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Drug-induced liver injury associated with atypical generation antipsychotics from the FDA Adverse Event Reporting System (FAERS)

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Abstract

Background Recent studies have shown that liver enzyme abnormalities were not only seen with typical antipsychotics (APs) but also with atypical antipsychotics (AAPs). During the last 20 years, the hepatotoxicity of various antipsychotics received much attention. However, systematic evaluations of hepatotoxicity associated with APs are limited.

Methods All drug related hepatic disorders cases were retrieved from the FDA Adverse Event Reporting System (FAERS) database using standardized MedDRA queries (SMQ) from the first quarter of 2017 to the first quarter of 2022. Patient characteristics and prognosis were assessed. In this study, a case/non-case approach was used to calculate reporting odds ratio (RORs) and 95% confidence intervals (CIs). We calculated the drug-induced liver injury (DILI) RORs for each AAPs.

Results A total of 408 DILI cases were attributed to AAPs during the study period. 18.6% of these were designated as serious adverse event (SAE), which include death (19.74%), hospitalization (68.42%), disability (2.63%), and life-threatening (9.21%) outcomes. The RORs values in descending order were: quetiapine (ROR = 0.782), clozapine (ROR = 0.665), aripiprazole (ROR = 0.507), amisulpride (ROR = 0.308), paliperidone (ROR = 0.212), risperidone (ROR = 0.198), ziprasidone (0.131).

Conclusion The result found in our study was that all AAPs didn't have a significant correlation with increased hepatotoxicity. Future analysis of the FAERS database in conjunction with other data sources will be essential for continuous monitoring of DILI.

Keywords AAPs, Hepatotoxicity, Reporting odds ratio (RORs), SAE, FAERS, DILI

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Introduction

Antipsychotics (APs) represent the basis for the pharmacological therapy of schizophrenia and other mental disorders, such as severe behavioral problems in autism, bipolar mania, and drug-induced psychosis. These medications are recommended to control acute episodes and induce remission of psychosis [1]. Atypical antipsychotics (AAPs) are characterized by beneficial efficacy and tolerance with few adverse reactions [2]. At present, they have replaced traditional APs and become internationally recognized first-line drugs for treating mental diseases [3]. To prevent the onset of psychosis and their potentially psychosocial consequences, individuals with mental illness often take APs for years to maintain treatment. However, APs also have a range of side effects, which can be very unpleasant and increase non-compliance [4, 5]. Therefore, drug safety is an important consideration when selecting APs.

Drug-induced liver injury (DILI) has diverse clinical manifestations, ranging from asymptomatic laboratory abnormalities to symptomatic acute liver disease to fulminant liver failure [6]. During the last 20 years, the hepatotoxicity of various APs received much attention. However, due to the limitations of clinical trials in identifying such rare events, the burden represented by DILI has been greatly underestimated [7]. A systematic review of 462 medical products withdrawn between 1953 and 2013 revealed that 18% were withdrawn from the market due to their hepatotoxicity [8]. The incidence rate of DILI is currently increasing year by year, which is now recognized as a major public health concern [9].

Recent studies have shown that liver enzyme abnormalities were not only seen with typical APs but also with AAPs [10–12]. AAPs commonly have been reported to lead asymptomatic elevation of liver enzymes and serum bilirubin levels [13]. However, serious hepatotoxicity caused by these drugs has been rarely reported [14]. The hepatotoxicity induced by typical APs has been confirmed in the literature, and many cases of chlorpromazine-induced DILI usually present as acute cholestatic hepatitis [15]. Conversely, AAPs frequently cause abnormalities in liver enzymes, but they are rarely linked to clinically significant liver injury with jaundice [16]. The prevalence of abnormal liver function in patients taking AAPs is unknown. It was difficult to comprehensively and systematically investigate the association between APs and liver function in cross-sectional or cohort studies with small samples.

