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Original Research

Age-stratified analysis of adverse event signals for clarithromycin: a disproportionality analysis using the FDA Adverse Event Reporting System

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Abstract

Background: Clarithromycin is a widely used antibiotic, but its safety profile, particularly in different age groups, remains inadequately explored.

Objectives: This study aims to characterize and illustrate the features of clarithromycin-related adverse events (AEs) across different age groups using the FDA Adverse Event Reporting System (FAERS) database, providing a reference for the clinical detection, prevention, and management of AEs in various age groups.

Design: A disproportionality analysis was performed using data from the FAERS database. The study included all AE reports related to clarithromycin, stratified by age groups.

Methods: Disproportionality analysis was conducted using reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and multiple gamma Poisson shrinkers. Statistical analyses included descriptive statistics and Chi-square tests.

Results: A total of 7319 reports of clarithromycin AEs were retrieved from the FAERS database. Vomiting, diarrhea, drug interactions, and drug interactions were reported most frequently in the age groups 0–17, 18–44, 45–64, and ⩾65 years, respectively. Abnormal product taste, taste disorder, and medication errors related to drug interactions specified in the package insert were the strongest signals in the age groups 0–17, 18–44, 45–64, and ⩾65 years, respectively. A total of 41 Preferred Terms signals were not explicitly included in the clarithromycin package insert and were mainly associated with psychiatric disorders, skin and subcutaneous tissue disorders, and gastrointestinal disorders, among others. Specific signals for age differences were identified, with 18 signals being age-specific, including 3 in children and 15 in elderly individuals.

Conclusion: The safety profile of clarithromycin varies across age groups. In children, it is mainly associated with vomiting, hypersensitivity, and dyspnea, while in adults, psychiatric AEs are more common. In the elderly, clarithromycin should be used cautiously, with attention to drug interactions.

Plain language summary

A study on the adverse effects of clarithromycin

Introduction: Clarithromycin is a relatively newer macrolide antibiotic derived from erythromycin, that is included in the WHO Model List of Essential Medicines, and is one of the important drugs needed in basic healthcare systems. Currently, there are no studies mining adverse events and outcomes related to the clinical use of clarithromycin in the FDA Adverse Event Reporting System (FAERS) database. This study investigated the safety signals related to clarithromycin.

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Methods: Disproportionality analysis, including reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multiple gamma Poisson shrinker (MGPS) algorithms, were used to quantify signals of clarithromycin-related adverse events (AEs) across different age groups.
Results: 7,319 AE reports were identified, 41 PT signals were not explicitly included in the clarithromycin package insert. Specific signals for age differences were identified, with 18 signals being age specific.
Conclusion: We discovered important safety concerns related to clarithromycin. The safety of clarithromycin is different in different age groups. Children are more closely associated with adverse events related to vomiting, drug-induced hypersensitivity, and dyspnea. In adults, it is more associated with psychiatric adverse events. In addition, the use of clarithromycin in the elderly should be strictly in accordance with the instructions and be alert to drug interactions.

Keywords: adverse event, children, clarithromycin, elderly, FAERS

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Introduction

Clarithromycin is a relatively newer macrolide antibiotic derived from erythromycin, that is included in the WHO Model List of Essential Medicines and is one of the important drugs needed in basic healthcare systems.[1,2] Compared to its parent compound erythromycin, clarithromycin has improved side effects, dosing regimens, and microbial activity. It is used to treat various bacterial infections, including *streptococcal* pharyngitis, pneumonia, skin infections, and *Helicobacter pylori* infection.[1,3]

Although clarithromycin plays an important role in treating various diseases, reports of adverse events (AEs) associated with it are gradually increasing. Currently, there are still deficiencies in the in-depth analysis of AEs related to clarithromycin. Studies have shown that adverse reactions to clarithromycin mainly include gastrointestinal reactions, allergic reactions, and liver function damage.[4] However, there has not been a comprehensive comparison and interpretation of risk factors and adverse reactions among different patient populations. The clarithromycin package clearly states that the safety of clarithromycin in pregnant and lactating women has not been confirmed, and special treatment is not recommended for children and elderly people.[5,6] Currently, there are no studies mining AEs and outcomes related to the clinical use of clarithromycin in the FDA Adverse Event Reporting System (FAERS) database. To further understand clarithromycin-related AEs and better protect patients of different ages, we need to conduct comparative analyses of clarithromycin AEs.

This study aimed to characterize and illustrate the features of clarithromycin-related AEs across different age groups using FAERS data. We aimed to explore the types, frequencies, severity, and relative risks of AEs induced by clarithromycin in different age groups. Through this research, we hope to provide more comprehensive and specific information about the safety of clarithromycin, thereby enhancing patient compliance and tolerance and providing more accurate and personalized guidance for its clinical use.

Methods

Data source

We conducted a pharmacovigilance study on AEs associated with clarithromycin using the FAERS database. The FAERS is a vital public database of the FDA, that is used to collect reports of AEs and medication errors related to approved drugs.[7,8] The clarithromycin reports were retrieved from the FAERS database covering the period from the first quarter of 2004 to the second

quarter of 2023, using either the brand name or the generic name of clarithromycin as keywords. Data were extracted using the open-source tool OpenVigil 2.1, and the selected role code was "PS" (primary suspect). AE reports in the FAERS database are encoded according to the Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA), with additional classification by System Organ Class (SOC).[9]

Data processing

We performed deduplication on the clarithromycin reports obtained from the FAERS database. When the CASE ID was identical, we selected the report with the most recent FDA_DT. In cases where both the CASE ID and FDA_DT were the same, the report with the larger PRIMARY_ID value was chosen. In addition, reports with identical values for fields such as gender, age, country, event date, adverse event, and indication were also identified as duplicates. Furthermore, we refined the dataset by categorizing clarithromycin reports based on the reported age, distinguishing between different age groups.

