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Post-marketing safety concerns with lecanemab: a pharmacovigilance study based on the FDA Adverse Event Reporting System database

Xiaoxuan Xing^{1†}, Xiaotong Zhang^{1†}, Ke Wang¹, Zhizhou Wang¹, Yingnan Feng¹, Xiaoxi Li¹, Yiming Hua¹, Lan Zhang^{1*} and Xianzhe Dong^{1*}

Abstract

Background The safety data of lecanemab in the post-marketing period has yet to be fully investigated in the current literature. We aimed to identify and characterise the safety profile of lecanemab in the post-marketing period.

Methods We searched and reviewed the reports submitted to the FDA's Adverse Event Reporting System (FAERS). We used a case/non-case approach to estimate the reporting odds ratio (ROR) and information component (IC) with 95% confidence intervals (CI) for lecanemab-related adverse events (AEs) reported at least four counts. We compared the difference between serious and non-serious reports using non-parametric tests.

Results The FAERS recorded 1,986 lecanemab-related AEs affecting 868 patients. Two hundred and three patients experienced serious AEs, including 22 deaths. The most frequently reported AEs were headache ($n = 193$), chills ($n = 100$), fatigue ($n = 93$), and amyloid-related imaging abnormality-oedema/effusion (ARIA-E) ($n = 91$). Safety signals were detected, such as headache (ROR: 10.4, 95%CI: 8.97, 12.07; IC: 3.25, 95%CI: 2.97, 3.40), ARIA-E (ROR: 18,299.69, 95%CI: 14,001.27, 23,917.73; IC: 13.37, 95%CI: 6.15, 6.87), and infusion-related reaction (ROR: 35.25, 95CI 27.58, 45.07; IC: 5.09, 95CI 4.15, 4.87). We also identified several new AEs, such as migraine and pancreatic carcinoma. Patients with serious AEs were more likely to be on polypharmacy for Alzheimer's disease and use aspirin, acid-suppressing medications, statins, antidepressants, or benzodiazepines compared to those with non-serious AEs.

Conclusions Lecanemab may have a significant potential for AEs. Our results provide evidence for healthcare professionals and patients to weigh the risks and benefits of lecanemab treatment. Further prospective studies are needed to explore rare and unexpected AEs.

Keywords Alzheimer's disease, Lecanemab, Drug safety, Adverse event, FAERS

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Background

Lecanemab, an amyloid-beta (A β) protofibril antibody, was the first medication for the target treatment of early Alzheimer's disease. It was fully approved by the US Food and Drug Administration (FDA) in July 2023 [1]. The drug previously received conditional approval by the FDA in January 2023 through its accelerated approval pathway [2]. The safety database leading to product approval included 1795 patients (898 patients received lecanemab; 897 controls) from a randomised, placebo-controlled Clarity clinical trial [3]. The most common adverse events (AEs) (affecting > 10% of the participants) during the treatment were infusion-related reactions (26.4%), Amyloid related imaging abnormalities (ARIA) with cerebral microhaemorrhage, cerebral macrohaemorrhages, or superficial siderosis (ARIA-H; 17.3% with lecanemab and 9.0% with placebo); ARIA-E (12.6%); headache (11.1%); and falls (10.4%). Serious AEs occurred in 24% of treated men and 25% of controls. The most commonly reported serious AEs were infusion-related reactions (1.2%), ARIA-E (0.8%), atrial fibrillation (0.7%), syncope (0.7%), and angina pectoris (0.7%). FDA issued a "black box" warning for lecanemab due to significant safety risks associated with ARIA [1]. Weighing the minor beneficial effects and potential harms, the European Medicines Agency rejected a marketing authorisation request for the lecanemab [4]. Lecanemab marketing authorisation triggered a vivid debate and significant concerns, mainly because of the lack of convincing evidence on its efficacy and safety [5–9]. Currently, the safety of lecanemab has not been thoroughly discussed in the literature except in the clinical trial submitted for drug application. Notably, safety data from the real world, such as long-term safety beyond 18 months, are unknown. In addition, the highly controlled environment of the clinical trial and strict inclusion/exclusion criteria for the trial population likely mitigated some of the complexities that are commonly noted in the clinical use of the medication, such as the Clarity trial excluded patients with a history of stroke in the year before enrolment.

Spontaneous reporting systems for post-marketing AEs provide an essential and accessible resource for identifying safety concerns in pharmacotherapy within real-world settings [10]. Spontaneous reporting should be cautiously approached due to inherent limitations such as reporting bias, data quality issues, and the inability to calculate incidence rates. Despite these challenges, post-marketing pharmacovigilance remains crucial for monitoring medication safety and new rare signals. We aimed to evaluate the safety of lecanemab in the post-marketing period by assessing the reports

submitted to the FDA's Adverse Event Reporting System (FAERS) [11].

Methods

Data source and data processing

The FAERS is a spontaneous database that contains AEs reports, medication error reports and product quality complaints resulting in AEs that were submitted to the FDA [12]. Healthcare professionals, consumers, and manufacturers submit reports to FAERS. The FAERS database supports post-marketing safety surveillance for drug and therapeutic biologic products, currently containing 21 million spontaneously reported AE cases. The AEs are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology [13, 14]. These coded terms are arranged in a hierarchy of 5 categories that include broad (system organ class [SOC]) and specific categories (e.g., preferred term [PT]).