The United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database is a post market repository for FDA approved treatment related adverse event reports. It contains real-world data from a large population, providing a valuable resource for clinicians, pharmaceutical companies and regulators to detect new associations in a timely way, evaluate the risk-benefit profile of drugs over time and ultimately promote the safe prescription of the drugs. Currently, many researchers explored the associations between drugs and adverse events based on the FAERS database.

At present, there are few systematic studies on DILI related to the use of AAPs [9, 17]. Therefore, this study conducted an exploratory analysis of pharmacovigilance data from the FAERS database to systematically evaluate the risk of DILI related to AAPs in order to raise awareness of drug safety and promote further research.

Materials and methods

Data acquisition

The data of this study was obtained from the FAERS, one of the most comprehensive spontaneous reporting system databases. The FDA publishes FAERS files every quarter. In this study we used FAERS quarterly data files, reports submitted between the first quarter of 2017 and the first quarter of 2022 were extracted. The AAPs we analyzed included: olanzapine, paliperidone, risperidone, amisulpride, clozapine, aripiprazole, quetiapine and ziprasidone.

This study used the standardized MedDRA queries (SMQ) to retrieve all cases of drug-related liver disease from the FAERS database (SMQ code 20000006), including: liver injury, hepatitis, transaminases increased, hepatic failure, hepatic steatosis, hepatitic cancer, hepatic congestion, hepatic pain, hepatocellular injury, hepatic cirrhosis, hepatomegaly, liver sarcoidosis, hepatic cytolysis, hepatic encephalopathy, hepatic fibrosis, hepatotoxicity, hepatic necrosis. We used the Medical Dictionary for Regulatory Activities (MedDRA version 25.0). Serious adverse events (SAE) in this study were classified as patients whose treatment resulted in hospitalization, death, disability, or other life-threatening consequences.

Inclusion and exclusion criteria

Inclusion criteria for this study: (1). Data from the first quarter of 2017–2022 in the FAERS database; (2). The drug names were the eight AAPs specified in this study; (3). The "Role cod" field was recorded as data for Primary suspect (PS) and Secondary suspect (SS).

Exclusion criteria for this study: (1). Gender, age and other personal information had significant missing data.

Processing

Each quarterly FAERS data file contains seven data tables: demographic characteristics (DEMO), details of medication (DRUG), adverse event (REAC), outcomes of patients treatment (OUTC), source of the report (RPSR), medication start and end date (THER), indications of drugs (INDI). In this study, three tables ("DEMO",

"DRUG", "REAC", "OUTC") were used for analysis. Adverse events were identified by preferred terms (PTs), as coded by the Medical Dictionary for Regulatory Activities (MedDRA). Each table used "$" as the separator to divide the file into several fields. To prevent drug name irregularities, we used The Drugbank database (https://go.drugbank.com/drugs), which contains comprehensive drug names that can be used as a reference for pharmacovigilance analysis.

Since the FAERS database contains reports from numerous sources, there may be multiple reports for the same adverse event, so the data in this study was cleaned and only one report was retained for the same adverse event. According to the method of eliminating duplicate reports recommended by FDA, the "Primaryid", "Caseid", and "FDA_DT" fields of DEMO table were selected and sorted in the order of "Caseid", "FDA_DT", and "primaryid". For reports with the same caseid, the one with the largest "FDA_DT" value was reserved in this study. Secondly, for reports with the same "Caseid" and "FDA_DT", the one with the largest "Primaryid" value was retained. As of 2019 Quarter one there is a new text file that lists deleted files. FDA or Manufacturers may delete cases for various reasons including combiningcases. According to this file, we deleted the reports according to Caseid in the deleted reports list to ensure the accuracy of the data.

The field "Role cod" represents the degree of relationship between adverse events and the drug, including Primary suspect (PS), Secondary suspect (SS), Concomitant (C), Interaction (I). To ensure the accuracy of the study, reports of AAPs recorded as "PS" and "SS" were included in the analysis. The data included in this study were age, gender, adverse reactions, weight, event date, initial FDA receipt date, latest FDA receipt date, reported country, reporter, drug name, outcomes.