Signal mining

In the context of pharmacovigilance studies, disproportionality analysis methods are primarily used as tools to assess potential associations between specific AEs and specific drugs. The reporting of this study conforms to the READUS-PV statement.[10] Disproportionality analysis methods include frequency-based data mining approaches such as the reporting odds ratio (ROR) and proportional reporting ratio (PRR), as well as Bayesian adverse drug reaction data mining approaches like the Bayesian Confidence Propagation Neural Network (BCPNN) and the multiple gamma Poisson shrinker (MGPS).[11–14]

The advantage of frequency-based methods lies in their high sensitivity, simplicity of principle, ease of algorithm, and fast computation. However, they have low specificity, unstable signals, and are easily influenced by outliers. Conversely, Bayesian methods offer high specificity, stable signals, and a lower likelihood of false positives, but they typically have lower sensitivity and are computationally complex.

Considering the core principles and pros and cons of each disproportionality analysis method, this study employed four methods—ROR, PRR, BCPNN, and MGPS—for AE signal detection to reduce the likelihood of false-positive signals. A potential risk signal is identified when all four algorithms indicate a positive signal, defined as follows: the frequency of the AE occurrence is $\geqslant 3$, the lower limit of the 95% confidence interval (CI) for the ROR is >1, the PRR is $\geqslant 2$ with a chi-square value $\geqslant 4$, the lower limit of the 95% CI for the Information Component is >0, and the lower limit of the 95% CI for the Empirical Bayes Geometric Mean (EBGM) is $\geqslant 2$.

Statistical analysis

In addition to signal detection at the PT level, we also conducted a comparison across different age groups. Descriptive analysis was employed to present the characteristics of all the AE reports related to clarithromycin. The Chi-square test was used to compare the distribution differences of patients between the age groups. All statistical analyses were performed using R software (The R Foundation, version 4.4.0).

Results

Baseline characteristics

The demographic characteristics of the patients included in the clarithromycin AE reports are shown in Table 1. From the first quarter of 2004 to the second quarter of 2023, a total of 7319 clarithromycin AE reports were retrieved from the FAERS database. Among them, 679 were in the age group of 0–17 years, 2056 were in the age group of 18–44 years, 2192 were in the age group of 45–64 years, and 2392 were in the age group of 65 years and above. The most common age group was $\geqslant$65 years (32.7%). The proportion of female reports (59.9%) was higher than that of male reports (38.5%). A total of 42.5% of the reports originated from the United Kingdom. A total of 16.3% of the AE reports did not specify the route of administration. Among the known routes of administration, oral administration accounted for 69.0%, while injection accounted for 1.4%. Except for unknown indications, the reported AEs associated with clarithromycin are primarily related to lower respiratory tract infection and pneumonia. The most reported outcome was Other (52.3%), followed by Hospitalization—Initial or Prolonged (31.1%) and Life-Threatening (6.3%).

Table 1. Demographic characteristics of patients who received clarithromycin and AE reports and percentages (*n* (%)).

Variables	0–17 (*N* = 679)	18–44 (*N* = 2056)	45–64 (*N* = 2192)	⩾65 (*N* = 2392)	*p*-Value
Gender					<0.001
Male	312 (45.9)	652 (31.7)	881 (40.2)	975 (40.8)	
Female	345 (50.8)	1384 (67.3)	1272 (58.0)	1382 (57.8)	
Unknown	22 (3.2)	20 (1.0)	39 (1.8)	35 (1.5)	
Reporter country					<0.001
United Kingdom	180 (26.5)	990 (48.2)	932 (42.5)	1008 (42.1)	
United States	74 (10.9)	184 (8.9)	252 (11.5)	201 (8.4)	
Italy	97 (14.3)	182 (8.9)	182 (8.3)	223 (9.3)	
Japan	31 (4.6)	85 (4.1)	141 (6.4)	209 (8.7)	
Other	297 (43.7)	615 (29.9)	685 (31.3)	751 (31.4)	
Route					<0.001
Oral	373 (54.9)	1209 (58.8)	1235 (56.3)	1407 (58.8)	
Injection	8 (1.2)	21 (1.0)	19 (0.9)	35 (1.5)	
Transplacental/transmammary	6 (0.9)	5 (0.2)	0 (0.0)	0 (0.0)	
Other	180 (26.5)	492 (23.9)	565 (25.8)	570 (23.8)	
Indication					<0.001
Lower respiratory tract infection	94 (13.8)	114 (5.5)	316 (14.4)	313 (13.1)	
Pneumonia	85 (12.5)	77 (3.7)	194 (8.9)	309 (12.9)	
Bronchitis	53 (7.8)	67 (3.3)	73 (3.3)	124 (5.2)	
Tonsillitis	30 (4.4)	145 (7.1)	37 (1.7)	7 (0.3)	
Helicobacter infection	20 (2.9)	154 (7.5)	304 (13.9)	272 (11.4)	
Other	202 (29.7)	884 (43.0)	615 (28.1)	621 (26.0)	
Unknown	195 (28.7)	615 (29.9)	653 (29.8)	746 (31.2)	
Outcome					<0.001
Death	16 (2.1)	42 (1.8)	107 (4.2)	193 (6.4)	
Life-threatening	32 (4.2)	99 (4.3)	160 (6.2)	256 (8.5)	
Disability	35 (4.6)	130 (5.6)	141 (5.5)	146 (4.9)	
Congenital anomaly	3 (0.4)	3 (0.1)	0 (0.0)	1 (0.0)	
Hospitalization—initial or prolonged	269 (35.1)	542 (23.4)	817 (31.8)	1066 (35.6)	
Required intervention to prevent permanent impairment/damage	3 (0.4)	19 (0.8)	23 (0.9)	23 (0.8)	
Other	408 (53.3)	1484 (64.0)	1321 (514)	1311 (43.8)	

AE, adverse event.

