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Safety and side effects of psychotropic medications, volume II

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Safety and side effects of psychotropic medications, volume II

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Table of contents

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Editorial: Safety and side effects of psychotropic medications, volume II

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adverse drug reaction (ADR), adverse effects, mental disorders, mental health, psychiatry, psychopharmacology, safety, tolerability

Editorial on the Research Topic
Safety and side effects of psychotropic medications, volume II

The safety and tolerability of psychotropic medications have always been a significant concern within the realm of mental health treatment (1, 2). Over recent years, there has been a noticeable uptick in the collection of evidence-based data and dedicated research endeavors aimed at gaining a more comprehensive understanding of the advantages and drawbacks tied to these medications (3, 4). This surge in empirical research has empowered healthcare providers to make more informed decisions when prescribing psychotropic drugs and personalizing treatment plans to meet each patient's unique needs (5, 6). Furthermore, research has been actively engaged in a collaborative effort to devise new strategies and medications boasting enhanced safety profiles and reduced adverse drug reactions (ADRs) (7, 8). As the field continually evolves, the focus on patient safety and the fine-tuning of psychotropic treatments remains an overarching priority, with the ultimate goal of improving mental health outcomes for individuals worldwide (9, 10).

Therefore, following the first volume of this Research Topic (11), our objective was to compile articles that delve into the safety and ADRs of psychotropic medications. We invited contributions from all sources that could potentially provide fresh insights and evidence to this critical subject matter.

Akbarzadeh et al. evaluated the effect of adding an extract of the plant Alpinia galanga, known for enhancing sexual function, to the treatment of adult males taking selective serotonin reuptake inhibitors (SSRIs) with the goal to improve SSRI-induced erectile dysfunction. They designed a triple-blind randomized clinical trial involving 60 adult male participants on SSRIs, receiving 500 mg of Alpinia galanga extract or placebo, and adding Alpinia galanga to the SSRIs treatment seems to be a promising approach to alleviate the SSRI-related sexual dysfunction in male.

Kimura et al. conducted a systematic review aimed to assess the heart safety of escitalopram in comparison to a placebo for patients with underlying cardiovascular issues (12). The analysis included five randomized controlled trials with a total of 773 participants.

Escitalopram did not significantly increase the risk of major adverse cardiovascular events, medication discontinuation, or QTc prolongation when compared to a placebo in patients with underlying cardiovascular disease.

Bonnett commented on a previous article (13) about the more attention needed in prescribing SSRIs during COVID-19 adding interesting discussion points. In particular, in the light of the increased SSRIs prescription trend in coronavirus infections (i.e., fluvoxamine) it should also be considered the potential occurrence of an anxiety/jitteriness syndrome (AJS, also known as "activation syndrome") as a common ADR of SSRIs. Therefore, the AJS might be mistakenly identified as neuropsychiatric or gastrointestinal symptoms of COVID-19 or as a worsening of an existing COVID-19 condition.

The team led by Xu et al. conducted a systematic review between the citalopram plasma concentration and treatment outcomes in depression. The review did not establish a clear correlation between citalopram plasma concentration and clinical or cost-related outcomes, but there was some limited evidence hinting at improved treatment effectiveness in patients with plasma concentrations above 50 or 53 ng/mL.

Xiang et al. aimed to examine the impact of a Chinese policy implemented on September 1, 2019, which classified oxycodone/acetaminophen as a psychotropic medicine due to its history of misuse, with the goal to regulate its use in medical institutions. Through a prescription data analysis from five tertiary hospitals in Xi'an city over 42 months, authors concluded that the stricter regulation of oxycodone/acetaminophen helped reduce the risk of misuse among short-term drug users.

In another retrospective analysis run in a long-term hospital with chronic schizophrenia patients with co-existing type 2 diabetes who were prescribed olanzapine or risperidone as primary antipsychotic medication with or without co-prescribing aripiprazole (Liu et al.). Liu et al. compared various parameters between the two groups and assessed the factors influencing prolactin levels. The results showed that the co-aripirazole group had significantly higher levels of fasting blood glucose, blood uric acid, cholesterol, and triglycerides, but there was no difference in prolactin levels between the two groups.

An EUDRAVigilance dataset screening led by Cicala et al. aimed to provide a more comprehensive understanding of the safety and tolerability of paliperidone palmitate (PP) using real-world pharmacovigilance data. This analysis of 8,152 reports suggested that the safety and tolerability profiles of PP are generally consistent with other second generation long- acting anitpychotics, with only higher probabilities of reporting specific ADRs in PP-related reports, particularly related to sexual dysfunctions, haemodynamic edema, effusions, fluid overload, and fertility disorders.

According to a nationwide retrospective study between 1998 and 2019 in Australia conducted by Alsaleh et al. potential errors in the administration of psychotropic drugs are a common cause of hospitalization in Australia, often requiring overnight stays. The concerning prevalence of such errors among individuals aged 20–39 years underscores the need for further investigation and research to understand the risk factors associated with hospitalization due to psychotropic drug administration errors.

Hamasaki and Yanai conducted a retrospective cohort study with the aim to investigate the impact of psychotropic drug use on handgrip strength and hospitalization in individuals with type 2 diabetes. Authors concluded that the use of psychotropic drugs may increase the likelihood of repeated hospitalizations among patients with type 2 diabetes. Morevoer, the study suggests that skeletal muscle strength, as reflected by handgrip strength, may have a role in reducing the risk of hospitalization in individuals receiving psychotropic drug treatment.

The study by Joung investigated the gender differences in ADRs associated with zolpidem, with data from the Korea voluntary adverse drug events reporting system (KAERS) for the years 2015–2019. Of all the ADRs with gender differences in reporting risk, somnambulism stood out as the most consistent and substantial difference. This suggests that women may have a higher susceptibility to somnambulism, which is a potentially serious adverse effect associated with zolpidem.

While psychopharmacological research has already generated a substantial amount of data on numerous facets, we contend that the clinical perspectives presented in these articles offer a practical and innovative viewpoint that could lead to a more precise allocation of resources, piquing the interest of both clinicians and researchers (14, 15). In light of the psychopharmacological trends discussed in the collected papers, it is crucial to underscore the pressing need for a deeper exploration of ADRs associated with psychotropic medications. The findings compiled in this Research Topic do not discourage the use of psychotropic drugs but rather advocate for their thoughtful and informed prescription.

Author contributions

RF: Conceptualization, Data curation, Writing – original draft. MSo: Conceptualization, Writing – review & editing. MSh: Conceptualization, Writing – review & editing.

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Co-prescription of aripiprazole on prolactin levels in long-term hospitalized chronic schizophrenic patients with co-morbid type 2 diabetes: A retrospective clinical study

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Background: One of the most frequent side effects of atypical antipsychotics is hyperprolactinemia (HPRL), and metformin or aripiprazole co-prescription is regarded as an effective therapy option for reducing prolactin (PRL) levels. However, whether either of the two drugs can reduce PRL levels in patients with long-term hospitalized chronic schizophrenia with co-morbid type 2 diabetes (T2DM) has not been adequately reported.

Methods: In our study, long-term hospitalized chronic schizophrenia patients with co-T2DM who were prescribed olanzapine or risperidone as the primary antipsychotic medication were enrolled. A total of 197 of these cases with co-prescribed aripiprazole were set up as the study group (co-Ari group), and the other 204 cases without co-prescribed aripiprazole were set up as the control group (non-Ari group). The two groups' variations in each target parameter were compared, and the variables affecting PRL levels were examined.

Results: Compared to the non-Ari group, fasting blood glucose (FBG), blood uric acid (UA), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in the co-Ari group, but there was no difference in PRL levels. Co-prescribing aripiprazole had no impact on PRL levels in all patients with co-T2DM, and aripiprazole dose had no impact on PRL levels in the clinical subgroup of the co-Ari group.

Conclusion: Aripiprazole not only worsened the severity of index disturbances associated to metabolism in long-term hospitalized chronic schizophrenia patients with co-T2DM on metformin-based hypoglycemic medications but also failed to lower PRL levels.

KEYWORDS

schizophrenia, aripiprazole, prolactin, type 2 diabetes, long-term hospitalized, chronic

1. Introduction

The most significant and fundamental form of treatment for schizophrenia is antipsychotic medication, as we all know. And one of the most prevalent and common adverse drug reactions to antipsychotic medications is hyperprolactinemia (HPRL) (1), but it is believed to have decreased with the broad and extensive clinical prescribing of second-generation antipsychotics as opposed to traditional antipsychotics (2). However, the real clinical situation may not be as optimistic as perceived. According to a significant Chinese study, the prevalence of HPRL in hospitalized schizophrenia patients is up to 61.3% and is similar in men and women (3). Among the many atypical antipsychotics, risperidone is considered to have one of the most significant effects on elevating prolactin (PRL) levels in psychiatric patients, and the PRL- increasing pharmacological effects of olanzapine should not be underestimated (1). A study from the Chinese province of Taiwan found that olanzapine can cause high levels of PRL (up to 51.6%) (4). What's more, risperidone and olanzapine are two of the top-ranked antipsychotic drugs in terms of prescription rates, according to reports of prescribing patterns for psychiatric patients from around the world, including China (5–8). It is therefore not surprising to observe that HPRL brought on by atypical antipsychotics, such as risperidone and olanzapine, continue to be widespread and require proper clinical attention.

Long-term exposure to excessive PRL levels is frequently linked to an increased risk of sexual dysfunction (9), weight gain (10), cardiovascular disease (11), osteoporosis (12), and even cancer (13). In order to decrease the risk of adverse events and accidents in psychiatric patients and to promote patient compliance with treatment, it is vital for psychiatrists to find effective ways to diminish or neutralize antipsychotic-induced HPRL. In clinical practice, metformin is a frequently used hypoglycemic drug that has been shown to have pharmacological effects in attenuating antipsychotic-induced HPRL (14), but the specific mechanism of action is uncertain. It has been found that metformin can cross the blood-brain barrier and appears at higher levels in the pituitary gland than in other brain tissues (15). This suggests that metformin may have a local interaction with PRL-secreting cells in the pituitary gland to suppress elevated PRL levels. Distinguishing from metformin, as a novel antipsychotic with "PRL-sparing" effects (16, 17), aripiprazole has an partial agonistic effect on D_2, as well as a partial agonistic effect on 5-HT_{1A} and/or an antagonistic effect on 5-HT_{2A} that exerts a PRL-lowering effect (18, 19). As a result, co-prescription of metformin or aripiprazole is considered an effective treatment option to reduce or alleviate HPRL caused by psychiatric drugs (20, 21). Unfortunately, the results of these studies or the specific recommendations given are for the general population with schizophrenia rather than for the group of long-term hospitalized chronic schizophrenia people with co-type 2 diabetes (T2DM).

We discovered by chance that aripiprazole did not lower PRL levels in a subclinical group of schizophrenic patients with co-T2DM in our earlier study when we examined the factors influencing PRL levels in chronically schizophrenic patients with long-term hospitalization for co-T2DM (22). However, due to the study's limited sample size of aripiprazole-prescribed cases, statistical efficacy was compromised, leaving the conclusions without any useful advice for clinical action. The purpose of this study was to clarify the specific effects of aripiprazole on the PRL levels in co-T2DM schizophrenic patients, to fill in the gaps of the aforementioned study, to provide a reasonable and effective approach to the specific prescription, and to increase the sample size of this clinical subgroup.

2. Materials and methods

2.1. Subjects

A total of 197 schizophrenic patients with long-term hospitalization and co-T2DM who were hospitalized at Wuhan Mental Health Center and Suzhou Guangji Hospital from June 2015 to August 2022 with co-prescription of aripiprazole were included as the study group in this study.

2.1.1. Inclusion criteria

(1) Meet the criteria for the diagnosis of schizophrenia in the QQInternational Classification of Diseases 10th Revision (ICD-10).

(2) Age range of 25–70 years old, male and female cannot be restricted.

(3) The duration of psychiatric illness was 6 years or more, and there were no adjustments in the dose or type of antipsychotic medication in the 2 months before collection of the target data.

(4) The duration of continuous uninterrupted inpatient treatment is not less than 2 years.

(5) The antipsychotic prescribed during hospitalization was olanzapine in combination with aripiprazole or risperidone in combination with aripiprazole, and the doses of the three antipsychotics involved were not limited.

(6) All enrolled patients were co-T2DM and were treated with oral hypoglycemic agents for glycemic control. Additionally, diabetes mellitus did not last less than 1 year.

2.1.2. Exclusion criteria

Exclude bipolar disorder, major depressive disorder, personality disorders, psychiatric disorders due to epilepsy, intellectual developmental disorders, psychiatric disorders due to somatic disorders, and other psychiatric disorders other than schizophrenia. Those with type 1 diabetes (T1DM) and T2DM who need extra exogenous insulin for glycemic control should be excluded. Patients with severe physical comorbidities were also disqualified, including those with cerebrovascular disease, severe heart disease, somatic dysfunction, and other conditions that limit free movement and affect executive function, as well as those with polycystic ovary syndrome and pituitary tumors that affect PRL levels.

In the course of gathering study group cases, we included 204 schizophrenic patients with co-T2DM as the control group, which had the same inclusion and exclusion criteria as the study group, except that aripiprazole was not prescribed.

This study was reviewed and approved by the Ethics Committee of Wuhan Mental Health Center.

2.2. Research design

The study design was a two-center retrospective case-control study. We studied long-term hospitalized chronic schizophrenic patients with co-T2DM, with the group of patients co-prescribed

TABLE 1 Demographic and general clinical data.

Index	Total patients (*n* = 401)	Co-Ari (*n* = 197)	Non-Ari (*n* = 204)	t/χ^2	*p*-value
Age–years	46.93 ± 10.33	47.18 ± 10.03	46.69 ± 10.63	0.48	0.634
Gender–*n* (%)				1.20	0.274
Female	259, 64.59%	122, 61.93%	137, 67.16%		
Male	142, 35.41%	75, 38.07%	67, 32.84%		
Schizophrenia duration–years	18.55 ± 10.03	18.38 ± 10.16	18.72 ± 9.93	−0.33	0.739
Onset age–years	28.38 ± 8.20	28.80 ± 8.23	27.97 ± 8.17	1.01	0.314
Length of hospital stays–years	4.59 ± 1.23	4.55 ± 1.13	4.63 ± 1.32	−0.65	0.519
Antipsychotic drugs–*n* (%)				0.45	0.505
Olanzapine	254, 63.34%	128, 64.97%	126, 61.76%		
Risperidone	147, 36.66%	69, 35.03%	78, 38.23%		
Diabetes duration–years	4.46 ± 1.97	4.32 ± 1.89	4.60 ± 2.04	−1.42	0.157
Anti-glycemic drugs–*n* (%)				3.07	0.080
Metformin alone	75, 32.86%	30, 15.23%	45, 22.06%		
Co-metformin	326, 81.30%	167, 84.77%	159, 77.94%		
Metformin dosage–g	1.14 ± 0.36	1.15 ± 0.37	1.13 ± 3.43	0.63	0.532
Educational background–*n* (%)				0.07	0.787
Junior school and below	245, 61.10%	122, 61.93%	129, 63.24%		
High school and above	156, 38.90%	75, 38.07%	75, 36.76%		
FBG–mmol/L	7.41 ± 2.74	7.69 ± 2.68	7.14 ± 2.77	2.00	0.046*
BUN–mmol/L	3.91 ± 3.17	4.21 ± 3.61	3.63 ± 2.66	1.83	0.068
CRE–mmol/L	64.18 ± 20.89	65.35 ± 22.09	63.05 ± 19.66	1.10	0.271
UA–mmol/L	412.54 ± 121.43	417.17 ± 120.67	408.07 ± 122.29	0.75	0.454
TC–mmol/L	4.54 ± 1.06	4.66 ± 0.96	4.43 ± 1.13	2.17	0.030*
TG–mmol/L	3.13 ± 2.35	3.43 ± 2.45	2.85 ± 2.22	2.50	0.013*
LDL-C–mmol/L	2.25 ± 0.84	2.41 ± 0.86	2.10 ± 0.79	3.81	<0.001*
HDL-C–mmol/L	0.99 ± 0.25	0.98 ± 0.26	1.01 ± 0.23	−0.27	0.091
BMI–kg/m^2	22.89 ± 9.20	23.25 ± 10.56	22.28 ± 7.65	1.35	0.177
BW–kg	60.49 ± 11.05	60.66 ± 11.05	60.32 ± 11.07	0.31	0.755
AC–cm	80.12 ± 8.74	80.23 ± 9.57	79.19 ± 8.02	1.18	0.054
PRL–ng/mL	31.58 ± 26.59	32.33 ± 25.77	30.86 ± 27.40	0.56	0.579

Co-Ari, co-prescribed aripiprazole, i.e., study group; non-Ari: non-prescribed aripiprazole, i.e., control group; FBG, fasting blood glucose; BMI, body mass index; BUN, blood urea nitrogen; CRE, blood creatinine; UA, blood uric acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BW, body weight; AC, abdominal circumference; PRL, prolactin. *$P < 0.05$.

with aripiprazole as the study group (co-Ari group) and the group of patients not co-prescribed with aripiprazole as the control group (non-Ari group), comparing the differences between the two clinical subgroups in terms of common demographic data and general clinical data, especially in terms of PRL levels. The factors influencing the PRL levels in the study group were also analyzed.

We extracted demographic information and general clinical data from the electronic case systems of the two centers for cases meeting the inclusion criteria for the study and control groups, including age, gender, educational background, body weight (BW), abdominal circumference (AC), body mass index (BMI), duration of psychiatric illness and age of onset, length of stay in the hospital, antipsychotic type and dose, glucose-lowering drug type and dose, fasting blood glucose (FBG), renal function [namely: blood urea nitrogen (BUN); blood creatinine (CRE); blood uric acid (UA)], blood lipids [namely: total cholesterol (TC); triglyceride (TG); low-density lipoprotein cholesterol (LDL-C); high-DL-C (HDL-C)], and PRL. The above indicators were recorded in a self-made spreadsheet.

We defined patients with continuous and uninterrupted hospitalization of greater than or equal to 2 years from the first day of the current hospitalization as long-term hospitalized patients. The time point at which the target parameters were tested and extracted for all samples was required to no history of antipsychotic drug type and dose adjustment and exogenous insulin supplementation in the 2 months before that time. All parameters involved that require the testing of venous blood were measured using morning fasting venous blood as the specimen. BW, AC, BMI were also measured and calculated values obtained in the morning fasting state.

2.3. Data analysis

The obtained continuous variables that fit the normal distribution were expressed as mean and standard deviation, and categorical variables were expressed as counts (percentages). First, we used independent samples *t*-tests or chi-square tests to compare the differences between the study and control groups for each target parameter. Secondly, we used Pearson's correlation analysis to obtain parameters related to PRL levels for all included samples (a total of 401 participants). Thirdly, a multiple linear regression model was constructed to analyze the factors influencing PRL levels in the total sample size. Finally, a second multiple linear regression model was constructed for the study group sample to analyze the factors influencing PRL levels in this clinical subgroup. All *P*-values were two-tailed, and the significance level was <0.05. Statistical analyses were performed using SPSS 27 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Differences in target parameters between the two clinical subgroups

In patients prescribed olanzapine, the average daily drug dose of olanzapine was (12.86 ± 5.42) mg, and the average daily drug dose of risperidone was (4.10 ± 1.38) mg. The average daily dose of aripiprazole in the co-Ari group was (13.96 ± 3.75) mg. FBG, UA, TC, TG, and LDL-C levels were significantly higher in the study group compared to the control group ($t = 2.00$, $p = 0.046$; $t = 2.17$, $p = 0.030$; $t = 2.50$, $p = 0.013$; $t = 3.81$, $p < 0.001$; respectively), but there was no difference in PRL levels ($t = 0.56$, $p = 0.579$) (Table 1).

3.2. Factors associated with PRL levels for all included patients

For all included co-T2DM schizophrenia patients, age ($r = 0.01$, $p = 0.017$), schizophrenia duration ($r = 0.17$, $p = 0.001$), prescription olanzapine ($r = 0.11$, $p = 0.035$), prescription risperidone ($r = -0.03$, $p = 0.035$), and LDL-C levels ($r = 0.27$, $p < 0.001$) were positively associated with PRL levels, while, prescription metformin ($r = -0.11$, $p = 0.048$), prescription aripiprazole ($r = -0.01$, $p = 0.009$), FBG levels ($r = -0.09$, $p = 0.041$), and UA levels ($r = -0.14$, $p = 0.007$) were positively associated with PRL levels (Table 2).

