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Evaluation of atypical antipsychotics associated rhabdomyolysis using the FDA adverse event reporting system database

Yi Yin✉, Jie Jiang & Youpeng Jin✉

Rhabdomyolysis is a potentially fatal adverse reaction mainly caused by certain medications. Few real-world studies have shown a clear association between atypical antipsychotics and rhabdomyolysis. This study aimed to evaluate the association between atypical antipsychotics and rhabdomyolysis using the FDA Adverse Event Report System (FAERS) database. The data were obtained from the FAERS database from January 1, 2004 to December 31, 2023. To identify potential risk signals from the FAERS database, a disproportionality analysis was conducted using the reporting odds ratio (ROR) and corresponding 95% confidence intervals (CIs) with *p*-values adjusted via Bonferroni correction. The time to onset, hospitalization rate, and mortality of atypical antipsychotics associated rhabdomyolysis were also investigated. A total of 2360 rhabdomyolysis case reports from the FAERS database were considered. Quetiapine had the greatest proportion (27.75%). Olanzapine had the highest positive signal values of rhabdomyolysis. Statistically significant rhabdomyolysis RORs (95% CI) for atypical antipsychotics were (in descending order): olanzapine 4.02 (3.72–4.35), quetiapine 3.81 (0.53–27.6), ziprasidone 2.76 (2.19–3.49), risperidone 2.12 (1.91–2.35), aripiprazole 2 (1.8–2.21), clozapine 1.47 (1.31–1.64). In the time to onset analysis, all atypical antipsychotics associated rhabdomyolysis had early failure type characteristics, the risk of rhabdomyolysis occurrence would be gradually decreased over time. Our study highlights the importance of vigilant patient monitoring following the prescription of atypical antipsychotics to reduce the risk of rhabdomyolysis. It is necessary to monitor serum creatinine kinase (CK) level early, especially during dose adjustment or initiation of new atypical antipsychotics. This research may provide a valuable information for patients, clinicians, and others concerned with the safety of atypical antipsychotics, and optimize clinical practice.

Keywords Rhabdomyolysis, Atypical antipsychotics, Pharmacovigilance, Adverse event, The FDA adverse event reporting system (FAERS)

Rhabdomyolysis is a clinical syndrome characterized by skeletal muscle injury, leading to the breakdown and necrosis of muscle tissue and the release of intracellular contents into the bloodstream[1]. The severity of rhabdomyolysis can range from an asymptomatic elevation in creatinine kinase (CK) to severe life-threatening symptoms such as cardiac arrhythmia, disseminated intravascular coagulation (DIC) and acute renal failure[1].

The etiology of rhabdomyolysis is diverse. It can be caused by infections (viral, bacterial, or other), drugs, physical factors, neuroleptic malignant syndrome or heat stroke[2–4]. The toxicity of exogenous drugs to skeletal muscles is a common non-traumatic cause of rhabdomyolysis, with the most commonly suspected drugs include alcohol, illicit drugs and lipid-lowering agents[3,5–8].

Mental illness has been a social and economic burden worldwide. The World Economic Forum reported that mental illness is the largest source of global gross domestic product (GDP) loss among non-communicable diseases in 2011[9]. Since the introduction of chlorpromazine, the first antipsychotic drug in the 1950s, the efficacy and side effects of antipsychotic drugs have been a concern[10]. Compared to traditional antipsychotics,

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atypical antipsychotics have comparable therapeutic effects with fewer extrapyramidal reactions[11]. However, the increasing usage of atypical antipsychotic drugs have also raised the concerns about their safety[12]. The common adverse events (AEs) of atypical antipsychotics include nausea, vomiting, constipation and weight gain. In addition, other AEs of atypical antipsychotics, such as rhabdomyolysis, have also been reported in recent years[13–15]. Although it is a rare event, these reports suggest that rhabdomyolysis may be an overlooked risk associated with these medications.

Considering the limitations of insufficient epidemiological data and clinical methods, it is difficult to conduct clinical studies and systematic reviews of rhabdomyolysis caused by different atypical antipsychotics. Therefore, it is a cost-effective method to assess adverse reactions of drugs by using a real-world FDA adverse Event Reporting System (FAERS) database. The FAERS database contains millions of real-world reports from various sources and has been widely used in pharmacovigilance research and drug safety evaluation[16].

Our study aims to quantify the safety signal strength between different atypical antipsychotic drugs and rhabdomyolysis, investigate the time to onset, hospitalization rates, and mortality of different atypical antipsychotics associated rhabdomyolysis, and further provide better insights into the safety evaluation of atypical antipsychotics and optimize clinical decision.