In the FAERS database, the reported AEs and the indications of drugs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA 27.0). The reported medication exposure data will be standardised using the World Health Organization Drug Dictionary (March 2024). We extracted the data from FAERS on August 28, 2024. In addition, we excluded duplicate reports according to FDA guidelines to ensure accuracy. Our study was exempt from institutional review board approval or informed patient consent.

Eligibility criteria

We searched the reports submitted to FAERS between January 1, 2023, and June 31, 2024, with lecanemab designated as the "primary suspect drug". A suspect product is a drug or biologic considered by the reporter to be associated with the reported AE.

Study design

We employed a case/non-case approach akin to a case-control study design [15]. Cases were defined as reports involving lecanemab, while non-cases included AE reports for all other medications in FAERS [16, 17]. Within this cohort, we assessed disproportionality: if the proportion of AEs of interest is higher in patients exposed to lecanemab (cases) compared to those not exposed (non-cases), an association between the medication and the event can be hypothesised, indicating a disproportionality signal [18].

We categorised AEs into four groups based on their predictability: (a) Expected AEs with a detected signal: Predictable events linked to lecanemab's mechanism of action or those anticipated from pre-marketing pivotal trials, where a safety signal was observed in at least 5% of participants; (b) Expected AEs without a signal:

Predictable events based on the above criteria but without a signal; (c) Disease-related AEs: Events associated with the Alzheimer's disease being treated; (d) Unexpected AEs: Events that were unexpected or not previously reported [19].

Statistical analysis

There is currently no gold standard methodology for detecting safety signals [15]. We used two disproportionality approaches: the reporting odds ratio (ROR) [20], the Bayesian information component (IC) and ninety-five per cent confidence intervals (CIs) [21]. The ROR was considered statistically significant if the lower limit of the CI was greater than 1, while the IC was deemed significant if the lower limit of the CI was above 0. The ROR method is easier to understand and analyse than the Bayesian one and is the most widely used [22]. Bayesian approaches may be more effective with increased confounding or larger effect sizes [22]. A safety signal for an AE was identified when both disproportionality measures met the criteria.

Secondary analysis

We also observed disproportionate reporting for females and males separately. We compared age, sex, time to onset, types of AEs, and polypharmacy for Alzheimer's disease (defined as the use of two or more Alzheimer's disease medications), aspirin, antipsychotics, anticoagulants, acid-suppressing medications, statins and benzodiazepines between serious and non-serious reports. Proportions were analysed using chi-square (χ^2) tests, while the Mann–Whitney U test (M-W-U) was applied for age comparisons. Time-to-onset differences between serious and non-serious AEs were analysed using the Wilcoxon Test. A "volcano map" was created to visualise differences in AE severity and sex.

Sensitivity analysis

As some AEs are disease-related and the detection of these signals might confound the association between lecanemab and its AEs [23], we conducted a sensitivity analysis using a patient population indicated for medication treatment. Donepezil and aducanumab share similar indications with lecanemab. Therefore, we re-evaluated the RORs and IC values for donepezil and aducanumab as comparators for lecanemab.

Results

We identified 1,986 AEs related to lecanemab, affecting 868 patients, with an average of 2.3 AEs per patient. Of these patients, 203 experienced serious AEs, including 22 deaths. Patients were distributed from 2023 through the second quarter of 2024. Age information was available for

Table 1 Characteristics of the patients submitted to the US FDA Adverse Event Reporting System for lecanemab

Characteristics	No (%)
Gender	
Female	478 (55.07)
Male	325 (37.44)
Not Specified	65 (7.49)
Age, y	
18–44	3 (0.35)
45–64	90 (10.37)
65–74	260 (29.95)
≥75	344 (39.63)
Not Specified	171 (19.70)
Reporting year	
2023	243 (28.00)
2024	625 (72.00)
Reporter	
Consumer	440 (50.69)
Physician	252 (29.03)
Pharmacist	164 (18.89)
Not Specified	12 (1.38)
Reporting country	
United States of America	809 (93.20)
Japan	31 (3.57)
China	5 (0.58)
France	4 (0.46)
Korea	3 (0.35)
Unknown	16 (1.84)
Patients with serious and nonserious reports	
Non-Serious	665 (76.61)
Serious	203 (23.39)
Reported outcome ^a	
Death	22 (2.53)
Nonfatal: hospitalization, disability, life-threatening, or required intervention	153 (17.63)
Nonfatal: other serious outcome	71 (8.18)
Time-to-onset, d ^b	
N (Missing)	467 (401)
Mean (SD)	86.28 (244.41)
Median (Q1,Q3)	0.00 (0.00,33.00)
Min,Max	0.00,1283.00

^a The patients can have multiple serious AE outcomes

^b the time from the start of therapy to the date the event occurred

697 patients (mean age 73.4 ± 7.7 years), and 478 patients were specified to be females (Table 1).

For 90 different AEs, at least four reports were recorded. The most frequently reported AEs were headache ($n=193$, 12.00%) with mean time-to-onset of 5.2 days, chills ($n=100$, 6.22%) with mean time-to-onset of 1.03 days, fatigue ($n=93$, 5.78%) with mean

time-to-onset of 9.84 days, ARIA-E ($n=91$, 5.66%) with mean time-to-onset of 206.85 days, ARIA-H ($n=70$, 4.35%) with mean time-to-onset of 127.07 days, infusion-related reaction ($n=66$, 4.10%) with mean time-to-onset of 15.26 days, pyrexia ($n=65$, 4.04%) with mean time-to-onset of 0.87 days, confusional state ($n=64$, 3.98%) with mean time-to-onset of 48.05 days, nausea($n=63$, 3.92%) with mean time-to-onset of 3.97 days, dizziness ($n=51$, 3.17%) with mean time-to-onset of 10.4 days (online supplementary Table 1). The characterisation of deaths is provided in Table 2. The time-to-onset distribution is shown in the online supplementary Fig. 1.