Statistical analysis

IBM SPSS V.26.0 and StataCorp Stata 12.0 software were used for analysis. Normally distributed data were presented in the form of mean (SD), and non- normally distributed data were represented by median (Q1, Q3). In this study, a case/non-case approach was used to calculate reporting odds ratio (RORs) and 95% confidence intervals (CIs) [18, 19]. The ROR represents the ratio of the odds of an adverse event for a specific drug against the odds of the same adverse event reported for all other drugs, p-value < 0.05 was considered significant.

Results

As shown in Fig. 1, after excluding the duplicate records and the records without age and sex, a total of 1,947,166 patients were extracted between January 2017 and March 2022, including 3,342,314 reports. The number of females was more than that of males among patients taking olanzapine (52.0%), aripiprazole (58.6%), quetiapine (56.7%) and ziprasidone (55.7%). The median age of total patients included was 60 years (interquartile ranges: 46–71 years). Most patients taking quetiapine (52 years (37–66)) were older, followed by clozapine (49 years (35–61)) and olanzapine (48 years (33–61)), while the patients taking risperidone (24 years (14–45)) and paliperidone (30 years (20–43) were younger. The specific details are shown in Table 1.

In 3,342,314 reports, the DILI reports numbered at 37,912 (1.1%), with 408 DILI cases attributed to an AAPs (1.1% of all DILI reports). Patients with AAPs-related DILI were a medium age of 46 years (interquartile ranges: 31–58 years). AAPs-related DILI reports originated from a total of 22 countries worldwide, with Canada (118 reports), the USA (61), the UK (59), France (30). The reporter role also varied, with 25.7% of reports originating from physicians, 3.9% from pharmacists, 40.4% from other health professionals, 0.2% from lawyers, 27.0% from consumers and 2.9% from undisclosed sources.

A total of 76 patients were designated as SAE, which include hospitalization (52 [68.42%]), death (15 [19.74%]), disability (2 [2.63%]), and life-threatening outcomes (7 [9.21%]). The medications with SAE in descending order were quetiapine (25 [32.89%]), aripiprazole (23 [30.26%]), olanzapine (12 [15.79%]), clozapine (10 [13.16%]), risperidone (3[3.95%]) and amisulpride (1 [1.32%]). The clinical characteristics of events with AAPs-related DILI were described in Table 2.

The DILI counts associated with each AAPs, along with corresponding RORs and 95% confidence intervals are included in Table 3. The RORs of all AAPs were less than 1, and p values of all other drugs except olanzapine were less than 0.05. The RORs values in descending order were: quetiapine (ROR=0.782), clozapine (ROR=0.665), aripiprazole (ROR=0.507), amisulpride (ROR=0.308), paliperidone (ROR=0.212), risperidone (ROR=0.198), ziprasidone (0.131) (Fig. 2).

Discussion

The adverse effects of the AAPs, which are routinely prescribed for a range of mental diseases, have raised concerns since they affect the choice of drug for long-term therapy. DILI is one of the most common adverse reactions of AAPs. However, the real prevalence of liver dysfunction in patients treated with a wide range of AAPs is unknown. In addition, there has been no agreement on the necessity and timing of evaluating liver functions in adult and young patients using AAPs [20]. This study analyzed data from the first quarter of 2017 to the first quarter of 2022 to evaluate the correlation between AAPs and DILI. The result found in our study was that all AAPs didn't have a significant correlation with increased hepatotoxicity.