3.3. Factors influencing PRL levels in all included patients

We constructed a multivariate linear model with PRL level as the dependent variable and the above clinical parameters associated with PRL level as independent variables. The three variables involved in the model, aripiprazole, olanzapine, and risperidone, were defined as dichotomous variables (0 = prescribed, 1 = unprescribed). Age ($B = -0.61$, $t = -3.64$, $p = 0.021$), prescription metformin ($B = -0.12$, $t = -1.04$, $p = 0.017$), and FBG ($B = -1.71$, $t = -3.42$, $p = 0.001$) levels were protective factors for HPRL, whereas prescription olanzapine ($B = 2.11$, $t = 1.05$, $p = 0.036$) and risperidone ($B = 7.21$, $t = 2.72$, $p = 0.007$) were risk factors for HPRL (Table 3).

TABLE 2 Factors associated with PRL levels in patients with schizophrenia co-type 2 diabetes (T2DM).

Characteristic	*n* = 401	
	r	*p*-value
Age–years	0.01	0.017*
Schizophrenia duration–years	0.17	0.001*
Onset age–years	−0.20	0.060
Length of hospital stays–years	−0.01	0.794
Diabetes duration–years	0.03	0.623
Educational background	0.07	0.184
Metformin	−0.11	0.048*
Aripiprazole	−0.03	0.009*
Olanzapine	0.11	0.035*
Risperidone	0.01	0.035*
FBG–mmol/L	−0.09	0.041*
BUN–mmol/L	−0.04	0.401
CRE–mmol/L	−0.06	0.257
UA–mmol/L	−0.14	0.007*
TC–mmol/L	0.12	0.018
TG–mmol/L	0.01	0.791
LDL-C–mmol/L	0.27	<0.001*
HDL-C–mmol/L	0.03	0.497
BMI–kg/m^2	0.04	0.455
BW–kg	0.12	0.059
AC–cm	0.01	0.809

FBG, fasting blood glucose; BMI, body mass index; BUN, blood urea nitrogen; CRE, blood creatinine; UA, blood uric acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BW, body weight; AC, abdominal circumference; PRL, prolactin. *$P < 0.05$.

3.4. Factors influencing PRL levels in clinical subgroups prescribed aripiprazole

In the clinical subgroup co-prescribed with aripiprazole, we constructed a multiple linear regression model again with PRL levels as the dependent variable and parameters associated with PRL levels as independent variables. Age ($B = -0.95$, $t = -2.93$, $p = 0.014$), prescription metformin ($B = -0.11$, $t = -0.89$, $p = 0.015$), FBG ($B = -3.63$, $t = -3.71$, $p < 0.001$) levels, and UA ($B = -0.07$, $t = -3.18$, $p = 0.002$) levels were protective factors for HPRL, whereas prescription risperidone ($B = 2.32$, $t = 3.23$, $p = 0.032$) were risk factors for HPRL (Table 4).

4. Discussion

According to us, this may be the only study to date to clarify whether aripiprazole can reduce PRL levels in schizophrenia patients with co-T2DM. The main findings of this study were that co-prescribing aripiprazole not only had no clinical value in reducing PRL levels in the target population of our study but also increased the severity of metabolic disorders compared to the clinical subgroup without co-prescribing aripiprazole.

TABLE 3 Influencing factors of prolactin (PRL) levels in include patients with type 2 diabetes (T2DM): multiple linear regression model.

	Coefficients	Std. error	*t*	*p*-value	95% CI for EXP (*B*)	
	B				Lower	Upper
Constant	65.63	9.76	6.72	<0.001	46.44	84.82
Age–years	−0.61	0.17	−3.64	0.021*	−0.94	−0.28
Schizophrenia duration–years	1.05	0.18	5.94	0.081	0.70	1.39
Metformin–g	−0.12	0.04	−1.04	0.017*	−0.21	0.00
Aripiprazole	−2.58	2.57	−1.00	0.317	−7.63	2.48
Olanzapine	2.11	1.46	1.05	0.036*	1.12	1.89
Risperidone	7.21	2.65	2.72	0.007*	1.99	12.42
FBG–mmol/L	−1.71	0.50	−3.42	0.001*	−2.70	−0.73
UA–mmol/L	−0.04	0.01	−3.38	0.051	−0.06	−0.02
LDL-C–mmol/L	2.20	1.55	1.41	0.158	−0.86	5.25

FBG, fasting blood glucose; UA, blood uric acid; LDL-C, low-density lipoprotein cholesterol. *$P < 0.05$.

TABLE 4 Influencing factors of prolactin (PRL) levels in clinical subgroups prescribed aripiprazole: multiple linear regression model.

	Coefficients	Std. error	*t*	*p*-value	95% CI for EXP (*B*)	
	B				Lower	Upper
Constant	39.61	25.34	5.51	<0.001	89.44	189.78
Age–years	−0.95	0.33	−2.93	0.014*	−1.59	−0.31
Schizophrenia duration–years	0.79	0.34	2.37	0.120	0.13	1.46
Metformin–g	−0.11	0.21	−0.89	0.015*	−0.15	0.01
Aripiprazole–mg	−0.28	0.91	−0.31	0.759	−2.08	1.52
Olanzapine–mg	−0.76	0.43	−1.74	0.084	−1.62	0.10
Risperidone–mg	2.32	1.97	3.23	0.032*	0.73	8.21
FBG–mmol/L	−3.63	0.98	−3.71	<0.001*	−5.57	−1.69
UA–mmol/L	−0.07	0.02	−3.18	0.002*	−0.11	−0.03
LDL-C–mmol/L	0.51	2.78	0.18	0.856	−4.99	6.01

FBG, fasting blood glucose; UA, blood uric acid; LDL-C, low-density lipoprotein cholesterol. *$P < 0.05$.

Our secondary findings also include: (1) in the group of schizophrenic patients with co-T2DM, higher age, prescription metformin, and higher FBG levels were protective factors for HPRL, and prescription olanzapine and risperidone were risk factors for HPRL, but aripiprazole did not affect PRL levels. (2) In the subclinical group with co-prescribed aripiprazole, higher age, metformin dose, and higher FBG and UA levels were protective factors for HPRL, and risperidone dose was a risk factor for HPRL, but aripiprazole dose had also no effect on PRL levels.

There are many clinical studies on the effectiveness of aripiprazole in reducing antipsychotic-induced HPRL (23–25). In China, it is relatively uniform and widely accepted that co-prescribing aripiprazole at doses less than 5 mg is the most effective and optimal prescribing regimen (14, 26). However, one meta-analysis gave differing conclusions, such as Zhang et al. (27) who included 53 randomized controlled double-blind studies and found that either adjuvant less than 5 mg or greater than 10 mg of aripiprazole was the best regimen to control antipsychotic-induced HPRL. In contrast to the above reports, a study from India found that the percentage reduction in PRL levels did not correlate with the specific dose of aripiprazole (28). A multicenter, open-label, prospective study from Korea also reported that administration of the maximum dose of co-prescribed aripiprazole (30 mg/day) similarly achieved a reduction in antipsychotic-induced HPRL (29). These above studies may suggest that the PRL-sparing effect of aripiprazole may not be dependent on the dose of the drug. Although there is a wide range of opinions about which dose of aripiprazole is optimal for improving HPRL, the conclusion that aripiprazole can reduce antipsychotic-induced HPRL is relatively uniform and clear. Puzzlingly, our findings all differ from the above studies in that we found no actual clinical value of co-prescribing aripiprazole for lowering PRL levels in the schizophrenia group with co-morbid T2DM. We speculate that this may be related to the more specific study population we enrolled in or the narrower range of aripiprazole doses (10–20 mg/day) that the study population was prescribed.

As a basic and primary therapeutic agent for T2DM, metformin also unsurprisingly showed a large prescription rate for controlling patients' blood glucose levels in the schizophrenia group included in our study, while its other significant pharmacological effect is its use for controlling antipsychotic-induced HPRL (14, 20, 27). There is similar controversy and uncertainty regarding the optimal dose of metformin for the treatment of antipsychotic-induced HPRL. The expert consensus from China and clinical studies from Poland

both conclude that high doses of metformin (2.55–3.0 g/day) are effective in reducing antipsychotic-derived HPRL (14, 30), but this dose exceeds the maximum daily dose limit (maximum 2 g/day) given in the metformin instructions, which may introduce other metformin-derived adverse drug reactions and ethical issues, and therefore should not be used as a routine clinical treatment regimen. A meta-analysis reported that metformin doses below 1 g/day were also effective in reducing PRL levels in patients with HPRL induced by atypical antipsychotics (27). In our study, the conventional metformin dose (1–2 g/day) used to treat diabetes mellitus in schizophrenia with co-morbid T2DM also had the same function of lowering PRL levels and showed a negative dose-dependence of metformin dose and PRL levels. Whether the reason for this phenomenon is related to the co-prescription of aripiprazole, resulting in a dose shift of metformin to lower PRL levels, is a question that deserves further investigation. And whether aripiprazole is competing with metformin for the failure of targets that inhibit the synthesis and/or release of PRL and thus losing its function in reducing the utility of PRL levels is likewise a question that needs to be further answered.

In the present study, although the function of lowering PRL levels was lost, the co-prescription of aripiprazole exacerbated the severity of abnormal metabolic markers in the included patients, although aripiprazole is considered to be one of the antipsychotics with the least metabolic adverse effects (31–33). In contrast to the more common extrapyramidal adverse effects of first-generation antipsychotics, atypical antipsychotics exhibit more prominent abnormalities in metabolic indicators (34). A study from Hong Kong, China, reported that the combination of multiple antipsychotics increased the risk of abnormal metabolic parameters associated with cardiovascular disease in patients with schizophrenia spectrum disorders (35). Another study reported a higher incidence of metabolic syndrome and lipid markers of insulin resistance in patients receiving antipsychotic polypharmacy compared to those receiving antipsychotic monotherapy (36). In contrast to our study, the participants we included were co-prescribed aripiprazole, which is thought to have no or minimal effect on metabolic indices, and two studies even reported that adjunctive use of 5–20 mg/day of aripiprazole improved metabolic disturbances, while the original atypical antipsychotic dose was maintained (37–40). However, a review of systematic reviews concludes that this possible protective effect of aripiprazole needs to be further elaborated by more robust studies (41), because longer-term observations and studies have found that the severity of metabolic adverse effects of aripiprazole is not superior to that of antipsychotics such as risperidone and quetiapine (42, 43). This is consistent with the results of our study, which found that long-term hospitalized chronic schizophrenia patients co-prescribed with aripiprazole exhibited metabolic abnormalities of even worse severity.

In the secondary findings, we found that older age was a protective factor for HPRL, and one study also found that antipsychotic-derived high levels of PRL decline with age in patients with schizophrenia (44), which may be attributed to the fact that the gonads shrink with age. Higher FBG levels were also a protective factor for HPRL, which is inconsistent with previous findings (45), and in our opinion may be related to the more aggressive addition of glucose-lowering agents represented by metformin for those patients with poorly controlled blood glucose levels. Risperidone remained an important contributor to HPRL, which was the same as the previous findings (1). And higher UA levels were a protective factor for HPRL, which was consistent with our previous report (22).

5. Conclusion

In conclusion, aripiprazole not only worsened the severity of index disturbances associated to metabolism in long-term hospitalized chronic schizophrenia patients with co-T2DM on metformin-based hypoglycemic medications but also failed to lower PRL levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by the Ethics Committee of Wuhan Mental Health Center. Written informed consent to participate was not required in accordance with institutional requirements and legislation.

Author contributions

JM and YG made substantial contributions to conception and design of the study. XL and XS drafted the manuscript. LL had polished and re-edited the language and logic of the manuscript. KZ and YL were responsible for setting up and complement and modify the contents of the manuscript. JM gave final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Initiation of antidepressants in patients infected with SARS-COV-2: Don't forget Caution for "Paradoxical" Anxiety/Jitteriness syndrome—Commentary: Prescription of selective serotonin reuptake inhibitors in COVID-19 infection needs caution

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A Commentary on
Prescription of selective serotonin reuptake inhibitors in COVID-19 infection needs caution

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With great interest, I read the informative Opinion Article of Borovcanin et al. (1) in a recent issue of *Front. Psychiatry* about the possible benefits and obstacles (including relevant adverse effects) of selective serotonin reuptake inhibitors (SSRIs) if prescribed for patients infected with SARS-CoV-2. The SSRI fluvoxamine and further antidepressants (ADs) are probably going to be increasingly used in this particular population mainly for two reasons. First, ADs may be useful in the treatment of depression and anxiety, which are found to be frequently associated with SARS-CoV-2 infections (e.g., "coronaphobia"), COVID-19, and long/post-COVID-19 (2–5). Second, there seems emerging, albeit preliminary and still inconsistent, evidence for reducing COVID-19-related mortality and hospitalizations using a couple of ADs (5–8). This applies especially to fluvoxamine, which is, as of November 2022, the most well-studied AD in this specific research area (5–11). The cheap and easy availability of this molecule and similar ADs might facilitate an increasing prescription by physicians who may be not experienced in psychopharmacology, especially in regions where vaccination programs are still far from realization.

Therefore, in an amendment to the article by Borovcanin et al. (1), I would like to add the potential occurrence of an anxiety/jitteriness syndrome (AJS, also known as "activation syndrome") as a common adverse reaction of ADs including SSRIs. AJS usually involves the "paradoxical" occurrence of a mild-to-severe mix of panic attacks, nausea, restlessness,

insomnia, tremor, hyperhidrosis, irritability, impulsivity, and rarely also suicidality and/or hostility/aggressiveness (12, 13). AJS occurs independently of the used AD class and is one of the main causes of the early discontinuation of a selected AD (12–14). Reported incidence rates diverged considerably from 4 to 65% in persons commencing AD treatment (12–16). This large range might reflect incongruent AJS definitions [mostly symptom clusters including suicidality or not (12, 13)] as well as a variation of interlinked underlying mechanisms including individual genetic/epigenetic vulnerability, exuberant sensitization of the monoamine neurotransmitter system, and/or dis-balancing within the cytokine orchestra, as well as psychological factors [e.g., the nocebo effect of the AD treatment (12–17)]. There is no model about a possible biological mechanism of AJS being reconciled with a psychological explanation into a comprehensive explanatory model. Patients, as well as their first-degree relatives, diagnosed with anxiety and mood disorders were found to be at increased risk for AJS (odds ratio $\geq$ 5) (14, 15). Patients on mirtazapine were found to be at a lower AJS risk than those on other ADs (15). Another prospective study described that escitalopram, mirtazapine, milnacipran, clomipramine, and trazodone were associated with a lower incidence of AJS than paroxetine, sertraline, and fluvoxamine (14). A further study showed that high-dose AD treatment was significantly associated with AJS (15).

Usually, anxiety/jitteriness syndrome disappears spontaneously within the first weeks after its emergence, highlighting a pertinent tolerance/de-sensitization phenomenon (12–16). Although currently not proven by well-controlled clinical studies, phenothiazine-type antipsychotics (the anticholinergic activity and potential QTc prolongation of which should be noted) and benzodiazepines were reported to be useful for AJS suppression (12–16) and, thereby, helpful for differentiating between AJS and a true worsening of COVID-19 or long COVID-19.

In my experience, AJS developed often immediately after starting with an SSRI or serotonin–norepinephrine reuptake inhibitor (SNRI) and disappeared rapidly within the next 2–4 days without stopping the administration of AD. Before starting with an AD, including information about AJS in the education about possibly occurring adverse events and outlining the usual transiency of AJS can stabilize the continuation of the administered AD. However, clinical studies on this specific subject are missing. Approximately two-thirds of these patients who were in the following indeed affected by an AJS continued the AD treatment in my practice using the aforementioned patient education for better clarity.

It is worth underscoring that AJS is a frequent adverse reaction in the early treatment period with an AD because this easy-to-manage, benign, and usually ephemeral condition may be overlooked if physicians are unaware of its occurrence. In this case, AJS could be more likely misdiagnosed as neuropsychiatric and/or gastrointestinal COVID-19 in patients infected with SARS-CoV-2 or worsening of pre-existing COVID-19. Nausea, tremor, anxiety, and restlessness occurring in particular within the first days after the onset of an AD treatment are more likely caused by an AJS than by COVID-19 in patients infected with SARS-CoV-2.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluation of the effect of managing oxycodone/acetaminophen as a psychotropic medicine: An interrupted time-series study

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Background: Oxycodone/acetaminophen has been reported for misuse for many times in China. To cope with that, Chinese national authorities jointly issued a policy, requiring that oxycodone/acetaminophen should be managed as a psychotropic medicine starting 1 September 2019. This paper aimed to evaluate the effect of this policy in medical institutions.

Methods: We used interrupted time-series analysis to examine the immediate level and slope changes in the mean number of tablets prescribed, proportion of oxycodone/acetaminophen prescription exceeding 30 pills, days supplied per prescription and the proportion of days supplied exceeding 10 days with prescription data from 5 tertiary hospitals in Xi'an city between 1 January 2018 and 30 June 2021 (42 months). We divided the prescriptions into two groups, one for long-term drug users, and the other for short-term drug users.

Results: In total, 12,491 prescriptions were included in the final study, with 8,941 and 3,550 prescriptions for the short-term and long-term drug users, respectively. Significant differences in the proportion of prescriptions issued by various departments, were observed between pre- and post-implementation of the policy for both short-term and long-term drug users ($p < 0.001$). For short-term drug users, the policy implementation was only associated with an immediate level decrease in proportion of prescriptions exceeding 30 tablets (–4.09%, $p < 0.001$). For long-term drug users, after the policy, the mean number of tablets prescribed and the mean proportion of prescriptions exceeding 30 tablets experienced a level decrease of 22.96 tablets ($p < 0.001$) and a level decrease of 41.13% ($p < 0.001$), respectively; the mean number of days supplied showed a significant level decrease (6.88 days per prescription) and slope increase (0.19 days per month), and the mean proportion of days supplied exceeding 10 days showed a significant level decrease (–10.51% per prescription) and a slope increase (0.27% per month).

Conclusion: Implementation of stricter management for oxycodone/acetaminophen achieved its goal of reducing the risk of misuse in short-term drug users. For those long-term drug users, policy needed to be strengthened as the prescription exceeding 10 days was still at a high level after the intervention.

Policies targeting patients with different drug demands are needed. Many other strategies can be implemented, including establishing specific guidelines/principles and conducting training programs.

KEYWORDS

Oxycodone/acetaminophen, policy, clinical effect, psychotropic medicine, interrupted time series

Introduction

The use of opioid analgesics is a growing problem all over the world. The consumption varied widely throughout the world, with overuse in some countries like the United States and underuse in some low-and middle-income countries (Berterame et al., 2016). The difference in the management strategy may be one of the reasons for that (Hamunen et al., 2009). In China, opioid analgesics are strictly regulated and its use was far below demand (Xie et al., 2020a; Huang et al., 2020). However, drug misuse with opioid, especially those compound formulations, were still reported in multiple studies (Wang et al., 2008; Zhao et al., 2018; Xie et al., 2020a; Tang and Che, 2020; Shen et al., 2021). One example is the oxycodone/acetaminophen.

