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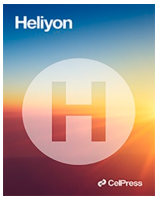

Research article

Post-marketing safety profile of solriamfetol: A real-world disproportionality analysis using FDA adverse event reporting system (FAERS) database

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ABSTRACT

Solriamfetol is a selective dopamine and noradrenalin reuptake inhibitor applied in adult patients with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA). However, the post-marketing safety profile of solriamfetol in large number of people was unrevealed. The purpose of our study is to unravel solriamfetol's adverse events (AEs) in real-world to refine medication safety using Food and Drug Administration Adverse Event Reporting System (FAERS) database. We derived the data associated with solriamfetol from FAERS between 2019 and 2023, and removed the duplicated entries. We evaluated the disproportionality of solriamfetol's AEs by reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN) and the multi-item gamma Poisson shrinker (MGPS). Among 8,846,085 AE reports, 1659 recorded solriamfetol as the 'primary suspected (PS)'. 74 significant disproportionality preferred terms (PTs) were retained across 27 organ systems. Moreover, 16 unexpected AEs not mentioned in the FDA label of solriamfetol were identified. Our findings provided the post-marketing safety profile of solriamfetol, highlighting potential solriamfetol's AEs. Further researches are significant to define the causality between solriamfetol and newly identified AEs.

1. Introduction

Solriamfetol, as a selective dopamine and noradrenalin reuptake inhibitor, inhibited reuptake without release of mono-amine [1]. In 2019, Solriamfetol was approved by the US Food and Drug Administration (FDA) to relief wakefulness in adult patients with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA) or narcolepsy [2]. The Committee for Medicinal Products for Human Use recommended European Medicines Agency approval for the same indications [3]. Several clinical trials have confirmed solriamfetol's safety and effectiveness, collectively highlight its good therapeutic effect in patients with OSA or narcolepsy [2,4,5].

With the FDA approval of solriamfetol, attention to real-world adverse events (AEs) is important because of its widespread use. A number of common AEs mentioned in FDA's prescribing information include headache, nausea, decreased appetite, insomnia, and anxiety. Subsequent safety trials have underscored these AEs, suggesting a correlation with dose [6,7]. Though insights provided by

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Abbreviations

FDA	Food and Drug Administration
EDS	excessive daytime sleepiness
OSA	obstructive sleep apnea
AE	Adverse event
FAERS	FDA Adverse Event Reporting System database
SOC	system organ class
HLGT	high-level group term
HLT	high-level term
PT	preferred term
LLT	lowest-level term
PS	primary suspected
PRR	Proportional reporting ratio
ROR	Reporting odds ratio
BCPNN	Bayesian confidence propagation neural Network
MGPS	multi-item gamma Poisson shrinker
SOC	System Organ Class
IC	Information Component
EBGM	Empirical Bayes Geometric Mean
RCT	Randomized clinical trial

clinical trials are valuable, they only offer a partial picture. Patient responses in real-world are variable due to individualized health conditions and other factors [8]. Therefore, comprehensive studies are crucial for understanding of solriamfetol's AEs across diverse patient populations in real-world. Nonetheless, there is no safety profile analysis with large sample size focusing on the post-marketing AE signals associated with solriamfetol.

The FDA Adverse Event Reporting System database (FAERS) is a large databases designed to support the FDA-approved drug safety surveillance program in real-world [9]. In recent years, more and more post-marketing pharmacovigilance analyses using FAERS database have been published, underscoring the recognized validity of this study protocol for drug safety profiles [10,11]. Although the FAERS database has some limitations, it remains an effective way to unearth adverse drug reactions by leveraging a large sample size.

The purpose of our study is to obtain the comprehensive post-marketing safety profile of solriamfetol. The exploration of unexpected AEs will help medical workers to understand the comprehensive safety profile of solriamfetol. Our study is the first to unravel the post-marketing safety profile of AEs associated with solriamfetol in large-scale population through the utilization of the FAERS database. This significant achievement lays the groundwork for future research endeavors, and the emergence of unexpected AEs are instrumental in refining therapeutic strategies.

2. Methods

Data in this study was harnessed from FAERS (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), a publicly accessible database encompassing an extensive spectrum of AE reports, medication error reports, and drug quality reports [12]. Due to the observational nature of our study and reliance on public anonymized data, no direct intervention or human sample collection was required, thus obviating the need for specific ethical approval and informed consent.