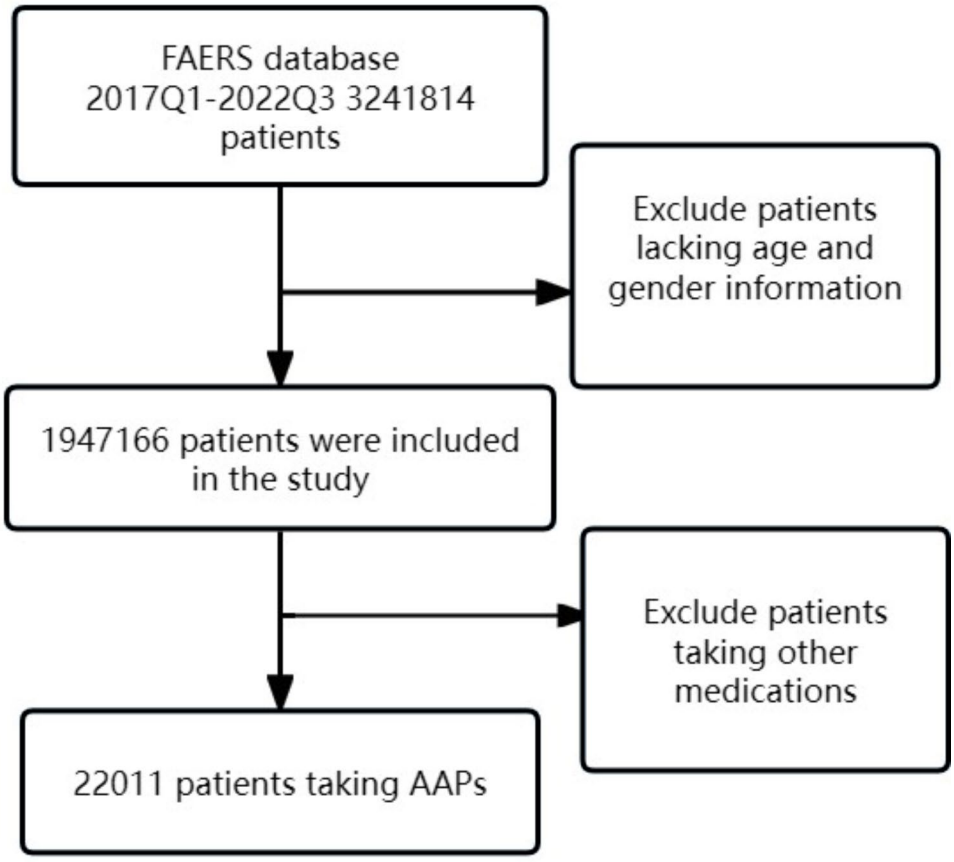

Fig. 1 Flowchart of the study

Table 1 Demographic characteristics of individuals taking AAP within the FAERS database

	N	Male	Female	Age
Total	22,001	14,769 (67.13%)	7232 (32.87%)	60 (46–71)
Aripiprazole	2845	1179 (5.36%)	1666 (7.57%)	42 (29–55)
Amisulpride	132	68 (0.31%)	64 (0.29%)	47 (32–56)
Clozapine	2381	1479 (6.72%)	902 (4.10%)	49 (35–61)
Olanzapine	1827	877 (3.99%)	950 (4.32%)	48 (33–61)
Paliperidone	1801	1549 (7.04%)	252 (1.15%)	30 (20–43)
Quetiapine	4210	1825 (8.30%)	2385 (10.84%)	52 (37–66)
Risperidone	8455	7637 (34.71%)	818 (3.72%)	24 (14–45)
Ziprasidone	350	155 (0.70%)	195 (0.89%)	38 (27–50)

Normal distribution (mean + standard deviation)

Non-normal distribution (median (Q1, Q3))

According to the previous research on liver function, AAPs may be less toxic to the liver and have fewer adverse effects than typical APs [21]. These variations could be partially explained by the distinct gene expression patterns induced by two various APs [22, 23]. It has been discovered that typical APs have an impact on the genes in the liver involved in stress response, nucleo protein, and phosphorylation. Numerous DNA-binding proteins and transcription factors that are essential for regulating the expression of other genes in the cell nucleus are found in the genes associated to nucleoproteins. For instance, haloperidol has been demonstrated to cause DNA methylation alterations in the rat brain and peripheral tissue [24]. In contrast, AAPs had an impact on the genes in the liver's golgi apparatus and endoplasmic reticulum. The consistent upregulation of genes associated with the category suggested that AAPs may influence transport processed in the cytoplasm rather than altering the gene expression cascades in the nucleus of cells. Therefore, there are significant differences between typical APs and AAPs in liver gene expression profiles of schizophrenia patients, which is consistent with the previous animal studies [25].