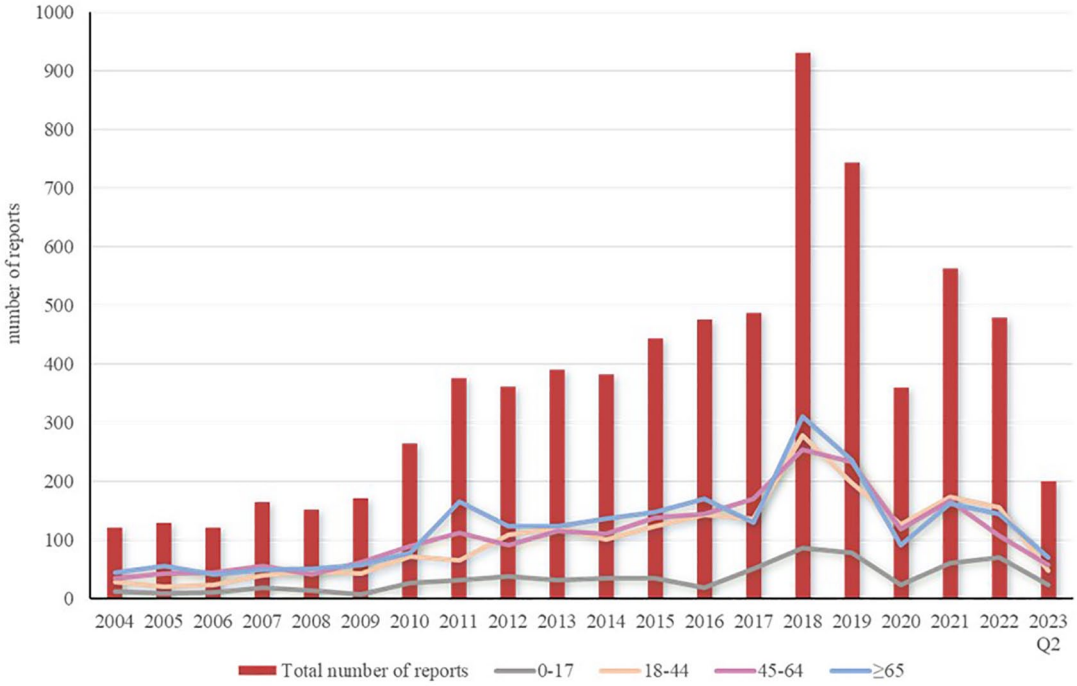

Figure 1. Annual AE reports of patients receiving clarithromycin.
AE, adverse event.

Reporting year

The trend of clarithromycin AE reports over time is illustrated in Figure 1. The number of reports was relatively low and stable from 2004 to 2009. There was an increase in the number of reports in 2010, followed by a slow increase from 2011 to 2017. The number of reports surged in 2018, reaching a peak of 931 cases. The number of reports decreased from 2019 to 2020. There was an increase in the number of reports in 2021. The distribution of clarithromycin AE reports across different age groups is shown in Figure 2.

Risk signals associated with clarithromycin

The detection of AE signals at the SOC and PT levels using five methods—ROR, PRR, comprehensive standard method, BCPNN, and MGPS—is illustrated in Figure 3 for clarithromycin-related AE signals across different age groups. The 45- to 64-year-old age group ($n = 37$) had the greatest number of signals, followed by the 18- to 44-year-old age group ($n = 34$), and the 65-year-old age group ($n = 30$), while the 0- to 17-year-old age group ($n = 11$) had the least signals. At the SOC level, AE signals in the 0–17 age group involved 7 SOCs, primarily concentrated in gastrointestinal disorders ($n = 3$) and skin and subcutaneous tissue disorders ($n = 3$). AE signals in the 18–44 age group involved 10 SOCs, mainly concentrated in psychiatric disorders ($n = 11$) and general disorders and administration site conditions ($n = 6$). AE signals in the 45–64 age group involved 12 SOCs, mainly concentrated in psychiatric disorders ($n = 10$), gastrointestinal disorders ($n = 4$), skin and subcutaneous tissue disorders ($n = 4$), and general disorders and administration site conditions ($n = 4$). AE signals in the age group of 65 years and above involved 12 SOCs, mainly concentrated in psychiatric disorders ($n = 7$), with the remaining signals distributed relatively evenly.

The AE signals detected at the PT level are shown in Table 2.

Vomiting ($n = 89$), diarrhea ($n = 179$), drug interactions ($n = 265$), and drug interactions ($n = 487$) were the most commonly reported in the age groups of 0–17, 18–44, 45–64, and 65 years and above, respectively.

In the 0–17 years age group, strong signals detected included abnormal product taste (EBGM 95% CI = 12.14) and dysgeusia (EBGM

