database. Subsequently, we performed a detailed statistical analysis of these reports, including the number of reports, patient characteristics, and the identification of individual and systemic adverse reactions caused by asenapine, with a focus on neuropsychiatric adverse reactions. Through this study, we hope to uncover the real-world adverse reactions associated with asenapine post-marketing, and the potential associations between these reactions and the drug. The findings aim to provide scientific evidence for clinical use, inform drug safety management, and ultimately improve patient medication safety.

Methods

Data source

We used the FAERS database for drug-related adverse reaction analysis. Considering that Asenapine was launched in 2009, we downloaded the report files from the FAERS website (https://open.fda.gov/data/faers/) spanning from Q1 2009 to Q3 2023. These data include individual case safety reports (DEMO), drug usage records (DRUG), outcomes, report sources, indications, and therapy methods. Subsequently, we used R 4.3.2 to analyze the downloaded data. We used asenapine as a keyword for the search, as detailed in the appendix file's Table 1.

Data extraction and Disproportionality Analysis

To ensure data accuracy, we first removed duplicate reports. Specifically, for data in the DEMO table with the same caseid, we retained only the most recent report based on the report date. We utilized the Medex_UIMA_1.3.8 system to standardize the drugs and classify adverse drug reactions (ADRs) caused by these drugs [11]. We focused on extracting reports where Asenapine was the primary suspected cause of the ADRs, based on user reports and data analysis. These reports included details such as report date, patient's age and gender, reporter, and region [12]. To encode, classify, and locate signals of ADRs, we used the Preferred Terms (PT) and System Organ Classes (SOC) from the MedDRA26.1 software. For our subsequent analysis, we included PTs with a report count of ≥ 3 [13, 14]. In this study, we employed four methods for signal detection and disproportionality analysis: Reporting Odds Ratio (ROR) [15], Proportional Reporting Ratio (PRR) [16], Bayesian Confidence Propagation Neural Network (BCPNN) [17], and Multi-Item Gamma Poisson Shrinker (MGPS) [18]. The goal was to leverage the strengths of each method to expand the detection range, validate results from multiple perspectives, and ensure comprehensive and reliable safety signal detection. The combined use of multiple algorithms allows for cross-validation to reduce false positives, and by adjusting thresholds and variances, it enables the detection of more potential rare ADRs. ROR identifies disproportionality in drug-event reporting compared to all other events, with a higher ROR suggesting a potential signal. PRR measures the proportion of

Table 1 Basic information on ADEs related to asenapine from the FAERS database

Variable	Total (%)
Sex	
Female	3484 (51.98)
Male	1863 (27.79)
Unknown	1356 (20.23)
Age	
<18	135 (2.01)
18 ~ 45	1574 (23.48)
45 ~ 65	1052 (15.69)
65 ~ 75	144 (2.15)
>=75	74 (1.10)
Unknown	3724 (55.56)
Reporter	
Physician	2914 (43.47)
Consumer	2297 (34.27)
Other health-professional	1040 (15.52)
Pharmacist	316 (4.71)
Unknown	131 (1.95)
Lawyer	3 (0.04)
Registered Nurse	2 (0.03)
Reported countries	
Other	3630 (54.15)
United States	2498 (37.27)
Japan	402 (6.00)
Canada	100 (1.49)
Australia	73 (1.09)
Route	
Sublingual	3658 (54.57)
Other	2247 (33.52)
Oral	798 (11.91)
Outcomes	
Other serious	1495 (48.81)
Hospitalization	903 (29.48)
Death	244 (7.97)
Life threatening	221 (7.22)
Disability	175 (5.71)
Required intervention to Prevent Permanent Impairment/Damage	22 (0.72)
Congenital anomaly	3 (0.10)
Adverse event occurrence time - medication date (days)	
<7	855 (31.51)
7 ~ 27	181 (6.67)
28 ~ 59	106 (3.91)
>=60	181 (6.67)
Unknown	1390 (51.23)
Indications	
Affective disorder	43 (0.63)
Anxiety	45 (0.65)
Bipolar disorder	1711 (24.89)
Bipolar I disorder	389 (5.66)
Bipolar II disorder	33 (0.48)
Delirium	13 (0.19)
Delusion	10 (0.15)
Depression	129 (1.88)
Drug use for unknown indication	681 (9.91)
Hallucination	512 (0.17)
Insomnia	34 (0.49)
Major depression	37 (0.54)
Mania	80 (1.16)
Mental disorder	18 (0.26)
Mood altered	10 (0.15)
Obsessive-compulsive disorder	11 (0.16)
Others	206 (3.00)
Paranoia	15 (0.22)
Post-traumatic stress disorder	20 (0.29)
Product used for unknown indication	1246 (18.13)
Psychotic disorder	108 (1.57)
Schizoaffective disorder	135 (1.96)
Schizoaffective disorder bipolar type	11 (0.16)
Schizophrenia	802 (11.67)
Schizophrenia, paranoid type	13 (0.19)
Sleep disorder	15 (0.22)
Unknown	1046 (15.22)