Disproportionality analyses

Table 3 presents disproportionality estimates for lecanemab-related AEs grouped according to the four predefined categories. AEs expected with detected signals are those mentioned in the lecanemab label or revealed in clinical trials, such as ARIA-E, ARIA-H, nausea, and chills. AEs categorised as disease-expected are highly likely to be associated with the disease itself, such as brain fog, lethargy and disorientation. Unexpected AEs include tremor, migraine, and pancreatic carcinoma. Figure 1 is a forest map showing the top 30 reported AEs, which were statistically significant. Safety signals were detected for a large number of AEs, such as ARIA (ROR 42298.55, 95% CI 24067.60, 74,339.24; IC 14, 95% CI 4.35,5.65), ARIA-H (ROR 18047.56, 95% CI 14001.27, 23,917.73; IC 13.37, 95% CI 5.73, 6.55), ARIA-E (ROR 18299.69, 95% CI 14001.27, 23,917.73; IC 13.37, 95% CI 6.15, 6.87), infusion-related reaction (ROR 35.25, 95% CI 27.58, 45.07; IC 5.09, 95% CI 4.15, 4.87), chills (ROR 27.4, 95% CI 22.40, 33.50; IC 4.7, 95% CI 4.09, 4.68).

Sex Differences in lecanemab AEs

The most common safety signals were similar in males and females. However, ARIA was more likely to be reported in female patients, whereas chills, blood pressure increased, Corona Virus Disease 2019 (COVID-19), asthenia and pyrexia were more likely to be reported in male patients ($p<0.05$) (online supplementary Fig. 2; online supplementary Table 2a, b).

Serious versus Non-Serious AEs

The time-to-onset has a significant difference between serious and non-serious AEs ($p<0.0001$) (Fig. 2). Likewise, the patients with serious AEs were more likely to receive polypharmacy for Alzheimer's disease ($p=0.009$), aspirin ($p<0.001$), acid-suppressing medications ($p=0.030$), statins ($p<0.001$), antidepressant ($p=0.015$) or benzodiazepines ($p=0.038$) compared to patients with non-serious AEs. By contrast, age and sex did not differ between groups ($p=0.076$ and $p=0.448$,

Table 2 Characterisation of deaths for US Adverse Event Reports submitted to the US FDA Adverse Event Reporting System for lecanemab

Characteristics	Total, No (%)
Total death cases	22 (100.00)
Gender	
Female	12 (55.00)
Male	10 (45.00)
Age,y	
65–74	5 (22.70)
≥ 75	17 (77.20)
Reporter	
Consumer (%)	1 (4.50)
Physician (%)	21 (95.40)
Cause of death according to SOC ^a	
Cardiac disorders	12 (33.33)
Nervous system disorders	8 (22.22)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (13.89)
Injury, poisoning and procedural complications	4(11.11)
Metabolism and nutrition disorders	2 (5.56)
Psychiatric disorders	2 (5.56)
Other specified ^b	3 (8.33)
Cause of death according to PT ^a	
Pancreatic carcinoma	4 (11.11)
ARIA-E	3 (8.33)
Acute myocardial infarction	3 (8.33)
Other specified ^c	26 (72.22)
Time-to-onset,d ^d	
N (Missing)	21 (1)
Mean (SD)	676.8 (464.66)
Median (Q1,Q3)	829.50 (119.00,1066.00)
Min,Max	0.00,1283.00

Abbreviations: FDA US Food and Drug Administration, SOC system organ class, PT Preferred Terms, ARIA-E Amyloid-related imaging abnormality with oedema/effusion

^a Total of 36 reports affecting 22 patients

^b One report: Gastrointestinal disorders, Infections and infestations, Respiratory, thoracic and mediastinal disorders

^c Two reports: Bradycardia, Cardiac failure, Electrocardiogram ST-segment elevation, Fall, Femur fracture, Ventricular fibrillation; one report: ARIA-H, Cardiac arrest, Cerebral haemorrhage, Colon cancer metastatic, Confusional state, Dehydration, Delirium, Haemorrhagic stroke, Hyponatraemia, Interstitial lung disease, Loss of consciousness, Pneumonia, Small intestinal obstruction, Status epilepticus

^d The time from the start of therapy to the date of death

respectively). ARIA-E, ARIA-H, cerebral haemorrhage, pneumonia, fall, syncope, hyperhidrosis, loss of consciousness and dehydration were more likely to be reported as severe. In contrast, headache, fatigue, chills, pain, somnolence and dizziness were more likely to be reported as non-serious (online supplementary Fig. 3).