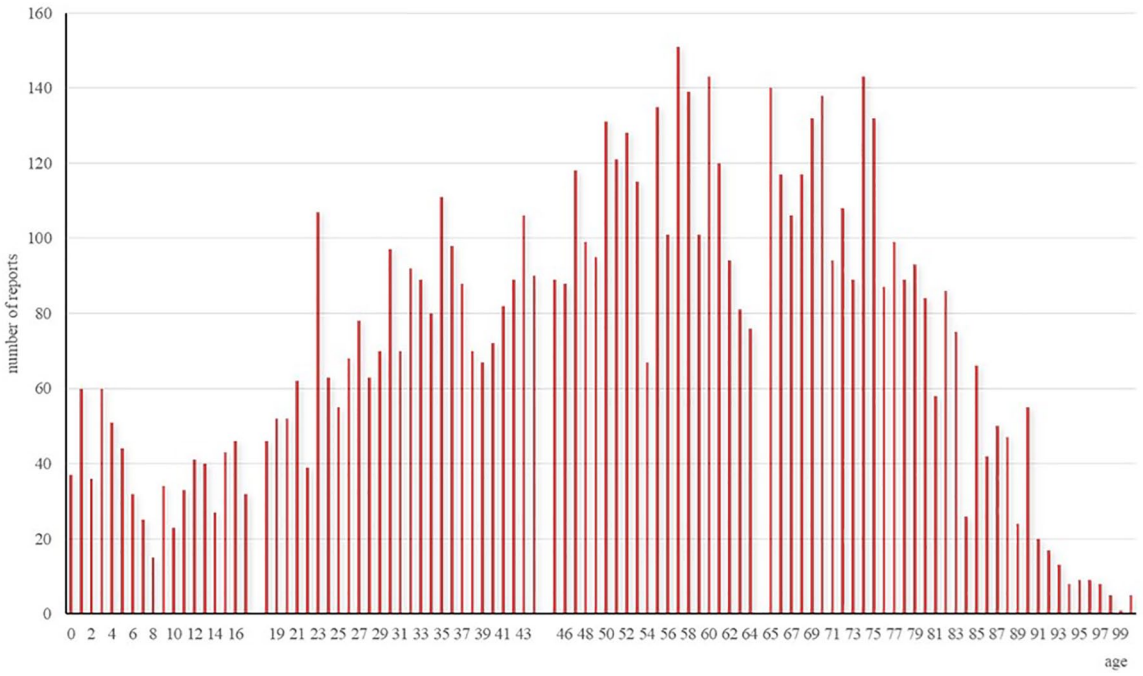

Figure 2. AE reports of clarithromycin across different age groups.
AE, adverse event.

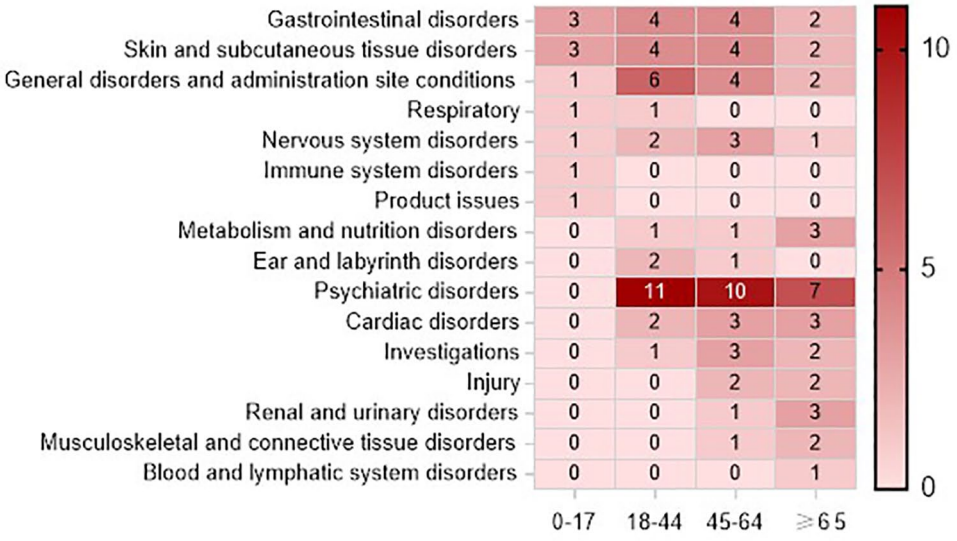

Figure 3. Clarithromycin AE signals detected using four algorithms.
AE, adverse event.

95% CI = 11.92). In the 18–44 years age group, strong signals detected included taste disorders (EBGM 95% CI = 20.53) and dysgeusia (EBGM 95% CI = 17.08). In the 45- to 64-year-old age group, strong signals detected included labeled drug-drug interaction medication errors (EBGM 95% CI = 36.29) and erythema multiforme (EBGM 95% CI = 19.88). In the 65 years and older age group, strong signals detected included labeled drug–drug interaction medication errors (EBGM 95% CI = 16.83) and drug interactions (EBGM 95% CI = 16.04).

Table 2. AE signals detected and strength of clarithromycin.

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
0–17 Years									
1	Product taste abnormal	Product issues	14	12.91	21.74	245.81	0.07	12.14	No
2	Dysgeusia	Nervous system disorders	17	12.69	20.25	280.74	0.41	11.92	Yes
3	Lip swelling	Gastrointestinal disorders	15	5.38	8.85	95.18	0.16	5.2	No
4	Drug interaction	General disorders and administration site conditions	38	4.27	5.66	140.95	1.58	4.04	Yes
5	Stevens-Johnson syndrome	Skin and subcutaneous tissue disorders	15	3.33	5.48	50.13	0.08	3.24	Yes
6	Urticaria	Skin and subcutaneous tissue disorders	35	3.09	4.18	81.88	1.08	2.95	Yes
7	Vomiting	Gastrointestinal disorders	89	2.79	3.16	134.21	1.31	2.52	Yes
8	Drug hypersensitivity	Immune system disorders	15	2.4	3.94	29.93	0.05	2.34	Yes
9	Dyspnea	Respiratory, thoracic and mediastinal disorders	36	2.32	3.14	50.81	0.88	2.23	No
10	Erythema	Skin and subcutaneous tissue disorders	20	2.08	3.19	27.98	0.23	2.03	No
11	Abdominal pain upper	Gastrointestinal disorders	23	2.07	3.08	30.33	0.37	2.02	Yes
18–44 Years									
1	Taste disorder	Nervous system disorders	23	21.8	32.87	645.85	0.02	20.53	Yes
2	Dysgeusia	Nervous system disorders	150	18.9	20.85	2734.49	3.34	17.08	Yes
3	Nightmare	Psychiatric disorders	51	7.31	9.46	373.06	0.86	7.06	No
4	Lip swelling	Gastrointestinal disorders	44	7.29	9.66	328.75	0.57	7.05	No
5	Hallucination	Psychiatric disorders	62	6.37	8.01	369.87	1.07	6.14	Yes