2.1. Data sources and procedures

We obtained FAERS data in the form of zipped package from the network. These datas contained seven sections, which are demographic and management information, drug information, AE information, patient outcomes information, reporting sources, starting and end dates of medications and indications of drugs. Base on the date of solriamfetol's FDA approval, We selectively derived the data from 2019 to 2023 from FAERS. Due to the existence of duplicate entries in the FAERS, a deduplication process based on FDA recommendations [13] was conducted. Specifically, we manually reviewed reports to remove entries with lower PRIMARYIDs when the CASEIDs are the same. Moreover, we further removed entries with CASEID listed in the deleted cases file. Finally, We identified solriamfetol-associated reports in both the "drugname" and "prod_ai" columns using "solriamfetol" and "SUNOSI" in the "DRUG" files.

The AE date labeled as (EVENT_DT) was in the "DEMO" file, and the therapy start date labeled as (START_DT) was in the "THER" file. The time-to-onset (TTO) was calculated by subtracting therapy start date from AE date. The correct date format (YYYYMMDD) was included and cases with incomplete date or incorrect input (EVENT_DT earlier than START_DT) was excluded. Furthermore, TTO analysis was proceeded based on medians, quartiles and the Weibull shape parameter (WSP) test. We used Minitab statistical software (v20.0; Minitab LLC, State College, PA, United States) for WSP analysis [14].

2.2. AE identification

AEs recorded in the FAERS were systematically coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0, which classifies medical terms into five levels, including system organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT). Our analysis concentrated on AEs linked to solriamfetol, identified through these classifications, as outlined in the carefully curated "REAC" file in the FAERS database.

The relationship between drugs and AEs was categorized using specific codes: 1 = suspect, 2 = concomitant, and 3 = interacting, and the individuals reporting the AEs assigned these codes. In order to increase the credibility of results, our study only labeled suspect drugs as "primary suspected (PS)" in the DRUG files.

2.3. Disproportionality analysis

We adopted disproportionality analysis, which is the most commonly used quantitative methods in pharmacovigilance analysis [15],to detect safety signals. The essence of this methodology is the comparison of the frequency of AEs related to a particular drug and the frequency of AEs related to all other drugs. It relies on a basic conception that a signal emerges when the frequency of a specific AE for a given drug significantly exceed the background frequency of all drugs in the entire database.

In our study, four methods were applied to determine the significance of these signals, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) [16]. The identification of AE signals required complying with criteria of all four algorithms simultaneously. The equations and criteria for all methods are presented in Supplementary Table S1 for a detailed understanding. The principles of calculation for disproportionality analysis are presented as the 2 × 2 table in Supplementary Table S2.

3. Results

3.1. General characteristics

In our study, we initially scrutinized 8,846,085 reports of AEs. Following a meticulous deduplication process, we isolated 1659 cases of solriamfetol as the PS and 3603 solriamfetol-induced AEs, as shown in Fig. 1.