Methods

Data source and extraction criteria

The data of the retrospective pharmacovigilance study was from FAERS database. FAERS is a publicly available database composed of adverse event reports voluntarily submitted to the FDA. FAERS data files consist of seven databases: demographic and administrative information (DEMO), adverse drug reaction information (REAC), patient outcome information (OUTC), drug information (DRUG), drug therapy starts and end dates (THER), information on report sources (RPSR), and indications for use/diagnosis (INDI). The data for this study were obtained from the ASCII files in the FAERS database from 2004 Quarter 1 (Q1) to 2023 Q4 with the open tool OpenVigil 2.1(https://openvigil.sourceforge.net/). OpenVigil 2.1 is a validated pharmacovigilance tool for analyzing cleaned FAERS drug-event data[17]. Our study investigated atypical antipsychotics that were approved by FDA before 2004 to minimize bias related to the time of market. Each atypical antipsychotic was identified in FAERS by generic names, brand names and chemical names. To improve the association between drugs and AEs, only the reported role coded as "PS" (Primary Suspect Drug) were evaluated for inclusion. The AEs of atypical antipsychotics were encoded using the preferred terms (PTs) in the Medical Dictionary for Regulatory Activities 26.1 (MedDRA). Standardized MedDRA Queries (SMQs) are groupings of MedDRA terms, usually at the PT level, which relate to an adverse drug reaction. Our study selects PTs in the narrow-scope search of "Rhabdomyolysis/Myopathy (SMQ 20000002)" to identify the target AE reports (Table 1). A detailed flow chart is shown in Fig. 1.

Data mining

Based on the classical two-by-two contingency table, a disproportionality analysis was conducted by computing Reporting Odds Ratios (ROR) and corresponding 95% confidence intervals (95%CI) for the association between rhabdomyolysis and each atypical antipsychotic[18]. ROR was calculated as the ratio of the odds of reporting rhabdomyolysis versus all other AEs for a given drug, compared with the reporting odds for all other drugs present in FAERS[18]. An association was considered statistically significant if the lower limit of 95%CI was above 1.0 and p-adjust < 0.05. P-adjust is the p-value adjusted by Bonferroni correction. The equations and criteria for the algorithm are shown in Supplementary Table S1. A higher ROR suggested a stronger association between the atypical antipsychotics and rhabdomyolysis.

PT	MedDRA code
Muscle infarction	10086278
Muscle necrosis	10028320
Myoglobin blood increased	10028625
Myoglobin blood present	10059888
Myoglobin urine present	10028631
Myoglobinaemia	10058735
Myoglobinuria	10028629
Myopathy	10028641
Myopathy toxic	10028648
Necrotising myositis	10074769
Rhabdomyolysis	10039020
Thyrotoxic myopathy	10081524

Table 1. PTs contained in the narrow-scope search of "rhabdomyolysis/myopathy (SMQ 20000002)". PT, preferred term; MedDRA, Medical dictionary for drug regulatory activities; SMQ, Standardized MedDRA querie.