Table 3 Safety signals for lecanemab-related adverse events with more than four counts are classified into four groups

Groups	PT	No	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI	Time-to-onset
Expected with signal*	Headache	193	10.40	8.97	12.07	3.25	2.97	3.40	5.2
	Chills	100	27.40	22.40	33.50	4.70	4.09	4.68	1.03
	ARIA-E	91	18,299.69	14,001.27	23,917.73	13.37	6.15	6.87	206.85
	ARIA-H	70	18,047.56	13,315.73	24,460.89	13.37	5.73	6.55	127.07
	Infusion related reaction	66	35.25	27.58	45.07	5.09	4.15	4.87	15.26
	Pyrexia	65	5.96	4.65	7.63	2.53	2.07	2.79	0.87
	Nausea	63	2.53	1.97	3.26	1.31	0.91	1.65	3.97
	Dizziness	51	3.21	2.43	4.24	1.66	1.19	2.00	10.4
	Vomiting	33	2.23	1.58	3.15	1.14	0.59	1.59	10
	ARIA	31	42,298.55	24,067.60	74,339.24	14.00	4.35	5.65	194.71
	Influenza like illness	26	9.46	6.43	13.93	3.22	2.28	3.39	1.7
	Fall	20	1.87	1.20	2.90	0.89	0.20	1.47	9.64
	Feeling cold	17	18.73	11.62	30.19	4.21	2.55	3.92	0.11
	Gait disturbance	17	2.65	1.64	4.27	1.40	0.59	1.95	11.27
	Cerebral haemorrhage	12	10.26	5.82	18.10	3.35	1.78	3.38	128.63
	Brain oedema	11	27.24	15.05	49.28	4.76	2.26	3.93	26.33
	Superficial siderosis of central nervous system	5	3060.36	1212.26	7725.94	11.42	1.33	3.83	36.25
	Body temperature increased	5	7.35	3.06	17.69	2.87	0.65	3.01	2.8
	Cerebral microhaemorrhage	4	485.00	180.26	1304.95	8.89	1.00	3.62	23.5
Disease-expected*	Fatigue	93	3.89	3.16	4.79	1.91	1.56	2.17	9.84
	Confusional state	64	12.48	9.73	16.01	3.60	3.01	3.73	48.05
	Asthenia	27	2.23	1.53	3.27	1.15	0.54	1.64	7.63
	Somnolence	25	3.87	2.61	5.74	1.94	1.22	2.36	3.36
	Memory impairment	15	3.35	2.01	5.56	1.73	0.81	2.26	4
	Decreased appetite	14	1.80	1.07	3.05	0.85	0.02	1.52	3.62
	Lethargy	9	4.76	2.47	9.15	2.24	0.87	2.70	37.5
	Brain fog	9	46.00	23.89	88.59	5.51	2.15	3.98	3
	Dementia Alzheimer's type	8	26.43	13.20	52.95	4.72	1.82	3.75	16
	Disorientation	8	6.01	3.00	12.04	2.58	0.98	2.91	0.17
	Cognitive disorder	8	5.39	2.69	10.79	2.42	0.89	2.82	28
	Anger	6	5.25	2.36	11.70	2.39	0.61	2.80	206.85
	Aphasia	6	5.93	2.66	13.21	2.56	0.70	2.89	17.5
	Abnormal dreams	6	6.35	2.85	14.15	2.66	0.75	2.94	118.67
	Heart rate decreased	5	4.29	1.78	10.32	2.10	0.29	2.65	3.5
	Poor quality sleep	5	7.43	3.09	17.87	2.89	0.66	3.02	9
	Pallor	4	4.42	1.66	11.78	2.14	0.10	2.68	5.33
	Incontinence	4	11.51	4.32	30.71	3.52	0.60	3.18	11.33
	Lacrimation increased	4	4.41	1.65	11.75	2.14	0.10	2.68	37.5

Table 3 (continued)

Groups	PT	No	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI	Time-to-onset
<i>Without signal-related</i>	Pain	27	1.34	0.92	1.96	0.42	-0.15	0.95	828
	Diarrhoea	22	1.09	0.71	1.65	0.12	-0.49	0.72	3.7
	Back pain	12	1.58	0.90	2.79	0.66	-0.21	1.40	13.57
	Arthralgia	10	0.76	0.41	1.42	-0.38	-1.23	0.52	0.6
	COVID-19	9	1.61	0.84	3.11	0.69	-0.31	1.52	48.67
	Pain in extremity	8	0.82	0.41	1.64	-0.29	-1.22	0.70	5.33
	Rash	8	0.55	0.28	1.11	-0.85	-1.74	0.19	8.67
	Dyspnoea	7	0.38	0.18	0.80	-1.39	-2.29	-0.25	12.25
	Hypertension	7	1.02	0.49	2.15	0.04	-0.99	1.05	22.75
	Anxiety	7	0.74	0.35	1.56	-0.43	-1.41	0.64	17.5
	Abdominal pain upper	6	0.92	0.41	2.05	-0.12	-1.20	0.99	118.67
	Visual impairment	6	1.48	0.66	3.30	0.56	-0.62	1.56	64
	Chest pain	5	0.81	0.34	1.96	-0.30	-1.43	0.93	17.67
	Hypotension	5	0.77	0.32	1.85	-0.38	-1.50	0.86	417
<i>Unexpected*</i>	Tremor	37	6.84	4.94	9.47	2.75	2.08	3.02	0.5
	Migraine	8	2.70	1.35	5.40	1.43	0.21	2.14	280
	Pancreatic carcinoma	4	4.00	1.50	10.66	2.00	0.03	2.61	1170

Abbreviations: * Signal detected, *PT* Preferred Terms, *CI* confidence interval, *ROR* reporting odds ratio, *IC* information component, *ARIA-E* amyloid-related imaging abnormality with oedema/effusion, *ARIA-H* amyloid-related imaging abnormality with cerebral microhaemorrhage, cerebral macrohaemorrhages, or superficial siderosis

Sensitivity analyses

After analysing donepezil as a comparator for disease-related AEs, safety signals were not detected for fatigue, poor quality sleep, and asthenia. However, signals were identified for other disease-related AEs compared to the list of AEs seen for lecanemab, except for brain fog and increased lacrimation, which were not reported. When using aducanumab as a comparator, safety signals were found for confusional state, disorientation, memory impairment, falls, and lethargy. At the same time, fatigue and somnolence, along with other unreported AEs, showed no signals. We identified several safety signals for lecanemab, donepezil, and lecanemab, including confusional state, memory impairment, lethargy, dementia Alzheimer's type, disorientation, cognitive disorder, anger, aphasia, abnormal dreams, somnolence, fall, decreased appetite, heart rate decreased, pallor and incontinence (online supplementary. Table 3).