reports for a specific event with a drug versus all other drugs, where a PRR significantly greater than 1 indicates a signal. BCPNN uses Bayesian logic to compute the information component (IC) value, with a positive IC suggesting a strong association. MGPS, a Bayesian data mining method, calculates the Empirical Bayes Geometric Mean (EBGM) to assess the strength of the association, with a higher EBGM indicating a stronger signal. An ADR is considered significant if it meets the following criteria: (1) ROR≥3 and 95% CI (lower limit)>1; (2) PRR≥2 and 95% CI (lower limit)>1; (3) IC025>0; (4) EBGM05>2. For detailed algorithms and formulas, refer to the appendix file's Table 2 [19].

Results

Screening results of asenapine adverse reactions

From the first quarter of 2009 to the third quarter of 2023, this study collected a total of 17,607,392 adverse event reports from the FAERS database. After removing 2,637,523 duplicate reports, we obtained 6703 reports which included 15,439 adverse reactions deemed as primary suspects. We performed demographic and clinical characteristic analysis on the 6703 reports and conducted disproportionality analysis on the 15,439 adverse reactions. Detailed information is shown in Fig. 1.

Basic characteristics of asenapine-related ADEs

In the basic characteristics of adverse event reports involving Asenapine, we observed a trend of initial increase followed by a decrease in the number of reports from 2009 to 2023. The highest number of reports was

Table 2 The signal strength of ADEs of Asenapine at the SOC level in FAERS database

SOC	Case reports	ROR (95% CI)	PRR (95% CI)	chisq	IC (IC025)	EBGM (EBGM05)
Psychiatric disorders	2641	3.42 (3.28, 3.56)	2.99 (2.88, 3.11)	3714.63	1.58 (1.52)	2.99 (2.88)
Nervous system disorders	3305	2.94 (2.83, 3.05)	2.51 (2.41, 2.61)	3285.74	1.33 (1.27)	2.51 (2.43)
Gastrointestinal disorders	2049	1.63 (1.55, 1.7)	1.54 (1.48, 1.6)	425.19	0.62 (0.56)	1.54 (1.48)
Reproductive system and breast disorders	125	0.97 (0.81, 1.15)	0.97 (0.81, 1.16)	0.14	-0.05 (-0.3)	0.97 (0.83)
Immune system disorders	172	0.96 (0.83, 1.12)	0.96 (0.82, 1.12)	0.25	-0.06 (-0.27)	0.96 (0.85)
Investigations	867	0.95 (0.89, 1.02)	0.96 (0.91, 1.02)	1.93	-0.07 (-0.16)	0.96 (0.9)
Metabolism and nutrition disorders	283	0.87 (0.77, 0.98)	0.87 (0.77, 0.98)	5.67	-0.2 (-0.37)	0.87 (0.79)
Injury, poisoning and procedural complications	1190	0.79 (0.74, 0.84)	0.81 (0.76, 0.86)	62.18	-0.31 (-0.4)	0.81 (0.77)
Respiratory, thoracic and mediastinal disorders	539	0.72 (0.66, 0.79)	0.73 (0.67, 0.79)	54.74	-0.45 (-0.57)	0.73 (0.68)
Vascular disorders	203	0.61 (0.53, 0.7)	0.61 (0.53, 0.7)	50.84	-0.71 (-0.91)	0.61 (0.55)
Musculoskeletal and connective tissue disorders	480	0.58 (0.53, 0.63)	0.59 (0.55, 0.64)	144.81	-0.76 (-0.89)	0.59 (0.55)
General disorders and administration site conditions	1757	0.58 (0.55, 0.6)	0.62 (0.6, 0.64)	486.75	-0.68 (-0.75)	0.63 (0.6)
Eye disorders	182	0.57 (0.5, 0.67)	0.58 (0.51, 0.67)	56.53	-0.79 (-1)	0.58 (0.51)
Ear and labyrinth disorders	38	0.57 (0.41, 0.78)	0.57 (0.42, 0.78)	12.3	-0.81 (-1.26)	0.57 (0.44)
Cardiac disorders	222	0.57 (0.5, 0.65)	0.57 (0.5, 0.65)	71.95	-0.8 (-0.99)	0.57 (0.51)
Skin and subcutaneous tissue disorders	488	0.55 (0.5, 0.6)	0.57 (0.53, 0.62)	172.38	-0.82 (-0.95)	0.57 (0.52)
Renal and urinary disorders	124	0.44 (0.36, 0.52)	0.44 (0.37, 0.52)	90.03	-1.18 (-1.44)	0.44 (0.38)
Endocrine disorders	14	0.37 (0.22, 0.62)	0.37 (0.22, 0.63)	15.33	-1.45 (-2.18)	0.37 (0.24)
Hepatobiliary disorders	44	0.33 (0.24, 0.44)	0.33 (0.25, 0.44)	59.92	-1.59 (-2.02)	0.33 (0.26)
Congenital, familial and genetic disorders	13	0.28 (0.16, 0.48)	0.28 (0.16, 0.48)	24.53	-1.85 (-2.61)	0.28 (0.18)
Blood and lymphatic system disorders	52	0.2 (0.15, 0.26)	0.2 (0.15, 0.26)	167.02	-2.31 (-2.7)	0.2 (0.16)
Infections and infestations	135	0.16 (0.13, 0.19)	0.17 (0.14, 0.2)	595.48	-2.59 (-2.83)	0.17 (0.14)
Pregnancy, puerperium and perinatal conditions	8	0.12 (0.06, 0.24)	0.12 (0.06, 0.24)	52.81	-3.08 (-4.02)	0.12 (0.07)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21	0.05 (0.03, 0.07)	0.05 (0.03, 0.08)	417.28	-4.41 (-5.01)	0.05 (0.03)