Pae et al. reviewed charts of 667 psychiatric patients treated with risperidone or olanzapine and compared differences in hepatic enzyme elevation during treatment with either risperidone or olanzapine alone. They discovered that the risperidone group not only had lower hepatic enzyme elevation, but also had a shorter recovery time [26]. There have been several effectiveness and safety studies with large samples that found no significant clinical abnormalities in liver function tests with risperidone treatment in adults and youths [10, 21, 26]. Moreover, previous animal studies reported that neither low nor high doses of risperidone resulted in damage to the

Table 2 Characteristics of AAPs-related DILI from January 2017 to March 2022

	AAPs-related DILI
Gender	
Female	213 (52.21%)
Male	175 (42.90%)
Unknown	20 (4.90%)
Age	
<20	37 (9.07%)
20–50	133 (32.60%)
50–80	166 (40.69%)
>80	10 (24.50%)
Unknown	62 (15.20%)
Reported countries	
Canada	118 (28.92%)
USA	61 (14.95%)
United Kingdom	59 (14.46%)
France	30 (7.35%)
Others	140 (34.31%)
Reported person	
Consumer	110 (26.96%)
Physician	105 (25.74%)
Other health professional	164 (40.20%)
Pharmacist	16 (3.92%)
Lawyers	1 (0.25%)
Unknown	12 (2.94%)
Serious adverse event	
Hospitalization	52 (68.42%)
Disability	2 (2.63%)
Life-threatening	7 (9.21%)
Death	15 (19.74%)

rat livers at the cellular level [27]. These results were in line with the findings of the present study.

The AAPs can cause hepatic enzyme abnormalities but they are rarely associated with clinically obvious liver damage [16]. A pharmacokinetic research found no difference in plasma amounts of free paliperidone in patients with moderate liver damage compared with healthy individuals. Paliperidone has not yet been linked to any serious liver damage cases that have been documented [28]. In individuals with mild, moderate, and severe liver impairment, respectively, the area under the aripiprazole curve increased by 31% and 8%, and dropped by 20% in a single dosage of 15 mg aripiprazole compared to healthy controls [28]. These findings suggest that individuals with hepatic impairment who take aripiprazole do not require dose adjustments [28]. Acute liver injury has not yet been recorded, despite reports of amisulpride temporarily elevating aminotransferases [17]. A retrospective study evaluated the abnormalities of liver enzymes induced by olanzapine, risperidone and quetiapine. According to the study, serious hepatotoxicity caused by AAPs is a rare event since only in two cases (1.8%) were found to have severe liver enzyme abnormalities [21]. With respect to ziprasidone, liver abnormalities have been rarely reported in short - and long-term clinical studies evaluating the safety and efficacy of ziprasidone [29]. There are only a few researches that investigate the potential hepatotoxicity of clozapine. To date, only five cases of mortality secondary to liver failure associated with clozapine therapy have been reported in the UK [30]. Hepatic enzyme elevations during the AAPs therapy may be adaptive changes of hepatic function under treatment rather than as liver function disturbance [12]. This also supports the results of this study.

Despite the widespread use of AAPs in clinical settings, comprehensive evaluations of DILI associated with AAPs are deficient in the current scientific literature. The spontaneous reports are the earliest methods of identifying previously undiscovered adverse medication events [31]. Based on the large amounts data from the FAERS database, our study comprehensively explored the risk of DILI related to treatment with AAPs and compared the effects of various AAPs on liver function, which provided useful evidence for clinical reference.