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
6	Tinnitus	Ear and labyrinth disorders	49	6.2	8.07	293.76	0.72	6.00	Yes
7	Psychotic disorder	Psychiatric disorders	58	5.76	7.31	307.21	0.92	5.57	Yes
8	Panic attack	Psychiatric disorders	63	5.54	6.94	312.6	1.06	5.35	No
9	Rash maculopapular	Skin and subcutaneous tissue disorders	24	5.36	7.96	137.61	0.05	5.25	No
10	Disorientation	Psychiatric disorders	37	5.2	7.11	186.46	0.36	5.08	Yes
11	Angioedema	Skin and subcutaneous tissue disorders	42	5.12	6.84	201.96	0.48	4.98	Yes
12	Adverse drug reaction	General disorders and administration site conditions	38	4.8	6.53	171.13	0.39	4.69	Yes
13	Palpitations	Cardiac disorders	102	4.86	5.69	389.57	1.69	4.63	Yes
14	Mania	Psychiatric disorders	27	4.36	6.31	114.55	0.1	4.27	Yes
15	Insomnia	Psychiatric disorders	166	4.42	4.85	507.56	1.94	4.11	Yes
16	Vertigo	Ear and labyrinth disorders	45	4.09	5.41	156.62	0.51	3.99	Yes
17	Paranoia	Psychiatric disorders	26	3.81	5.55	91.99	0.07	3.74	No
18	Drug interaction	General disorders and administration site conditions	90	3.83	4.58	248.8	1.4	3.68	Yes
19	Confusional state	Psychiatric disorders	76	3.79	4.63	212.98	1.13	3.66	Yes
20	Swelling face	General disorders and administration site conditions	38	3.35	4.56	101.77	0.3	3.29	No
21	Diarrhea	Gastrointestinal disorders	179	3.39	3.7	355.83	1.62	3.16	Yes
22	Abdominal pain upper	Gastrointestinal disorders	88	3.05	3.67	168.91	1.13	2.95	Yes
23	Peripheral swelling	General disorders and administration site conditions	32	2.88	4.04	70.03	0.14	2.83	No
24	Erythema	Skin and subcutaneous tissue disorders	63	2.7	3.4	104.64	0.72	2.63	No

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
25	Heart rate increased	Investigations	48	2.68	3.52	84.1	0.44	2.63	No
26	Nervousness	Psychiatric disorders	25	2.66	3.91	51.2	0.01	2.62	Yes
27	Urticaria	Skin and subcutaneous tissue disorders	78	2.69	3.28	122.17	0.93	2.61	Yes
28	Anxiety	Psychiatric disorders	158	2.75	3.06	221.87	1.3	2.59	Yes
29	Dyspnea	Respiratory, thoracic, and mediastinal disorders	150	2.66	2.99	200.18	1.22	2.52	No
30	Chest discomfort	General disorders and administration site conditions	44	2.49	3.3	68.5	0.33	2.44	Yes
31	Decreased appetite	Metabolism and nutrition disorders	49	2.48	3.24	73.77	0.45	2.43	Yes
32	Dyspepsia	Gastrointestinal disorders	32	2.29	3.21	46.51	0.1	2.25	Yes
33	Tachycardia	Cardiac disorders	50	2.12	2.77	54.93	0.39	2.08	Yes
34	Chest pain	General disorders and administration site conditions	65	2.1	2.64	64.92	0.57	2.05	Yes
45–64 Years									
1	Labeled drug–drug interaction medication error	Injury, poisoning, and procedural complications	55	39.06	50.16	2474.46	1.22	36.29	Yes
2	Erythema multiforme	Skin and subcutaneous tissue disorders	37	20.77	28.43	925.23	0.5	19.88	No
3	Mania	Psychiatric disorders	42	15.32	20.49	744.36	0.71	14.76	Yes
4	Dysgeusia	Nervous system disorders	159	15.72	17.27	2388.76	3.57	14.44	Yes
5	Drug interaction	General disorders and administration site conditions	265	13.97	14.15	3206.48	3.55	12.27	Yes
6	Drug level increased	Investigations	35	12.11	16.71	493.24	0.42	11.74	No
7	Electrocardiogram QT prolonged	Investigations	53	9.47	12.19	527.59	1.03	9.16	Yes

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
8	Paranoia	Psychiatric disorders	27	8.67	12.57	272.73	0.13	8.48	No
9	Face edema	General disorders and administration site conditions	27	8.07	11.7	250.76	0.13	7.9	No
10	Psychotic disorder	Psychiatric disorders	32	7.31	10.25	255.59	0.29	7.15	Yes
11	Drug eruption	Skin and subcutaneous tissue disorders	23	7.21	10.8	192.96	0.03	7.08	Yes
12	Hallucination	Psychiatric disorders	53	7.21	9.29	381	0.95	7	Yes
13	Nightmare	Psychiatric disorders	40	6.82	9.19	281.61	0.54	6.65	No
14	Ageusia	Nervous system disorders	23	6.73	10.07	177.31	0.03	6.6	Yes
15	Swollen tongue	Gastrointestinal disorders	39	6.58	8.9	263.77	0.51	6.42	No
16	Lip swelling	Gastrointestinal disorders	33	5.71	7.96	192.79	0.3	5.6	No
17	Rhabdomyolysis	Musculoskeletal and connective tissue disorders	47	5.54	7.27	246.83	0.73	5.41	Yes
18	Tinnitus	Ear and labyrinth disorders	41	5.54	7.43	220.56	0.54	5.41	Yes
19	Disorientation	Psychiatric disorders	35	5.17	7.13	177.38	0.35	5.07	Yes
20	Confusional state	Psychiatric disorders	102	5.04	5.92	412.47	1.91	4.82	Yes
21	Dysarthria	Nervous system disorders	34	4.91	6.81	162.02	0.3	4.82	No
22	Hypoglycemia	Metabolism and nutrition disorders	28	3.52	5.06	87.05	0.09	3.47	Yes
23	Adverse drug reaction	General disorders and administration site conditions	29	3.47	4.96	87.45	0.13	3.42	Yes
24	Agitation	Psychiatric disorders	38	3.33	4.53	100.95	0.35	3.27	No
25	Arrhythmia	Cardiac disorders	26	3.21	4.69	71.75	0.04	3.17	Yes
26	Erythema	Skin and subcutaneous tissue disorders	75	3.26	4	166.29	1.19	3.16	No
27	Acute kidney injury	Renal and urinary disorders	66	3.18	3.98	144.65	0.96	3.1	No

