A pharmacovigilance study of the association between antipsychotic drugs and Venous thromboembolism based on Food and Drug Administration adverse event reporting system data

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Abstract

Aims Venous thromboembolism (VTE) is a rare but serious adverse drug reaction could be caused by antipsychotic drugs. However, the specific correlation of VTE caused by antipsychotic drugs is still controversial. This study explored the potential association between antipsychotics and VTE. Method All VTE cases of antipsychotic drugs as primary suspected medicines were extracted from the US Food and Drug Administration adverse event reporting system (FAERS) from 2004 to 2021. Disproportionality analyses were conducted by estimating the reporting odds ratio (ROR) and the information component (IC). Results 4,455 VTE cases with antipsychotics as primary suspected drugs were identified. The VTE signal was detected in haloperidol, olanzapine, quetiapine and paliperidone. The RORs and the 95% confidence intervals (95% CI) of haloperidol, olanzapine, quetiapine and paliperidone were (ROR=2.17, 95% CI(2.17-1.91), IC=1.1, 95%CI(1.52-0.66)), (ROR 2.53 95% CI 2.69–2.38 IC 1.31 95%CI 1.52-1.1), (ROR 1.37, 95% CI 1.47–1.28 IC 0.45 95%CI 0.67-0.23) and (ROR 1.6 95% CI 1.83–1.4 IC 0.67 95%CI 1.11-0.22), respectively. Pulmonary embolism occurred in more than 50% of VTE events (2760 cases, 52.84%). The outcome indicated that venous thrombosis caused by antipsychotics is usually a serious consequence. Conclusion The current data mining of FAERS suggested an association between VTE and antipsychotic drugs including olanzapine, haloperidol, paliperidone and quetiapine, which reminds health professionals to pay attention to the serious adverse drug effects of antipsychotic drugs leading to venous thromboembolism.
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Conclusion The current data mining of FAERS suggested an association between VTE and antipsychotic drugs including olanzapine, haloperidol, paliperidone and quetiapine, which reminds health professionals to pay attention to the serious adverse drug effects of antipsychotic drugs leading to venous thromboembolism.

Key word 
Pharmacovigilance, Pulmonary thromboembolism, Deep venous thrombosis, Venous thromboembolism, Antipsychotics

Introduction
Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT and PE are two clinical manifestations in different stages of VTE, and they share the same risk factors. VTE is the third most frequent acute cardiovascular syndrome globally, behind myocardial infarction and stroke. In some epidemiological studies, annual incidence rates for PE range from 39 to 115 per 100 000 population; for DVT, incidence rates range from 53 to 162 per 100 000 population [1, 2]. VTE has significant morbidity and mortality for both the inpatient and outpatient populations.

VTE is a heterogeneous disease. A major theory delineating the pathogenesis of VTE, often called the Virchow triad [3, 4], proposes that VTE occurs as a result of blood stasis, vascular endothelial injury, and alterations in the constituents of the blood. According to this theory, any factor that affects the three elements will lead to the occurrence of a thrombus. The causes of VTE can be divided into two groups: hereditary and acquired, and are often multiple in each patient. Medication is one of the risks acquired factors for VTE. To date, the drugs that may induce VTE include oral contraceptives, hormone replacement therapy, and chemotherapy drugs [2]. In recent years, studies have confirmed that antipsychotic medications may be associated with VTE, and patients with severe mental illness have a higher risk of developing the condition compared to the general population [5-7]. However, there are few comprehensive reports on the association between antipsychotics and venous thromboembolism.

VTE caused by antipsychotic drugs is one of the adverse drug reactions. Adverse event reporting system data are an outstanding source of post-marketing drug safety monitoring and pharmacovigilance analysis World widely. The US Food and Drug Administration’s Adverse Event Reporting System (FAERS) is one of the largest databases available to the public. By the end of 2019, FAERS had collected more than 10 million cases, including adverse drug event reports submitted by medical professionals, manufacturers, consumers, and lawyers. These reports can be quantitatively analyzed using data mining methods to detect signals of drug-related adverse events [8-9]. The purpose of this study was to detect the signal of antipsychotics causing VTE by systematically evaluating spontaneous reports submitted to the FAERS database.

2. Aims
The study aimed to assess the association between Venous thromboembolism and antipsychotic drug by comprehensively evaluating spontaneous reports submitted to the FAERS database.