Discussion

Our findings reveal notable safety concerns, and we identified four key findings.

First, the rapidly increasing trend in the number of lecanemab reports per quarter is noteworthy. In the first

six months of 2023, 45 cases were registered, with an average of 7.5 cases per month. In the last six months of 2023, this number rose to 198 cases, which means about 33 cases per month. In contrast, 625 cases were registered in the first six months of 2024, with a mean of 104 cases per month. If the Weber effect holds-suggesting a reporting peak occurs two years after medication approval-lecanemab reports may continue to rise, justifying concerns about its safety [24]. This trend may be partially attributable to the uptake of the drug following its availability. In addition, this drug has been highly discussed in the scientific and public arena. It may increase the safety concern among healthcare professionals and patients, leading to reporting bias. This increase underscores the need for ongoing epidemiological surveillance and post-marketing safety studies. Our findings align with a previous pharmacovigilance study about post-marketing safety concerns with esketamine, which reported 591 cases in the last nine months of 2019 (since April) compared to 371 reports in the first three months of 2020 [19].

Second, this analysis identified several AEs not reported in regulatory trials (or noted in < 5% of patients), such as tremors, migraine, and pancreatic carcinoma.

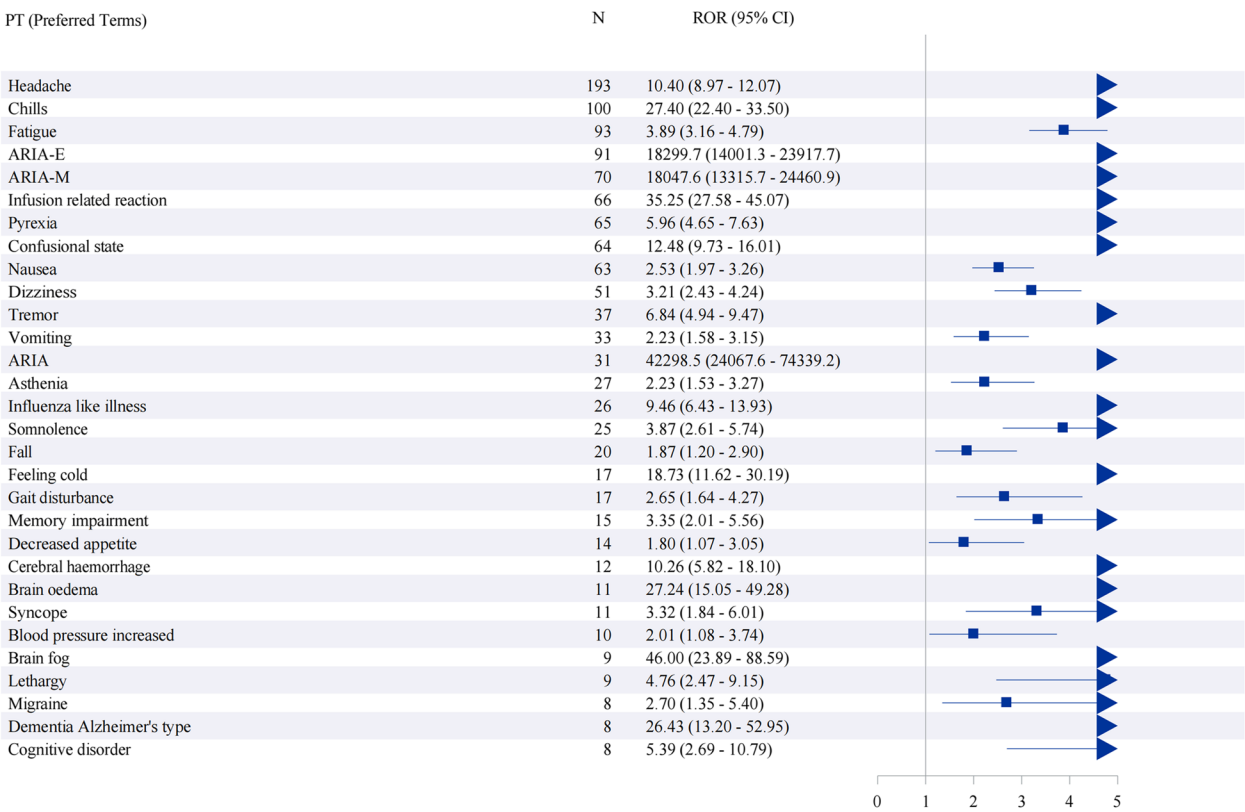


Fig. 1 The Forest Map Showing the Top 30 Safety Signals. We used disproportionality approaches: the reporting odds ratio (ROR). The ROR was considered statistically significant if the lower limit of the confidence intervals (CIs) was greater than 1. We shows the top 30 reported adverse events which were statistically significant