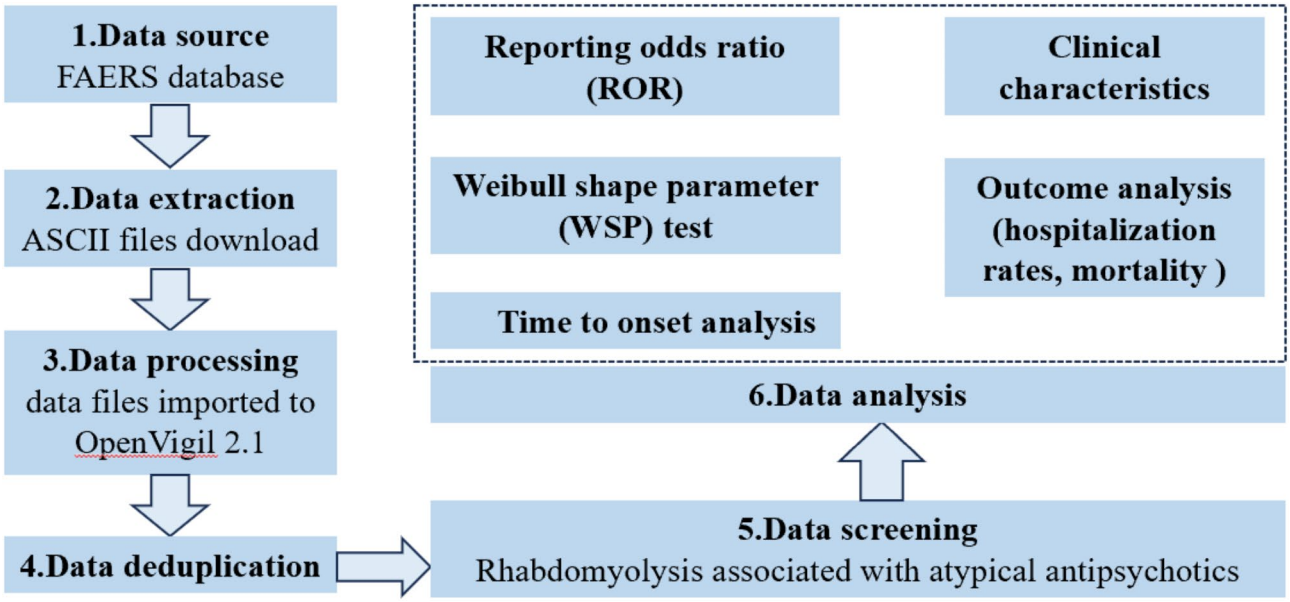

Fig. 1. Flow chart of data extraction, processing, and analysis from the FAERS database.

Time to onset of atypical antipsychotics associated rhabdomyolysis

Time to onset (TTO) was defined as the duration time between the START_DT in THER file (date of atypical antipsychotics treatment initiation) and EVENT_DT in DEMO file (date of adverse event onset)[19]. Only the reports with available TTO data were analyzed. Inaccurate and missing data, input error reports were excluded to ensure the accuracy of TTO.

The incidence of adverse events varies over time after the initiation of drug treatment. TTO analysis was conducted using the Weibull shape parameter (WSP) test to describe the risk that the incidence of AEs increases or decreases over time[20].

The shape of Weibull distribution was described by two parameters: scale (α) and shape (β). The scale parameter α of the Weibull distribution determines the scale of the distribution function. The shape parameter β of the Weibull distribution determines the shape of the distribution function. Three hazard types are described in WSP test: early failure type means the hazard of the AEs decreases over time ($\beta < 1$ and 95% CI < 1); random failure type means the hazard of the AEs constantly occurs over time (β was equal to or nearly 1 and its 95% CI included the value 1); wear-out failure type means the hazard of the AEs increases over time ($\beta > 1$ and 95% CI > 1).

Statistical analysis

Descriptive analysis was applied to summarize the clinical characteristics of rhabdomyolysis patients resulting from atypical antipsychotics in the FAERS database. As the data were not normally distributed, the Kruskal-Wallis test was used to compare the time to onset of atypical antipsychotics associated rhabdomyolysis. Fisher's exact test was utilized to compare the outcome of events(including hospitalization rates and mortality) between different atypical antipsychotics. The statistical significance was set at $p < 0.01$ with 95% confidence intervals. All statistical analysis was conducted using R version 4.4.1 software.

Results

Descriptive analysis of atypical antipsychotics associated with rhabdomyolysis in the FAERS database

From 2004 Q1 to 2023 Q4, a total of 52,159,321 atypical antipsychotics associated AE cases were recorded in the FAERS database, among which 2360 cases were for rhabdomyolysis. The annual AE cases were shown in Fig. 2. Quetiapine was the most reported drug in rhabdomyolysis cases ($n = 655$, 27.75%), followed by olanzapine ($n = 621$, 26.31%), aripiprazole ($n = 364$, 15.42%), risperidone ($n = 362$, 15.34%), clozapine ($n = 290$, 12.29%), ziprasidone ($n = 67$, 2.84%), zotepine ($n = 1$, 0.04%). In terms of age, the group of 18 ~ 64.9 accounted for majority of the proportion. In terms of regions, Europe and North America had higher proportions.

In terms of gender, all six drugs were more commonly reported in men than in women. Most reports were submitted by clinicians, other health professionals, and pharmacists. The reported clinical characteristics of atypical antipsychotics associated rhabdomyolysis are described in Table 2.