Oxycodone/acetaminophen is a compound formulation consisting of acetaminophen and oxycodone (Chinese Association for the Study of Pain Committee, 2018). It entered the Chinese market in 1998 and was managed as psychotropic medicine of Category II in the initial stage (Ma et al., 2012). In 2004, it was adjusted to be common medicine (National Medical Products Administration, 2004). Since the management policy of this medicine was relaxed, misuse of that has been reported for many times. In 2010, misuse of oxycodone/acetaminophen in hospitals was detected for the first time (Ma et al., 2012). In 2014, a study reported its overselling in retail pharmacies (Li et al., 2018). In addition, the addiction and dependence was also reported in many studies in the past 5 years (Hu and Cao, 2018; Zhao et al., 2018; Xu et al., 2019; Tang and Che, 2020). Studies on the analysis of rational use of oxycodone/acetaminophen have also found that it was in excessive use in medical institutions (Niu and Zhang, 2017; Geng et al., 2021). The main reason for that was the big difference in the management of common medicines and psychotropic medicines of Category II in China. All the drugs are divided into common drugs and special managed drugs for management in China (Man et al., 2017). The special managed drugs mainly included anesthetic drugs, psychotropic drugs, toxic drugs, radioactive drugs, etc. The psychotropic drugs were further refined and divided into Category I and II. Special managed drugs were subject to a stricter regulation, and supervised by the China National Medical Products Administration, who implemented whole-chain supervision and monitored the usage regularly. To be specific, the differences in the management of common drugs and psychotropic medicines of Category II included production, selling and use (National Health Commission of the People's Republic of China, 2005; National Health Commission of the People's Republic of China, 2007). In terms of production, psychotropic medicines of Category II are produced by designated enterprises, while common medicines are produced in enterprises which have the corresponding producing qualifications. In addition to the business license, the institutions selling psychotropic medicines of Category II need to get a specific qualification authentication. In term of use, these two kinds of medicines are also quite different. For common medicine, the prescription duration limit was generally 7 days but it can be appropriately extended to 3 months, while psychotropic medicine of Category II is strictly limited to 7 days. If the prescription duration need to exceed the time limit, the doctor needs to state it clearly and provides an extra signature on the prescription, and the total duration should not exceed 15 days. In addition to the risk of misuse posed by the oxycodone, there are also risks of hepatotoxicity and nephrotoxicity because of the acetaminophen. Nowadays, many studies reported that improper use of acetaminophen, including excessive use and combining with other drugs inappropriately, would cause serious damages, including liver toxicity kidney toxicity and even death (Hiragi et al., 2018; Hopkins et al., 2018; Janković, 2022). In order to avoid the risks of that, the Pharmacopoeia, revised in 2015, clearly stated that the prescription duration of acetaminophen should not exceed 10 days.

In order to cope with the growing misuse of oxycodone/acetaminophen and reduce the risk of that, three Chinese national authorities, including Food and Drug Administration, the Ministry of Public Security, and the National Health Commission, jointly issued a document, requiring that the oxycodone/acetaminophen should be managed as a psychotropic medicine starting 1 September 2019 (National Medical Products Administration, 2019a). This means that stricter restrictions would be applied on the use of oxycodone/acetaminophen.

Until now, several researchers have evaluated the effect of strengthening the management of oxycodone/acetaminophen in medical institutions. An investigation found that the single dose, daily dose, and prescription volume of oxycodone/acetaminophen were all significantly lower after the implementation of the stricter management policy (Tian et al., 2021). Another report also came to similar conclusions (Liu and Wang, 2021). However, all the above studies were conducted in single medical institution and used before-and-after comparative analysis (covering a few months) to describe the short term changes. To comprehensively evaluate the policy effect and obtain reliable conclusion, we conducted a multicenter prescription-based study, quantitatively evaluated the effect of policy and analyzed both the short-term and long-term effects.

Methods

Study design and setting

We conducted a retrospective interrupted time-series analysis of oxycodone/acetaminophen prescriptions filled between 1 January 2018 and 30 June 2021 in Xi'an, the capital city of Shaanxi Province.

Shaanxi is a major pilot province of the northwestern health system reform. It has a population of 39.55 million and 11 cities,

ranked 12th for gross domestic product *per capita* in Mainland China (China Economic and Social Big Data Research Platform, 2021; Statistics Bureau of Shanxi Province, 2021). In Shaanxi Province, there were 35,300 medical institutions, including 60 tertiary hospitals; most tertiary hospitals were located in its capital city-Xi'an (National Health Commission 2021 of the People's Republic of China, 2021).

Data source

We invited the top 10 tertiary hospitals in Xi'an in terms of oxycodone/acetaminophen consumption in 2020 to participate the study, and three refused. Among the seven agreed hospitals, two upgraded their Hospital Information System (HIS) in last two years, and could not provide prescriptions during the periods before upgrading. Finally, we extracted the prescriptions data from HIS of five tertiary hospitals. The oxycodone/acetaminophen consumption in these five hospitals accounted for 20% of the total oxycodone/acetaminophen consumption in Shaanxi Province in 2020.

The prescription information included unique prescription code and patients' code, sex, age of patient, diagnosis, department of physician, drug name and dosage.

Study cohort and measures

We identified all prescriptions for oxycodone/acetaminophen dispensed between 1 January 2018 and 30 June 2021. Based on the following principal, we excluded the invalid prescriptions and determined the final study cohort: 1) Firstly, we eliminated the prescriptions without key information such as department, age, gender, diagnosis, frequency or dosage; 2) Secondly, the prescriptions prescribed by non-clinical departments were excluded from the study; 3) Thirdly, given that the prescriptions issued by emergency department followed the principle of a 3-day limit, we also excluded prescriptions from that department.

Based on the definition of chronic pain given by WHO (pain which lasts for 3 months or recurs in 3 months), we divided all the drug users into two groups (short-term and long-term drug users) using the information of the total prescription volume, frequency of prescription and the interval between prescriptions. Patients who met one of the following two criteria were considered as long-term drug users: 1) 360 or more tablets (usage covering 3 months) were prescribed during the whole study period; 2) More than one prescription was prescribed between 7 and 90 days and the total number of tablets prescribed was more than 120 tablets, which could be used for pain relief for more than one month. Those who do not met the criteria was regarded short-term drug users. Our analysis was based on the prescriptions prescribed to the short-term and long-term drug users.

The primary outcome for the two groups was mean number of tablets prescribed, which can be used to estimate the consumption of oxycodone/acetaminophen. We also analyzed three secondary outcomes. The first was proportion of oxycodone/acetaminophen prescriptions exceeding 30 pills. The recommended dosage and frequency for oxycodone/acetaminophen is 1 tablet every 6 h (4 pills a day). While according to the policy requirement, one prescription shall not exceed a 7-day supply. In other word, no more than 28 pills would be prescribed for one prescription. And given the facts that there are 10 tablets in a box of oxycodone/acetaminophen and medicines are usually not sold in pieces, we set the standard as 30 tablets. The second indicator was days supplied per prescription, which are calculated based on the pills prescribed and the dosage and frequency. The last indicator was the proportion of days supplied exceeding 10 days which evaluated the relational use of acetaminophen. Acetaminophen is one of the main components of oxycodone/acetaminophen and it is required that the days supplied should not exceed 10 days in the "Instructions for clinical medication in Chinese Pharmacopoeia".

Statistical analysis

Firstly, descriptive statistics were used to compare the demographic and characteristics of patients before and after the implementation of the policy. Secondly, to estimate the effect of the policy, we conducted an interrupted time-series analysis of application of oxycodone/acetaminophen. The outcomes and covariates were all aggregated to the level of months. Segmented regression model was used to estimate the changes in the mean number of tablets prescribed, proportion of oxycodone/acetaminophen prescription exceeding 30 pills, mean number of supplied days and proportion of days supplied exceeding 10 days. Two segments with one interruption point were constructed, with 20 months before (January 2018 to August 2019) and 22 months after (September 2019 to June 2021) the intervention. Totally, 42 months were covered in the regression. The model is as follows:

$$Y_t = \beta_0+\beta_1*\text{time}_t+\beta_2*\text{intervention}+\beta_3*\text{time after intervention}_t + e_t$$

Y_t represented the four outcomes. β_0 is the intercept of the outcome variable, estimating the baseline level. β_1 represent the slope of the outcome before the introduction of the policy. β_2 estimates the change in the level of the outcomes immediately after the introduction of the policy. β_3 represents the difference between pre-intervention and post-intervention slopes of the outcome.

The Durbin-Watson and Bgodfrey statistic were used to test for serial autocorrelation. When needed, Feasible Generalized Least Square was used for adjusting for the serial autocorrelation. Breusch-Pagan test was used for heteroscedasticity. In addition, we also tested the normality of the series. All analysis was performed on Stata MP 16.0.

Results

We extracted 16,133 prescriptions for oxycodone/acetaminophen between 1 January 2018 and 30 June 2021. After exclusion, the final study cohort contained 7,789 drug user, involving 12,491 prescriptions. There were 7,440 short-term and 349 long-term drug users, involving 8,941 and 3,550 prescriptions, respectively. For short-term and long-term drug users, differences in the characteristics were frequent (Table 1). For short-term drug users, the proportion of prescriptions for elderly patients (> 65)

TABLE 1 Demographic and clinical characteristics of the short-term and long-term drug users before and after the policy.

Characteristic		Short-term (n = 7,440)			Long-term (n = 349)		
		Before (n = 3,801)	After (n = 3,639)	p	Before (n = 142)	After (n = 207)	p
Age	≤18	135 (3.55%)	40 (1.10%)	<0.001	0 (0.00%)	0 (0.00%)	<0.001
	19–64	2,716 (71.45%)	2,462 (67.66%)		70 (49.30%)	111 (53.62%)	
	≥65	950 (24.99%)	1,137 (31.24%)		72 (50.70%)	96 (46.38%)	
Sex	male	2,234 (58.77%)	2,141 (58.83%)	>0.05	87 (61.27%)	106 (51.21%)	<0.001
	female	1,567 (41.23%)	1,498 (41.17%)		55 (38.73%)	101 (48.79%)	
Departments	Surgery	2,288 (60.19%)	1,652 (45.40%)	<0.001	49 (34.51%)	54 (26.09%)	
	Internal medicine	303 (7.97%)	683 (18.77%)		30 (21.13%)	66 (31.88%)	
	Pain medicine	296 (7.79%)	392 (10.77%)		14 (9.86%)	48 (23.19%)	
	Oncology	256 (6.74%)	542 (14.89%)		10 (7.04%)	21 (10.14%)	
	Convenience clinic	233 (6.13%)	38 (1.04%)		29 (20.42%)	3 (1.45%)	<0.001
	Traditional Chinese Medicine	185 (4.87%)	60 (1.65%)		2 (1.41%)	7 (3.38%)	
	Dermatology	141 (3.71%)	41 (1.13%)		1 (0.70%)	0 (0.00%)	
	Infectious Diseases	58 (1.53%)	99 (2.72%)		6 (4.23%)	7 (3.38%)	
	Others	41 (1.08%)	132 (3.63%)		1 (0.70%)	1 (0.48%)	

increased, while for young patients (≤ 18) decreased after the policy. There is no significant difference in the proportion of prescriptions for male and female before and after the policy for short-term drug users. However, the proportion of prescriptions for short-term and long-term drug users issued by various departments changed greatly. To be specific, the proportion in convenience clinics and surgery dropped, while the proportion prescribed by pain, internal and oncology departments increased.

Changes in the mean number of tablets prescribed and proportion of oxycodone/acetaminophen exceeding 30 pills

For all users, before the policy, the mean number of tablets prescribed was 22.26 with an upward trend (0.18 per month, p = 0.011) and the mean proportion of prescriptions exceeding 30 tablets was 14.35%. After the policy intervention, the mean number of tablets prescribed experienced a level decrease of 3.9 tablets ($p < 0.01$), and the mean proportion of prescriptions exceeding 30 tablets had a significant immediate decrease (-12.24%, $p < 0.01$).

For short-term drug users, prior to the implementation of the policy, the mean number of tablets prescribed was 16.50 and the mean proportion of prescriptions exceeding 30 tablets was 4.86%. After the policy intervention, the mean proportion of prescriptions exceeding 30 tablets experienced a level decrease of 4.09% ($p < 0.01$), with a downward trend (0.34% per month, $p = 0.01$) (Figures 1, 2; Table 2).

For long-term drug users, before the policy, the mean number of tablets prescribed was 63.38, and it experienced a level decrease of 22.96 tablets ($p < 0.001$) after the policy. The mean proportion of prescriptions exceeding 30 tablets was 66.35% before the policy, and we observed a significant decrease of 41.13% in level ($p < 0.001$) after the policy (Figures 1, 2; Table 2).

Changes in the days supplied and proportion of days supplied exceeding 10 days

For all users, before September 2019, the mean number of days supplied was 8.54, and the mean proportion of days supplied exceeding 10 days was 17.03%. After the policy intervention, the mean number of days supplied showed an immediate level decrease (−1.37 days) and a significant slope increase (0.08 days per month); the mean proportion of days supplied exceeding 10 days decreased significantly by 10.51% immediately ($p < 0.01$), but no significant change in the trend.

For short-term drug users, before September 2019, the mean number of days supplied was 6.97 and the mean proportion of days supplied exceeding 10 days was 9.81%. After policy intervention, the mean number of days supplied had a significant slope increase (0.06 days per month), while the mean proportion of days supplied exceeding 10 days did not show any significant changes (Figures 3, 4; Table 3).

For long-term drug users, before September 2019, the mean number of days supplied was 17.67 and the mean proportion of days supplied exceeding 10 days was 60.54%. After policy

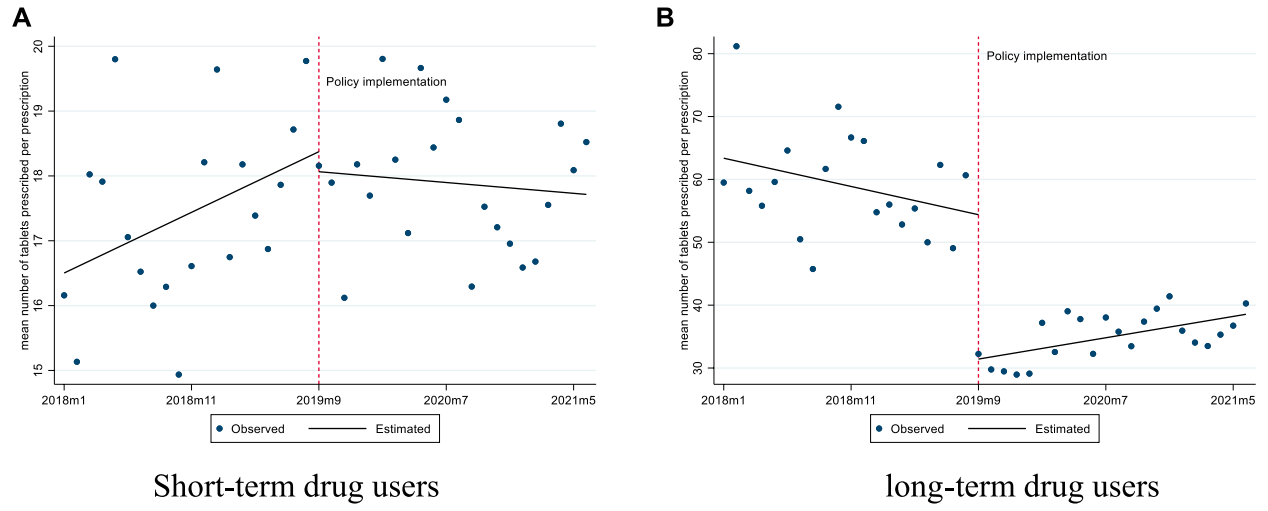

FIGURE 1
Changes in the mean number of tablets prescribed per prescription for short-term and long-term drug users. **(A)** Short-term drug users **(B)** long-term drug users.

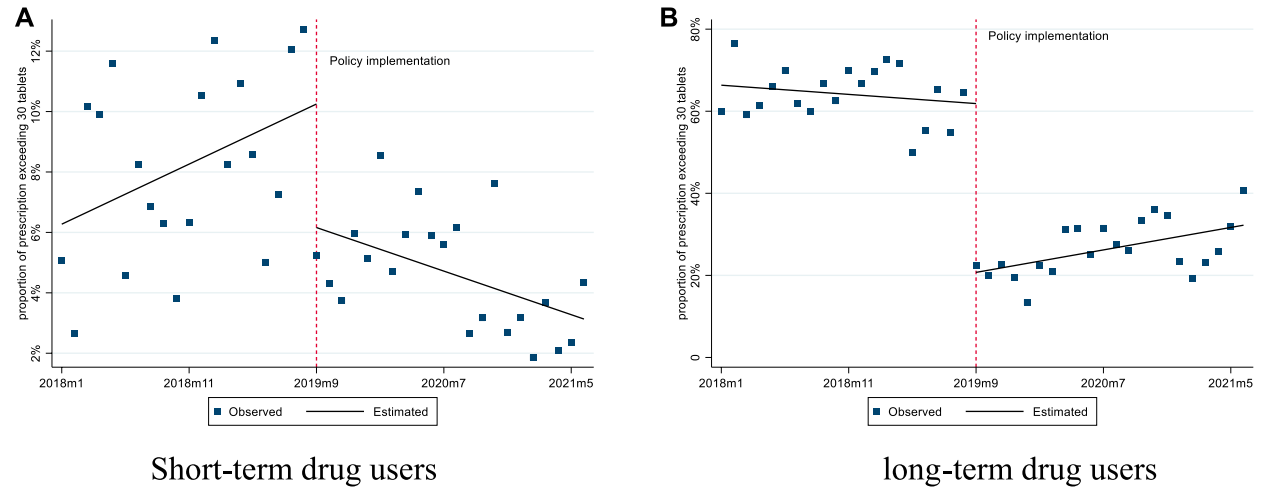

FIGURE 2
Changes in the proportion of prescription exceeding 30 pills for short-term and long-term drug users. **(A)** Short-term drug users **(B)** long-term drug users.

intervention, the mean number of days supplied showed a significant level decrease (6.88 days per prescription) and slope increase (0.19 days per month); the mean proportion of days supplied exceeding 10 days also had a significant level decrease (−10.51%) (Figures 3, 4; Table 3).

Discussion

Previously, some studies have found that strengthening the management significantly reduced the risk of misuse of oxycodone/acetaminophen. The number of prescriptions, dosage, DDDs, drug utilization index, irrational prescription proportion of oxycodone/acetaminophen decreased after the implementation of stricter management (Liu and Wang, 2021; Tian et al., 2021). Our study also confirmed that. In addition, we found the exact effects of the inclusion of oxycodone/acetaminophen in psychotropic drugs and the implementation of stricter regulatory on different group of drug users.

For those short-term drug users, the policy had an impact on the proportion of prescription exceeding 30 tablets, which had a significant level decrease and slope decrease. It also had a level decrease on the proportion of prescription exceeding 10 days (significantly at the level of 0.1). Before the policy, we can find some irrational drug use, as the mean proportion of prescriptions exceeding 30 tablets was 6.27% and the mean proportion of days supplied exceeding 10 days was 9.82%. After the policy implementation, these two indicators decreased. From this

TABLE 2 Estimates from Interrupted Time-Series models of the impacts of the policy on the number of tablets prescribed and proportion of prescription exceeding 30 tablets.

		Short-term drug users		Long-term drug users		All users	
		coefficient	*p*-value	coefficient	*p*-value	coefficient	*p*-value
Number of tablets prescribed per prescription							
Intercept	β0	16.50	<0.001***	63.38	<0.001***	22.26	<0.01***
Pre-intervention slope	β1	0.09	0.058*	−0.45	0.172	0.18	0.011**
Level change	β2	−0.31	0.644	−22.96	<0.001***	−3.90	0.001***
Slope change	β3	−0.11	0.062*	0.79	0.024**	0.02	0.797
Proportion of prescription exceeding 30 tablets (%)							
Intercept	β0	6.27%	<0.001***	66.35%	<0.001***	14.35%	<0.01***
Pre-intervention slope	β1	0.20%	0.094*	−0.22%	0.424	0.34%	0.079*
Level change	β2	−4.09%	0.008***	−41.13%	<0.001***	−12.24%	<0.01***
Slope change	β3	−0.34%	0.010**	0.77%	0.028**	−0.02%	0.922

*p < 0.1, **p < 0.05, ***p < 0.01.