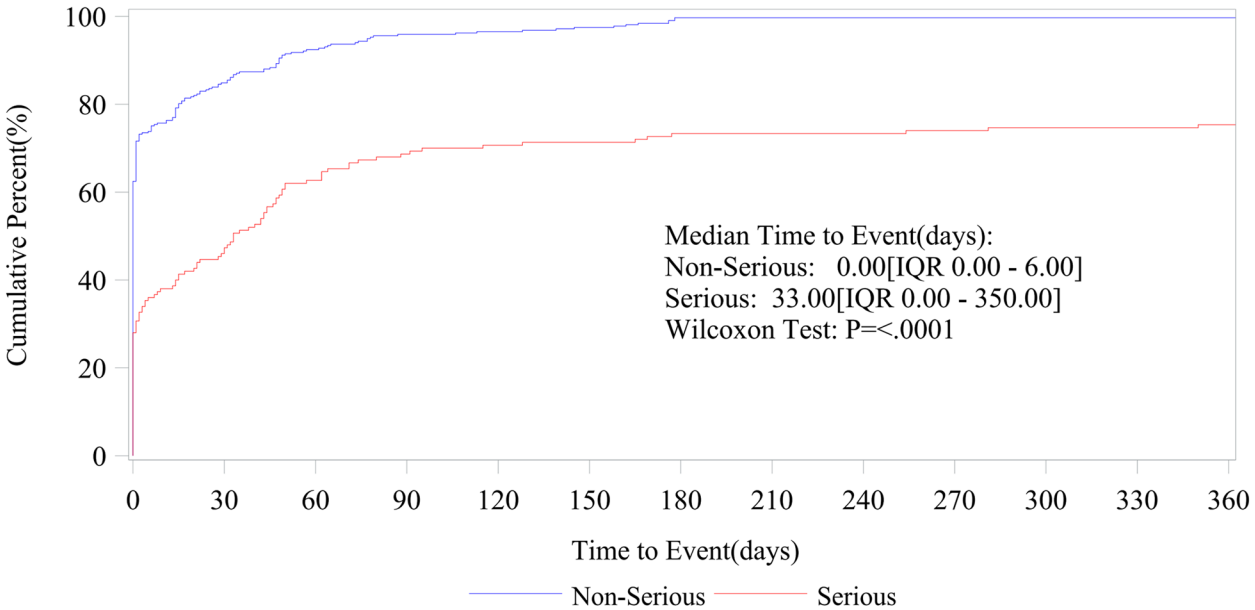


Fig. 2 The Time-to-onset Difference Between Serious and Non-serious AEs. Legends: The time-to-onset difference between serious and non-serious AEs was analysed using the Wilcoxon Test. The result shows that time-to-onset significantly differs between serious and non-serious AEs($p < 0.0001$)

Additionally, we uncovered numerous disease-related AEs. Tremor is a defining feature of Parkinson's disease, which is the second most prevalent neurodegenerative movement disorder after Alzheimer's disease. In a nationwide cohort study by Kim colleagues [25], individuals with a migraine history are more susceptible to Alzheimer's disease than those without a migraine history. However, a two-sample Mendelian randomisation (MR) study suggests that there is no causal association between migraine and the risk of Alzheimer's disease [26].

To determine whether these AEs were associated with Alzheimer's disease, we compared patients using donepezil and aducanumab as control groups. Donepezil is a classic first-line FDA-approved medication which was widely used in mild Alzheimer's disease [27]. Aducanumab was the first FDA-approved monoclonal antibody for early Alzheimer's disease [28]. Several safety signals detected in lecanemab, donepezil, and lecanemab suggest that these AEs may be associated with Alzheimer's disease rather than specific to lecanemab. In contrast, fatigue, poor quality sleep, asthenia, brain fog, and increased lacrimation were specific to lecanemab. The efficacy results of two phase 3 clinical trials of aducanumab are conflicting, the incidence of AEs in ARIA is as high as 41%, so the clinical benefit is unclear [29]. In April 2022, the Centers for Medicare & Medicaid Services (CMS) formally decided to restrict aducanumab coverage strictly to patients participating in FDA-approved and NIH-funded clinical trials [30]. Given that we speculate that the number of patients using aducanumab is limited, AE reports should be interpreted cautiously.

Third, our results reveal strong and consistent disproportionality estimates, with ROR values significantly exceeding the threshold for relevance across several AEs. A recent study highlighted a substantial concordance between disproportionality measures and relative risk estimates in analytical studies for medications with established usage, suggesting a rough indication of the clinical significance of signal strength [19]. For instance, our analysis indicates notably high reporting RORs for ARIA. Although the FDA granted full approval for lecanemab, it also issued a "black box" warning due to significant safety risks associated with ARIA [1]. This may raise awareness and understanding of lecanemab-related ARIA, potentially leading to an increase in reports in the FAERS database. Such scrutiny could introduce notoriety bias, inflating the number of reports and estimated RORs [31].

Some of the AEs detected are reasonably likely to be symptoms of ARIA, such as headache, dizziness, nausea, and gait difficulty [32]. ARIA usually does not cause any symptoms, and only some patients experience mild headaches, cloudiness of consciousness, dizziness, vision changes, and nausea. 1% to 2% of patients

with ARIA experience long-term symptoms such as ARIA-E, ARIA-H, or seizures [33]. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

On the other hand, the incidence of ARIA (including ARIA-E and ARIA-H) reported in clinical trials was 26.61%, higher than the 22.12% observed in our analysis [3]. However, the 22.12% is based on reporting rates and not incidence, the results should be interpreted cautiously. The apolipoprotein E (ApoE) $\epsilon 4$ genotype is strongly associated with ARIA and exhibits a gene dose effect [34]. ARIA-E and ARIA-H were numerically less common among ApoE $\epsilon 4$ noncarriers than among carriers, with higher frequency among ApoE $\epsilon 4$ homozygotes than among ApoE $\epsilon 4$ heterozygotes. We recommend that clinicians conduct ApoE $\epsilon 4$ genetic testing to facilitate prior to treatment initiation. In real-world Settings, patients who are ApoE $\epsilon 4$ homozygous after genetic testing may abstain from taking the drug, which may also account for lower-than-expected real-world use reports.