Disproportionality analysis

Rhabdomyolysis signals for the atypical antipsychotics under the criteria of the ROR are summarized in Fig. 3. A total of 2,359 rhabdomyolysis reports from the FAERS database were considered. Olanzapine had the highest positive signal values of rhabdomyolysis. Statistically significant rhabdomyolysis RORs (95% CI) for atypical

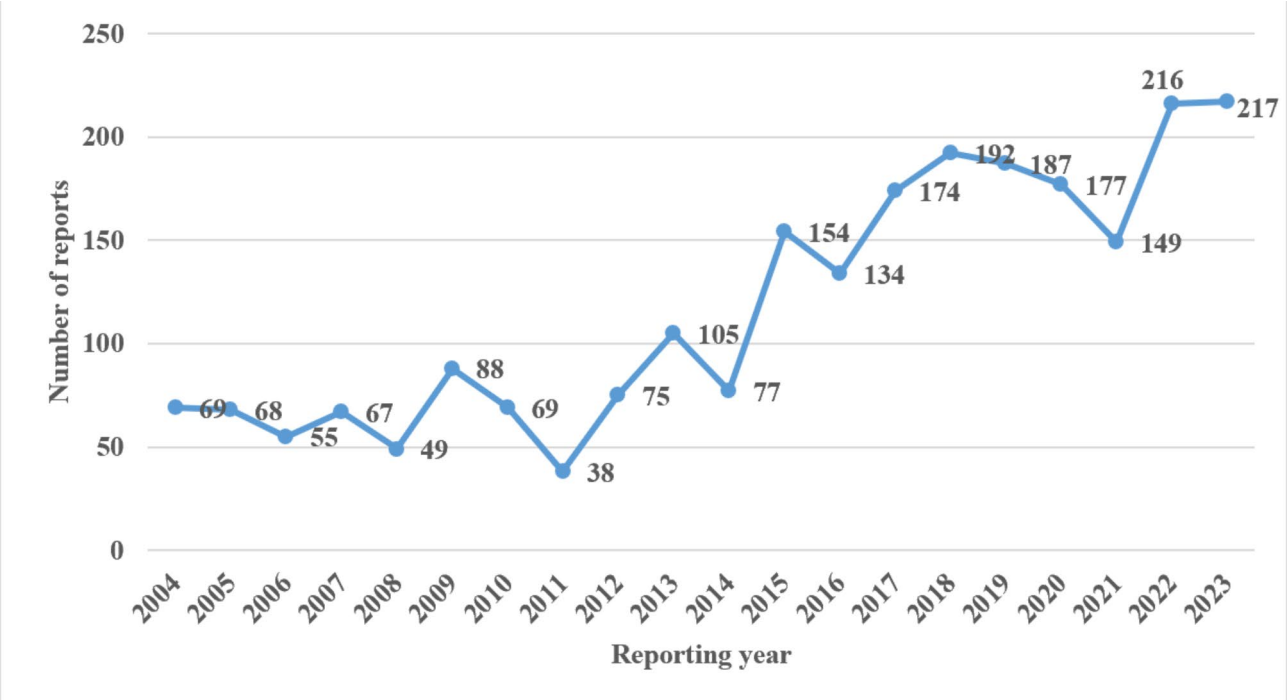

Fig. 2. The annual AE case reports of atypical antipsychotics associated rhabdomyolysis in the FAERS database.

antipsychotics were (in descending order): olanzapine 4.02 (3.72–4.35), quetiapine 3.81 (0.53–27.6), ziprasidone 2.76 (2.19–3.49), risperidone 2.12 (1.91–2.35), aripiprazole 2 (1.8–2.21), clozapine 1.47 (1.31–1.64).

Time to onset of atypical antipsychotics associated rhabdomyolysis

The time to onset of atypical antipsychotics associated rhabdomyolysis is illustrated in Table 3. According to the data, the median onset time of clozapine associated rhabdomyolysis was 595.0 days [interquartile range (IQR) 82.5–2616.0], which was significantly longer than that of olanzapine (174.0 days, IQR 10.0–551.0), aripiprazole (35.5 days, IQR 14.0–131.5), quetiapine (31.0 days, IQR 7.0–143.0), ziprasidone (25.0 days, IQR 6.0–36.5), risperidone (11.0 days, IQR 8.0–93.5) (Kruskal-Wallis test, $p < 0.001$). In the WSP analysis, the upper limits of 95% CI of the shape parameters β were < 1, suggesting the risk of rhabdomyolysis occurrence gradually decreased over time. The detailed information is shown in Supplementary Table S2.