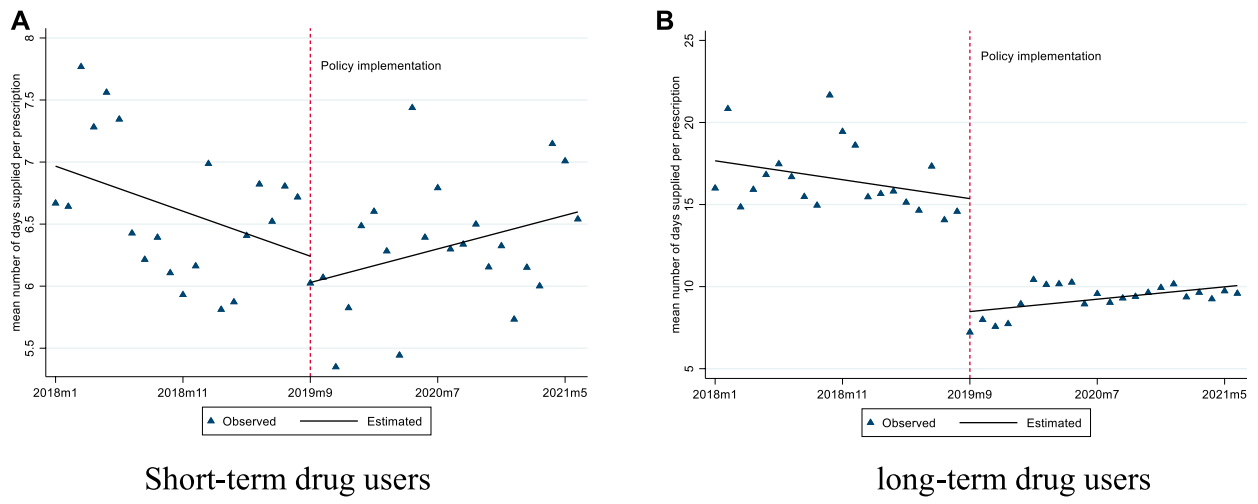

FIGURE 3
Changes in the mean number of days supplied per prescription for short-term and long-term drug users. **(A)** Short-term drug users **(B)** long-term drug users.

aspect, the policy did achieve its anticipated goal of reducing the risks of drug misuse.

For those long-term drug users, all the four indicators decreased immediately. One possibility for the decline was that the longest supply of one prescription was three months before the policy, while after the policy it decreased to 15 days. This has both pros and cons. Long-term drug users have to visit hospitals more frequently which may benefit them as it can help physicians track the progress of the disease, evaluate the efficacy of the treatment, find the adverse effects of drugs and adjust the dosage in time. However, more visits to the hospital for these needful medicines, which increased the cost for patients. More importantly, it caused inconvenience, especially in the time of COVID-19 as cities were locked down frequently.

Besides, we found the proportion of prescription exceeding 10 days supplied among long-term drug users was high, with about 60% and 20% before and after the implementation of the policy, respectively. This should be of high concern, for that the prolonged use of acetaminophen would cause liver and kidney toxicity. One possible reason for this was that oxycodone/acetaminophen was a kind of compound preparation, and doctors was not familiar with it and had no knowledge of the ingredients of that (Chen, 2000; Huang, 2007). Improving the knowledge of doctors about medicine through lectures, training and other ways, was the key to promote the rational use of that.

With the implementation of the policy, the four indicators for long-term drug user increased to a certain extent. The reasons for that are likely multifactorial. Firstly, the administrative supervision of psychotropic drugs of Category II was in certain deficiencies (Xie et al., 2020b). The supervision of "special drugs" focused on anesthetic drugs and psychotropic drugs of Category I, while the

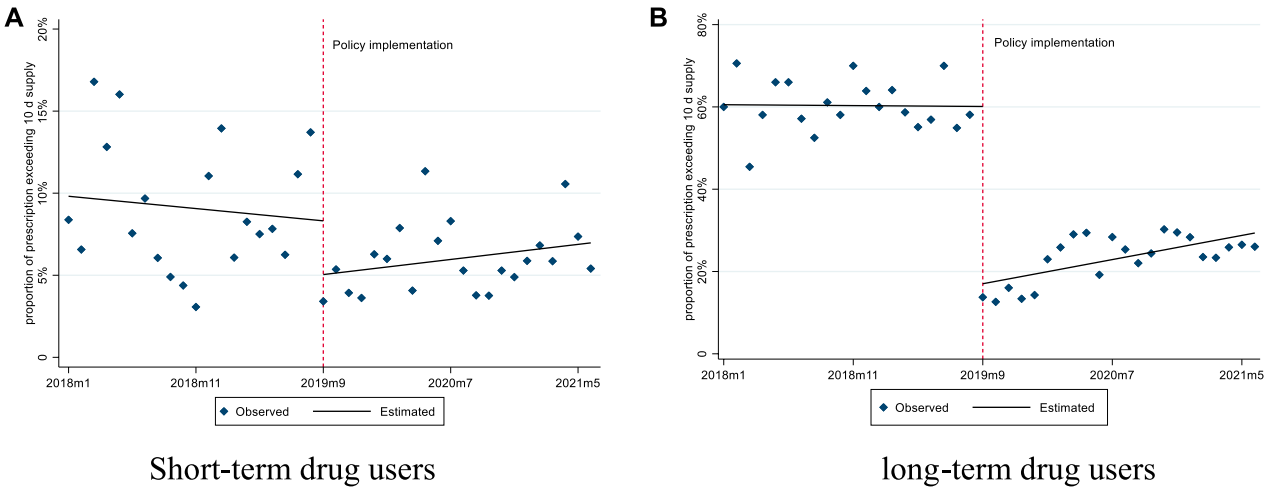

FIGURE 4
Changes in the proportion of prescription exceeding 10 days' supply for short-term and long-term drug users. **(A)** Short-term drug users **(B)** long-term drug users.

TABLE 3 Estimates from Interrupted Time-Series models of the impacts of the policy on days supplied and proportion of prescription exceeding 10 days.

		Short-term drug users		Long-term drug users		All users	
		coefficient	*p*-value	coefficient	*p*-value	coefficient	*p*-value
Days supplied per prescription							
Intercept	β0	6.97	<0.001***	17.67	<0.001***	8.54	<0.001***
Pre-intervention slope	β1	−0.04	0.068*	−0.12	0.113	−0.02	0.41
Level change	β2	−0.21	0.468	−6.88	<0.001***	−1.37	<0.001***
Slope change	β3	0.06	0.013**	0.19	0.017**	0.08	0.006***
Proportion of prescription exceeding 10 days(%)							
Intercept	β0	9.81%	<0.001***	60.54%	<0.001***	17.03%	<0.001***
Pre-intervention slope	β1	−0.07%	0.682	−0.02%	0.940	0.11%	0.359
Level change	β2	−3.27%	0.08*	−43.08%	<0.001***	−10.51%	<0.001***
Slope change	β3	0.17%	0.316	0.61%	0.058*	0.27%	0.091*

*$p < 0.1$, **$p < 0.05$, ***$p < 0.01$.

supervision of psychotropic drugs of Category II is relatively loose, and corresponding documents on supervision are rare. Therefore, in the initial stage of the policy, medical practitioners may comply with the requirement of the policy as they expected strict regulation. However, if regulation is loose and they think the new policy just caused inconvenience for their patients, practitioners may revert to their old prescription pattern.

Including drugs at risk of misuse in the list of psychotropic drugs, and then adopting stricter management measures are commonly used methods in China to reduce the risk of drug misuse. Until now, three kinds of drugs, including codeine-containing oral liquid preparations, oxycodone/acetaminophen, and remimazolam, have been added to the list of psychotropic drugs due to their increased risk of misuse (National Medical Products Administration, 2015; National Medical Products Administration, 2019a; National Medical Products Administration, 2019b). Our research found that the policy reduced the risk of misuse in short-term drug users but also caused inconvenience for those long-term drug users. Thus, different policies targeting patients with different drug demands are needed. And more importantly, we need promote rational and appropriate use of these medicines by implementing multiple strategies. First of all, it is recommended to further enrich the supporting documents and measures to guide the use of psychotropic drugs and to supervise drug application regulations on the basis of existing laws. Government need further formulate and issue standardized guidelines and principles to guide the clinical use of special drugs in medical institutions. Secondly, the relevant regulatory process and content also need be further developed. Conducting prescription review on such medicine is a good way to ensure its appropriate use in medical institutions. Because prescription review can timely detect relevant problems and avoid improper prescriptions in time. What's more, training medical

practitioners is also needed to provide enough information of how to use it properly and what's the harm of improper use. Finally, the role of pharmacists should also be brought into full play. Pharmacists are professionals who have better knowledge of drugs and can provide advice about medicines to physicians. Involving pharmacists in the medication process can promote the rational use of drugs and avoid the occurrence of inappropriate drug use to the great extent.

This is the first study to comprehensively evaluate the effects of a policy intervention for including oxycodone/acetaminophen as a psychotropic medicine and the short- and long-term effects are described intuitively. However, our research also has several limitations. Firstly, our data was derived from 5 tertiary medical institutions, not all the medical institutions. However, the consumption in these 5 medical institutions accounted for 20% of all the oxycodone/acetaminophen consumption in Shaanxi, which also makes our sample representative to a certain extent. Secondly, the prescriptions involved in our study was only oxycodone/acetaminophen, and other kinds of opioid analgesics was not involved. In other words, we only evaluated the changes in the prescription of oxycodone/acetaminophen. How many patients shifted to other kinds of opioid analgesics and the changes of prescription pattern of them after policy implementation were not assessed. Thirdly, we divided the patients into long-term and short-term users, but impact of the policy on specific diseases were not included in the analysis.

Conclusion

This study showed that the policy administrating oxycodone/acetaminophen as a psychotropic medicine achieved its goal of reducing the risk of misuse in short-term drug users. But for those long-term drug users, policies needed to be strengthened as the prescription exceeding 10 days was still at a high level after the intervention. Policies targeting patients with different drug demands are needed. Many other strategies can be implemented, including establishing specific guidelines/principles and conducting training programs.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data will be made available on reasonable request. Requests to access these datasets should be directed to JZ, xjtu705010314@163.com.

Author contributions

CX: Conceptualization, investigation, formal analysis, writing–original draft; SL: Investigation, formal analysis, writing–Review and editing; JwZ: Investigation, writing–review and editing; JqZ: Investigation, writing–review and editing; SH: Investigation, writing–review and editing; MP: Investigation; CY: Conceptualization, investigation, formal analysis, visualization, supervision; KZ: Conceptualization, investigation, formal analysis, visualization, supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tolerability profile of paliperidone palmitate formulations: A pharmacovigilance analysis of the EUDRAVigilance database

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Introduction: Long-acting injectable antipsychotics (LAIs) have proven to be effective in the maintenance treatment of patients suffering from schizophrenia, and their safety and tolerability profiles represent a key factor in their long-term use and choice in clinical practice. Paliperidone palmitate (PP) is the only second-generation LAI (SGA-LAI), available in both one- (PP1M) and 3-month (PP3M) formulations. However, real-world prospective studies on PP1M and PP3M are still few and mostly conducted on small samples. In this context, we aimed to better define the safety and tolerability profile of PP using real world pharmacovigilance data.

Methods: We retrospectively analyzed the publicly available data regarding Individual Case Safety Reports (ICSRs), presenting PP1M and/or PP3M as suspected drugs, reported on EUDRAVigilance between 2011 and June 30th, 2022. ICSRs relative to at least one SGA-LAI other than PP, reported between 2003 and June 30th, 2022, were also examined as reference group. Data were evaluated with a descriptive analysis, and then, as disproportionality measures, crude reporting odds ratio (ROR) and 95% confidence interval (CI) were calculated.

Results: A total of 8,152 ICSRs met the inclusion criteria, of those 77.7% (n = 6,332) presented as suspected drug PP1M, 21.2% (n = 1,731) PP3M, while 89 cases indicated both PP1M and PP3M. Significantly higher probabilities of reporting in PP-related reports were observed for the primary Standardized MedDRA Queries "Sexual Dysfunctions" (ROR = 1.45; 95% CI 1.23-1.70), "Haemodynamic oedema, effusions and fluid overload" (ROR = 1.42; 1.18-1.70), as well as "Fertility disorders" (ROR = 2.69; 1.51-4.80).

Discussion: Our analysis indicates that the tolerability and safety profiles of PP are in line with what is known for the other SGA-LAIs. However, differences regarding endocrine system ADRs have been noticed. The results presented in this work do not discourage the prescription of SGA-LAI formulations but aim to enhance their safety.

KEYWORDS

adverse drug reaction, antipsychotics, schizophrenia, pharmacovigilance, paliperidone palmitate, long-acting injectable, drug-induced reaction, EUDRAVigliance

1. Introduction

Antipsychotic medications represent the mainstay of the pharmacological treatment of schizophrenia (SCZ) (1). They are commonly categorized into three drug classes, first- (FGAs), second- (SGAs) and third-generation antipsychotics (TGAs) (2). Poor adherence to antipsychotic treatment is a critical aspect of the clinical management of patients affected by schizophrenia spectrum disorders (SSDs). In addition, treatment discontinuation represents a relevant risk factor for relapse and rehospitalization (3–6). To improve antipsychotic adherence in patients affected by SCZ in the 1960s the long-acting injectable (LAI) antipsychotic formulations, initially based on FGAs (FGA-LAIs), were introduced (7, 8).

The LAI formulations have proven to reduce the risk of relapse and re-hospitalization due to non-adherence (9). This makes them valuable therapeutic options for the long-term management of patients suffering from SSDs (10–13). Furthermore, robust literature evidence suggests that LAIs may also provide an effective treatment strategy for patients in the early-phase or with a first-episode of psychosis (FEP) (12, 14–16).

As for their oral counterparts, FGA-LAIs have been gradually less prescribed due to the risk of extrapyramidal symptoms and tardive dyskinesia (17, 18). However, over the past 20 years, several SGAs, including olanzapine, risperidone, and paliperidone, and one TGA, aripiprazole, have become available, partially replacing FGA-LAIs thanks to a lower liability for movement disorders (19). There are considerable differences between second-generation LAIs (SGA-LAIs) regarding pharmacodynamic and pharmacokinetic profiles, injection interval, cost, requirements for oral supplementation, and risks of adverse events (20, 21). Safety profiles of SGA-LAIs generally follow the known profiles of the oral molecule, although unexpected safety signals were occasionally observed in clinical practice (22).

Among the currently available SGA-LAIs, paliperidone palmitate (PP) (the esterified form of paliperidone, an active metabolite of risperidone) is the only one already available in both a monthly (PP1M) and a quarterly formulation (PP3M), with a recently approved 6-month PP (PP6M) formulation (23). In particular, the PP3M formulation has shown significant efficacy in delaying the time to relapse in patients suffering from SCZ (24, 25). Candidates for PP3M are patients previously prescribed PP1M (26). In other words, patients introduced to PP3M have been previously exposed PP1M, which they may tolerate well before clinicians switch them to PP3M. This could be related to the low incidence of adverse drug reactions (ADRs) (27).

The aim of the present study was to analyze the ADRs related to PP1M and PP3M and to compare them to those related to the other SGA-LAIs, in the Spontaneous Reporting System (SRS) database (i.e., European Union Drug Regulating Authorities Vigilance database; EUDRAVigilance) of the European Medicines Agency (EMA).

2. Materials and methods

2.1. Data source

Data on Individual Case Safety Reports (ICSRs) presenting as suspected drugs LAI formulations of PP (i.e., PP1M and/or PP3M) were retrieved using the EUDRAVigilance access platform (publicly available at www.adrreports.eu). EUDRAVigilance functions as a management and analysis platform for information on suspected ADRs regarding drugs that have obtained marketing authorization or are currently under evaluation in clinical trials across the European Economic Area (EEA). More specifically, EUDRAVigilance represents the collection point for all the ICSRs (regarding either drugs or vaccines), reported by healthcare professionals (HCPs) and non-HCP figures to any of the European Union (EU) competent authorities at the national level or the marketing authorization holder. The EU medicines regulatory network, in the form of the EMA, acts as the responsible authority for the maintenance and constant update of EUDRAVigilance. For transparency's sake, data collected on EUDRAVigilance are publicly available through the previously cited access portal. Data are made available in different tiers of completeness, with the more specific ones requiring access authorization directly licensed from the EMA. The data access level used for the analysis was the one indicated as "Stakeholder Group II: Healthcare professionals, patients and the general public" in the EUDRAVigilance access policy (28).

2.2. Selection of individual case safety reports

All ICSRs reported as suspected drugs LAI formulations of PP were retrieved using the line-listing function of the EUDRAVigilance platform. The timeframe used for report collection spanned between January 1st, 2011 (the year of the first market approval for PP1M) and June 30th, 2022. The reference Group (RG) for the analyses was constituted by ICSRs showing at least one SGA-LAI other than PP (i.e., LAI formulations of aripiprazole, olanzapine, and risperidone) as suspected drugs reported to EUDRAVigilance between January 1st, 2003, the year of commercialization of risperidone LAI, and June 30th, 2021. The authors acknowledge that aripiprazole belongs to the class of TGAs (2). However, concerning LAI formulations, a number of literature sources enlist aripiprazole-based LAIs as part of SGA-LAIs (29, 30). Thus, after careful consideration, to improve the applicability of the analysis results, aripiprazole LAI-related ICSRs were considered in the reference group. The retrieved dataset included the following fields: ICSR identification number in EUDRAVigilance; date of receipt; primary source qualification; the presence of an eventual literature reference; patients' sex and age group; ADRs characteristics (type of ADR, duration, outcome, and seriousness status) and characteristics of suspected and concomitant drugs (Type of drug, use indication, duration of therapy, drug dose and administration route). The level of data completion varied for each ICSR. Once retrieved, ICSRs identified as "non-spontaneous," ICSRs linked to literature sources, and ICSRs that presented as suspected drugs vaccines have all been excluded.

2.3. Data analysis

Data regarding the available demographic characteristics of patients (i.e., sex and age group) were evaluated by means of a descriptive analysis. The descriptive analysis also included adverse event characteristics (i.e., outcome and seriousness), primary source qualification, and the number of suspected drugs other than the LAI

formulations of PP. The latter is described cumulatively for all PP-related and for each PP formulation. In addition to that, the annual trend in ICSRs reporting was also evaluated. All the ADRs were classified in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®), which follows a hierarchical structure in which terms are organized into five levels. Observations are codified, at first with more specific lowest-level terms (LLT), to resemble the clinical condition reported closely. Multiple LLTs converge into only one "preferred term" (PT) representing the next structural level. Several PTs can then be grouped using anatomical, pathological, physiological, etiological, or functional criteria in "High-Level Terms" (HLTs). HLTs can then be categorized in "High-Level Group Terms" (HLGTs). Finally, the highest-level terms of this classification are represented by the so-called "System Organ Classes" (SOCs), which provide a broader data overview. As far as seriousness was concerned, a case was defined as 'serious' when highlighted at least an ADR resulting in death, hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect or conditions deemed as medically important by the reporter, prolonging hospitalization or being life-threatening. For the ADRs outcomes standardized terminology was used with ADRs classified as: 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae', 'not recovered/not resolved', 'fatal', and 'unknown' on the bases of what was reported in the ICSR. The ADR expectedness was verified based on the Summary of Product Characteristics (SmPCs) available in the EMA database (31). If two or more ADR Symptoms reported in the same ICSR presented different outcomes a global outcome for the case described in the ICSR was computed using the "Lower Level of Resolution" methodology previously described by other authors (32).

2.4. Statistical analysis

For ICSRs characteristics comparisons, we used the Chi-square test and the U Mann–Whitney test for categorical and continuous variables, respectively. The distribution of variables was tested using Shapiro-Wilks and Kolmogorov–Smirnov tests. Continuous variables were reported as median values with associated interquartile ranges (IQRs). Categorical variables were synthesized as frequencies and percentages. ICSRs simultaneously involving a PP-based formulation and another SGA-LAI as suspected drugs were excluded from comparisons between the two groups. The Chi-square test was applied to evaluate differences for ADR characteristics between PP-related ICSRs and the reference group. Values of $p < 0.001$ were considered statistically significant.

Disproportionalities in the observed ADR frequencies for PP-related ICSRs compared to those of ICSRs presenting as suspected drugs other SGA-LAIs were evaluated by calculating the Reporting Odds Ratios (RORs) and associated 95% confidence intervals (95% CI). The statistical significance threshold was defined as 95% CI lower bound >1 in the presence of ≥3 reports per PP formulation. For ADR regrouping purposes, we used the standardized MedDRA® queries (SMQs), which are groups of MedDRA® terms related to a defined medical condition or area of interest (33). Regrouping terms by SMQs can be done by using either 'narrow' or 'broad' search strategies. For this analysis, we used the more narrow-scope approach, with terms characterized by a higher likelihood of representing the condition of interest (34). In addition, a sub-analysis using the Chi-square test methodology was performed to compare the ADR reporting frequencies between PP3M and PP1M. All the analyses were carried out using the Statistical Package for Social Science (SPSS, International Business Machines Corporation) Version 28.