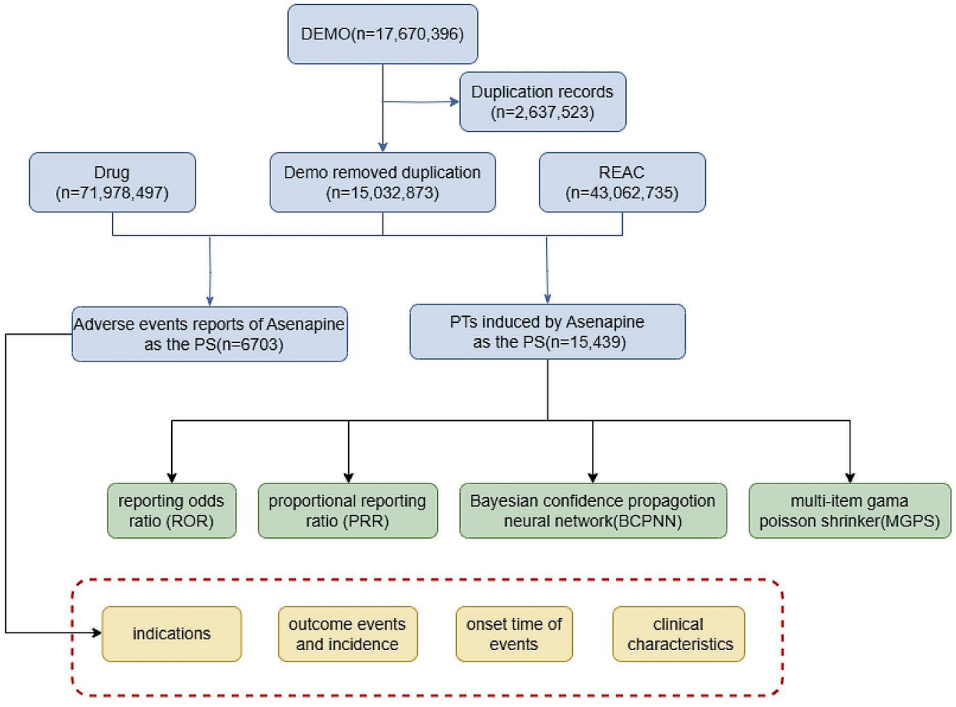

Fig. 1 The flow diagram of selecting Asenapine-related AEs from FAES database

in 2010 (25.65%), followed by 2013 (22.48%). The lowest number was in 2009 (0.33%), followed by 2015 and 2023, both at (1.24%), as detailed in Fig. 2. In terms of gender, the number of reports involving females was significantly higher than that of males (51.98% vs. 27.79%). Regarding age, more than half of the data (55.56%) did not provide age information, limiting the potential for our study on the relationship between age and adverse reactions. Nevertheless, among the reports with specific age data, the age group of 18 to 45 years was the most common (23.48%), followed by the age group of 45 to 65 years (15.69%). The majority of Asenapine adverse reaction reports were from physician (43.47%), followed by consumers (34.27%). Excluding the "other" category (54.15%), the primary reporting country was the United States (37.27%). In terms of the route of administration, more than half were sublingual (54.57%). Regarding clinical outcomes, apart from other serious, the most common outcome was hospitalization (29.48%), followed by death (7.97%). Concerning the time from drug administration to the appearance of adverse reactions, about half of the reports did not specify this duration (51.23%). Approximately one-third of the adverse reactions were reported to occur within less than 7 days of drug administration (31.51%), with the remainder occurring between 7 and 27 days and ≥60 days (6.67%). For indications, the drug was primarily used for the treatment of bipolar disorder (30.55%). Detailed information is provided in Table 1.