Outcome of events due to atypical antipsychotics associated rhabdomyolysis

Table 2 showed the congenital anomaly rate of olanzapine associated with rhabdomyolysis was 0.5%, none were found for the other five drugs. The rates of mortality and hospitalization due to rhabdomyolysis associated with atypical antipsychotics were assessed. The hospitalization rate of all six atypical antipsychotics was above 40%. There were no statistically significant differences between the groups. However, the mortality rate of rhabdomyolysis caused by aripiprazole is1.9%, which was significantly lower than that of olanzapine, quetiapine, risperidone and clozapine (Fisher's exact test, $p < 0.01$). Details of the statistical analysis can be found in Supplementary Table S3.

Discussion

To the best of our knowledge, this is the largest real-world comparative study reporting rhabdomyolysis after treatment with atypical antipsychotics along with a supportive disproportionality analysis. Most of our data were collected from professionals, including physicians, pharmacists, and other health professionals. Those ensured the reliability and accuracy of our study.

Our study found the highest rates of reporting in Europe and North America, which may be related to differences in regional perceptions and cognition of mental disease. Interestingly, the incidence of rhabdomyolysis associated with atypical antipsychotics in our study was significantly higher in men than in women, which is consistent with the literature[7]. A possible reason is the protective effect that increased estrogen levels in women have on muscle[21,22]. Another possible reason is geographical and racial differences. Most of our data comes from Europe and North America, and African Americans have a higher risk of developing rhabdomyolysis than Caucasians[23].

Of all atypical antipsychotics approved before 2004, we identified six drugs that had significant reporting associations with rhabdomyolysis at the ROR level. The founding may be attributed to the comprehensive nature of our study, which analyzed a large, real-world dataset from the FAERS database. The safety and side

Characteristics	Reports (*N*, %)					
	Olanzapine (621)	Quetiapine (655)	Ziprasidone (67)	Risperidone (362)	Aripiprazole (364)	Clozapine (290)
Patient age (year)						
< 18	41 (6.60)	35 (5.34)	2 (2.99)	27 (7.46)	12 (3.30)	8 (2.76)
18～64.9	386 (62.16)	440 (67.18)	41 (61.19)	226 (62.43)	193 (53.02)	202 (69.66)
65～85	85 (13.69)	66 (10.08)	5 (7.46)	52 (14.36)	50 (13.74)	23 (7.93)
> 85	5 (0.81)	9 (1.37)	0 (0.00)	3 (0.83)	5 (1.37)	2 (0.69)
Unknown	104 (16.75)	105 (16.03)	19 (28.36)	54 (14.92)	104 (28.57)	55 (18.97)
Patient gender						
Female	204 (32.85)	217 (33.13)	18 (26.87)	82 (22.65)	122 (33.52)	68 (23.45)
Male	363 (58.45)	391 (59.69)	40 (59.70)	240 (66.30)	194 (53.30)	209 (72.07)
Unknown	54 (8.70)	47 (7.18)	9 (13.43)	40 (11.05)	48 (13.19)	13 (4.48)
Reporting regions						
Africa	2 (0.32)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Asia	78 (12.56)	63 (9.62)	4 (5.97)	54 (14.92)	87 (23.90)	8 (2.76)
Europe	337 (54.27)	351 (53.59)	7 (10.45)	203 (56.08)	159 (43.68)	146 (50.34)
Oceania	13 (2.09)	27 (4.12)	0 (0.00)	1 (0.28)	3 (0.82)	16 (5.52)
North America	145 (23.35)	182 (27.79)	44 (65.67)	84 (23.20)	103 (28.30)	97 (33.45)
South America	0 (0.00)	8 (1.22)	0 (0.00)	2 (0.55)	0 (0.00)	0 (0.00)
Unknown	46 (7.41)	24 (3.66)	12 (17.91)	18 (4.97)	12 (3.30)	23 (7.93)
Reporters						
Consumer	123 (19.81)	44 (6.72)	3 (4.48)	15 (4.14)	98 (26.92)	11 (3.79)
Health professional	80 (12.88)	89 (13.59)	3 (4.48)	50 (13.81)	16 (4.40)	32 (11.03)
Lawyer	10 (1.61)	2 (0.31)	1 (1.49)	0 (0.00)	1 (0.27)	0 (0.00)
Physician	264 (42.51)	241 (36.79)	34 (50.75)	127 (35.08)	145 (39.84)	109 (37.59)
Other health-professional	96 (15.46)	143 (21.83)	11 (16.42)	121 (33.43)	71 (19.51)	79 (27.24)
Pharmacist	43 (6.92)	90 (13.74)	11 (16.42)	33 (9.12)	31 (8.52)	44 (15.17)
Unknown	5 (0.81)	46 (7.02)	4 (5.97)	16 (4.42)	2 (0.55)	15 (5.17)
Outcome of events						
CA	6 (0.54)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
DE	57 (5.11)	59 (5.34)	2 (1.57)	27 (4.85)	12 (1.91)	28 (5.51)
DS	9 (0.81)	42 (3.80)	3 (2.36)	7 (1.26)	17 (2.71)	5 (0.98)
HO	516 (46.28)	457 (41.36)	55 (43.31)	262 (47.04)	252 (40.19)	229 (45.08)
LT	152 (13.63)	167 (15.11)	19 (14.96)	57 (10.23)	69 (11.00)	69 (13.58)
OT	354 (31.75)	335 (30.32)	44 (34.65)	199 (35.73)	266 (42.42)	168 (33.07)
RI	3 (0.27)	12 (1.09)	4 (3.15)	3 (0.54)	3 (0.48)	1 (0.20)
Unknown	18 (1.61)	33 (2.99)	0 (0.00)	2 (0.36)	8 (1.28)	8 (1.57)