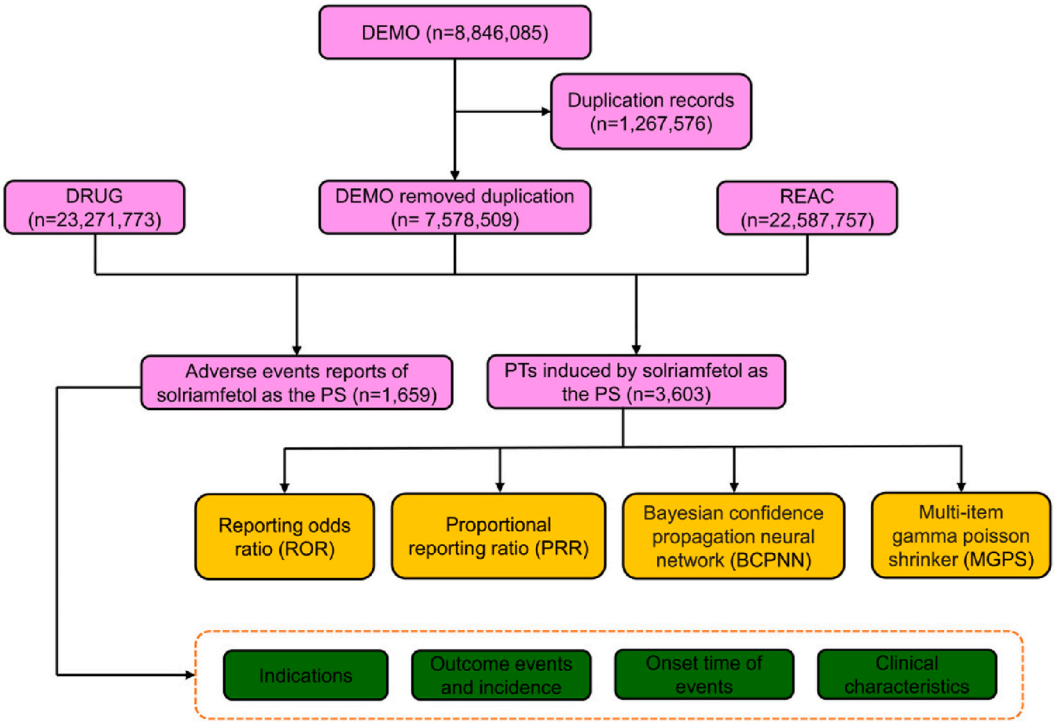

Fig. 1. The flow diagram of selecting solriamfetol-related AEs from FAERS database.
DEMO: demographic file.
DRUG: drug file.
REAC: reaction file.
PS: primary suspect.

To illuminate the demographics and baseline characteristics of patients with solriamfetol-induced AEs, a concise summary was meticulously presented in Table 1. Gender analysis reveals a higher frequency of AEs in females (1,076, 71.21 %) compared to males (435, 28.79 %). Regarding age distribution, individuals aged between 18 and 65 years comprise the majority (n = 361, 92.09 %). Among patients with solriamfetol-induced AEs, those weighing less than 80 kg constitute the majority (n = 85, 50.60 %). Geographically, most AEs are reported from the US (n = 1,497, 92.52 %). The most common indications in AE reports related to solriamfetol are narcolepsy and somnolence. The main concomitant medications reported with solriamfetol include Xyrem, Adderall, Xywav, Modafinil, and Wakix. Among the serious outcomes related to solriamfetol-induced AEs, hospitalization is the most frequent (n = 51, 15.18 %). The time-to-onset for solriamfetol's AEs is 2 days (range 0–11 days). The highest number of AE reports occurred in 2022 (589, 35.50 %), followed by 2021 (431, 25.98 %).

3.2. Disproportionality analysis

We identified AEs associated with solriamfetol affecting 27 different System Organ Classes (SOCs) and presented in Table 2. The top three categories are "General disorders and administration site conditions" (SOC: 10018065, n = 791), "Psychiatric disorders" (SOC: 10037175, n = 392), and "Nervous system disorders" (SOC: 10029205, n = 363). The first one exhibits a positive signal detection according to four indicators, which included ROR, PRR, information component (IC) and empirical bayes geometric mean (EBGM).

Table 1
Clinical characteristics of reports with solriamfetol from the FAERS database.

Characteristics	Solriamfetol-induced AE reports (n = 1659)		
Number of events	Available number, n	Case number, n	Case proportion, %
Gender, n (%)	1511	–	91.08 %
Female	–	1076	71.21 %
Male	–	435	28.79 %
Age (years), n (%)	392	–	23.63 %
<18	–	11	2.81 %
18 ≤ and ≤65	–	361	92.09 %
>65	–	20	5.10 %
Median (IQR)	–	40 (31–51)	–
Weight (Kg), n (%)	168	–	10.13 %
<80	–	85	50.60 %
80 ≤ and ≤100	–	45	26.79 %
>100	–	38	22.62 %
Median (IQR)	–	79.45 (63.08–100)	–
Reported countries, n (%)	1618	–	97.53 %
US		1497	92.52 %
FR		65	4.02 %
DE	–	28	1.73 %
Other country	–	28	1.73 %
Indications, n (%)	900	–	54.25 %
Narcolepsy	–	570	63.33 %
Somnolence		262	29.11 %
Others	–	68	7.56 %
Combination drugs, n (%)	667	–	40.20 %
Xyrem	–	192	28.79 %
Adderall	–	136	20.39 %
Xywav	–	121	18.14 %
Modafinil	–	66	9.90 %
Wakix	–	50	7.50 %
Outcomes, n (%)	1659	–	100.00 %
Non-serious Outcome	–	1323	79.75 %
Serious Outcomea	–	336	20.25 %
Death	–	8	2.38 %
Life-threatening	–	5	1.49 %
Hospitalization	–	51	15.18 %
Disability	–	4	1.19 %
Other serious outcomes	–	300	89.29 %
Time-to-onset (days)	25		1.51 %
Median (IQR)		2 (0–11)	
Reporters, n (%)	1602	–	96.56 %
Health professional	–	721	45.01 %
Consumer	–	881	54.99 %
Reporting year, n (%)	1659	–	100.00 %
2023	–	283	17.06 %
2022	–	589	35.50 %
2021	–	431	25.98 %
2020		306	18.44 %
2019	–	50	3.01 %

The other two categories have positive signals only in ROR and IC.