Asenapine signal mining

In this study, the analysis of adverse event reports related to Asenapine revealed associations with 24 System Organ Classes (SOCs). The research indicates that the three most common systems affected are various nervous system disorders (n=3305, ROR 2.94, PRR 2.51, IC 2.33, EBGM 2.51), mental disorders (n=2641, ROR 3.42, PRR 2.99, IC 1.58, EBGM 2.99), and gastrointestinal system disorders (n=2049, ROR 1.63, PRR 1.54, IC 0.62, EBGM 1.54), consistent with Asenapine's characteristics as a psychiatric drug. Details are outlined in Table 2.

At the Preferred Term (PT) level, four algorithms were employed to analyze drug adverse reactions and assess their compliance with various screening criteria, resulting in 204 PTs. According to the ROR algorithm ranking, the top 30 PTs are shown in Table 3. The results indicate high signal strength for PTs, such as in gastrointestinal system disorders, where the adverse reaction primarily manifested as reduced oral sensation (n=354, ROR 64.64, PRR 92.43, IC 6.4, EBGM 89.4). In the nervous

Fig. 2 Total number of Asenapine induced adverse event reports by season over the years

Table 3 The top 30 signal strength of adverse events of Asenapine ranked by ROR at the PTs level in FAERS database

SOC	PT	Case reports	ROR (95% CI)	PRR (95% CI)	chisq	IC (IC025)	EBGM (EBGM05)
Gastrointestinal disorders	Hypoaesthesia oral	354	94.64 (85.03, 105.35)	92.43 (83.8, 101.95)	30964.65	6.48 (6.33)	89.4 (81.74)
Gastrointestinal disorders	Glossoptosis	3	62.39 (19.86, 195.98)	62.37 (20.01, 194.39)	177.08	5.93 (4.5)	60.99 (23.4)
Gastrointestinal disorders	Tooth discolouration	41	61.7 (45.25, 84.12)	61.53 (44.97, 84.19)	2387.19	5.91 (5.47)	60.18 (46.43)
Gastrointestinal disorders	Oral dysaesthesia	3	58.35 (18.59, 183.14)	58.33 (18.71, 181.8)	165.48	5.84 (4.4)	57.12 (21.94)
Gastrointestinal disorders	Tongue blistering	34	55.58 (39.56, 78.09)	55.46 (39.74, 77.39)	1781.76	5.76 (5.28)	54.36 (40.91)
Gastrointestinal disorders	Tongue exfoliation	5	52.2 (21.54, 126.48)	52.18 (21.6, 126.05)	246.24	5.68 (4.51)	51.21 (24.42)
Gastrointestinal disorders	Tongue spasm	4	49.38 (18.37, 132.77)	49.37 (18.53, 131.54)	186.15	5.6 (4.32)	48.5 (21.2)
Gastrointestinal disorders	Tongue ulceration	30	35 (24.41, 50.2)	34.94 (24.55, 49.72)	976.36	5.11 (4.6)	34.5 (25.52)
Gastrointestinal disorders	Protrusion tongue	5	29.39 (12.17, 70.95)	29.38 (12.16, 70.97)	135.59	4.86 (3.7)	29.07 (13.91)
Nervous system disorders	Anosognosia	18	78.56 (49.16, 125.56)	78.47 (49.02, 125.6)	1337.86	6.25 (5.59)	76.28 (51.53)
Nervous system disorders	Akathisia	238	65.77 (57.77, 74.86)	64.74 (56.44, 74.26)	14589.06	5.98 (5.8)	63.24 (56.75)
Nervous system disorders	Oromandibular dystonia	8	39.48 (19.64, 79.36)	39.46 (19.49, 79.91)	295.55	5.28 (4.33)	38.9 (21.69)
Nervous system disorders	Spasmodic dysphonia	3	38.62 (12.35, 120.73)	38.61 (12.39, 120.34)	108.37	5.25 (3.82)	38.08 (14.67)
Nervous system disorders	Sedation	217	35.78 (31.27, 40.95)	35.28 (30.76, 40.47)	7137.58	5.12 (4.93)	34.84 (31.12)
Nervous system disorders	Cogwheel rigidity	7	28.04 (13.32, 59.06)	28.03 (13.31, 59.03)	180.59	4.79 (3.79)	27.75 (14.88)
Nervous system disorders	Drooling	44	26.61 (19.76, 35.82)	26.53 (19.77, 35.6)	1070.76	4.72 (4.29)	26.29 (20.5)
Psychiatric disorders	Self esteem inflated	3	83.61 (26.5, 263.81)	83.59 (26.3, 265.69)	237.47	6.34 (4.9)	81.12 (31.01)
Psychiatric disorders	Thought blocking	7	49.81 (23.58, 105.22)	49.79 (23.64, 104.86)	328.61	5.61 (4.6)	48.91 (26.16)
Psychiatric disorders	Activation syndrome	4	41.59 (15.49, 111.67)	41.58 (15.61, 110.79)	156.03	5.36 (4.08)	40.97 (17.93)
Psychiatric disorders	Flight of ideas	3	32.06 (10.27, 100.07)	32.05 (10.28, 99.89)	89.19	4.99 (3.56)	31.69 (12.22)
Psychiatric disorders	Distractibility	9	30.35 (15.73, 58.55)	30.33 (15.58, 59.06)	252.45	4.91 (4.01)	30.01 (17.31)
Respiratory, thoracic and mediastinal disorders	Pharyngeal hypoaesthesia	21	90.36 (58.48, 139.62)	90.24 (58.63, 138.89)	1793.38	6.45 (5.84)	87.35 (60.7)
Respiratory, thoracic and mediastinal disorders	Larynx irritation	3	54.43 (17.35, 170.71)	54.42 (17.46, 169.62)	154.21	5.74 (4.31)	53.37 (20.51)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal blistering	21	47.25 (30.68, 72.76)	47.18 (30.65, 72.61)	933	5.54 (4.93)	46.39 (32.32)
Investigations	Acid base balance abnormal	4	72.58 (26.88, 195.95)	72.56 (26.7, 197.16)	274.91	6.14 (4.86)	70.69 (30.79)
Investigations	Blood prolactin abnormal	17	62.58 (38.68, 101.25)	62.51 (38.3, 102.04)	1005.78	5.93 (5.26)	61.12 (40.87)
Investigations	Antipsychotic drug level below therapeutic	5	30.24 (12.52, 73.03)	30.23 (12.51, 73.03)	139.77	4.9 (3.74)	29.91 (14.3)
Vascular disorders	Orthostatic hypertension	6	40.26 (17.98, 90.16)	40.24 (18.02, 89.88)	226.23	5.31 (4.23)	39.67 (20.2)
Metabolism and nutrition disorders	Water intoxication	9	75.59 (38.97, 146.63)	75.55 (38.8, 147.11)	644.03	6.2 (5.29)	73.52 (42.23)
Injury, poisoning and procedural complications	Mucosal excoriation	4	327.7 (116.08, 925.13)	327.62 (115.94, 925.8)	1161.67	8.19 (6.85)	292.31 (122.66)