Table 2. Clinical characteristics of patients with atypical antipsychotic drugs associated rhabdomyolysis collected from the FAERS database (2004 Q1 to 2023 Q4). FAERS, The Food and Drug Administration Adverse Event Reporting System; CA, Congenital anomaly; DE, Death; DS, Disability; HO, Hospitalization-initial or prolonged; LT, Life-threatening; OT, Other serious (important medical event); RI, Required intervention to prevent permanent impairment/damage.

effects of atypical antipsychotics have been a focus of concern[10,11,24–28]. Currently only olanzapine, aripiprazole, risperidone, and clozapine list rhabdomyolysis as a possible adverse event on their labels. Our study will help to arouse the clinician's concern of rhabdomyolysis caused by atypical antipsychotics, guide the precautions in clinical treatment and improve the prognosis.

Olanzapine had the highest positive signal values. The other atypical antipsychotics associated rhabdomyolysis reports included quetiapine, ziprasidone, risperidone, aripiprazole, clozapine. A possible mechanism is that olanzapine has a higher affinity for 5-hydroxytryptamine (5-HT) 2a receptors in skeletal muscle (Ki = 2.5 nM) compared with five other atypical antipsychotic drugs, which may reduce the density or block the receptor, thereby affecting glucose uptake and causing changes in the muscle membrane. These lead to increased permeability of CK, resulting in the diffusion of large amounts of CK from skeletal muscle into the circulation[27–30].

Our study found that quetiapine had the most cases (n = 655) of all atypical antipsychotics associated rhabdomyolysis. A quality review of patients with rhabdomyolysis and a retrospective chart review published in 2009 both indicated that quetiapine was the most commonly associated drug other than statin therapy[31,32]. Additionally, as the most commonly prescribed antipsychotic[33,34], the increased use of quetiapine in the population may also be a contributing factor.

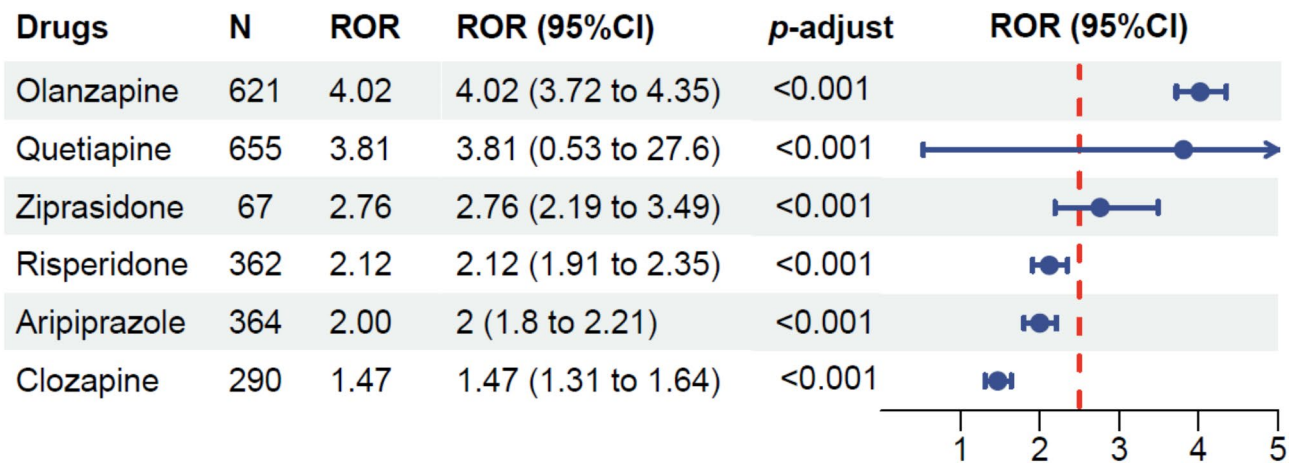

Fig. 3. RORs with 95% CI of atypical antipsychotic drugs associated rhabdomyolysis from the FAERS Database.