Some of the identified AEs are not related to solriamfetol intake, obviously. PTs related to solriamfetol were organized based on number of cases, arranged in a descending order in Table 3. Table 4 illustrated the AEs related to primary disease, medication misuse, poor drug efficacy, or secondary to other underlying causes, with each category having more than 10 cases. And the AEs with fewer than 10 cases were summarized in Supplementary Table S3. The largest number of PT species belong to the SOC labeled "Psychiatric disorders". PTs with more than 50 cases of reports include "Drug ineffective" (n = 374), "Off label use" (n = 158), "Headache" (n = 151), "Anxiety" (n = 129), "Blood pressure increased" (n = 62), and "Depression" (n = 57). Our study uncovered 16 unexpected AEs not mentioned in the FDA label of solriamfetol, including impaired gastric emptying, feeling of body temperature change, obesity, vitamin D deficiency, uterine leiomyoma, restless legs syndrome, carpal tunnel syndrome, spontaneous abortion, abnormal dreams, somnambulism, post-traumatic stress disorder, urinary tract hemorrhage, endometriosis, exercise-induced asthma, impaired driving ability, and Raynaud's phenomenon. An asterisk (*) is used to mark those unexpected AEs not previously identified or mentioned in the official drug instructions.

4. Discussion

Based on the FAERS database, our study provide a comprehensive safety profile of solriamfetol. Women accounted for the majority of the cases we obtained from FAERS. The incidence of EDS was not significantly sex-specific [17,18], and phase 3 clinical studies [2,5] of solriamfetol have not yet assessed the drug plasma concentration in people of different gender. Use of solriamfetol in population of specific gender needs further research to refine medication safety. Among the solriamfetol's AE cases in the FAERS database, 5 medications treating excessive sleepiness [19] were used in combination with solriamfetol commonly. The low number of deaths and disabilities indicated the good safety profile of solriamfetol. Previous clinical study and small sample size post-marketing study showed that serious AEs associated with solriamfetol was rare [5,20]. However, due to the absence of accurate numbers of patient treated by solriamfetol, further research is required to determine the true incidence of AEs.

In our data collected from FAERS, 29.11 % of the patients used solriamfetol to treat "somnolence", which is not mentioned in FDA prescribing information. Because the reporters who submitted AEs to FAERS include not only Health professional but also consumers, a part of reporters may have not use specialized medical terms normatively. In our study, 54.99 % of cases associated with solriamfetol's

Table 2
Signal strength of reports of solriamfetol at the System Organ Class (SOC) level in FAERS database.

System Organ Class(SOC)	Solriamfetol Cases Reporting SOC	ROR(95 % two-sided CI)	PRR (χ2)	IC(IC025)	EBGM (EBGM05)
Psychiatric disorders	392	3.03 (2.72–3.37)	2.76 (460.64)	1.46 (1.31)	2.75 (2.48)
Nervous system disorders	363	1.85 (1.65–2.06)	1.74 (123.23)	0.80 (0.72)	1.74 (1.56)
Endocrine disorders	17	1.77 (1.10–2.85)	1.77 (5.66)	0.82 (0.51)	1.77 (1.10)
General disorders and administration site conditions	761	1.66 (1.53–1.81)	1.49 (148.45)	0.58 (0.53)	1.49 (1.37)
Pregnancy, puerperium and perinatal conditions	18	1.53 (0.96–2.43)	1.53 (3.29)	0.61 (0.38)	1.53 (0.96)
Cardiac disorders	90	1.41 (1.14–1.74)	1.40 (10.46)	0.48 (0.39)	1.40 (1.13)
Investigations	180	1.14 (0.98–1.33)	1.14 (3.09)	0.18 (0.16)	1.14 (0.98)
Immune system disorders	51	1.09 (0.82–1.43)	1.09 (0.35)	0.12 (0.09)	1.09 (0.82)
Social circumstances	18	1.02 (0.64–1.63)	1.02 (0.01)	0.03 (0.02)	1.02 (0.64)
Congenital, familial and genetic disorders	8	0.99 (0.50–1.99)	0.99 (0.00)	−0.01 (−0.02)	0.99 (0.50)
Ear and labyrinth disorders	14	0.93 (0.55–1.57)	0.93 (0.08)	−0.11 (−0.18)	0.93 (0.55)
Gastrointestinal disorders	180	0.90 (0.77–1.04)	0.90 (1.94)	−0.14 (−0.17)	0.90 (0.78)
Surgical and medical procedures	45	0.85 (0.63–1.14)	0.85 (1.25)	−0.24 (−0.32)	0.85 (0.63)
Metabolism and nutrition disorders	56	0.84 (0.65–1.10)	0.84 (1.64)	−0.24 (−0.32)	0.84 (0.65)
Vascular disorders	57	0.82 (0.63–1.07)	0.82 (2.22)	−0.28 (−0.36)	0.82 (0.63)
Injury, poisoning and procedural complications	304	0.82 (0.73–0.92)	0.84 (10.88)	−0.26 (−0.29)	0.84 (0.74)
Respiratory, thoracic and mediastinal disorders	77	0.61 (0.49–0.77)	0.62 (18.11)	−0.68 (−0.85)	0.62 (0.50)
Reproductive system and breast disorders	13	0.61 (0.36–1.06)	0.61 (3.18)	−0.70 (−1.21)	0.61 (0.36)
Skin and subcutaneous tissue disorders	86	0.54 (0.44–0.67)	0.56 (32.13)	−0.85 (−1.05)	0.56 (0.45)
Renal and urinary disorders	30	0.49 (0.34–0.71)	0.50 (15.41)	−1.00 (−1.44)	0.50 (0.35)
Musculoskeletal and connective tissue disorders	63	0.49 (0.38–0.62)	0.50 (33.56)	−1.01 (−1.30)	0.50 (0.39)
Hepatobiliary disorders	13	0.46 (0.27–0.80)	0.46 (8.08)	−1.10 (−1.90)	0.47 (0.27)
Eye disorders	22	0.41 (0.27–0.62)	0.41 (18.60)	−1.27 (−1.94)	0.41 (0.27)
Infections and infestations	51	0.29 (0.22–0.39)	0.31 (84.63)	−1.70 (−2.25)	0.31 (0.23)
Product issues	8	0.12 (0.06–0.25)	0.13 (49.40)	−2.98 (−5.97)	0.13 (0.06)
Blood and lymphatic system disorders	3	0.05 (0.02–0.16)	0.05 (50.77)	−4.21 (−13.07)	0.05 (0.02)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	0.05 (0.02–0.11)	0.05 (122.78)	−4.22 (−8.87)	0.05 (0.03)

ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ^2, chi-information component; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

Table 3
Signal strength of AE reports related with solriamfetol at the Preferred Term (PT) level in FAERS database(*: The instruction does not mention).

SOC	Preferred Terms (PTs)	Solriamfetol Cases Reporting PT	ROR(95 % two-sided CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	Headache	151	4.66 (3.96–5.49)	4.51 (415.88)	2.17 (1.85)	4.51 (3.83)
Psychiatric disorders	Anxiety	129	8.48 (7.11–10.11)	8.21 (819.45)	3.04 (2.55)	8.20 (6.88)
Investigations	Blood pressure increased	62	6.96 (5.41–8.95)	6.86 (310.67)	2.78 (2.16)	6.85 (5.33)
Psychiatric disorders	Depression	57	5.44 (4.19–7.07)	5.37 (203.32)	2.42 (1.87)	5.37 (4.13)
	Suicidal ideation	48	11.91 (8.96–15.84)	11.77 (472.54)	3.55 (2.67)	11.75 (8.83)
Cardiac disorders	Palpitations	40	6.96 (5.10–9.51)	6.90 (201.81)	2.78 (2.04)	6.89 (5.05)
General disorders and administration site conditions	Feeling abnormal	40	3.18 (2.33–4.35)	3.16 (59.22)	1.66 (1.21)	3.16 (2.31)
Psychiatric disorders	Insomnia	38	2.99 (2.17–4.11)	2.96 (49.62)	1.57 (1.14)	2.96 (2.15)
Nervous system disorders	Somnolence	35	3.34 (2.39–4.66)	3.32 (56.74)	1.73 (1.24)	3.31 (2.38)
Investigations	Heart rate increased	34	6.51 (4.64–9.13)	6.46 (156.89)	2.69 (1.92)	6.45 (4.60)
Nervous system disorders	Migraine	33	5.89 (4.18–8.30)	5.85 (132.69)	2.55 (1.81)	5.84 (4.15)
Skin and subcutaneous tissue disorders	Hyperhidrosis	31	5.03 (3.53–7.16)	5.00 (99.16)	2.32 (1.63)	4.99 (3.51)
General disorders and administration site conditions	Feeling jittery	28	37.24 (25.65–54.08)	36.96 (974.18)	5.20 (3.58)	36.75 (25.31)
Nervous system disorders	Tremor	27	3.42 (2.34–4.99)	3.40 (45.77)	1.76 (1.21)	3.40 (2.33)
Cardiac disorders	Tachycardia	25	5.32 (3.59–7.88)	5.29 (86.91)	2.40 (1.62)	5.28 (3.56)
Psychiatric disorders	Irritability	23	9.86 (6.54–14.87)	9.81 (181.75)	3.29 (2.18)	9.79 (6.50)
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	23	19.91 (13.20–30.01)	19.79 (409.08)	4.30 (2.85)	19.73 (13.08)
Gastrointestinal disorders	Dry mouth	19	4.91 (3.12–7.70)	4.88 (58.72)	2.29 (1.46)	4.88 (3.11)
Surgical and medical procedures	Surgery	18	5.50 (3.46–8.75)	5.48 (65.95)	2.45 (1.54)	5.48 (3.45)
Nervous system disorders	Disturbance in attention	17	6.41 (3.98–10.32)	6.38 (77.12)	2.67 (1.66)	6.38 (3.96)
Psychiatric disorders	Agitation	16	5.30 (3.24–8.66)	5.28 (55.47)	2.40 (1.47)	5.27 (3.23)
	Panic attack	10	5.87 (3.15–10.92)	5.85 (40.22)	2.55 (1.37)	5.85 (3.14)
Nervous system disorders	Hypersomnia	9	5.82 (3.02–11.20)	5.81 (35.79)	2.54 (1.32)	5.80 (3.02)
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous*	9	4.55 (2.36–8.75)	4.54 (24.81)	2.18 (1.13)	4.53 (2.36)
Psychiatric disorders	Anger	9	6.27 (3.26–12.06)	6.25 (39.69)	2.64 (1.37)	6.25 (3.25)
	Persecutory delusion	9	71.49 (37.03–138.02)	71.32 (616.97)	6.14 (3.18)	70.52 (36.53)
	Somnambulism*	8	31.80 (15.87–63.76)	31.74 (236.96)	4.98 (2.48)	31.58 (15.75)
Nervous system disorders	Restless legs syndrome*	7	7.42 (3.53–15.59)	7.41 (38.78)	2.89 (1.38)	7.40 (3.52)
Psychiatric disorders	Thinking abnormal	7	8.42 (4.01–17.68)	8.40 (45.60)	3.07 (1.46)	8.39 (4.00)
Hepatobiliary disorders	Hepatic cytolysis	6	6.68 (3.00–14.88)	6.67 (28.88)	2.74 (1.23)	6.66 (2.99)
Psychiatric disorders	Post-traumatic stress disorder*	6	12.34 (5.53–27.50)	12.32 (62.28)	3.62 (1.62)	12.30 (5.52)
Vascular disorders	Raynaud's phenomenon*	6	22.33 (10.01–49.80)	22.29 (121.60)	4.47 (2.01)	22.22 (9.96)
Metabolism and nutrition disorders	Obesity*	5	6.37 (2.65–15.32)	6.36 (22.58)	2.67 (1.11)	6.36 (2.64)

(*continued on next page*)

Table 3 (*continued*)