3. Results

Overall, 20,226 ICSRs related to SGA-LAIs were retrieved from the EUDRAVigilance dataset during the observation period. Of those, 8,152 ICSRs indicated PP-based formulations as suspected culprit drugs. Among the PP-related reports, 6,332 (77.7%) presented as suspected drug PP1M and 1,731 (21.2%) PP3M, while 89 ICSRs indicated involvement of both PP formulations. As far as the ICSRs in the reference group were concerned, risperidone LAI was the SGA-LAI most frequently reported ($n = 5,317$; 43.7%), followed by aripiprazole LAI ($n = 4,038$; 33.2%) and olanzapine pamoate ($n = 2,802$; 23%). In the ICSRs for the reference group, 13 cases presenting referred to patients treated with multiple SGA-LAIs. In addition, 96 retrieved cases simultaneously involved a PP-based formulation and another SGA-LAI as suspected drugs. For PP-related ICSRs an initially steady trend was followed by a peak in 2018 ($n = 1,569$) after the introduction of PP3M in the market and a decreasing trend afterwards (Figure 1).

PP injection dose data were available in 6,312 (75.2%) ICSRs. The mean observed dose for PP-based formulations was 121,2 mg (±39 SD) for PP1M and 383,9 mg (±132.8 SD) for PP3M. Data for PP treatment duration were available in 430 (5.3%) ICSRs with a median PP treatment duration of 120 days for PP1M (IQR 31–337) and 244 (IQR 91–452) days for PP3.

Treatment indication information for PP based formulations were available in 57.1% ($n = 4,655$) of ICSRs. Among those, SCZ was the most frequently observed ($n = 3,486$; 74.9%), followed by psychotic disorders ($n = 446$; 9.6%), and schizoaffective disorders ($n = 253$; 5.4%). Table 1 summarizes the main characteristics of PP-related ICSRs compared to those related to the other SGA-LAIs.

Considering the suspected drugs other than PP, 36.8% ($n = 3,082$) of all PP-related ICSRs presented at least an additional suspected drug. A median value of 1 (IQR 1–2) for the number of co-reported suspected drugs was reported. Stratifying ICSRs by PP formulation, the number of co-reported suspected drugs remained constant for PP1M and PP3M-related ICSRs with the PP3M-related ones exhibited a narrower IQR (1-1). In qualitative terms the most frequently co-reported suspected drugs 65.4% ($n = 1,311$) belonged to the N05A ATC class (i.e., antipsychotics) namely, risperidone ($n = 516$; 39.4%), olanzapine ($n = 125$; 9.5%), and aripiprazole ($n = 117$; 8.9). Following the N05A was the N03A class (i.e., antiepileptics) ($n = 120$; 6%), with valproic acid ($n = 71$; 59.2%), clonazepam ($n = 14$; 11.7%), and lamotrigine ($n = 10$; 8.3%). After that, the N06A class drugs (i.e., antidepressants) had the higher frequency ($n = 106$; 5.3%), namely, escitalopram ($n = 15$; 14.2%), sertraline ($n = 13$; 12.3%), and paroxetine ($n = 12$; 11.3%). More details on the distribution of suspect drugs groups according to the ATC classification, per single PP-derived formulation is available in the Electronic Supplementary Material (ESM) Table 1.

In terms of ADR seriousness, 64.6% ($n = 5,264$) of PP-related ICSRs indicated at least one ADR classifiable as serious, less frequently than in the reference group ($n = 10,091$; 64.6%, $p < 0.001$). Outcome

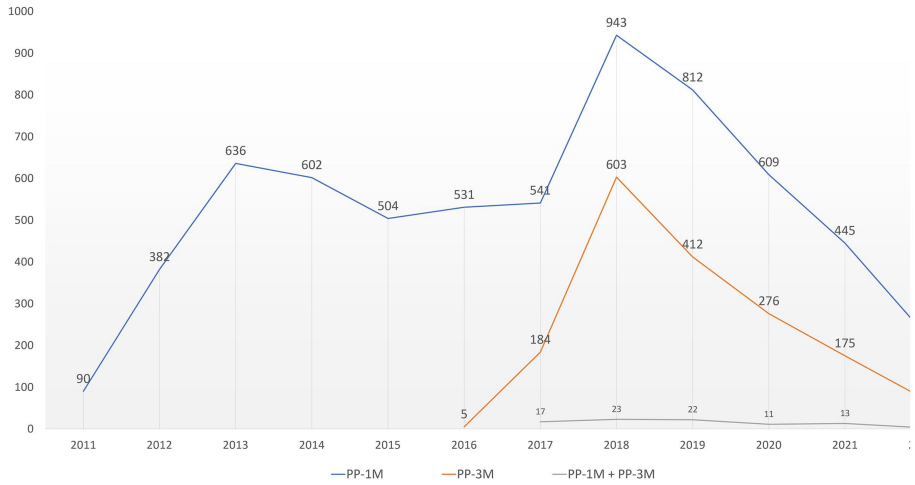

FIGURE 1
PP-related ICSRs temporal distribution. ICSRs, Individual Case Safety Reports; PP, paliperidone palmitate; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month.

data were available in 52.3% of PP-related ICSRs. In detail 1,543 cases (36.2%) described one ADR deemed as "Recovered/Resolved," 1,344 (31.5%) cases one labelled as "Not Recovered/Not Resolved," and 856 (20.1%) one ADR that was still "Recovering/Resolving" at the time of the last available follow-up (Table 1).

ADRs observed in PP-related ICSRs mainly concerned the SOCs "Psychiatric disorders" ($n = 2,898$; 19.3%), "General disorders and administration site conditions" ($n = 2,608$; 17.4%), "Nervous system disorders" ($n = 1946$; 13.0%), "Injury, poisoning and procedural complications" ($n = 1,321$; 8.8%), and "Investigations" ($n = 1,554$ 179; 7.9%).

ADRs labelled "Endocrine disorders" were more frequently reported in PP-related ICSRs, compared to the reference group (Table 2). The specific ADRs related to this SOC, classified at the MedDRA PT level for PP were hyperprolactinaemia ($n = 226$; 88.6%), followed by inappropriate antidiuretic hormone secretion ($n = 9$; 3.5%), hypothyroidism ($n = 4$; 1.6%), thyroid disorder ($n = 3$; 1.2%), and diabetes insipidus ($n = 2$; 0.8%).

There were 468 ICSRs reporting fatal outcomes. Most of them ($n = 303$; 64.7%) regarded male patients, and 330 cases (70.5%) were in the 18 to 64 years age group. The number of reported suspected drugs other than PP in this ICSRs was higher when compared to all other PP related ICSR (2.4 ± 2.1 SD vs. 1.6 ± 1.3 SD; $p < 0.001$) without however, major differences in terms of the type of co-reported suspected drugs. In these ICSRs the most frequently observed ADRs were related to the MedDRA HLTs "Death and sudden death" ($n = 181$; 17.4%), "Suicidal and self-injurious behavior" ($n = 103$; 9.9%), "Ischemic coronary artery disorders ($n = 26$; 2.5%)," "Ventricular arrhythmias and cardiac arrest" and "Product administration errors and issues" (both with $n = 24$; 2.3%). Among the specific ADRs leading to fatal outcomes those observed with higher frequencies were, aside from death ($n = 129$; 21.8%) and sudden death ($n = 47$; 7.9%), completed suicide ($n = 98$; 16.5%), pulmonary embolism ($n = 16$; 2.7%), myocardial infarction (n = 14; 2.4%), cardiac failure ($n = 13$; 2.2%), and cardio-respiratory arrest ($n = 12$; 2%).

Comparing to PP1M-related ICSRs, the PP3M-related ICSRs more frequently contained the SOCs "psychiatric disorders," "general disorder and administration site conditions," and "product issues" ($p < 0.001$). The relative reporting frequencies for the 10 major SOCs are reported in Figure 2, while full details are available in Table 3. In PP3M-related ICSRs, the specific ADRs more frequently reported as "psychiatric disorders" were SCZ ($n = 174$; 16.7%), psychotic disorder ($n = 97$; 9.3%), psychotic symptom ($n = 69$ 6.6%), delusion ($n = 54$; 5.2%), psychiatric decompensation ($n = 53$; 5.1%), and anxiety ($n = 47$; 4.5%). The specific ADRs in PP3M ICSRs, relative to "general disorder and administration site conditions" were mainly "drug ineffective" ($n = 158$; 20.8%), "condition aggravated" ($n = 101$; 13.3%), "malaise" ($n = 49$; 6.5%), "fatigue" ($n = 48$; 6.3%), and "injection site pain" ($n = 36$; 4.7%). While for the SOC "product issues" the ADRs observed with the highest frequency in PP3M ICSRs were "device occlusion" ($n = 7$; 17.9%), "syringe issue" ($n = 6$; 15.4%), "product complaint" ($n = 6$; 15.4%), "needle issue" ($n = 5$; 12.8%), and "product quality issue" ($n = 4$; 10.3%). More details on specific ADRs related to each SOC at the MedDRA PT level is available in Electronic Supplementary Material (ESM) Table 2.

Significantly disproportionate reporting, for PP-related reports compared to the reference group, was observed for SMQs "Sexual Dysfunctions" (ROR = 1.45; 95% CI 1.23–1.70), "Haemodynamic oedema, effusions and fluid overload" (ROR = 1.42; 1.18–1.70), as well as "Fertility disorders" (ROR = 2.69; 1.51–4.80) (Table 4). In terms of secondary SMQs only "Parkinson-like events" (ROR = 1.27; 1.06–1.53) were disproportionately reported for PP formulations compared to the reference group Electronic Supplementary Material (ESM) (Table 3).

4. Discussion

4.1. General ICSRs characteristics and frequently observed ADRs

Among SGA-LAIs PP is the only one currently available not only in a monthly but also a quarterly and more recently a half-yearly administration formulation, thus making it one of the most interesting therapeutic options to maintain treatment adherence in long-term treatment of patients suffering from SCZ (35). Therefore, the constant

TABLE 1 Characteristics of PP-related ICSRs compared to those of other SGAs related ICSRs.

Characteristic	PP-related ICSRs *n*=8,152 (%)	Other SGA-LAIs (reference group; RG) ICSRs (RG) *n*=12,170 (%)	*p*-value[a,b] PP-related ICSRs versus RG
Age categories (years)			
Less than 18	60 (0.7)	146 (1.2)	0.007
18–64	5,255 (64.5)	8,306 (68.2)	0.083
65–85	460 (5.6)	751 (6.2)	0.524
More then 85	18 (0.2)	30 (0.2)	0.773
Not specified	2,359 (28.9)	2,937 (24.1)	–
Sex			
Male	4,814 (59.1)	6,764 (55.6)	0.001
Female	3,213 (39.4)	4,932 (40.5)	
Not specified	125 (1.5)	474 (3.9)	–
Seriousness			
Non-serious	2,888 (35.4)	2,079 (17.1)	<0.001
Serious	5,264 (64.6)	10,091 (82.9)	
Outcome			
Recovered/resolved	1,543 (18.9)	3,390 (27.9)	<0.001
Not recovered/not resolved	1,344 (16.5)	2,532 (20.8)	<0.001
Recovering/resolving	856 (10.5)	886 (7.3)	<0.001
Fatal	468 (5.7)	679 (5.6)	0.693
Recovered/resolved with sequelae	52 (0.6)	92 (0.8)	0.307
Not available	3,889 (47.7)	4,591 (37.7)	–

ICSRs, Individual Case Safety Reports; LAI, long-acting injectable; PP, paliperidone palmitate; RG, reference group; SGA, second-generation antipsychotic.

[a]*p*-values were calculated using the Chi-square test.

[b]ICSRs presenting both PP formulations and Other SGA LAIs as suspected drugs ($n=96$) were excluded from the calculations.

rising number of ICSRS per year observed in our analysis reflects this continuous level of increasing attention on PP since its market introduction. Furthermore, the ICSRs reporting peak of 2018 following the market introduction of the PP3M formulation shows that this event also had an increasing effect on the yearly reporting frequency of the PP1M-related ICSRs. Thus, we expect an increase for ADRs reports in the coming years following the introduction of the six-monthly formulation as use and clinical experience increase. It must be pointed out however, that the market approval process of SGA-LAIs has not happened simultaneously in all the countries covered by the EUDRAVigilance database. Moreover, differences in the availability of these drugs still persist today.

As far as patient characteristics are concerned, the observed differences in terms of reported patients' age, between PP and RG-related ICSRs, seem to be in line with routinely clinical practice. PP-based formulations have been introduced more recently than the other LAIs which makes them less likely to be selected by clinicians for treating patients before the age of 18. Also, the lack of EMA-approved indications for their use in pediatric patients limits the use of both PP1M and PP3M in this context (36, 37). The observed differences in terms of reported patient sex may be more attributable to ADRs commonly associated with PP than to effective sex differences in tolerability. In fact, ADRs related to prolactin increases are frequently observed with PP, but they could be considered more in women as they are clinically more impactful (e.g., amenorrhea). This could lead to considering more carefully the administration of PP based in women and by consequence to an observation bias. However, our findings prevent us from formulating any conclusion in this regard.

The data regarding the types of co-reported suspected drugs highlight that almost 40% of ICSRs involved at least one co-medication. Most of the observed co-reported suspected drugs were oral antipsychotics. Adding an oral antipsychotic to LAI-based therapeutic regimens is a common practice in the initial phases to mitigate risks related to the slow release of the LAI formulations (38). Also, antipsychotic polypharmacy (APP) is frequently used in clinical practice. It has been estimated that 10–20% of outpatients and up to 40% of inpatients diagnosed with SCZ are treated with APP mainly as augmentation (39). The frequent combination of PP with mood stabilizers and/or antidepressants and benzodiazepines in the relevant ICSRs highlights the risks that may emerge in the context of such therapeutic regimens (40).

Regarding seriousness of ADRs, PP-related ICSRs were less frequently serious compared to other SGA-LAIs. This is in line with findings from other types of literature that highlighted overall good tolerability for PP when compared to other SGA-LAIs (41). As far as ADR outcomes are concerned, significantly higher ($p<0.001$) frequencies of cases describing ADRs deemed as "recovering/resolving" were observed in PP-related ICSRs when compared to the reference group. Significant differences but in a diminutive sense were observed for ADR cases with a complete recovery and with reactions not resolved at the time of the last follow-up between ICSRs PP-related and in the reference group. This data correlates well with the type of observed ADRs in PP-related ICSRs as several of the most frequently observed ADRs such as those relative to "Psychiatric disorders" and "Nervous system disorders" are generally characterized by long resolution periods (e.g., literature sources report a median of 91 days for extrapyramidal symptoms) (42, 43).

In terms of specific ADRs, "Psychiatric disorders" related ones were mainly associated to the onset of psychotic episodes, anxious manifestations, and insomnia (ESM Table 2). While anxiety and insomnia are listed as ADRs frequently associated with PP (36, 37), some considerations must be made regarding symptoms related to SCZ reported as suspected ADRs. Among the ICSRs reporting "schizophrenia" as one of the described specific ADRs, 22.2% presented at least an ADR classifiable within the high-level term "therapeutic and non-therapeutic responses (e.g., Drug ineffective, Treatment noncompliance, Therapeutic product effect decreased) and 12.3% at least one ADR relative to "Product administration errors and issues" (e.g., Inappropriate schedule of product administration; Product dose omission issue; Incorrect dose administered). Furthermore, literature sources indicate that 20 to 30% of patients affected by SCZ are known to not respond to treatment with antipsychotics (44, 45), and data suggest a form of secondary treatment-resistant SCZ (46, 47). Considering this, we could reasonably say that most of these ADRs are more likely to derive from insufficient therapeutic control or relapses of pre-existing diseases

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TABLE 2 Relative ADRs frequencies observed in PP-related ICSRs formulations as compared to reference group ICSRs, stratified by system organ class.

System organ classes	PP-related[a] ICSRs *N*=8,056 (%[b])	Other SGA-LAIs (reference group; RG) *N*=12,170 (%[b])	*p* value PP versus RG[a]
Blood and lymphatic system disorders	135 (1.7)	210 (1.7)	0.789
Cardiac disorders	353 (4.4)	742 (6.1)	<0.001
Congenital, familial and genetic disorders	17 (0.2)	22 (0.2)	0.631
Ear and labyrinth disorders	59 (0.7)	160 (1.3)	<0.001
Endocrine disorders	246 (3.1)	257 (2.1)	<0.001
Eye disorders	260 (3.2)	460 (3.8)	0.038
Gastrointestinal disorders	439 (5.4)	890 (7.3)	<0.001
General disorders and administration site conditions	2,576 (32)	4,100 (33.7)	0.011
Hepatobiliary disorders	70 (0.9)	116 (1)	0.539
Immune system disorders	65 (0.8)	98 (0.8)	0.990
Infections and infestations	295 (3.7)	470 (3.9)	0.465
Injury, poisoning and procedural complications	1,301 (16.1)	2,818 (23.2)	<0.001
Investigations	1,162 (14.4)	2,426 (19.9)	<0.001
Metabolism and nutrition disorders	335 (4.2)	813 (6.7)	<0.001
Musculoskeletal and connective tissue disorders	490 (6.1)	859 (7.1)	0.006
Neoplasms benign, malignant and unspecified (including cysts and polyps)	85 (1.1)	146 (1.2)	0.344
Nervous system disorders	1,904 (23.6)	4,602 (37.8)	<0.001
Pregnancy, puerperium and perinatal conditions	28 (0.3)	79 (0.6)	0.004
Product issues	76 (0.9)	264 (2.2)	<0.001
Psychiatric disorders	2,862 (35.5)	4,644 (38.2)	<0.001
Renal and urinary disorders	159 (2)	337 (2.8)	<0.001
Reproductive system and breast disorders	620 (7.7)	836 (6.9)	0.026
Respiratory, thoracic and mediastinal disorders	358 (4.4)	555 (4.6)	0.696
Skin and subcutaneous tissue disorders	339 (4.2)	545 (4.5)	0.358
Social circumstances	106 (1.3)	348 (2.9)	<0.001
Surgical and medical procedures	149 (1.8)	526 (4.3)	<0.001
Vascular disorders	244 (3)	732 (6)	<0.001

ADR, adverse drug reaction; ICSRs, Individual Case Safety Reports; PP, paliperidone palmitate; RG, reference group; SOC, system organ class.

[a]ICSRs presenting both categories of drugs as suspected ($n=96$) were excluded from the calculations.

[b]For each SOC, the number of reports with at least one ADR related to the SOC are reported. The sum of the distribution of reports of ADRs by SOC (%) is higher than the total number of reports, since a single report could contain ADRs related to more than one SOC.

rather than from exposure to the drug. This is also confirmed to what is reported for the General disorders and administration site conditions SOC, in which ADRs such as "drug ineffective" and "Condition aggravated" were characterized by the higher frequencies of reporting.