system, the predominant adverse reactions were akathisia (n=238, ROR 65.77, PRR 64.74, IC 5.98, EBGM 63.24), followed by sedation (n=217, ROR 35.78, PRR 35.28, IC 5.12, EBGM 34.84). Adverse reactions in mental disorders were mainly characterized by distractibility (n=9, ROR 30.35, PRR 30.33, IC 4.91, EBGM 30.01). Details are provided in Table 3.

As Asenapine is a psychiatric drug, we explored its effects on the neuro-psychiatric system. In mental disorders, we identified 30 PTs meeting the criteria, and in nervous system disorders, we obtained 20 PTs meeting the criteria. Adverse reaction reports in mental disorders included mania (n=106, ROR 9.92, PRR 9.77, IC 3.28, EBGM 9.68) and agitation (n=100, ROR 4, PRR 3.95, IC 1.98, EBGM 3.94). In nervous system disorders, the main adverse reaction reported was taste perversion (n=345, ROR 6.77, PRR 6.43, IC 2.68, EBGM 6.4) in Table 4.

Discussion

Asenapine, introduced to the market in 2009, is an atypical antipsychotic that is unique in being available solely as a sublingual, rapidly dissolving formulation. It primarily

Table 4 The signal strength of adverse events related to the neuro-psychiatric system associated with Asenapine, ranked by ROR at the PTs level in the FAERS database