SOC	Preferred Terms (PTs)	Solriamfetol Cases Reporting PT	ROR(95 % two-sided CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	Carpal tunnel syndrome*	5	6.30 (2.62–15.15)	6.29 (22.23)	2.65 (1.10)	6.29 (2.61)
	Cataplexy	5	80.88 (33.46–195.54)	80.77 (388.91)	6.32 (2.61)	79.76 (32.99)
Psychiatric disorders	Abnormal dreams*	5	5.96 (2.48–14.33)	5.95 (20.59)	2.57 (1.07)	5.95 (2.47)
	Paranoia	5	7.01 (2.92–16.87)	7.01 (25.72)	2.81 (1.17)	7.00 (2.91)
Social circumstances	Impaired driving ability*	5	11.84 (4.92–28.48)	11.82 (49.44)	3.56 (1.48)	11.80 (4.90)
Metabolism and nutrition disorders	Vitamin D deficiency*	4	7.27 (2.72–19.39)	7.26 (21.57)	2.86 (1.07)	7.25 (2.72)
Nervous system disorders	Psychomotor hyperactivity	4	5.55 (2.08–14.81)	5.55 (14.90)	2.47 (0.93)	5.54 (2.08)
	Tardive dyskinesia	4	6.34 (2.38–16.91)	6.33 (17.95)	2.66 (1.00)	6.33 (2.37)
Psychiatric disorders	Libido decreased	4	8.13 (3.05–21.70)	8.13 (24.97)	3.02 (1.13)	8.12 (3.04)
	Bipolar disorder	4	8.32 (3.12–22.18)	8.31 (25.68)	3.05 (1.14)	8.30 (3.11)
	Mania	4	6.08 (2.28–16.21)	6.07 (16.94)	2.60 (0.98)	6.07 (2.28)
	Initial insomnia	4	8.71 (3.27–23.24)	8.70 (27.23)	3.12 (1.17)	8.69 (3.26)
	Sleep attacks	4	302.40 (110.82–825.19)	302.06 (1145.09)	8.17 (2.99)	288.22 (105.62)
	Major depression	4	10.24 (3.84–27.31)	10.22 (33.24)	3.35 (1.26)	10.21 (3.83)
Respiratory, thoracic and mediastinal disorders	Asthma exercise induced*	4	181.88 (67.27–491.75)	181.68 (698.49)	7.46 (2.76)	176.59 (65.31)
Gastrointestinal disorders	Impaired gastric emptying*	3	6.54 (2.11–20.29)	6.53 (14.05)	2.71 (0.87)	6.53 (2.10)
	Lip dry	3	7.94 (2.56–24.65)	7.93 (18.16)	2.99 (0.96)	7.93 (2.55)
General disorders and administration site conditions	Feeling of body temperature change*	3	10.39 (3.34–32.25)	10.38 (25.38)	3.37 (1.09)	10.36 (3.34)
	Tachyphylaxis	3	163.64 (51.99–515.14)	163.51 (472.23)	7.32 (2.32)	159.38 (50.63)
	Feeling drunk	3	10.13 (3.26–31.46)	10.13 (24.64)	3.34 (1.08)	10.11 (3.26)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma*	3	9.84 (3.17–30.56)	9.83 (23.77)	3.30 (1.06)	9.82 (3.16)
Psychiatric disorders	Parasomnia	3	94.10 (30.08–294.37)	94.02 (272.01)	6.53 (2.09)	92.64 (29.61)
Renal and urinary disorders	Hemorrhage urinary tract*	3	21.22 (6.83–65.94)	21.20 (57.55)	4.40 (1.42)	21.13 (6.80)
Reproductive system and breast disorders	Endometriosis*	3	11.82 (3.81–36.71)	11.81 (29.63)	3.56 (1.15)	11.79 (3.80)
Respiratory, thoracic and mediastinal disorders	Throat clearing	3	6.85 (2.21–21.25)	6.84 (14.94)	2.77 (0.89)	6.83 (2.20)
Surgical and medical procedures	Cholecystectomy	3	6.42 (2.07–19.93)	6.42 (13.71)	2.68 (0.86)	6.41 (2.07)

ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-information component; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