In ICSRs reporting fatal cases, the most frequently reported specific ADRs described suicidal and self-injurious behaviors. These behaviors have been associated with SCZ; a recent study has estimated an increase of 4.5 times of the incidence of these conditions over the general population for patients with SSDs (48). The risk factors for these types of manifestations are highly complex and range from demographic characteristics to psychosocial factors (49). This complexity requires an in-depth case-by-case assessment approach to properly evaluate these reactions, which could require a different study design to investigate. Other common types of ADRs observed in this subgroup of ICSRs included pulmonary embolism and cardiac failure. These ADRs have already been reported in the context of antipsychotic treatment data (50). Data regarding a link between paliperidone and pulmonary thromboembolism, however, are limited to few cases (51, 52). Moreover, the underlying mechanism of this ADR is still largely unknown, although some hypotheses regarding prolactin and its potential role as a platelet aggregation coactivator have been proposed (53). However, the influence of other factors such as obesity, increased levels of antiphospholipid antibodies, and hyperhomocysteinemia remains unclear. On this matter, some authors suggested that using aripiprazole would be preferable in patients presenting possible risk factors (52), but the clinical experience in this sense remains limited. In addition, 8.9% of the total neuroleptic malignant syndrome (NMS) cases observed ($n=113$) presented a fatal outcome for the patient. This severe idiosyncratic reaction is linked to the administration of dopamine-blocking agents such as antipsychotics. It presents with symptoms such as fever, muscle rigidity, alterations in mental

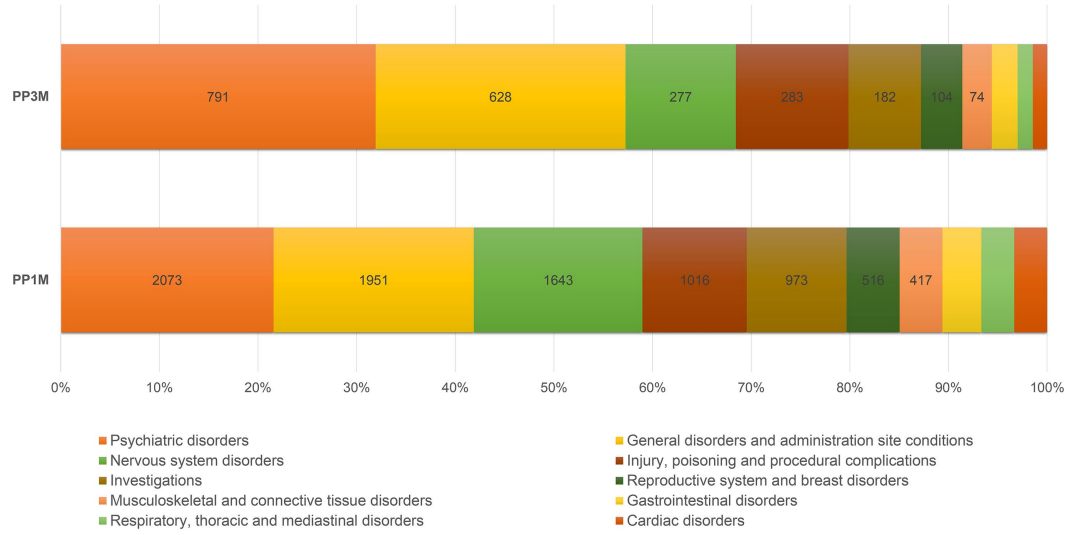

FIGURE 2
Relative reporting frequencies of ADRs belonging to the 10 most frequently observed SOCs. ADR, adverse drug reaction; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; SOCs, system organ classes.

status, and autonomic functioning (54–56). Since LAI antipsychotics cannot be cleared quickly from the patient's system, using these formulations can be perceived by the clinicians as limiting in terms of NMS management options, negatively impacting their perceived safety (57). Some recent retrospective studies have, however, estimated a low incidence of NMS cases over the antipsychotic-treated population, equal to 1.99 (95%CI 1.98–2.00) per 10,000 person-years, without any statistically significant differences between oral and LAI antipsychotics formulations (58, 59). This is in line with the results from our analysis, showing no disproportionality in the reporting of NMS between ICSRs PP-related and in the reference group (Table 4).

4.2. Disproportional ADRs

4.2.1. Sexual and fertility disorders

Our analysis has highlighted an increased probability of reporting for ADRs relative to the SMQs "sexual dysfunction" and "fertility disorder" between PP and the reference group. Sexual dysfunctions are commonly associated with antipsychotics. Literature sources state that up to 75% of treated patients experienced sexual dysfunction (60). However, their incidence could be underestimated due to the reluctancy of patients and physicians to spontaneously discuss and report these kind of reactions (61). These ADRs have multifactorial processes regarding underlying mechanisms. One of the most widely embraced factors is the increase in prolactin levels resulting from the antagonistic action on D2 dopamine receptors that characterizes antipsychotics. Dopaminergic receptors in the hypothalamic tuberoinfundibular tract act as inhibitors for prolactin secretion; thus, inhibition of dopamine D2 receptors in this tract increases prolactin release. This increase results in an inhibition of the release of follicle-stimulating and luteinizing hormones from the pituitary gland. With consequent low gonadal steroids and hypogonadism (62). The impact of these ADRs cannot be underestimated as they can negatively influence patient's quality of life and potentially reduce treatment compliance (63, 64). The importance of these aspects is particularly central for LAI-treated patients, considering that candidate patients for LAI treatment are usually middle-aged adults, already stabilized in treatment with an AP, for which clinicians seek therapies that could help them improve their quality of life and regain as much social functionality as possible (65). Prolactin-related ADRs could also limit the use of these LAIs in populations of youth with serious mental illness who are at risk for relapse, for which SGA-LAIs could represent an effective treatment strategy (66). A previous prospective study highlighted significant increases in mean prolactin values in risperidone-treated young patients, with long-term consequences of these ADRs still on patients' development to be clarified (66, 67).

4.2.2. Oedema related ADRs

ADRs relative to various forms of peripheral oedema constituted the vast majority of the SMQ "Haemodynamic oedema, effusions and fluid overload" for which a higher probability of reporting in PP-related when compared to RG-related ICSRs emerged from our analysis. These ADRs are already acknowledged as class effects related to the administration of SGA-LAIs. The mechanism underlying this type of ADRs remains unclear; however, several hypotheses have been formulated. Paliperidone being chemically a derivate of risperidone acts with a similar mechanism by blocking the serotonin (5-hydroxytryptamine, 5-HT) $5HT_2$, Dopaminergic D2, Adrenergic α1, α2 and histaminergic H1 receptors (68). The blockage of α1 receptors results in vasodilation with a consequential increase in hydrostatic pressure in the capillaries that could facilitate the onset of oedema (69). Also, the antagonistic action on 5HT2 receptors could

TABLE 3 Relative ADRs frequencies observed in PP3M-related ICSRs formulations as compared to PP1M-related ICSRs, stratified by system organ class.

System organ classes	PP3M-related[a] ICSRS	PP1M-related[a] ICSRs (RG)	*p* value PP3M versus PP1M[a]
	N=1,731 (%[b])	*N*=6,332 (%[b])	
Blood and lymphatic system disorders	19 (1.1)	115 (1.8)	0.038
Cardiac disorders	36 (2.1)	320 (5.1)	<0.001
Congenital, familial and genetic disorders	4 (0.2)	13 (0.2)	0.836
Ear and labyrinth disorders	13 (0.8)	46 (0.7)	0.915
Endocrine disorders	34 (2)	213 (3.4)	0.003
Eye disorders	37 (2.1)	230 (3.6)	0.002
Gastrointestinal disorders	65 (3.8)	379 (6)	<0.001
General disorders and administration site conditions	628 (36.3)	1951 (30.8)	<0.001
Hepatobiliary disorders	7 (0.4)	63 (1)	0.019
Immune system disorders	3 (0.2)	63 (1)	0.001
Infections and infestations	37 (2.1)	259 (4.1)	<0.001
Injury, poisoning and procedural complications	283 (16.3)	1,016 (16)	0.761
Investigations	182 (10.5)	973 (15.4)	<0.001
Metabolism and nutrition disorders	47 (2.7)	295 (4.7)	<0.001
Musculoskeletal and connective tissue disorders	74 (4.3)	417 (6.6)	<0.001
Neoplasms benign, malignant and unspecified (including cysts and polyps)	14 (0.8)	72 (1.1)	0.239
Nervous system disorders	277 (16)	1,643 (25.9)	<0.001
Pregnancy, puerperium and perinatal conditions	4 (0.2)	24 (0.4)	0.354
Product issues	36 (2.1)	40 (0.6)	<0.001
Psychiatric disorders	791 (45.7)	2073 (32.7)	<0.001
Renal and urinary disorders	32 (1.8)	127 (2)	0.677
Reproductive system and breast disorders	104 (6)	516 (8.1)	0.003
Respiratory, thoracic and mediastinal disorders	38 (2.2)	321 (5.1)	<0.001
Skin and subcutaneous tissue disorders	45 (2.6)	296 (4.7)	<0.001
Social circumstances	19 (1.1)	85 (1.3)	0.424
Surgical and medical procedures	22 (1.3)	126 (2)	0.048
Vascular disorders	32 (1.8)	216 (3.4)	0.001

ADR, adverse drug reaction; ICSRs, Individual Case Safety Reports; PP, paliperidone palmitate; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; SOC, system organ class.

[a]ICSRs presenting both categories drugs as suspected (n=89) were excluded from the calculations.

[b]For each SOC, the number of reports with at least one ADR related to the SOC are reported. The sum of the distribution of reports of ADRs by SOC (%) is higher than the total number of reports, since a single report could contain ADRs related to more than one SOC.

TABLE 4 Reporting odds ratios for PP-related ICSRs as compared to RG using standardized MedDRA queries.

Individual SMQ[a]	PP related ICSRs *N*=8,056[b]	95% CI	ROR
Psychosis and psychotic disorders	1,331	0.85–0.99	0.92
Medication errors	642	0.92–1.14	1.03
Lack of efficacy/effect	640	0.97–1.19	1.07
Extrapyramidal syndrome	601	0.65–0.79	0.72
Depression and suicide/self-injury	430	0.68–0.86	0.76
Sexual dysfunction	287	1.23–1.7	1.45
Hypersensitivity	264	0.81–1.11	0.95
Embolic and thrombotic events	253	0.68–0.92	0.79
Gastrointestinal nonspecific inflammation and dysfunctional conditions	231	0.57–0.78	0.66
Haemodynamic oedema, effusions and fluid overload	229	1.18–1.7	1.42
Oropharyngeal disorders	178	0.68–0.99	0.82
Hepatic disorders	158	0.72–1.07	0.88
Hostility/aggression	143	0.41–0.61	0.50
Haematopoietic cytopenias	130	0.81–1.26	1.01
Accidents and injuries	127	0.54–0.83	0.67
Cardiac arrhythmias	125	0.69–1.07	0.86
Shock	121	0.81–1.3	1.03
Hyperglycaemia/new onset diabetes mellitus	115	0.34–0.51	0.42
Noninfectious encephalopathy/delirium	113	0.54–0.84	0.67
Neuroleptic malignant syndrome	110	0.71–1.15	0.91
Ocular motility disorders	98	0.73–1.21	0.94
Haemorrhages	91	0.6–1	0.77
Convulsions	81	0.41–0.69	0.53
Generalised convulsive seizures following immunisation	79	0.42–0.71	0.55
Hypertension	74	0.21–0.35	0.27
Pregnancy and neonatal topics	71	0.44–0.75	0.57
Angioedema	70	0.55–0.97	0.73
Central nervous system vascular disorders	70	0.53–0.93	0.70
Malignancies	69	0.65–1.19	0.88
Drug abuse, dependence and withdrawal	67	0.64–1.17	0.86
Rhabdomyolysis/myopathy	58	0.96–1.96	1.37
Torsade de pointes/QT prolongation	58	0.93–1.89	1.33
Hearing and vestibular disorders	55	0.4–0.75	0.55
Ischaemic heart disease	55	0.47–0.9	0.65
Acute renal failure	48	0.68–1.41	0.98

(Continued)

TABLE 4 (Continued)

Individual SMQ[a]	PP related ICSRs N=8,056[b]	95% CI	ROR
Dyslipidaemia	48	0.42–0.82	0.59
Immune-mediated/autoimmune disorders	44	0.79–1.73	1.17
Infective pneumonia	44	0.51–1.05	0.73
Hyponatraemia/SIADH	40	0.64–1.43	0.96
Cardiac failure	38	0.61–1.36	0.91
Noninfectious diarrhoea	37	0.52–1.15	0.78
Gastrointestinal perforation, ulceration, haemorrhage or obstruction	36	0.5–1.11	0.74
Fertility disorders	32	1.51–4.8	2.69
Respiratory failure	29	0.4–0.95	0.62
Periorbital and eyelid disorders	26	0.69–1.93	1.16
Acute central respiratory depression	25	0.38–0.97	0.61
Anaphylactic reaction	22	0.53–1.52	0.90
Peripheral neuropathy	22	0.66–2	1.15
Conjunctival disorders	20	0.85–2.98	1.59
Biliary disorders	19	0.36–1.04	0.61
Acute pancreatitis	18	0.42–1.29	0.73
Agranulocytosis	18	0.54–1.76	0.97
Dehydration	18	0.52–1.69	0.94
Lacrimal disorders	18	0.61–2.09	1.13
Taste and smell disorders	16	0.53–1.9	1.01
Chronic kidney disease	15	0.28–0.9	0.50

COVID-19, coronavirus disease; ICSRs, Individual Case Safety Reports; PP, paliperidone palmitate; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
[a]Primary SMQs with less than 15 associated cases have been excluded from this table. Full details regarding primary and secondary SMQs are available in ESM Table 3.
[b]ICSRs distribution by SMQ is not mutually exclusive.

be associated to oedema due to the increase in cyclic adenosine monophosphate concentrations, leading to the relaxation of vascular smooth muscle (70).

4.2.3. Extrapyramidal disorders

Regarding ADRs related to nervous system no disproportionality in primary reporting was reported for the PP-related ICSRs compared to the reference range. However, secondary reports of Extrapyramidal syndrome and Parkinson-like events were more frequent for PP compared to the reference group. However, in these ICSRs there was a higher number of co-reported suspected drugs for extrapyramidal syndrome and Parkinson-like events compared to the rest of PP-related ICSRs (2.2 ± 1.8 SD vs. 1.6 ± 1.3 SD; $p = 0.014$). When repeating the ROR calculations including on ICSRs with only one suspected drug (either PP or other SGA-LAI) we did not detect disproportionality between PP and the reference group [PP cases = 98; ROR = 1.19 (95%CI: 0.91–1.57)]. Furthermore, the most frequently reported drugs other than PP in these reports were other antipsychotics. Considering these data, we can reasonably assume pharmacodynamic interactions in combination therapies underlying the risk of these ADRs.

4.2.4. Other considerations

The observed disproportionalities in ADR reporting probability while being mostly in line with what is already known about paliperidone-based formulations, might seem puzzling at first since the 44% of ICSRs in the reference group presented LAI formulations of risperidone, which is a chemical precursor of paliperidone (9-hydroxyrisperidone), as a suspected drug. However, risperidone differs substantially from paliperidone from a pharmacokinetic standpoint. In fact, the not negligible fist passage effect, the presence of other metabolites (7-hydroxyrisperidone), and possible influences of cytochrome P450-2D6 and 3A4 individual efficiency status, all represent differentiating factors between the two drugs (71). It has been pointed out by several literature sources that these differences could significantly impact the safety and tolerability profile of these two drugs, as well as provide a different efficacy profile in clinical practice (72, 73). In addition to that, the relative novelty of PP-based formulations compared to risperidone LAI could constitute an attention-increasing factor for ADRs already well-known in previously introduced LAIs for such as those regarding sexual disorders and extrapyramidal manifestations.

4.3. ADR reporting patterns' differences between PP1M and PP3M

Some differences in terms of relative reporting frequencies were noticed between the two PP formulations. Increased reporting frequencies in relation to the SOCs "psychiatric disorders," "general disorder and administration site conditions," and "product Issues" were observed for PP3M-related ICSRs when compared to the PP1M-related ones. The reporting of product issues could be linked to the relative novelty of PP3M compared to PP1M and the resulting limited clinical experience with PP3M. A recently marketed drug could be, in fact, more prone to initial product-related issues than a long-time marketed one. In this sense, it must be considered that currently, no meaningful Therapeutic Drug Monitoring (TDM) data are available for PP3M (74). However, from a recently published prospective study, no significant differences were observed for PP3M compared to PP1M in terms of safety (75). In addition, it is well known that in the initial phases of market presence, the attention reserved to the safety and tolerability aspects of a drug is higher. Potentially, the tendency of clinicians to propose newer treatments to patients that have performed well with existing options also needs to be considered (75). This underlines the necessity of further prospective studies involving large patient cohorts and clinicians more directly to properly assess these differences.

5. Strengths and limitations

To the best of our knowledge, this is one of the first pharmacovigilance studies to evaluate the safety and tolerability

profiles of PP-based formulation using data from a European scale pharmacovigilance database.

Considering the relatively recent approval of PP3M and given the general paucity of real-world derived safety data for PP-based LAI formulations, data deriving from large scale SRS databases analyses can contribute to a better characterization of their safety profiles.

Although our findings provide a comprehensive perspective in the evaluation of PP-related ADRs, the results of the present study should be interpreted in the light of some limitations.

First, the granularity of data provided by the EUDRAVigilance platform is limited and frequently managed in a categorical fashion. We acknowledge that we followed a conservative approach in case of lack of sufficient data, frequently leading to case exclusion or downgrade of reported items if information was not consistent. In addition to that, public data access does not allow to use all other drugs reported in the EUDRAVigilance database as a reference group as for other datasets (76). Moreover, we acknowledge that the publicly accessible EUDRAVigilance data level did not allow to access to detailed information about the reporting country, for privacy reasons. We were therefore unable to differentiate the results by reporting country. Likewise, FGA-LAI were not used as a reference group due to the lack of pharmacovigilance data related to the first years of their market presence. Additionally, the provided data limited considerations regarding aspects such as the presence of multiple suspected drugs in ICSRs. It also has to be pointed out that the retrieval of ICSRs regarding formulations with limited geographical availability was not possible due to database limitations.

Second, we performed a retrospective evaluation of cases reported by clinicians without the homogeneous structure of a single research protocol by applying a cluster analysis method not foreseen at the time of original reporting to the EUDRAVigilance platform. This makes secondary analysis of these data speculative, although the use of large pharmacovigilance databases inherently presents this limitation without necessarily limiting the validity of the conclusions.

Third, pharmacovigilance data should be read considering some technical concerns, including under-reporting compared to global clinical population and difficulty in identifying confounders. Indeed, this implies that the ADRs reported may represent only a partial, probably under-representative, percentage of all ADRs which occur in everyday clinical practice. Also, the lack of data related to the number of patients effectively treated with these drugs within the considered period (i.e., the denominator of the incidence fraction) does not allow incidence calculations.

Thus, future prospective clinical studies using a longitudinal design are required to improve the understanding of tolerability and security profile of PP1M, PP3M, and PP6M.

Similarly, further large-scale pharmacovigilance studies of international datasets, and with full access to Level 2A EUDRAVigilance data (77), are required to provide a more reliable estimate of incidence, clinical characteristics, and outcomes of PP-related ADRs compared to other LAIs.

6. Conclusion

In light of pharmacoepidemiological trends, there is an urgent need to understand SGA-LAI-related ADRs. Compared to other SGA-LAIs increased probabilities of reporting for ADR categorized as referring to the endocrine system impacting patient sexuality and fertility were observed for PP formulations. Also, some clinically irrelevant differences in the ICSRs reporting pattern between PP1M and PP3M emerged requiring further investigation as clinical experience with PP3M increases. The results presented in this work do not discourage the prescription of SGA-LAI formulations but aim to enhance their safety.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

GC and MAB retrieved and analyzed the data. GC and RdF drafted the paper and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are investigated appropriately. ES, GS, and PMC revised the paper for important intellectual content. ES, GS, and PDF approved the final version of the manuscript to be published. ES, GS, PMC, GC, and RdF developed the concept. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1130636/full#supplementary-material

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Assessing the effect of *Alpinia galanga* extract on the treatment of SSRI-induced erectile dysfunction: A randomized triple-blind clinical trial

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Objective: SSRIs are considered the first line in the medical treatment of depression and anxiety disorders. One of their most common side effects, sexual dysfunction, has led many patients to discontinuing their medication and treatment course. *Alpinia galanga*, a plant from the ginger family, has been shown to enhance androgenic activity and sexual function. This study aimed to assess whether the addition of *Alpinia galanga* extract to the treatment regimen of adult males consuming SSRIs can improve SSRI-induced erectile dysfunction.

Materials and methods: This triple-blind randomized clinical trial was conducted on 60 adult males who were being treated with SSRIs at the time of the study. The participants were divided into two groups, a group of 30 people receiving 500mg of *Alpinia galanga* extract and a group of 30 subjects receiving placebo. The population were re-assessed on week 2 and week 4 of the study using the international index of erectile function (IIEF), the Beck Depression Inventory, and the Beck Anxiety Inventory. In all the tests, a p-value of 0.05 was considered as the cut-off for significance.