There are some limitations in the present study. The FAERS database is a spontaneous reporting system that depends on reports of adverse events that are voluntarily reported, which may result in material underreporting. Another limitation is the heterogeneity of the data in the pharmacovigilance database. Since the information derives from different sources, it is quite possible that the causality assessment does not always adhere to the same principles. Furthermore, variables such as dose, weight

Table 3 The association of DILI with AAPs

Drugs	Number of DILI reports	Number of non-DILI reports	ROR (95% CI)	*P*-value
Aripiprazole	66	11,304	0.507 (0.398–0.646)	<0.0001**
Amisulpride	3	847	0.308 (0.099–0.957)	0.042*
Clozapine	59	7709	0.665 (0.515–0.860)	0.002*
Olanzapine	74	6698	0.961 (0.764–1.209)	0.736
Paliperidone	16	6564	0.212 (0.130–0.346)	<0.0001**
Quetiapine	121	13,452	0.782 (0.654–0.936)	0.007*
Risperidone	63	27,527	0.198 (0.154–0.253)	<0.0001**
Ziprasidone	3	1992	0.131 (0.042–0.406)	<0.0001**

ROR reporting odds ratio. *: $p \leq 0.05$; **: $p \leq 0.001$

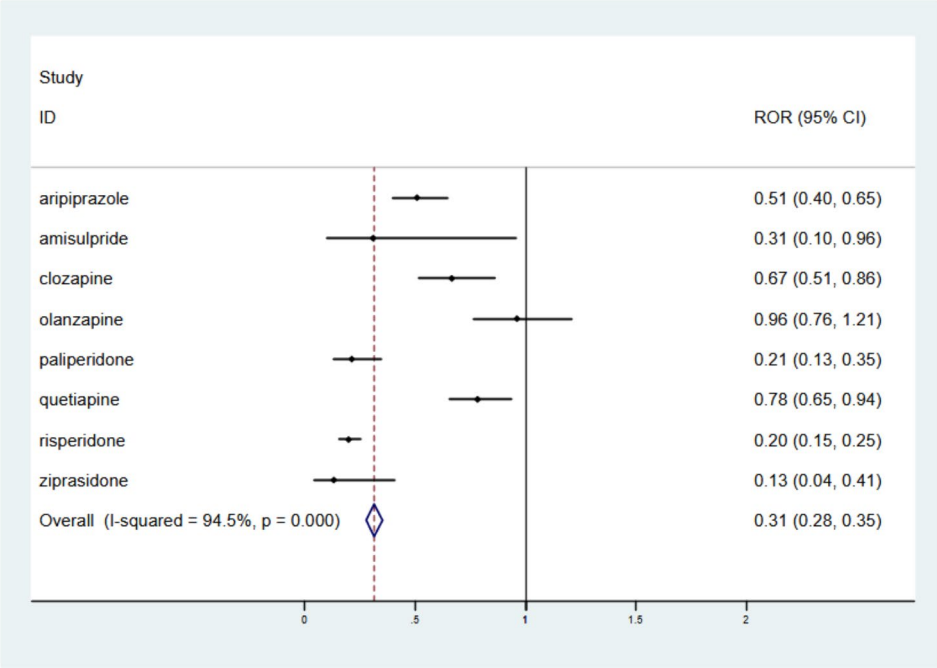

Fig. 2 Plot displaying the ROR with 95% CI of DILI for each AAPs reports from the FAERS database, January 2017–March 2022

and time to onset were not included in the study, so we are unable to calculate the relationship between dose and risk. Finally, we only considered AAPs monotherapy and ignored the complex polypharmacy of AAPs. Therefore, the relationship between changes in liver function test associated with AAPs should be investigated in further studies.

Conclusion

This study conducted a comprehensive analysis of the potential DILI induced by AAPs. The result found in our study was that all AAPs didn't have a significant correlation with increased hepatotoxicity.

Author contributions

SH: designed and performed the research, collected and analyzed the data, wrote the paper. BC collected and analyzed the data. CL: checked the data and revised the article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. This project was submitted for review through Advocate Health and was waived as this study was deemed non-human subject related research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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