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
28	Palpitations	Cardiac disorders	60	2.99	3.79	121.09	0.8	2.93	Yes
29	Anxiety	Psychiatric disorders	99	2.57	3.05	136.25	1.13	2.49	Yes
30	Abdominal pain upper	Gastrointestinal disorders	71	2.43	3.01	94.21	0.84	2.37	Yes
31	Swelling face	General disorders and administration site conditions	28	2.36	3.39	44.94	0.03	2.33	No
32	Toxicity to various agents	Injury, poisoning, and procedural complications	67	2.34	2.92	83.46	0.75	2.29	No
33	Urticaria	Skin and subcutaneous tissue disorders	56	2.31	2.96	71.1	0.57	2.26	Yes
34	Insomnia	Psychiatric disorders	91	2.26	2.71	98.05	0.92	2.2	Yes
35	Tachycardia	Cardiac disorders	31	2.19	3.09	41.92	0.08	2.16	Yes
36	Heart rate increased	Investigations	35	2.17	3	44.69	0.15	2.14	No
37	Dry mouth	Gastrointestinal disorders	27	2.12	3.07	35.72	0	2.1	Yes
⩾65 Years									
1	Labeled drug–drug interaction medication error	Injury, poisoning, and procedural complications	62	17.67	22.26	1207.73	1.66	16.83	Yes
2	Drug interaction	General disorders and administration site conditions	487	20.16	18.08	7764.35	3.95	16.04	Yes
3	Torsade de pointes	Cardiac disorders	32	14.29	20.09	548.97	0.32	13.81	Yes
4	Erythema multiforme	Skin and subcutaneous tissue disorders	30	13.72	19.51	497.45	0.24	13.27	No
5	Dysgeusia	Nervous system disorders	97	10.26	12.14	969.6	2.55	9.77	Yes
6	Electrocardiogram QT prolonged	Investigations	58	8.71	11.07	515.77	1.29	8.42	Yes
7	Drug resistance	General disorders and administration site conditions	26	8.04	11.74	241.78	0.11	7.86	Yes

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
8	Gout	Metabolism and nutrition disorders	32	7.85	11.02	278.36	0.32	7.67	No
9	Nightmare	Psychiatric disorders	32	7.29	10.23	254.61	0.3	7.13	No
10	Chromaturia	Renal and urinary disorders	29	7.02	10.04	224.61	0.18	6.87	No
11	Rhabdomyolysis	Musculoskeletal and connective tissue disorders	68	7.03	8.74	455.17	1.55	6.8	Yes
12	International normalized ratio increased	Investigations	62	5.44	6.86	303.18	1.31	5.29	Yes
13	Hallucination	Psychiatric disorders	26	5.2	7.59	141.14	0.08	5.11	Yes
14	Hypoglycemia	Metabolism and nutrition disorders	60	5.17	6.54	275.25	1.16	5.03	Yes
15	Oral pain	Gastrointestinal disorders	23	4.99	7.48	121.72	0.01	4.91	Yes
16	Lip swelling	Gastrointestinal disorders	25	4.11	6.05	99.77	0.04	4.05	No
17	Delirium	Psychiatric disorders	39	3.85	5.22	128.4	0.41	3.78	No
18	Renal failure acute	Renal and urinary disorders	47	3.74	4.92	142.52	0.61	3.66	No
19	Pancytopenia	Blood and lymphatic system disorders	47	3.71	4.88	140.69	0.63	3.63	No
20	Hallucination	Psychiatric disorders	49	3.48	4.55	131.9	0.7	3.41	Yes
21	Toxicity to various agents	Injury, poisoning, and procedural complications	62	3.02	3.82	126.32	0.89	2.95	No
22	Hyperkalemia	Metabolism and nutrition disorders	36	2.95	4.06	79.85	0.27	2.91	No
23	Agitation	Psychiatric disorders	27	2.65	3.84	53.79	0.04	2.62	No
24	Bradycardia	Cardiac disorders	41	2.55	3.43	68.32	0.37	2.51	No
25	Acute kidney injury	Renal and urinary disorders	85	2.52	3.05	116.02	1.03	2.45	No
26	Palpitations	Cardiac disorders	39	2.46	3.33	61.47	0.27	2.42	Yes
27	Confusional state	Psychiatric disorders	80	2.28	2.79	91.03	0.89	2.23	Yes

(Continued)

Table 2. (Continued)

No.	PT	SOC	*N*	ROR_{025}	PRR	χ^2	IC – 2 SD	EB05	Whether included in the package insert
28	Insomnia	Psychiatric disorders	70	2.22	2.77	77.66	0.8	2.17	Yes
29	Muscular weakness	Musculoskeletal and connective tissue disorders	41	2.07	2.79	45.48	0.27	2.04	No
30	Hyperhidrosis	Skin and subcutaneous tissue disorders	35	2.04	2.83	39.68	0.14	2.02	Yes

AE, adverse event; IC, Information Component; PT, preferred term; PRR, proportional reporting ratio; ROR, reporting odds ratio; SOC, system organ class.

A total of 41 PT signals were not explicitly listed in the clarithromycin package insert, and were primarily concentrated in psychiatric disorders ($n=9$), skin and subcutaneous tissue disorders ($n=6$), gastrointestinal disorders ($n=5$), etc. Among these signals, 4 signals were not explicitly listed in the package insert for the age group of 0–17 years, 9 signals for the age group of 18–44 years, 14 signals for the age group of 45–64 years, and 14 signals for the age group of 65 years and above.

Signals related to age differences

Using the ROR method, the above warning signals are separately calculated for age-related signals. When the ratio of the signal value for children to the signal value for other age groups is >1.5, or when children produce signals while other age groups do not, these signals are considered specific to children; similarly, when the ratio of the signal value for elderly people to the signal value for other age groups is >1.5, or when elderly people produce signals while other age groups do not, these signals are considered specific to the elderly.[15–17] Through computation, it was found that there were 18 age-specific signals, including 3 for children and 15 for elderly people. Table 3 shows the results.