AEs were submitted by consumers. Therefore, some people may have used "somnolence" to describe their symptoms without using professional medical terms such as "narcolepsy" or "obstructive sleep apnea". Even so, there may still be off-label use of solriamfetol, and previous studies have shown the good therapeutic effect of solriamfetol in central sleepiness or excessive daytime sleepiness in Parkinson's Disease [21,22].

Our study underscored a clustering of SOCs and PTs. Among these PTs, occurrences such as drug ineffective, off label use, therapeutic response decreased, product administration interrupted, exposure during pregnancy, therapeutic response unexpected, drug ineffective for unapproved indication, therapeutic response shortened, pre-existing condition improved, drug effect less than expected, prescribed overdose, drug dose titration not performed, drug titration error, narcolepsy and obstructive sleep apnoea syndrome were not considered to be solriamfetol-induced AEs. These PTs are more likely to be related with primary disease, misuse of medication and poor drug efficacy, rather than being direct consequences of solriamfetol treatment. Correct identification of these PTs is of great

Table 4
Signal strength of AE reports not related with solriamfetol at the Preferred Term (PT) level in FAERS database(case number >10).

SOC	Preferred Terms (PTs)	Solriamfetol Cases Reporting PT	ROR(95 % two-sided CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	Drug ineffective	374	4.78 (4.29–5.32)	4.38 (999.80)	2.13 (1.91)	4.38 (3.94)
Injury, poisoning and procedural complications	Off label use	158	2.64 (2.25–3.10)	2.57 (153.95)	1.36 (1.16)	2.57 (2.19)
General disorders and administration site conditions	Therapeutic response decreased	35	11.51 (8.25–16.07)	11.41 (332.11)	3.51 (2.52)	11.39 (8.16)
Injury, poisoning and procedural complications	Product administration interrupted	28	36.39 (25.07–52.84)	36.12 (950.82)	5.17 (3.56)	35.92 (24.74)
	Exposure during pregnancy	26	6.57 (4.47–9.66)	6.53 (121.76)	2.71 (1.84)	6.52 (4.43)
General disorders and administration site conditions	Therapeutic response unexpected	23	9.92 (6.58–14.95)	9.86 (182.97)	3.30 (2.19)	9.85 (6.53)
	Drug ineffective for unapproved indication	23	6.11 (4.06–9.21)	6.08 (97.65)	2.60 (1.73)	6.08 (4.03)
	Therapeutic response shortened	20	7.77 (5.01–12.07)	7.74 (117.27)	2.95 (1.90)	7.73 (4.98)
	Pre-existing condition improved	18	53.28 (33.46–84.83)	53.02 (911.04)	5.72 (3.59)	52.58 (33.03)
Nervous system disorders	Narcolepsy	14	140.05 (82.38–238.08)	139.51 (1883.33)	7.09 (4.17)	136.49 (80.29)

ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-information component; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

importance for a accurate presentation of the drug safety profiles.