Drugs	TTO (Days)	Weibull distribution		Failure type
	Median (IQR)	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	
Olanzapine	174.0 (10.0,551.0)	261.27 (180.48,342.07)	0.52 (0.46,0.58)	Early failure
Quetiapine	31.0 (7.0,143.0)	97.73 (56.57,138.89)	0.47 (0.40,0.53)	Early failure
Ziprasidone	25.0 (6.0,36.5)	31.96 (7.38,56.54)	0.70 (0.44,0.96)	Early failure
Risperidone	11.0 (8.0,93.5)	100.92 (20.16,181.68)	0.38 (0.31,0.46)	Early failure
Aripiprazole	35.5 (14.0,131.5)	89.24 (59.13,119.34)	0.61 (0.53,0.69)	Early failure
Clozapine	595.0 (82.5,2616.0)	1108.08 (718.53,1497.62)	0.58 (0.49,0.67)	Early failure

Table 3. The time to onset (TTO) of atypical antipsychotics associated rhabdomyolysis. FAERS: the Food and Drug Administration Adverse Event Reporting System. AE: adverse event; FAERS: the Food and Drug Administration Adverse Event Reporting System. ROR: reporting odds ratio; CI: confidence interval; FAERS: the Food and Drug Administration Adverse Event Reporting System; *p*-adjust is the *p*-value adjusted by Bonferroni correction.

In the TTO analysis, the median TTO of atypical antipsychotics associated rhabdomyolysis varied, with the median time for adverse events ranging from 11 days to 595 days. Of note, clozapine associated rhabdomyolysis had the longest median time to onset. The mechanism remains unclear, and there are limited reports in the literature. Previous pharmacovigilance studies on clozapine have reported adverse reactions such as rhabdomyolysis[35], but data of TTO are lacking. A descriptive and exploratory study reported 16 cases of antipsychotic-related rhabdomyolysis in children and adolescents, including one case with the longest time to onset (TTO) of 1.5 years, although the specific drug involved was not described[36].

In addition, WSP test was conducted to observe the relationship between adverse events and time after the initiation of atypical antipsychotics treatment. All atypical antipsychotics associated rhabdomyolysis had early failure type characteristics, suggesting that the AE of rhabdomyolysis may develop in a few days with atypical antipsychotics treatment, and the risk of rhabdomyolysis occurrence would be gradually decreased over time. Clinicians should be aware of the potential toxicity of rhabdomyolysis induced by atypical antipsychotics, especially in the early stages of treatment. Early monitoring of serum CK level and timely detection of potential risks can help patients to maintain long-term medication and improve prognosis. Further prospective studies and long-term follow-up are needed to validate our results.

The dose of atypical antipsychotic medications may also be an important consideration for the development of rhabdomyolysis. Ezequiel Martí-Bonmatí et al. reported a case of a patient taking olanzapine, where the serum CK levels were significantly higher at a dose of 10 mg/day compared to 5 mg/day[37]. Another retrospective review showed that significant CK elevations were observed in 17% of patients who presented to the hospital after olanzapine treatment. Moreover, the myotoxicity gradually increased with the high doses of olanzapine[38]. These findings suggest that olanzapine has a dose-dependent effect. However, different outcomes have been observed with other atypical antipsychotics such as quetiapine and clozapine[14,39,40]. Due to the small sample sizes of these studies, further large-scale research is needed to confirm the relationship between atypical antipsychotics and serum CK level.