3. Method
3.1 Data source
The FAERS datasets comprises seven data tables, including patient demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start states and end dates for reported drugs (THER), and indications for drug administration (INDI). Raw FAERS data can be downloaded for free from the FDA website. Data from
the first quarter of 2004 to the end of 2021 were downloaded from the FAERS Quarterly Data Extract Files [10]. Duplicate records were excluded based on FDA recommendations. If the CASEIDs (a number for identifying a FAERS case) were the same, the latest FDA_DT (date FDA received the case) was selected. If the CASEID and FDA_DT were the same, the higher PRIMARYID (a unique number for identifying a FAERS report) was established. Deleted cases from 2019 were further removed from the local database. FAERS data were managed locally using Microsoft SQL Server 2017.

### 3.2 Antipsychotic drugs and venous thrombosis adverse event identification

Drug names in the DRUG table can be documented in various forms, including generic, brand, synonymous, or abbreviations. Before identifying target drugs, we standardized different names of the same drug into a "generic name" using MedEx software (MedEx UIMA 1.3.8, Vanderbilt University, USA) [11, 12]. We attempted to identify 47 single-component antipsychotic drugs according to the WHO Anatomical Therapeutic Chemical (ATC) classification (ATC code: J01AA) from the local FAERS database. The 47 agents (ATC codes) (Supplementary Information for detail)

### 3.3 Data mining

The characteristics of venous thrombosis adverse event cases and antipsychotic drugs were collected, including age, sex, reporter, report country, report year, case outcome Reporting odds ratio (ROR, a frequency method) and the information component (IC, a Bayesian approach) were used to detect the "signal" (a significant association between venous thrombosis adverse event and antipsychotic drugs). For ROR, a signal is detected if the case number is ≥3 and the lower limit of the two-sided 95% confidence interval (95% CI) is > 1. For the IC, a signal is detected if the lower limit of 95% CI is > 0. Both methods were used for signal detection, and venous thrombosis adverse event was considered drug-associated if ROR and IC met the above-mentioned criteria.

### 3.4 Statistical analysis

A descriptive analysis was used to describe the clinical characteristics of included cases. Data management and statistical analyses were performed with Microsoft Excel 2013 (Microsoft, Redmond, Washington, USA) and SPSS version 25.0 (IBM, Armonk, New York, USA).

### 4. Results

A total of 376,344 adverse reaction cases were reported by antipsychiatry as preferred suspected drugs, of which 4,455 were VTE cases. We tried to identify 43 antipsychotic drugs. However, only the following twenty-four drugs were identified: olanzapine, quetiapine, clozapine, risperidone, aripiprazole, haloperidol, paliperidone, ziprasidone, lurasidone, asenapine, lithium, chlorpromazine, brexpiprazole, olanzapine, droperidol, prochlorperazine, cariprazine, thioridazine, fluphenazine, amisulpride, pimozide, loxapine. The male-to-female ratio with VTE (2125/1964) was 1.08. Most VTE cases occurred in the 18 to 64-year group (64.29%). Health professionals reported 75.76% of VTEI cases. The top three VTE reporting regions were Europe (2666 cases, 59.84%), North America (1103 cases, 24.76%), and Asia (357 cases, 8.01%). The details are in Table 1. The top ten of the most reported cases of VTE antipsychotic drug are olanzapine, quetiapine and clozapine and risperidone, aripiprazole, haloperidol, paliperidone, paliperidone, and lurasidone(Table 2). The data mining of FAERS suggested an association between VTE and haloperidol, olanzapine, quetiapine, and paliperidone. The RORs and the 95% confidence intervals (95% CI) of t haloperidol, olanzapine, quetiapine, and paliperidone were (ROR 2.17, 95% CI 2.17-1.91 IC 1.1 95%CI 1.52-0.66), (ROR 2.53 95% CI 2.69–2.38 IC 1.31 95%CI 1.52-1.1), (ROR 1.37, 95% CI 1.47–1.28 IC 0.45 95%CI 0.67-0.23) and (ROR 1.6 95% CI 1.83–1.4 IC 0.67 95%CI 1.11-0.22). So, clinicians should monitor patients for potential VTE while they are taking these antipsychotic drugs.