Moreover, comparing serious versus non-serious AEs helps identify high-risk patient subgroups. Patients on polypharmacy for Alzheimer's disease, as well as those taking aspirin, acid-suppressing medications, statins, antidepressants, or benzodiazepines, showed an increased risk for serious lecanemab-related AEs, likely due to bias (i.e., patients have more severe disease and comorbidities) [35], and potential medication interactions compromising the therapeutic outcome. In addition, ARIA-E, ARIA-H, cerebral haemorrhage, pneumonia, fall, syncope, hyperhidrosis, loss of consciousness and dehydration were more likely to be reported as serious AEs. Consequently, careful benefit-risk assessments and stringent monitoring are essential. The time-to-onset for serious AEs was significantly longer than for non-serious AEs, with non-serious events typically occurring soon after the first dose. Notably, infusion-related reactions were mostly mild to moderate (grade 1 or 2, 96%) and predominantly occurred with the first dose (75%), aligning with clinical trial data [3].

An important strength of our study was the inclusion of a large number of lecanemab reports, thereby presenting the first real-world data on the safety profile of lecanemab, to our knowledge. However, our study should be approached with caution due to inherent limitations in pharmacovigilance research, such as voluntary (under-reporting), the inability to establish causality, reporting bias, data quality issues, and the absence of a denominator, which precludes calculating incidence rates. Despite these challenges, pharmacovigilance remains crucial

for monitoring medication safety and uncovering rare signals.

Conclusion

Our analysis identified new and unexpected lecanemab-related AEs not previously reported in regulatory trials, such as tremor, migraine, pancreatic carcinoma and brain fog, highlighting the need for prescribers to be vigilant about these AEs. Certain patient subgroups, particularly for polypharmacy for Alzheimer's disease, aspirin, acid-suppressing medications, statins, antidepressants or benzodiazepines, may be more vulnerable to serious AEs. This underscores the importance of careful monitoring and risk assessment in these vulnerable populations to enhance patient safety and help with the clinical decision-making process. These results have significant implications for clinicians, patients, and policy-makers regarding lecanemab. Further clinical practice data is essential to gain a clearer understanding of lecanemab safety.

Abbreviations

Aβ	Amyloid-beta
FDA	Food and Drug Administration
AEs	Adverse events
ARIA-H	Amyloid-related imaging abnormalities with cerebral microhaemorrhage, cerebral macrohaemorrhages, or superficial siderosis
ARIA-E	Amyloid-related imaging abnormality with oedema/effusion
FAERS	FDA's Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System organ class
PT	Preferred term
ROR	The reporting odds ratio
IC	Information component
95%CI	Ninety-five per cent confidence intervals
ApoE	Apolipoprotein E

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

X.X. and X.D. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design: X.X., L.Z., X.D.; Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: X.X. and X.D.; Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Supervision: L.Z., X.D.

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Data availability

The datasets generated and/or analyzed during the current study are available in the US FAERS database (<https://fs.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>). The code generated and/or analyzed in the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was not required as the study was conducted using de-identified publicly available data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Mahase E. Alzheimer's disease: Lecanemab gets full FDA approval and black box safety warning. *BMJ*. 2023;382:1580. <https://doi.org/10.1136/bmj.p1580>.
- Mahase E. Alzheimer's disease: FDA approves lecanemab amid cost and safety concerns. *BMJ*. 2023;380:73. <https://doi.org/10.1136/bmj.p73>.
- Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9–21. <https://doi.org/10.1056/NEJMoA2212948>.
- Mahase E. Lecanemab: European drug agency rejects Alzheimer's drug amid debate over efficacy and safety. *BMJ*. 2024;386:q1692. <https://doi.org/10.1136/bmj.q1692>.
- Withington CG, Turner RS. Amyloid-related imaging abnormalities with anti-amyloid antibodies for the treatment of dementia due to Alzheimer's disease. *Front Neurol*. 2022;13:862369. <https://doi.org/10.3389/fneur.2022.862369>.
- Reish NJ, Jamshidi P, Stamm B, et al. Multiple cerebral haemorrhages in a patient receiving lecanemab and treated with t-PA for stroke. *N Engl J Med*. 2023;388(5):478–9. <https://doi.org/10.1056/nejmc221514>.
- Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimers Res Ther*. 2021;13:80. <https://doi.org/10.1186/s13195-021-00813-8>.
- Söderberg L, Johannesson M, Nygren P, et al. Lecanemab, Aducanumab, and Gantenerumab-binding profiles to different forms of amyloid-Beta might explain Efficacy and Side effects in clinical trials for Alzheimer's Disease. *Neurotherapeutics*. 2023;20:195–206. <https://doi.org/10.1007/s13311-022-01308-6>.
- McDade E, Cummings JL, Dhadda S, et al. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. *Alzheimers Res Ther*. 2022;14:191. <https://doi.org/10.1186/s13195-022-01124-2>.
- Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. *Drug Discov Today*. 2009;14(7–8):343–57. <https://doi.org/10.1016/j.drudis.2008.12.012>.
- US Food & Drug Administration. FDA Adverse Event Reporting System (FAERS) Quarterly Data Extract Files. <https://www.fda.gov/drugs/queries-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files>, Accessed September 25, 2024.
- US Food and Drug Administration. Questions and answers on FDA's Adverse Event Reporting System. <https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers>. Accessed September 25, 2024.
- MedDRA. Introductory Guide: MedDRA version 27.1. https://admin.new.meddra.org/sites/default/files/guidance/file/intguide_27_1_English.pdf. Published September 2024. Accessed September 25, 2024.