SOC	PT	Case reports	ROR (95% CI)	PRR (95% CI)	chisq	IC (IC025)	EBGM (EBGM05)
Psychiatric disorders	Self esteem inflated	3	30.95 (9.81, 97.68)	30.94 (9.73, 98.34)	84.3	4.91 (3.47)	30.04 (11.48)
Psychiatric disorders	Thought blocking	7	18.45 (8.73, 38.98)	18.43 (8.75, 38.81)	113.28	4.18 (3.17)	18.11 (9.69)
Psychiatric disorders	Activation syndrome	4	15.4 (5.73, 41.35)	15.39 (5.78, 41.01)	53	3.92 (2.65)	15.17 (6.64)
Psychiatric disorders	Flight of ideas	3	11.87 (3.8, 37.05)	11.86 (3.81, 36.96)	29.49	3.55 (2.13)	11.73 (4.53)
Psychiatric disorders	Distractibility	9	11.24 (5.82, 21.69)	11.23 (5.88, 21.44)	82.91	3.47 (2.57)	11.11 (6.41)
Psychiatric disorders	Mania	106	9.92 (8.18, 12.04)	9.77 (8.03, 11.89)	827.42	3.28 (3)	9.68 (8.24)
Psychiatric disorders	Binge eating	6	9.4 (4.21, 21.01)	9.39 (4.2, 20.97)	44.58	3.22 (2.14)	9.31 (4.75)
Psychiatric disorders	Abulia	6	9.21 (4.12, 20.59)	9.21 (4.12, 20.57)	43.49	3.19 (2.12)	9.13 (4.66)
Psychiatric disorders	Hypomania	22	9.21 (6.05, 14.03)	9.18 (6.08, 13.85)	158.98	3.19 (2.59)	9.11 (6.4)
Psychiatric disorders	Schizophrenia	71	8.56 (6.77, 10.83)	8.47 (6.69, 10.72)	464.62	3.07 (2.74)	8.41 (6.91)
Psychiatric disorders	Enuresis	22	8.4 (5.52, 12.79)	8.37 (5.55, 12.63)	141.66	3.05 (2.46)	8.31 (5.85)
Psychiatric disorders	Bipolar I disorder	12	8.3 (4.7, 14.66)	8.28 (4.69, 14.62)	76.24	3.04 (2.25)	8.22 (5.11)
Psychiatric disorders	Disturbance in social behaviour	14	7.24 (4.28, 12.26)	7.23 (4.26, 12.27)	74.59	2.84 (2.11)	7.18 (4.62)
Psychiatric disorders	Feelings of worthlessness	7	7.19 (3.42, 15.13)	7.18 (3.41, 15.12)	36.99	2.84 (1.83)	7.14 (3.83)
Psychiatric disorders	Soliloquy	4	6.93 (2.59, 18.52)	6.92 (2.6, 18.44)	20.13	2.78 (1.51)	6.88 (3.02)
Psychiatric disorders	Psychiatric decompensation	9	6.44 (3.34, 12.42)	6.43 (3.37, 12.28)	41.06	2.68 (1.78)	6.4 (3.7)
Psychiatric disorders	Feeling guilty	6	5.83 (2.61, 13)	5.82 (2.61, 13)	23.82	2.53 (1.46)	5.79 (2.96)
Psychiatric disorders	Disinhibition	6	5.22 (2.34, 11.65)	5.21 (2.33, 11.64)	20.33	2.38 (1.3)	5.19 (2.65)
Psychiatric disorders	Hallucination, auditory	53	5.05 (3.85, 6.62)	5.01 (3.81, 6.59)	169.77	2.32 (1.93)	4.99 (3.98)
Psychiatric disorders	Tachyphrenia	13	4.92 (2.85, 8.49)	4.91 (2.84, 8.5)	40.31	2.29 (1.53)	4.89 (3.1)
Psychiatric disorders	Logorrhoea	12	4.9 (2.78, 8.64)	4.89 (2.77, 8.63)	36.96	2.28 (1.5)	4.87 (3.03)
Psychiatric disorders	Emotional poverty	6	4.68 (2.1, 10.44)	4.68 (2.1, 10.45)	17.27	2.22 (1.15)	4.66 (2.38)
Psychiatric disorders	Somnambulism	22	4.64 (3.05, 7.06)	4.63 (3.07, 6.99)	62.35	2.21 (1.61)	4.61 (3.25)
Psychiatric disorders	Dysphemia	13	4.26 (2.47, 7.36)	4.26 (2.46, 7.37)	32.27	2.08 (1.33)	4.24 (2.69)
Psychiatric disorders	Restlessness	100	4 (3.28, 4.87)	3.95 (3.25, 4.81)	220.25	1.98 (1.69)	3.94 (3.34)
Psychiatric disorders	Delusion	33	3.37 (2.39, 4.75)	3.36 (2.41, 4.69)	54.51	1.74 (1.26)	3.35 (2.51)
Psychiatric disorders	Euphoric mood	24	3.2 (2.14, 4.78)	3.19 (2.16, 4.72)	35.98	1.67 (1.1)	3.18 (2.27)
Psychiatric disorders	Psychotic disorder	60	3.09 (2.39, 3.98)	3.06 (2.37, 3.95)	83.47	1.61 (1.25)	3.06 (2.47)
Psychiatric disorders	Personality change	20	3.09 (1.99, 4.79)	3.08 (2, 4.74)	28.01	1.62 (1)	3.07 (2.13)
Psychiatric disorders	Agitation	145	2.96 (2.51, 3.49)	2.91 (2.49, 3.4)	183.14	1.54 (1.3)	2.91 (2.53)
Nervous system disorders	Anosognosia	18	29.13 (18.22, 46.57)	29.04 (18.14, 46.48)	473.65	4.82 (4.16)	28.25 (19.07)
Nervous system disorders	Akathisia	238	24.91 (21.85, 28.41)	23.96 (21.3, 26.95)	5122.13	4.55 (4.36)	23.42 (20.99)
Nervous system disorders	Oromandibular dystonia	8	14.62 (7.27, 29.4)	14.6 (7.21, 29.57)	99.92	3.85 (2.9)	14.41 (8.03)
Nervous system disorders	Spasmodic dysphonia	3	14.3 (4.57, 44.7)	14.29 (4.58, 44.54)	36.56	3.82 (2.39)	14.1 (5.43)
Nervous system disorders	Sedation	217	13.51 (11.79, 15.49)	13.06 (11.39, 14.98)	2391.47	3.69 (3.49)	12.9 (11.51)
Nervous system disorders	Cogwheel rigidity	7	10.38 (4.93, 21.88)	10.37 (4.92, 21.84)	58.69	3.36 (2.36)	10.28 (5.51)
Nervous system disorders	Drooling	44	9.89 (7.34, 13.32)	9.82 (7.32, 13.18)	345.43	3.28 (2.86)	9.73 (7.59)
Nervous system disorders	Dystonia	114	7.65 (6.36, 9.22)	7.53 (6.31, 8.98)	642.03	2.9 (2.64)	7.48 (6.4)
Nervous system disorders	Facial spasm	6	7.57 (3.39, 16.92)	7.57 (3.39, 16.91)	33.95	2.91 (1.84)	7.52 (3.84)
Nervous system disorders	Grimacing	4	7.12 (2.66, 19.05)	7.12 (2.67, 18.97)	20.89	2.82 (1.55)	7.08 (3.11)
Nervous system disorders	Restless legs syndrome	90	7.06 (5.73, 8.7)	6.97 (5.73, 8.48)	458.08	2.79 (2.49)	6.93 (5.82)
Nervous system disorders	Dysgeusia	345	6.77 (6.07, 7.55)	6.43 (5.83, 7.09)	1586.92	2.68 (2.52)	6.4 (5.84)
Nervous system disorders	Sudden onset of sleep	6	6.27 (2.81, 14)	6.26 (2.8, 13.98)	26.39	2.64 (1.57)	6.23 (3.18)
Nervous system disorders	Extrapyramidal disorder	109	5.52 (4.56, 6.67)	5.43 (4.46, 6.61)	393.5	2.44 (2.16)	5.41 (4.61)
Nervous system disorders	Head titubation	5	5.25 (2.18, 12.65)	5.25 (2.17, 12.68)	17.11	2.39 (1.23)	5.23 (2.5)
Nervous system disorders	Parkinsonism	31	4.76 (3.34, 6.78)	4.74 (3.33, 6.75)	91.19	2.24 (1.74)	4.72 (3.51)