Most AEs detected by our study coincided with information provided in the FDA's drug label and pre-marketing clinical researches. For example, a randomized clinical trial (RCT) of solriamfetol for EDS in narcolepsy revealed that main AEs included headache, nausea, decreased appetite, nasopharyngitis, dry mouth and anxiety [5]. Another RCT of solriamfetol for treatment of EDS in OSA highlighted the most common AEs such as headache, nausea, decreased appetite, anxiety and nasopharyngitis [2]. This consistency of our founding with previous studies highlight the reliability of our study, confirming the established safety profile of solriamfetol.

In addition to known AEs, our research has revealed several potential AEs of solriamfetol that extend beyond those listed by the FDA. Solriamfetol's real world experience studies with small sample size (START and SURWEY) in the past two years did not displayed the same unexpected AEs with our study [20,23]. The previously unrecognized AEs may have been overshadowed by more frequent reactions in the smaller-scale studies. These unexpected AEs in our study are detected for the first time, which is significant for solriamfetol's pharmacovigilance activities. Clinicians should pay more attention to these AEs when solriamfetol was used in patients, and further prospective trials and mechanism studies associated with the phenomenon are urgently needed.

Abortion spontaneous is an meaningful unexpected AE we detected based on FAERS database, and caution about solriamfetol usage in pregnant population. Several previous studies revealed that drug exposure was a significant risk factor for spontaneous abortion. According to drug prescribing information, solriamfetol is not prohibited by the FDA for use in pregnant women. However, it is not clear if the abortion is an AE associated with solriamfetol or due to other underlying causes at present. It is critical to proceed further research to reevaluate the safety of solriamfetol in pregnant women. However, some of the newly found unexpected AEs do not really seem to be causally related to solriamfetol. Obesity is known to be a risk factors for OSA development [24], and weight decrease was recorded as AE in solriamfetol's FDA label. Therefore, Obesity should be associated with the primary disease. Posttraumatic stress disorder (PTSD) is secondary to trauma [25], and could not be the intake of solriamfetol. Similarly, restless legs syndrome may be primary or secondary to iron deficiency or chronic renal insufficiency [26], and carpal tunnel syndrome is induced by median nerve compression [27]. If AEs are not displayed in the drug describing information, it is difficult for clinicians or nurses to distinguish. Therefor, these confusions underscore the necessary of further prospective multi-center trials.

Though the advantage of conducting studies based on large-scale population are undeniable, the inherent limitations of this research cannot be avoided. Firstly, the voluntary nature of the FAERS database can lead to biases, randomness, and underreporting in the data, potentially affecting the accuracy of the findings. Secondly, because of the absence of comprehensive clinical information, especially treatment for patients after the occurrence of AEs, the combination drug of solriamfetol poses a challenge in addressing confounding factors, thereby impacting the determination of causality between AE and the drug of interest [28]. Furthermore, due to the absence of accurate number of patients treated by solriamfetol, we can not calculate the true incidence of each identified AE. Despite these limitations, employing the spontaneous reporting systems remain irreplaceable for efficient detection of rare and unpredictable drug AEs [28].

5. Conclusion

Our study assessed post-marketing safety profile of solriamfetol through a comprehensive and systematic analysis of the FAERS

database. The AE signals identified in our study are largely in line with those already documented in the FDA's official prescribing information. Our findings highlighted 16 unexpected AEs potentially associated with solriamfetol. This addition fills in the limitations of pre-marketing trials. However, these unexpected AEs are not all necessarily related to solriamfetol. It is crucial to carry out the further prospective clinical trials to establish causality between solriamfetol and these newly identified AEs.

Data availability statement

Data associated with our study has been deposited into a publicly available repository(https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html)

Ethics statement

Our study is a secondary analysis of publicly available summary statistics and requires no specific ethical approval.

CRediT authorship contribution statement

Beili He: Writing – review & editing, Writing – original draft, Conceptualization. **Wei Zheng:** Visualization, Validation, Supervision, Software, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38450.

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