To our surprise, in the outcome of atypical antipsychotics associated rhabdomyolysis, there were six congenital anomaly cases with olanzapine but none with the other drugs. A large study in the United States of nearly 1,400 live births exposed to olanzapine during fetal development showed teratogenic risks [RR = 1.09, 95%CI (0.85,

1.41)][41]. A cohort study from five Nordic countries and the United States between 1996 and 2018 found that increased risks for oral cleft after olanzapine exposure (adjusted relative risks, 2.1 [95% CI, 1.1–4.3])[42]. A large, retrospective, population-based cohort study from Finland found that first-trimester gestational exposure to atypical antipsychotics was not associated with a significantly increased major congenital malformation (MCM) risk relative to either no exposure or exposure to first-generation antipsychotics. However, in exploratory analyses, olanzapine was associated with increased risk relative to unexposed pregnancies, specifically for musculoskeletal malformations[42]. A case has been reported of a Nepalese woman with schizophrenia who was treated with olanzapine throughout her pregnancy delivering a baby boy with congenital talipes equinovarus deformity[43]. Negative effects of olanzapine on bone development have also been found in animal experiments in mice[44]. Further research is needed to strengthen the potential link between olanzapine exposure in the first trimester and the development of clubfoot in infants. Therefore, olanzapine should only be used when the potential benefits outweigh the possible risks to the fetus, suggesting that clinicians need to be mindful of pregnancy status when prescribing this medication.

The prognosis of rhabdomyolysis largely depends on the underlying cause and associated complications. Rhabdomyolysis can be life-threatening due to acute renal failure[1,45], early and aggressive treatment can improve patient outcomes[46]. Our study found that more than 40% of rhabdomyolysis caused by atypical antipsychotics required hospitalization. This suggests that clinicians should be more aware of this risk and teach patients to recognize the signs of rhabdomyolysis early, such as myalgia, myasthenia, or brown urine during the course of medication.

In terms of mortality related to antipsychotic-induced rhabdomyolysis, aripiprazole had a lower mortality compared to other drugs like olanzapine, quetiapine, risperidone and clozapine. This may be due to the fact that aripiprazole has no effect on histamine H1 and H2 receptors, but has antagonistic effect on 5-HT2A receptors and only partially activates 5-HT1A and D2 receptors. This can regulate dopamine neurotransmission in the brain according to the activity of endogenous dopamine receptors[47], making aripiprazole a "dopamine-serotonin stabilizer"[48]. Along with its high D2 receptor occupancy[49,50], aripiprazole can play a better role in reducing the occurrence of mortality. Another possible reason is that aripiprazole has a lower risk of metabolic and cardiovascular adverse events[51–54]. Further prospective and randomized controlled studies are required to validate our findings.

The mechanism of atypical antipsychotics associated rhabdomyolysis has not been determined so far. On one hand, as previously mentioned, atypical antipsychotics may increase the permeability of CK in skeletal muscle cell membrane through the 5-HT2a receptor[27–30]. Additionally, elevated intracellular sodium concentrations can increase calcium levels, activating intracellular proteolytic enzymes, which further damage intramuscular cells. These changes also increase the permeability to CK[55–57]. Another mechanism has also been mentioned, the blockade of the nigrostriatal pathway, which leads to involuntary excessive movements such as stiffness, Parkins-like movement, and sedentary movement, resulting in elevated CK levels[39]. In addition, gene polymorphism of CYP2D6 may also be related to the occurrence of CK elevation[14,58]. The CYP2D6 genotype can significantly affect plasma concentrations of some atypical antipsychotics such as risperidone and may impact the efficacy and safety of risperidone[59]. Future genetic research may help unravel some of these mechanisms.

Our study fully demonstrates the advantages of real-world research and data mining technology, but there are some limitations. First of all, significant bias may occur because of the spontaneous and voluntary reporting of AEs, such as input errors, underreporting, lacking denominator information for the reported drugs, underreporting of mild or moderate cases and overrepresentation of severe cases. Secondly, Although we can see the basic information, the disease status of patients is not clear, which brings many confounding factors and uncertainty to our analysis. For example, the patient may have a history of concurrent statin use, polypharmacy, strenuous exercise, illicit drugs and temperature, which can also lead to rhabdomyolysis[1,3,6]. Furthermore, it is important to note that the statistical method of disproportionality analysis is only applicable to hypothesis generation. Thus, the association of atypical antipsychotics with rhabdomyolysis is correlational rather than causal. Despite these limitations do exist, our study quantified the association between different atypical antipsychotics and rhabdomyolysis. This founding can further improve the awareness of this serious adverse event and call for regular monitoring relevant indicators in the early stage of atypical antipsychotics treatment.

Conclusion

Our study highlights the importance of vigilant patient monitoring following the prescription of atypical antipsychotics to reduce the risk of rhabdomyolysis. It is necessary to monitor serum CK level early, especially during dose adjustment or initiation of new atypical antipsychotics. This research may provide a valuable information for patients, clinicians, and others concerned with the safety of atypical antipsychotics. and optimize clinical practice.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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