Table 4 (continued)

SOC	PT	Case reports	ROR (95% CI)	PRR (95% CI)	chisq	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	Neuroleptic malignant syndrome	36	4.6 (3.31, 6.38)	4.57 (3.27, 6.38)	100.19	2.19 (1.72)	4.56 (3.46)
Nervous system disorders	Dyskinesia	107	3.8 (3.14, 4.6)	3.75 (3.08, 4.56)	216.06	1.9 (1.63)	3.74 (3.19)
Nervous system disorders	Tardive dyskinesia	75	3.1 (2.47, 3.9)	3.08 (2.48, 3.82)	105.34	1.62 (1.29)	3.07 (2.54)
Nervous system disorders	Dysarthria	73	2.91 (2.31, 3.67)	2.89 (2.28, 3.66)	90.17	1.53 (1.2)	2.88 (2.37)

exerts its therapeutic effects by modulating dopamine and serotonin levels [20, 21], and it has no significant affinity for muscarinic receptors [22]. Currently, asenapine is mainly used in the treatment of schizophrenia and bipolar disorder [23, 24]. As a novel multi-target antipsychotic, asenapine demonstrates efficacy comparable to other atypical antipsychotics, and is associated with favorable metabolic characteristics and minimal weight gain [25]. Studies have shown no significant difference between asenapine and placebo regarding adverse reactions such as insomnia, extrapyramidal symptoms, akathisia, dizziness, or somnolence/sedation. Moreover, research indicates that asenapine offers more significant long-term benefits compared to drugs like risperidone [8, 26]. As a new multi-target antipsychotic drug, Asenapine has potential therapeutic and safety advantages. However, as new drugs enter the market, it is necessary to monitor their actual usage and adverse events to ensure their safety and efficacy. This study, by comprehensive statistical analysis of the FAERS database from the first quarter of 2009 to the third quarter of 2023, systematically evaluated Asenapine-related adverse reactions. Through this process, the study confirmed some existing safety information, providing more comprehensive and accurate data support for medical practice and public health decision-making. The following is an comprehensive statistical discussion of the research results.