Discussion

Although adverse reactions related to clarithromycin have been reported and studied in clinical trials, there is a lack of comprehensive research on these AEs and insufficient studies focusing on specific populations. This study is the first pharmacovigilance investigation of clarithromycin-related AEs based on real-world data from the FAERS database. By utilizing a specific time frame of FAERS data for comparison, we conducted a disproportionality analysis to identify AEs significantly associated with clarithromycin therapy, revealing differences in AE risks across various age groups. Our research represents the largest post-marketing study of clarithromycin AEs conducted in a real-world setting to date. Through this large-scale, widely encompassing database, we can provide a more comprehensive depiction of the potential AEs encountered by different age groups during clarithromycin use, particularly in elderly and pediatric populations, where specific risks are highlighted.

Analysis of signals in children

In the 0–17 age group, the highest number of reports occurred in the 1–4 age group. This may be related to the relatively lower safety profile of clarithromycin in this age group, possibly due to factors such as increased susceptibility to adverse effects. Studies by Bourgeois et al. and Kimland et al. have shown that adverse reactions are more common in younger children, with 43%–61% of events originating from children aged 0 to 4.[18,19] The most frequently reported adverse reactions to clarithromycin in the 0–17 age group are gastrointestinal disorders, mainly vomiting and

Table 3. Signals related to age differences.

Child-specific signals			Elderly specific signals		
Adverse event	**Frequency**	**Signal risk ratio**	**Adverse event**	**Frequency**	**Signal risk ratio**
Vomiting[a]	89	2.79	Gout[b]	32	7.85
Drug hypersensitivity[a]	15	2.4	Pancytopenia[b]	47	3.71
Dyspnea	36	2.32	Hyperkalemia[b]	36	2.95
			Chromaturia	29	2.86
			Bradycardia[b]	41	2.55
			Drug resistance	26	2.43
			Drug interaction	487	2.38
			Torsade de pointes	32	2.36
			Rhabdomyolysis	68	2.25
			Electrocardiogram QT prolonged	58	2.22
			Muscular weakness[b]	41	2.07
			Hyperhidrosis[b]	35	2.04
			Hypoglycemia	60	1.97
			Oral pain	23	1.88
			Renal failure acute	85	1.76

[a]Signals generated by children rather than signals not generated by children.
[b]Signals generated by elderly individuals rather than signals not generated by elderly individuals.

upper abdominal pain, which is consistent with the clarithromycin label.[5] Among them, vomiting is also a high-risk signal for clarithromycin in children, with a high frequency of occurrence. Vomiting is a common symptom in children and is usually benign. However, clinical physicians must be able to identify this complication promptly and avoid serious complications.[20] The adverse reaction with the strongest signal intensity was abnormal product taste, which was not mentioned in the clarithromycin label. Clarithromycin has a strong bitter taste, which affects patient compliance and treatment efficacy. Therefore, improvements in design can optimize taste masking.[21]

In addition to vomiting, two specific signals were detected in children receiving clarithromycin (drug hypersensitivity, dyspnea). Research by Marrs et al. indicated that children under 4 years old most commonly present to drug allergy clinics, suggesting that young children may be more susceptible to antibiotic allergies.[22] Guvenir et al. evaluated hypersensitivity reactions in children to non-β-lactam antibiotics, among which clarithromycin (63.6%) was the most commonly reported cause of hypersensitivity reactions.[23] Conducting oral provocation tests to diagnose clarithromycin-induced hypersensitivity reactions is crucial because they can manifest in various clinical presentations, ranging from mild skin reactions to life-threatening severe skin reactions.[24] Skin reactions are closely associated with hypersensitivity reactions, with rash being the most common hypersensitivity reaction.[25] In addition, there are severe adverse skin reactions, including

Stevens-Johnson syndrome.[26] Suleyman et al. reported that confirmed β-lactam allergy is a risk factor for clarithromycin hypersensitivity reactions, especially in patients who develop rash following amoxicillin–clavulanic acid treatment before clarithromycin therapy.[27] For individuals allergic to this drug, its use should be prohibited. Dyspnea is a specific signal in children and is not included in the label. Research by Gangemi et al. during drug provocation tests revealed that after administering a 1/4 therapeutic dose of clarithromycin, patients exhibited dyspnea, coughing, and bronchospasm in all lung fields.[28] Clinical physicians should note that dyspnea is a pediatric-specific adverse reaction not listed on the label.

Signal analysis in adults

The signals detected in the 18- to 44-year-old and 45- to 64-year-old age groups for clarithromycin were similar, with AE signals predominantly related to psychiatric disorders in these populations. The signals mainly included nightmare, hallucination, psychotic disorder, panic attack, disorientation, mania, insomnia, paranoia, confusional state, nervousness, anxiety, and agitation, among which four signals—nightmare, panic attack, paranoia, and agitation—were not labeled in the instructions. Wallace et al. first reported clarithromycin-induced neurotoxicity in 1993, describing central nervous system side effects in seven patients receiving high-dose antibiotics (1200 mg/day) with mild renal impairment. The observed adverse reactions included altered consciousness, dizziness, and insomnia, but these symptoms improved when the dose was reduced to 1000 mg/day.[29] Rare neurological and psychiatric sequelae of clarithromycin have been reported.[30] Bandettini di Poggio et al. reviewed the literature on adult neurotoxicity induced by clarithromycin and reported adverse reactions in the central nervous system, including central nervous system depression (altered consciousness and lethargy) or excitation (agitation, insomnia, delirium, and psychosis).[3] Studies have shown that both high and low doses of clarithromycin may cause neurological side effects, and drug interactions are important underlying causes of neurotoxicity. When patients simultaneously use clarithromycin and other drugs metabolized by the cytochrome P450 enzyme of the CYP3A family, the risk of neurotoxicity is greater.[3, 31–35]

Due to the widespread use of clarithromycin, clinicians should be aware of its neurotoxicity and be vigilant for potential neurological and psychiatric symptoms. Early detection of clarithromycin (CLA)-induced neurotoxicity and prompt discontinuation of the drug are crucial. Bandettini di Poggio et al. recommend performing electroencephalography (EEG) in the diagnostic evaluation of CLA-induced neurotoxicity.[3]

Signal analysis in elderly

In elderly individuals (⩾65 years), strong signals for clarithromycin infection mainly include labeled drug–drug interaction medication errors, drug interactions, and cardiac-related AEs such as prolonged torsade de pointes and electrocardiogram QT, all of which are specific signals for clarithromycin in the elderly population.