14. ICH. Harmonisation for better health: MedDRA work products. <http://www.ich.org/products/meddra.html>, Accessed September 25, 2024.
15. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf.* 2009;18(6):427–36. <https://doi.org/10.1002/pds.1742>.
16. Raschi E, Poluzzi E, Salvo F, et al. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: what a clinician should know on disproportionality analysis of spontaneous reporting systems. *Nutr Metab Cardiovasc Dis.* 2018;28(6):533–42. <https://doi.org/10.1016/j.numecd.2018.02.014>.
17. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA Adverse Event Reporting System. *Int J Med Sci.* 2013;10(7):796–803. <https://doi.org/10.7150/ijms.6048>.
18. Pace ND, Multani JK. On the reporting of odds ratios and risk ratios. *Nutrients.* 2018;10(10):E1512. <https://doi.org/10.7150/ijms.6048>.
19. Gastaldon C, Raschi E, Kane JM, Barbui C, Schoretsanis G. Post-Marketing Safety Concerns with Esketamine: A Disproportionality Analysis of Spontaneous Reports Submitted to the FDA Adverse Event Reporting System. *Psychother Psychosom.* 2021;90(1):41–8. <https://doi.org/10.1159/000510703>.
20. Van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 2002;11(1):3–10. <https://doi.org/10.1002/pds.668>.
21. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol.* 1998;54(4):315–21. <https://doi.org/10.1007/s002280050466>.
22. Dijkstra L, Garling M, Foraita R, Pigeot I. Adverse drug reaction or innocent bystander? A systematic comparison of statistical discovery methods for spontaneous reporting systems. *Pharmacoepidemiol Drug Saf.* 2020;29(4):396–403. <https://doi.org/10.1002/pds.4970>.
23. Umetsu R, Abe J, Ueda N, et al. Association between selective serotonin reuptake inhibitor therapy and suicidality: Analysis of US Food and Drug Administration Adverse Event Reporting System data. *Biol Pharma Bull.* 2015;38(11):1689–99. <https://doi.org/10.1248/bpb.b15-00243>.
24. Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug Saf.* 2014;37(4):283–94. <https://doi.org/10.1007/s40264-014-0150-2>.
25. Kim J, Ha WS, Park SH, Han K, Baek MS. Association between migraine and Alzheimer's disease: a nationwide cohort study. *Front Aging Neurosci.* 2023;15:1196185. <https://doi.org/10.3389/fnagi.2023.1196185>.
26. Xue H, Zeng L, Liu S. Unraveling the link: exploring the causal relationship between diabetes, multiple sclerosis, migraine, and Alzheimer's disease through Mendelian randomization. *Front Neurosci.* 2023;17:1233601. <https://doi.org/10.3389/fnins.2023.1233601>.
27. Wang H, Zong Y, Han Y, Zhao J, Liu H, Liu Y. Compared of efficacy and safety of high-dose donepezil vs standard-dose donepezil among elderly patients with Alzheimer's disease: a systematic review and meta-analysis. *Expert Opin Drug Saf.* 2022;21(3):407–15. <https://doi.org/10.1080/14740338.2022.2027905>.
28. Rahman A, Hossen MA, Chowdhury MF, et al. Aducanumab for the treatment of Alzheimer's disease: a systematic review. *Psychogeriatrics.* 2023;23(3):512–22. <https://doi.org/10.1111/psyg.12944>.
29. Alexander GC, Emerson S, Kesselheim AS. Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility. *JAMA.* 2021;325(17):1717–8. <https://doi.org/10.1001/jama.2021.3854>.
30. CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. <https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-mono-clonal-antibodies-directed-against-amyloid-treatment>, Published April 2022. Accessed December 10, 2024.
31. Weber JC. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. In: Rainsford KD, Velo GD, editors. Side-effects of anti-inflammatory drugs, advances in inflammation research. New York: Raven Press; 1984. p. 1–7.
32. Roytman M, Mashriqi F, Al-Tawil K, et al. Amyloid-Related Imaging Abnormalities: An Update. *AJR Am J Roentgenol.* 2023;220(4):562–74. <https://doi.org/10.2214/AJR.22.28461>.
33. Hampel H, Elhage A, Cho M, et al. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. *Brain.* 2023;146(11):4414–24. <https://doi.org/10.1093/brain/awad188>.
34. Cummings J, Rabinovici GD, Atri A, et al. Aducanumab: Appropriate Use Recommendations Update. *J Prev Alzheimers Dis.* 2022;9(2):221–30. <https://doi.org/10.14283/jpad.2022.34>.
35. Borgen NT. Collider bias (aka sample selection bias) in observational studies: why the effects of hyperandrogenism in elite women's sport are likely underestimated. *Br J Sports Med.* 2020;54(12):750–2. <https://doi.org/10.1136/bjsports-2018-100054>.

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