This study observed that adverse event reports related to Asenapine were more common in female patients than in male patients. This may be related to the tendency of females to report adverse events more frequently [19]. Regarding age, due to a substantial amount of missing age data, our understanding of adverse event occurrences in different age groups was limited. Further research requires accurate age data and exploration of differences in drug reactions among different age groups. In contrast to other studies [27, 28], our study found that the reporters of Asenapineadverse reactions were mainly doctors rather than consumers. This may be related to Asenapine's target population, which includes schizophrenia and bipolar I disorder, emphasizing the need for doctors to pay more attention to adverse reactions in medication recipients [29]. Therefore, doctors should be more attentive to adverse reactions in patients taking medications. Among drug-induced outcomes, the proportion of deaths is 7.97%, which may be related to allergic reactions and sudden death caused by asenapine [30, 31]. Both clinical studies and post-marketing reports of asenapine have documented allergic reactions, angioedema, tongue swelling, wheezing, and rashes. Additionally, an increase in the QTc interval has been reported during asenapine use [32]. This may lead to arrhythmia and sudden cardiac death [33]. In elderly patients with dementia, Asenapine may increase the risk of mortality, resulting in a black box warning for Asenapine [34, 35].

As a psychiatric drug, adverse events related to Asenapine primarily involved various nervous system disorders, mental disorders, and digestive system issues, consistent with its pharmacological action and indications [36]. At the PT level, in addition to a high incidence of abnormal oral sensation and akathisia, this study identified adverse events not mentioned in the drug label, such as anosognosia, distractibility, psychogenic compensation disorder, emotional poverty, somnambulism, restless legs syndrome, and sudden sleep onset. This indicates the value of quantitative signal detection technology in monitoring drug adverse events, providing potential risk information. Studies suggest that oral paresthesia is associated with the sublingual administration of Asenapine. Therefore, researchers found that administering a single dose of d-sorbitol before Asenapine can significantly improve its bitter taste, and a black cherry-flavored version of asenapine has been introduced. Akathisia and sedation are common adverse effects of antipsychotics. A meta-analysis by Stefan Leucht and colleagues showed that asenapine has a higher association with the occurrence of akathisia (RR = 2.57, 95% CI: 1.54–4.12). In contrast, asenapine exhibits a significant difference in the incidence of sedation compared to other antipsychotics [37, 38]. Restless legs syndrome had a relatively high frequency among these adverse reaction reports, with 90 occurrences. Although anosognosia and distractibility were rare, they exhibited strong signal intensity, requiring special attention. The occurrences of akathisia and restless legs syndrome with the use of Asenapine are related to common dopamine dysfunction and require clinical differentiation [37].

This study explores the adverse reactions to asenapine reported in current clinical settings, but it has certain limitations. It primarily relies on spontaneous reports,

which may lead to reporting bias and incomplete information. Due to database limitations, we cannot determine whether patients were taking other medications concurrently with asenapine. Furthermore, while the results show that deaths account for 7.97% of the reported adverse reactions, it is unclear whether these events occurred at normal doses or due to overdoses. Given the uncertain efficacy of asenapine in improving depressive symptoms, it is difficult to ascertain whether these severe outcomes were caused by the disease itself or by the use of asenapine [36]. Consumer reports may be less reliable and comprehensive compared to reports from healthcare professionals, and higher reporting rates in certain countries and regions may introduce sampling bias. Additionally, asenapine has been on the market for a relatively short time, resulting in a relatively low number of adverse event reports. Therefore, it is crucial to invest more time in exploring the adverse reactions associated with asenapine in future clinical use. Further investigation into the causes of death is also necessary. Future studies should compare the adverse reactions of asenapine with those caused by other antipsychotic drugs to obtain more comprehensive and accurate clinical information on asenapine. Additionally, future research could use more rigorous prospective study designs, combining clinical trials and epidemiological studies, to more accurately assess the safety risks of asenapine.

Conclusion

Based on the analysis of adverse event reports and adverse reactions related to Asenapine in the FAERS system, the following conclusions were drawn. The number of reports peaked in 2010. Most reporters were female, and the majority of reports came from individuals aged 18 to 45 years old. Reports were predominantly from healthcare providers in the United States, and sublingual administration was the main route of administration. Hospitalization was the most common clinical outcome. Furthermore, we identified several adverse reactions associated with Asenapine, with neurological disorders, psychiatric disorders, and gastrointestinal disorders being the most common. Neurological disorders manifested as akathisia and sedation, psychiatric disorders included attention disturbance, mania, and agitation, and gastrointestinal adverse reactions mainly presented as decreased oral sensation. Future research could compare Asenapine with adverse reactions caused by other antipsychotic drugs to obtain more clinical medication information.

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

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Supplementary Material 1

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Author contributions

Conceptualization, LJ and JG. Methodology, LJ Validation, LJ and JG Formal analysis, LJ and Y. Writing— original draft preparation, LJ and JG. Writing—review and editing, HX. Visualization, GZ Supervision, GZ and GX. Project administration, GZ and GX. Funding acquisition, GZ and GX. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. 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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