Pulmonary embolism occurred in more than 50% of VTE events (2760 cases, 52.84%), deep vein thrombosis is 24.79%(1295 cases), and Another non-standardized diagnosis of VTE is 22.36%(1168 cases) in Fig 1. It is indicated that venous thrombosis caused by antipsychotics is usually a severe consequence, which is confirmed
by our analysis of the outcome, including death (883 cases), life-threatening (693 cases), hospitalization (1643 cases), and other serious events (1164 cases) in Fig 2.

Signal detection

According to the chemical structure of antipsychotics, it can be divided into butyrophenone derivatives, indole derivatives, thioxanthene derivatives, and diphenylbutylpiperidine derivatives, phenothiazines with aliphatic side-chain, phenothiazines with piperazine structure, diazepines, oxazepines, thiazepines and oxepines and lithium and other antipsychotics. Table 3 shows that Diazepines, oxazepines, thiazepines and oxepines and diphenylbutylpiperidine derivatives antipsychotics have the strongest signal in FARES. In terms of specific drugs, haloperidol, olanzapine, quetiapine and paliperidone show the strongest correlation (Table 4 for details).

Discussion

Psychiatric disorders such as schizophrenia, anxiety disorder, depression disorder, bipolar disorder, etc., are bringing heavy disease burden and social burdens to more and more people. Take schizophrenia as an example, which is among the most disabling and economically catastrophic medical disorders. Schizophrenia occurs throughout the World. The prevalence of schizophrenia approaches 1 percent internationally. The number of new cases annually is about 1.5 per 10,000 people[13]. Medication is the primary treatment method for schizophrenia.

Antipsychotics are divided into traditional antipsychotics (first-generation antipsychotics FGAs) and atypical antipsychotics (second-generation antipsychotics SGAs). SGAs generally have a lower risk of extrapyramidal symptoms and tardive dyskinesia than FGAs. VTE is a rare but severe adverse drug reaction to antipsychotics. VTE is one of the causes of sudden death in many psychiatric patients, and many studies revealed the association between antipsychotic drugs and VTE. Some studies have reported that there is an association between psychotropic drug use and the occurrence of VTE[14-25].

A systematic review of 28 observational studies published in 2021 showed that the risk of VTE was 1.55 times that of those who did not use antipsychotic drugs, and the risk of PE was 3.68 times that of those who did not use antipsychotic drugs, indicating that antipsychotic drugs significantly increased VTE risk, especially the risk of PE[26]. One study of psychiatric hospitals in Europe showed that risperidone (55/100,000) and pipamperone (61/100,000) were the most common examples of antipsychotics causing VTE in hospitalized psychotic patients[27].

At present, the underline mechanisms of VTE caused by antipsychotics are unknown, and no single cause can fully explain this drug-induced disease[28-29]. The hypotheses include that sedation, weight gain, and hyperprolactinemia induced by psychotropic drugs may increase the risk of VTE. Paliperidone and risperidone have the double blocking effect of the dopamine 2(D2) receptor and serotonin 2 receptor, and compared with other antipsychotic drugs, paliperidone, and risperidone have a strong antagonistic effect on dopamine. Dopamine is the main prolactin inhibitor, and dopamine inhibition can lead to high prolactin lipids. Prolactin may affect platelet aggregation. But platelet aggregation mainly leads to arterial clots, not venous clots. But VTE patients with acute psychosis may be induced by pathogenic mechanisms related to psychosis rather than by antipsychotic drugs. Thus, the mechanism by which antipsychotic drugs lead to venous thrombosis needs further study.

Conclusion

There is an increased risk of venous thrombosis due to psychiatric medications; therefore, when treating patients with these drugs, clinicians must pay special attention to possible signs and symptoms of VTE since early diagnosis and prompt treatment can improve the outcome. In addition, more studies are needed in order further to elucidate the association between antidepressant drugs and VTE and explore the possible mechanisms causing this adverse effect.

References:


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COMPETING INTERESTS
The authors have no conflicts of interest that are directly relevant to the content of this study.

CONTRIBUTORS
B.W. and Y.Y. designed the research. Y.Y., L.W., Y.L.Y performed data analysis of the paper. Y.Y, Y.X.C. and J.Y.X contributed to data interpretation. B.W. and Y.Y. had overall oversight of the paper construction.

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