Medication interactions are a common reason for hospital admission in elderly individuals.[36] Clarithromycin interacts with a variety of drugs, being a stronger CYP450 inhibitor than erythromycin, and appears to have more frequent and severe drug interactions.[37] Clarithromycin interacts with statin drugs, particularly those metabolized by CYP3A4, increasing the risk of skeletal muscle toxicity.[38] Kunakorntham et al. and Pasqualetti et al. reported associations between clarithromycin and rhabdomyolysis.[39,40] Rhabdomyolysis is a clinical syndrome of skeletal muscle injury characterized by muscle pain, weakness, dark-colored urine, and acute kidney injury, with the most common presenting symptoms being muscle pain, weakness, and tea-colored urine.[41] Rhabdomyolysis, pigmenturia, muscle weakness, and acute kidney injury are specific signals in elderly individuals, possibly resulting from interactions between clarithromycin drugs. Coadministration of clarithromycin with calcium channel blockers can also cause acute kidney injury. A large retrospective cohort study revealed that patients prescribed both calcium channel blockers and clarithromycin had an increased risk of hospitalization and acute kidney injury.[42] The Girardeau algorithm confirmed previously identified signals of acute kidney injury associated with clarithromycin and calcium channel blockers.[43] Interactions between clarithromycin and colchicine can also lead to renal impairment.[44] Villa Zapata et al.'s retrospective study revealed that concurrent use of colchicine

and clarithromycin can result in leukopenia, thrombocytopenia, rhabdomyolysis, and renal failure.[45] Clinicians should monitor white blood cell count, creatine kinase (CK), renal function, and liver function, with symptom monitoring including identification of the aforementioned symptoms. Concurrent use of clarithromycin and sulfonylureas can lead to hypoglycemia,[46] which is also a specific signal in elderly individuals using clarithromycin. Case reports have shown severe hypoglycemia related to the interaction between clarithromycin and repaglinide.[47] Kennedy et al. found a significant association between clarithromycin and hypoglycemia through analysis of adverse reactions of hypoglycemia in the FAERS.[48] Adverse reactions involving cardiac organs, such as torsades de pointes and prolonged QT intervals on electrocardiograms, have been reported, suggesting an increased risk of adverse cardiac reactions with clarithromycin.[49,50] Currently, the Summary of Product Characteristics for clarithromycin advises caution in patients with coronary artery disease and recommends against use in patients with a history of ventricular arrhythmias.[51]

Drug interactions are preventable causes of morbidity and mortality. Before prescribing clarithromycin, clinicians should strictly adhere to the label instructions and review the patient's medication list. Patients with heart disease should not use clarithromycin. Electrolyte levels should be monitored during oral clarithromycin therapy. Patients with diabetes using sulfonylureas and patients with hyperlipidemia undergoing lipid-lowering therapy should use clarithromycin cautiously, with timely monitoring of blood glucose and biochemical markers related to rhabdomyolysis, including renal function, CK, blood potassium, and myoglobinuria. Patients using calcium channel blockers should closely monitor related drug concentrations.[52–54]

Limitations

This study has several limitations. First, the FAERS database is a global spontaneous reporting system that has inherent issues such as underreporting, overreporting, misreporting, incomplete information, and non-standardized data.[55] The number of patients receiving clarithromycin treatment who did not report AEs is unknown, and there is a lack of denominator data. As a result, we cannot establish a causal relationship between clarithromycin and AEs, nor can we calculate the true incidence of clarithromycin-related AEs. Furthermore, each report lacks specific treatment duration data, which hinders our ability to conduct further risk analysis on clarithromycin-related AEs. Third, there is a lack of certain key information, such as the patient's medical history, concomitant medications, or treatment regimen, which may influence the occurrence of AEs. It is challenging to fully obtain this information. This study also did not completely differentiate between the drug indications, as reports of unknown indications were relatively common, and missing values were frequent. In addition, spontaneous reporting data are typically less reliable than data collected in clinical trials and cohort studies, and comparisons between different age groups are limited by potential imbalances in patient characteristics. Despite the limitations of FAERS, our findings provide insights into the basic aspects of clarithromycin-related AEs across different age groups and may serve as a foundation for subsequent rigorous prospective studies.

Conclusion

In summary, this study provides an objective reference for pharmacovigilance by exploring the safety signals of clarithromycin use across different age groups. The safety of clarithromycin is different in different age groups. Children are more closely associated with AEs related to vomiting, drug-induced hypersensitivity, and dyspnea. In adults, it is more associated with psychiatric AEs. In addition, the use of clarithromycin in the elderly should be strictly in accordance with the instructions and be alert to drug interactions.

Declarations

Ethics approval and consent to participate

Not applicable. FDA Adverse Event Reporting System is a spontaneous reporting system, the publicly available data are anonymized, and therefore, obtaining consent to participate is not applicable. The present pharmacovigilance study was conducted using a public database of spontaneous reports. Given the use of deidentified data, ethical approval was not considered necessary.

Consent for publication

Not applicable.

Author contributions

Haiyan Mai: Data curation; Resources; Writing – original draft; Writing – review & editing.

Zhenpo Zhang: Data curation; Resources; Writing – original draft; Writing – review & editing.

Yankun Liang: Investigation; Methodology; Software.

Jingping Zheng: Software; Supervision.

Ling Su: Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the US FAERS repository (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers).

Code availability

The R script developed for the analyses is available from the corresponding author upon reasonable request.

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