Results: At the beginning of the study, the IIEF scores of the placebo group and the intervention group were 10.6 ± 3.8 and 11.2 ± 4.8, respectively, which were not significantly different (p-value=0.577). By week 4 of the study, the IIEF scores of the control group and the *Alpinia galanga* group had increased to 13.7 ± 4.3 and 17.4 ± 3.7 respectively, which demonstrates a remarkably larger increase in the group receiving *Alpinia galanga* extract in comparison to the placebo group (p-value<0.001).

Conclusion: In this study, the effect of the addition of *Alpinia galanga* extract to the treatment regimen of male patients using SSRIs on the sexual dysfunction experienced by this group has been promising. Similar results, if proven, can aid both patients and clinicians in making and following better treatment plans with more pleasant outcomes.

Clinical trial registration: [https://clinicaltrials.gov/], identifier [IRCT20101130005280N41].

KEYWORDS

SSRI (selective serotonergic reuptake inhibitors), sexual dysfunction, erectile dysfunction, *Alpinia galanga*, libido, side effect, clinical trial

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants and one of the most frequently prescribed medications worldwide (1). The higher tolerability and overall safety of SSRIs in comparison with older antidepressants, have made them a common and popular component of the treatment regimen of disorders such as depression and anxiety (2). SSRIs are used to treat a variety of psychiatric conditions and mental disorders including major depressive disorder, obsessive–compulsive disorder (OCD), anxiety disorders including generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), eating disorders, chronic pain, phobias, and depersonalization disorder. In addition, they are also used off-label in the treatment of other disorders such as irritable bowel syndrome, fibromyalgia, premenstrual syndrome, and chronic pain disorder (3). SSRIs have been shown to significantly reduce mortality and morbidity rates associated with depression (4). The diverse therapeutic effect of SSRIs can be explained taking into consideration their mechanism of action, which is mainly increasing serotonin levels in certain synapses and brain regions as a result of somatodendritic 5HT1A autoreceptor desensitization. It is hypothesized that their side effects are due to an increase in serotonin levels in specific serotonin receptor subtypes in other regions of the body where the regulation of physiological processes occur (5). SSRIs have also been associated with side effects including nausea and vomiting, headaches, diarrhea and/or constipation, drowsiness, blurred vision, insomnia, agitation, dizziness, serotonin syndrome, bruxism, bipolar switch, akathisia, weight loss and/or weight gain, as well as sexual side effects such as a decrease in libido, erectile dysfunction, dysorgasmia, and anorgasmia (6). Regardless of how bothersome certain experienced side effects may be, only around 40% of patients report these side effects to their prescribing physician; this is even more significant for sexual side effects (7). The prevalence of sexual dysfunction among SSRI consumers has been reported to be as high as 30 to 50% (8). SSRI-induced sexual dysfunction is often temporary, and resolves after the discontinuation of the medication. A small percentage of patients, however, experience post SSRI dysfunction, a condition in which sexual dysfunction persists even after treatment termination (9).

Sexual behavior and desire is regulated by both cortical areas of the human brain as well as subcortical structures including the hypothalamus, spinal cord, and brainstem. At the central level, serotonergic as well as dopaminergic systems have been shown to play a significant role. In addition, cholinergic, adrenergic, and other transmitter systems contribute to this function. Loss or decrease in proper sexual function has been shown to significantly impair the quality of life of affected individuals as sexual well-being is considered one of the most important aspects of a person's quality of life (10). Patients being treated with SSRIs should routinely be asked about their sexual function in order to be able to identify such problems early. Medication-induced sexual dysfunction, if ignored, may lead to non-compliance, decrease in patient compliance, relapse, compromisation of treatment outcomes, lower quality of life, and lengthening of depressive episodes, which significantly contradict treatment goals in depressed patients (11). A variety of pharmacological and non-pharmacological methods have been proposed to manage SSRI-induced symptoms of sexual dysfunction. Methods such as the "wait and observe" approach and "drug holiday" have been used in the management of SSRI-associated sexual dysfunction. Some studies have reported withdrawal syndrome and a disturbance in therapeutic efficiency caused by these management methods (12). It has also been reported that switching the SSRI medication can result in a decrease in sexual side effects (13). In the treatment of psychiatric disorders, the "augmentation approach" has also been used to enhance medication efficacy as well as decrease certain side effects. Some studies have reported a significant increase in patients' libidos as a result of bupropion augmentation treatment. In addition, exercise has been shown to improve sexual function and desire due to the activation of sympathetic nervous system (14). Despite the use and practice of the various methods mentioned, most patients (80%) report little or no improvement after 6 months of treatment. Given the serious and harmful effects of depression and untreated mental disorders on the affected individual, the necessity to treat mental illnesses properly and adequately, as well as the wide use of SSRIs for this means, it is necessary and crucial to investigate and use efficient methods to reduce the inevitable side effects of these medications to the highest possible extent (15). Loss of sexual function and libido has been reported to affect 25–50% of patients with unipolar depression (16). Therefore, the proper management of sexual function in depressed patients is of high importance. *Alpinia galanga*, also called blue ginger, is a plant in the ginger family which has been used as a herb in Unani medicine and as a spice in many traditional cookeries, including Southeast Asian cuisine. It has widely been used to treat microbial infections, rheumatic pains, fever, dyspnea, gastritis, inflammations, and otitis internal. The major compound isolated from *Alpinia galanga* with various biological functions is 1′S-1′-acetoxychavicol acetate (ACE). Anti-fungal, anti-inflammatory, anti-malarial, and anti-oxidant activity, as well as anti-diabetic and anti-ulcer properties have been attributed to *Alpinia galanga* (17).

Another study conducted by Ratnasooriya et al. concluded that rhizomes of *Alpinia calcarata* Roscoe significantly increased the erectile ability as well as the serum testosterone levels in male rats. However, a slight impair in sexual motivation in the partner preference test was observed (18). A study on 40 rats conducted by Negm et al. also reported that *Alpinia officinarum* (known as lesser galanga, another plant from the ginger family) significantly increased testosterone serum levels, follicular stimulating hormone (FSH), luteinizing hormone (LH), and superoxide dismutase (SOD) levels. They inferred that *Alpinia officinarum* could potentially lead to an improvement in human fertility as well as sexual function (19).

Some studies have reported increases in androgenic activity as well as improvements in sexual function and libido as a result of *Alpinia galanga* (18). In this study, we aimed to assess the possible effects of *Alpinia galanga* extract on the erectile function and medication-induced sexual side effects of adult male patients under treatment with SSRIs.

Materials and methods

This randomized triple-blind clinical trial study was conducted on 60 patients diagnosed with anxiety and/or depression who were being treated with SSRI medications. This project was approved by the "Research Ethics Committee of Mashhad University of Medical Sciences" on 25 May 2021 under the code IR.MUMS.MEDICAL.REC.1400.189. The participants were all male consumers of SSRI medications who complained of new-onset sexual dysfunction; they were selected through convenience sampling method and were referred to outpatient psychiatric clinics of Ibn-Sina, Imam Reza, and Ghaem Hospitals in Mashhad, Iran from March 2020 to March 2021.

Considering the fact that no clinical study has previously investigated the possible effect(s) of the *Alpinia galanga* extract on SSRI-associated male sexual dysfunction, this project was considered a pilot study, and therefore, a minimum of 30 participants were assigned to each of the two groups. Thus, a total number of 60 people were selected as the sample population. Informed oral and written consent was obtained from all participants after the project was thoroughly explained to them and the participants were assured they were free to leave the study at any time that they wished.

In this triple-blind clinical trial, the participants, the data collectors, as well as the data analysts were blinded. The participants were chosen through convenience sampling method and randomly divided into two groups using a computerized randomizer. The permuted block randomization technique was used to divide the participants into two equal groups, each consisting of 30 subjects.

Inclusion criteria

The inclusion criteria for the study were as follows: male gender, age under 60 and over 18, use of SSRI medication for at least the past 6 consecutive weeks, sexual dysfunction (confirmed by examiner physician's diagnosis), lack of substance abuse, lack of co-existing other mental illnesses (as ruled out by a clinical psychiatrist), lack of physical/somatic illnesses, and lack of using medications other than SSRIs.

The exclusion criteria for the study included: symptoms of liver, kidney, or thyroid dysfunction, use of any medication other than SSRIs, age 18–60, substance use disorder, other somatic illnesses, co-existing mental disorders other than major depression or anxiety. In addition, the participants were routinely checked during the study and those who were found to meet any of the above criteria were removed from the sample population.

Medications

One group received *Alpinia galanga* extract in the form of a 500-mg tablet, while the other received similar looking placebo tablets containing Avicel (a starch-like substance). Both groups were told to consume their medication with a glass of milk on an empty stomach. The participants were assessed on week 2 and week 4 of the study. Additionally, in order to investigate the possible side effects, the participants were regularly assess using a self-report medication side effect questionnaire, as well as laboratory tests including complete blood count (CBC), blood urea nitrogen (BUN), Creatinine, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and thyroid stimulating hormone (TSH).

Questionnaires and evaluations

The International Index of Erectile Function (IIEF) was used to evaluate the participants. It is a widely used, multidimensional, self-report questionnaire used to assess the sexual function of males. The validity and reliability of this questionnaire has also been proven for the Iranian population (20). It contains 15 questions which assess different aspects of the test-taker's sexual function such as erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction over the past 4 weeks. There are 6 possible answers for every question and a score of 0–5 is awarded to each question. The total score is calculated by summing the score of each individual question. A maximum score of 75 can be obtained from this questionnaire with higher scores indicating better sexual function. A total score of 5–7, 8–11, 12–16, 17–21, and 22–30 indicate no dysfunction, mild dysfunction, mild to moderate dysfunction, moderate dysfunction, and severe dysfunction, respectively (21). The validity and reliability of this questionnaire has been approved for the Iranian population (22).

Throughout the years, different inventories and questionnaires have been used to measure the severity and prevalence of depression among populations. The Beck Depression Inventory (BDI) is one of the most widely used inventories for this means. It is a 21-question multi-choice self-report inventory. There are three versions of this inventory: BDI, BDI-1A, and BDI-II. The current version (BDI-II) was used in this study and is designed for ages 13 and up. This version was published in 1996 and takes into account physical as well as cognitive symptoms of depression. Previous studies have confirmed a high degree of reliability and validity for this inventory in the Iranian population (23). A value of 0 to 3 has been assigned for every answer to each question. The total score is calculated by summing up the scores attained in every question and can range from 0 to 63. Higher scores indicated higher levels of depression. The standard cut-off scores are as follows: A total score of 0–13, 14–19, 20–28, and 29–63 demonstrate normal, mild, medium, and sever levels of depression, respectively, (24). Its reliability and validity has been proven for the Iranian population (25).

The Beck Anxiety Inventory (BAI), a multiple-choice self-report inventory consisting of 21 questions, has been widely used to measure the prevalence and severity of anxiety in different studies. It has been designed for ages 17 and up and takes into consideration physical, cognitive, and emotional symptoms of anxiety in the last week such as numbness, palpitations, fear of future events, and fear of losing control of oneself. The reliability and persistence of the Beck Anxiety Inventory has been proven in Persian studies (26). In this 21-question inventory, each answer is scored on a scale value

TABLE 1 Comparison of the placebo group and the *Alpinia galanga* group.

	Placebo group		*Alpinia galanga* group		*p*-value
Age [median and (range)]	43 (25–62)		45 (22–63)		0.865
Beck Depression Score [mean ± standard deviation]	Baseline	20.5 ± 6.7	Baseline	21.3 ± 5.9	0.657
	Week 2	17.3 ± 6.2	Week 2	17.4 ± 5.4	0.974
	Week 4	12.9 ± 7.5	Week 4	13.0 ± 4.6	0.962
Beck Anxiety Score [mean ± standard deviation]	Baseline	22.7 ± 8.9	Baseline	23.4 ± 4.7	0.851
	Week 2	18.1 ± 7.2	Week 2	17.7 ± 3.8	0.903
	Week 4	10.6 ± 6.2	Week 4	8.6 ± 4.2	0.456
IIEF Score [mean ± standard deviation]	Baseline	10.6 ± 3.8	Baseline	11.2 ± 4.8	0.577
	Week 2	11.4 ± 3.8	Week 2	14.1 ± 4.4	0.015
	Week 4	13.7 ± 4.3	Week 4	17.4 ± 3.7	0.001

of 0–3. The total score can range from 0 to 63, with lower scores indicating lower anxiety levels. The standardized cut-offs used for interpretation are as follows: A total score of 0–7, 8–15, 16–25, and 26–63 indicate normal, mild, medium, and severe anxiety levels, respectively, (27). This inventory has been proven to be valid and reliable for use the Iranian population (28).

Data were analyzed using IBM SPSS 26.0 software using tests such as paired *t*-test and Chi-square. In all of the tests, 0.05 was considered as the cut-off for significance.

This clinical trial was registered under the code IRCT20101130005280N41 in the Iranian Registry of Clinical Trials.

Results

This triple-blind randomized clinical trial study was conducted on 60 adult males who were under treatment with SSRI medications and had complained new-onset sexual side effects. The participants were randomly divided into two groups, one group receiving *Alpinia galanga*, while their counterparts received placebo.

Table 1 demonstrates the information of the two groups.

There was no significant difference between the two groups in terms of age (p-value = 0.865). As shown in Table 1, there was no statistically significant difference between the Beck depression scores of the two groups at the beginning of the study, as well as by week 2, and week 4 of the study (p-value>0.05).

By the end of the study both groups had experienced a significant decrease in their Beck depression scores compared to the beginning of the project (p-value<0.001). In addition, the Beck depression scores of both groups were significantly lower by the end of the study compared to week 2 of the study (p-value<0.001). However, these changes were not significantly different among the two groups (p-value = 0.679).

No statistically significant difference was observed between group A and group B in terms of Beck anxiety score at the beginning of the study, as well as by week 2 and week 4 of the study (p-value>0.05). The Beck anxiety score had notably decreased in both groups by week 4 of the study compared to the beginning of the project (p-value<0.001). Moreover, both the control and the intervention group had obtained remarkably lower scores on the Beck anxiety inventory on week 4 of the study compared to the second week of the project (p-value<0.001). However, these changes were not significantly different among the two groups (p-value = 0.470).

The International Index of Erectile Function scores of the placebo group and the *Alpinia galanga* group at the beginning of the study were 10.6 ± 3.8 and 11.2 ± 4.8, respectively (mean ± standard deviation). The initial IIEF score was not significantly different between the two groups at the beginning of the study (p-value = 0.577). By week 2 and week 4 of the study, however, the *Alpinia galanga* group had obtained significantly higher marks on the IIEF compared to the placebo group (p-value<0.05; Figure 1).

The IIEF score of both groups had significantly increased by week 4 of the study in comparison to the beginning of the study (p-value<0.001). Furthermore, both groups had significant increases in their IIEF scores on week 4 of the study compared to week 2 of the project (p-value<0.001). In addition, the IIEF scores of both groups had significantly increased by the end of week 2 of the study compared to the beginning of the project (p-value<0.001).

Repeated measures design was applied to assess and compare changes in the IIEF scores of the two groups. Mauchly's sphericity test (considering $w = 0.673$) and Greenhouse–Geisser correction (considering $\varepsilon = 0.75$) were used to evaluate the two groups. There was a notably remarkable difference among the two groups in terms of the change in their IIEF scores, with the *Alpinia galanga* group experiencing a significantly higher increase in their IIEF scores compared with their placebo-consuming counterparts (p-value<0.001).

No significant correlation was observed between changes in IIEF scores and changes in Beck Depression Inventory scores in both groups (p-value>0.05). In addition, there was no significant correlation between changes in IIEF scores and changes in Beck Anxiety Inventory scores of the two groups (p-value>0.05).

The two groups showed no significant changes in their AST, ALT, or ALP laboratory values (p-value>0.05). The creatinine level of the participants consuming *Alpinia galanga* at the beginning and end of the study was 0.78 ± 0.16 and 0.82 ± 0.21, respectively (p-value = 0.091). Considering the normal range of creatinine within 0.6–1.2 mg/dL (53–106 μmol/L) (29), the AST, ALT, ALP, and creatinine results of the participants were within the normal range throughout the study. There was no significant association between the laboratory values and the use of *Alpinia galanga* (Table 2)

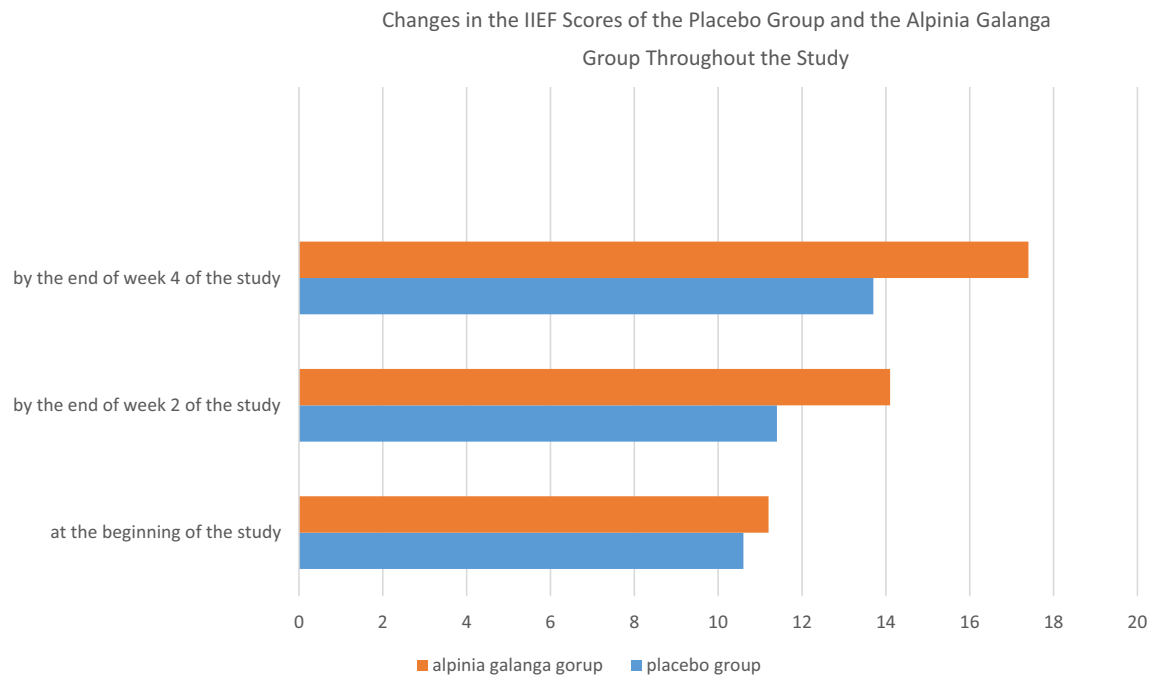

FIGURE 1
Changes in the IIEF scores of the placebo group and the *Alpinia galanga* group throughout the study.

TABLE 2 Laboratory values of the participants throughout the study.

	Placebo group	*p*-value	Intervention group	*p*-value
Primary AST	27.32 ± 11.82	0.236	24.65 ± 9.48	0.349
Week 4 AST	27.83 ± 12.13		23.96 ± 9.71	
Primary ALT	32.06 ± 10.27	0.455	27.17 ± 11.19	0.287
Week 4 ALT	32.67 ± 9.97		26.41 ± 11.52	
Primary ALP	96.74 ± 34.72	0.587	73.79 ± 32.57	0.385
Week 4 ALP	91.38 ± 34.39		72.55 ± 29.18	

Effect sized was calculated using Cohen's d statistic. Cohen's *d* was equal to 0.49, which can indicate an acceptable effect size (Figure 2).

Discussion

This triple-blind clinical trial aimed to assess the possible effects of *Alpinia galanga* extract on SSRI-associated male sexual dysfunction. Sixty male SSRI consumers were randomly assigned to two groups; one group consuming *Alpinia galanga* extract and the other receiving placebo. Both groups showed a significant decrease in their Beck Depression and Anxiety Inventory scores. This decrease was possibly due to the use of SSRI medications. The intervention group showed a notably higher increase in their IIEF scores by the end the study compared to the control group. Similar results, if proven by further studies, could suggest that *Alpinia galanga* may have a positive effect on enhancing male sexual dysfunction and may be used to reduce sexual side effects in patients consuming SSRI medications. Various other studies on both animals and human subjects have suggested sexual function enhancement as a result of *Alpinia galanga* use.

A 2021 narrative review study by Farahmand et al. also reported that plants of the ginger family may improve erectile function and augment sexual satisfaction. In addition, they concluded that plants such as Tribulus can increase testosterone levels as well as the number of sperms (30). This further suggests that plants of the Alpinia family may play a role in improving sexual function in males.

A 2019 literature review by Chen et al. found that 15% of heterosexual couples worldwide suffer from sexual disharmony, and that 40–50% of these cases are due to male sexual dysfunction factors. They wrote that the use of herbal medicine can be an effective method for reducing sexual dysfunction due to the increasing interest in the consumption of these medicines as well as their low cost and minimal side effects. They found that numerous herbal medications, including *Anacyclus pyrethrum*, *Anethum graveolens* L, and *Alpinia calcarata* Roscoe (from the ginger family) may serve as "aphrodisiac" agents as evident by their augmentation of erectile function and durability, sexual arousability, and sexual

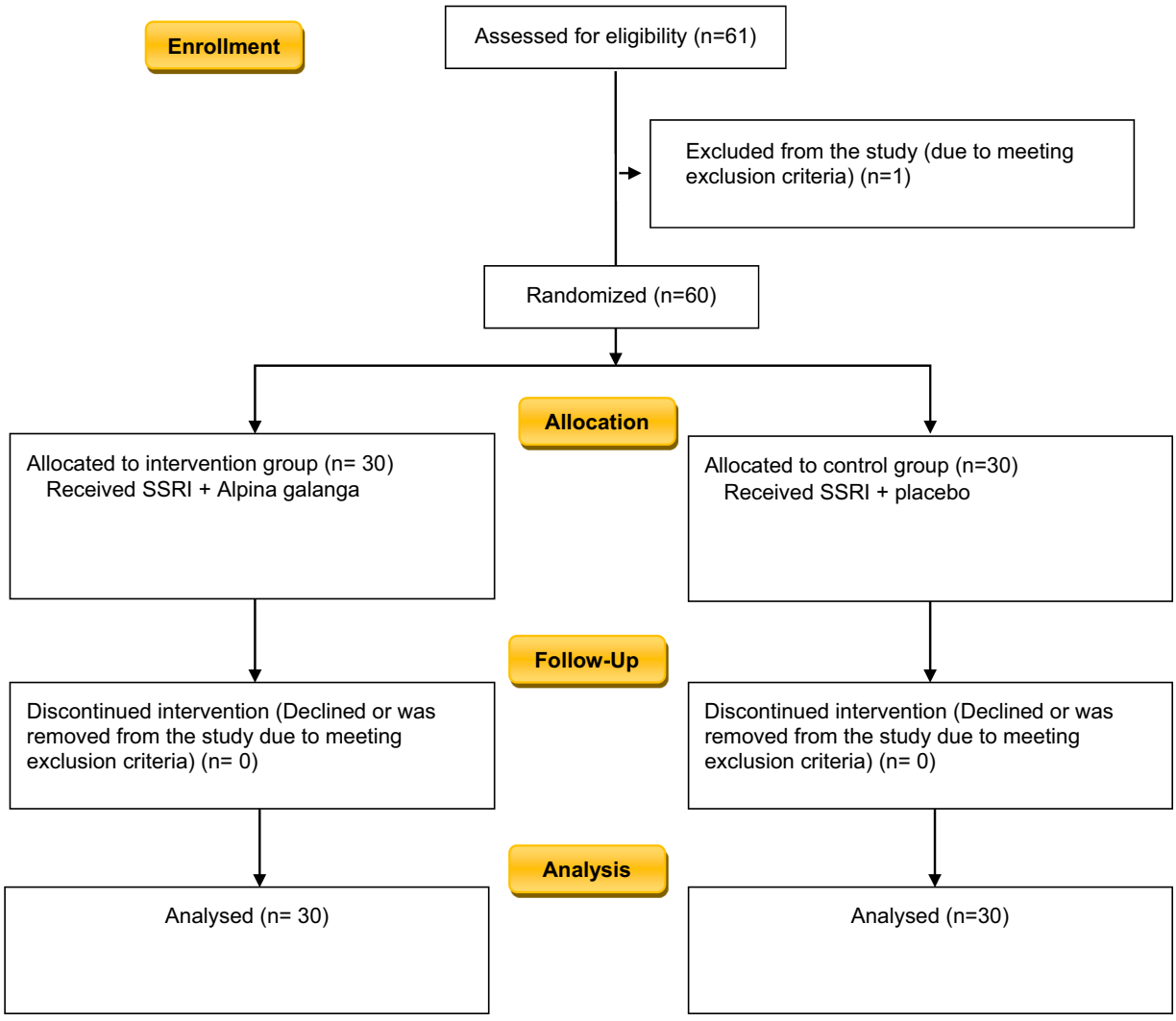

FIGURE 2
Study flow chart.

performance (31). These findings are in line with our results that herbal medications such as *Alpinia galanga* can play a role in improving male sexual function.

A review article by Banihani inferred that the use of ginger, or its derivatives, particularly in conditions of oxidative stress, enhances the production of testosterone. The presumed mechanism is that this effect is induced by the increase in luteinizing hormone (LH), reduction of lipid peroxidation and oxidative stress in the testes, increasing cholesterol levels, and enhancing blood flow to the testicles (32). These reports also align with our findings and provide a possible theory of the mechanism of action of plants of the ginger family in ameliorating erectile function.

A study by Qureshi et al. reported increases in sperm motility and sperm count as well as weight gain of the testes of mice being treated with *Alpinia galanga* and curcuma longa; the increases however were significantly higher in mice who had received *Alpinia galanga* extract (33). Similar to our study, their findings suggest that *Alpinia galanga* may play a role in the enhancement of sexual function.

A systematic review by da Cruz et al. found aphrodisiac effects for various herbal medications. They concluded that *Tribulus terrestris* and *Eurycoma longifólia* increase testosterone serum levels, ginseng stimulates smooth muscle relaxation with nitrous oxide, Lepidium meyenii improves sexual function, and that *Mondia whitei* (White's ginger) improved libido and erection (34). The findings of this study are also in line with our results and suggest that plants of the ginger family (including *Alpinia galanga*) may play a role in the enhancement of sexual function, desire, and fertility.

A 2021 systematic review by Luft et al. on the pharmacological interventions in SSRI-associated sexual dysfunction reported that

medications such as sildenafil and pycnogenol have been shown to enhance SSRI-induced sexual dysfunction in comparison with placebo (35). Some studies, including a systematic review by Maleki-Saghooni et al. have reported the positive effect of other herbal medications such as saffron (*Crocus sativus*) in the treatment of male sexual dysfunction (36). Further assessments are required on the use of herbal medications in treating erectile dysfunction as well as to compare their effectiveness and side effects.

This study was the first clinical trial to investigate the effects of the consumption of *Alpinia galanga* extract on the sexual side effects experienced by male patients being treated with SSRIs. As shown by a Cohen's d of 0.49, the effect size was acceptable and a significant improvement was observed in the sexual function of the intervention group. Similar results, if proven, could lead to more effective treatment plans and higher compliance in psychiatric patients consuming SSRIs. In addition, due to the popularity of herbal medications and the participants' enthusiasm, almost all the participants willingly completed the study and were content with their results and there was very little loss to follow-up.

It should be noted, however, that due to cultural and/or personal reasons, obtaining precise and accurate information about the sexual function of patients may be challenging. One of the limitations of this study could be that it was conducted in a limited group (heterosexual married males aged 18–60 who were being treated with SSRIs) and that the population was followed up for 4 weeks. Although significant changes were seen, we suggest future projects study similar possible effects in other groups such as females, the transgender population, people of other sexual orientations, or ages above 60 to better understand and address sexual side effects experienced by these populations.

It is also suggested that future researches assess similar possible effects on female sexual dysfunction as well in order to provide a better pathophysiological understanding as well as efficient treatment methods for females dealing with sexual side effects. Further studies on larger populations are required to investigate the possible effects of herbal medications such as *Alpinia galanga* extract on the sexual side effects of SSRIs.

The use of herbal medications such as *Alpinia galanga* needs to be assessed in patients with more severe levels of depression/anxiety as well to investigate whether the severity of the underlying mental illness can impact the effects of this medication. In this study, we found no significant relationship between the consumption of *Alpinia galanga* and AST, ALT, ALP, and creatinine laboratory values. We recommend future studies further investigate possible side effects of herbal medications such as *Alpinia galanga* to provide a better understanding of their possible benefits, risks, or usage in treatment. We also suggest future studies investigate and compare the possible efficacy and side effects of *Alpinia galanga* with other drugs such as sildenafil. It is hoped that by bringing more attention to subjects such as sexual function, enhancing the patient-physician relationship, and providing adequate education to people of different groups, discussions such as sexual function and activity will be easier and more fruitful. It is suggested that possible drug interactions and long-term and short-term side effects of herbal medications such as *Alpinia galanga* be studied as well before they are routinely prescribed to patients to enhance their sexual function.

Conclusion

According to the results of this study as well as similar studies, the use of *Alpinia galanga* for the management and reduction of SSRI-associated sexual dysfunction has been promising. The reported effects, if further proven by future studies, may lead to a better understanding of the causes and mechanisms of medication-induced sexual dysfunction, as well as provide more effective methods of reducing or treating sexual side effects of different medications including psychotropic medications. It is hoped that more efficient treatment guidelines and protocols that effectively address possible side effects experienced by patients lead to better patient-physician communication, higher compliance, more fruitful treatment outcomes, and higher satisfaction rates among patients and clinicians alike which can, in turn, play a role in the reduction in the prevalence and burden of mental illnesses worldwide.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Mashhad University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors contributed to the data collection, analysis, and manuscript preparation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Toward therapeutic drug monitoring of citalopram in depression? Insights from a systematic review

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Background: Within the framework of individualized psychopharmacotherapy, therapeutic drug monitoring (TDM) has gained increasing relevance. In the absence of high-quality evidence, the TDM of citalopram (CIT) and the recommended therapeutic ranges of the plasma concentrations have been proposed by guidelines. However, the correlation between the plasma concentration of CIT and treatment outcomes has not been well established. Therefore, the aim of this systematic review was to evaluate the relationship between plasma CIT concentration and treatment outcomes in depression.

Research design and methods: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese databases (CNKI, Wanfang Data and Sinomed) were searched up to August 6, 2022. We included clinical studies evaluating the correlation between the plasma CIT concentration and treatment outcomes in patients with depression receiving CIT treatment. Outcomes measured included efficacy, safety, medication adherence, and cost-related outcomes. A narrative synthesis was performed to summarize findings from individual studies. This study was performed according to the Preferred Reporting Items for Systematic Reviews, Meta-Analysis (PRISMA) and the reporting guideline for Synthesis without meta-analysis (SWiM).

Results: Eleven studies involving 538 patients were included in total. The reported outcomes were mainly efficacy (n = 11) and safety (n = 3); one study reported the duration of hospitalization, and no study reported medication adherence. Regarding the efficacy outcomes, three studies revealed the plasma CIT concentration-response relationship and proposed a lower limit of 50 or 53 ng/mL, whereas this was not found in the rest of the studies. Regarding adverse drug events (ADEs), one study reported more ADEs in the low-concentration group (<50 ng/mL vs. >50 ng/mL), which is not convincing from the perspective of pharmacokinetics/pharmacodynamics. Regarding the cost-related outcomes, only one study reported that the high CIT concentration group (≥50 ng/mL) contributed to shortening the hospitalization duration, but it did not provide detailed information, including direct medical expenses and multiple potential factors contributing to longer hospital stays.

Conclusions: A definite correlation between plasma concentration and clinical or cost-related outcomes of CIT cannot be drawn, whereas a tendency toward improved efficacy in patients with plasma concentration above 50 or 53 ng/mL was suggestive from limited evidence.

KEYWORDS

citalopram, therapeutic drug monitoring, plasma concentration, depression, treatment outcome

1. Introduction

Depression is a common psychological condition affecting more than 322 million people worldwide (1). Selective serotonin reuptake inhibitors (SSRIs) constitute a large part of antidepressants (2). As one of the representative SSRI drugs, citalopram (CIT) is a widely used and well-tolerated antidepressant in the treatment of depression. However, the response rates in trials have been estimated at only 50–60% (3). Therapeutic drug monitoring (TDM) is the clinical practice of measuring drug exposure at designated intervals to tailor drug doses, thereby optimizing outcomes in individual patients (4). The past years have witnessed great progress in TDM in the field of psychotropic drugs (5).

Within the framework of individualized psychopharmacotherapy, TDM has gained increasing relevance (6). With regard to CIT, polymorphism of CYP2C19 plays an important role in the N-demethylation of CIT *in vivo*. Extensive and poor metabolizers of CYP2C19 caused a significant difference in the behavior of CIT (7). Therefore, TDM has the potential to improve the outcomes of patients receiving CIT therapy. Currently, the TDM of CIT and the definition of therapeutic ranges of the plasma concentrations are recommended as the first level by the TDM expert group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guideline (2017) (4) as well as a Chinese expert consensus (2022) (8), whereas the TDM of other SSRIs is at the secondary or tertiary level. However, these recommendations were formulated in the absence of high-quality evidence.

The process of TDM is predicated on the assumption that there is a definable relationship between concentration and therapeutic or adverse effects (9), since the dose modifications must rely on the definable relationship. Nevertheless, although TDM is widely used in CIT, the relationship between CIT exposure and treatment outcomes has not been well established in depression. Furthermore, to a certain extent, TDM is costly and time consuming for patients and clinical staff.

Herein, we conducted a systematic review to evaluate the relationship between plasma CIT concentration and treatment outcomes in patients with depression to provide an evidence-based reference for further implementation of TDM in depression.

2. Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews, Meta-Analysis (PRISMA) statement (10) and the reporting guideline for Synthesis without meta-analysis (SWiM) in systematic reviews (11). The PRISMA checklist is included in Supplementary Table S1. The protocol for this systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42022356425).

2.1. Search strategy

Electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese databases (CNKI, Wanfang Data, and SineMed), were searched for potentially relevant studies from inception to August 6, 2022. Specific search strategies were developed for each database. The combination of keywords ("Citalopram" OR "CIT" OR "Celexa" OR "Lu10171" OR "SSRIs") AND ("Drug monitoring" OR "Plasma level" OR "TDM" OR "Pharmacokinetics" OR "Drug clearance") was used to search the title and abstract of the queried literature (Supplementary material II). No restrictions were placed on the study design or language. The search strategy was confirmed by an experienced information library specialist. The reference lists of previous guidelines, expert consensus, reviews (4, 6–8, 12) and included literature were searched for relevant studies.

2.2. Eligibility criteria and study selection

Studies were considered eligible if they satisfied all the following inclusion criteria: (1) type of studies: any study evaluating the correlation between the plasma concentration and treatment outcomes; (2) type of subject: patients with depression (including depressed or major depression) received CIT treatment, with no restrictions on ethnicity, sex or age; (3) types of exposure/comparison: measuring the plasma levels of CIT and its metabolites, and determining the correlation between drug exposure and efficacy, safety, adherence or cost-related outcomes; and (4) types of outcomes measured: (i) Efficacy: improvement measured by the Hamilton Depression Scale (HAMD/HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S), Children's Depression Rating Scale Revised (CDRS-R), and Cronholm-Ottosson Depression Rating Scale (CORS); (ii) Safety: adverse drug events (ADEs) during the CIT treatment, including dry mouth, gastrointestinal reactions, neuropsychiatric side effects, palpitations or QT interval prolongation, etc.; (iii) Medication adherence: the extent to which a patient's behavior corresponds with the prescribed medication dosing regimen; and (iv) Cost-related outcomes: hospitalization length, drug cost, hospitalization cost and other medical expense. Duplicate publications, literatures published in non-English or non-Chinese language, abstracts with not available full texts, unqualified data or unable to extract data were excluded, and only the most recent and comprehensive data were included in the systematic review in the case of overlapping data.

Two authors (X.N. and J.D.) independently assessed the eligibility of all studies based on the inclusion and exclusion criteria above after reviewing the study title, abstract and full text in succession. Studies were included in only the systematic review (but not the meta-analysis) if their findings were relevant to the research question but data were not available for quantitative analysis. Any disagreement among authors was discussed and reconciled by the corresponding author (Z.R.S.).

2.3. Data extraction

Two authors (X.N. and S.Z.W.) independently extracted data based on a predesigned standardized extraction form, including the first author, publication year, country, study design, disease, diagnostic criteria, rating scales, age, outcomes, number of

patients, therapy duration, clinical efficacy outcome measures, and correlation between efficacy, safety, and plasma CIT levels.

2.4. Quality assessment/risk of bias assessment

Two authors (X.N. and S.Z.W.) independently assessed the quality of the included studies. The cohort studies and case-control studies were assessed under the Newcastle-Ottawa Scale (NOS) (13). The NOS attributes a maximum of 9 points to studies based on methodological design and formal reporting, involving "selection", "comparability" and "exposure/outcome". NOS scores ranging from 7 to 9 points indicate high quality, 5 to 6 indicate medium quality, and 0 to 4 indicate low quality (14). The Quality In Prognosis Studies (QUIPS) tool (15) was used to assess the quality of the prognosis studies. The QUIPS tool contains six domains, and each domain contains 3–7 prompting items and considerations. Each domain is rated as having a high, moderate, or low risk of bias considering the prompting items. To judge overall risk, the review authors described studies with a low risk of bias as those in which at least 5 of the 6 important bias domains were rated as having a low risk of bias. If there was at least 1 domain rated as high risk or more than 3 domains rated as moderate risk of bias, the overall risk of bias was deemed high. All other variations were determined to have a moderate risk of bias (16). Disagreements regarding quality assessment were resolved by consensus or, when necessary, by consulting the corresponding author.

2.5. Statistical analyses

Data were extracted and recorded in Microsoft Excel 2019 by two investigators and subsequently checked by another investigator. Baseline study characteristics were extracted and presented using descriptive statistics. Clinical heterogeneity was estimated by comparing the diagnosis, exposure/comparison, efficacy definition, and other clinical features among studies. Initially, this review was intended as a meta-analysis if valid data assessing the association between CIT plasma concentration and treatment outcomes were available from sufficiently homogeneous studies. However, because of great heterogeneity and a lack of data among different studies, no meta-analysis but a narrative synthesis was performed.

3. Results

3.1. Electronic searches and study selection

A total of 10,890 candidate references were identified in electronic database searches, and 1 candidate reference was identified using a manual search. After removing duplicate references and carefully reviewing the titles and abstracts, only 58 references were recognized as relevant, and then we assessed all full texts. Of the 58 references, 23 did not focus on TDM or CIT, 14 did not report the targeted outcomes, 7 did not focus on patients with depression, and 4 were reviews. Finally, according to the aforementioned inclusion and exclusion criteria, 11 studies were included in this systematic review. Eleven studies (17–27) were included in the descriptive analysis since the meta-analysis was not feasible. The PRISMA 2020 flow diagram is shown in Figure 1.

3.2. Study characteristics and quality assessment

In total, 11 studies involving 538 patients with depression were included. All studies included were published in English. Five studies focused on the correlation between clinical response or non-response and plasma CIT concentration (grouping according to concentration exposure or clinical response), and 6 studies focused on the correlation between score reduction of the rating scales and concentration. In addition, three and one studies focused on the outcomes of ADEs and cost-related outcomes, respectively. In most studies, blood samples were drawn immediately prior to the morning dose of CIT or 8 to 16 h after the night-time dose, when the plasma concentration reached the steady state. The median age of the participants varied from 18 to 88 years. The median follow-up time ranged from 4 to 12 months. The main characteristics of the included studies are summarized in Table 1.

Regarding the depression screening instruments, HAMD/HDRS, MADRS, CGI-S, CDRS-R, and CORS were used as instruments for the evaluation of the extent of depression and indicators for the efficacy of the drugs. Seven studies (19–25) reported that patients with depression were scaled as mild-moderate depression by the HAMD, MADRS, and CORS scales. Other studies did not report the patients' scale scores. Regarding the definition of dichotomous clinical response, a percentage reduction of patients' initial HAMD/HDRS score $\geq$50%, MADRS cutoff scores $\leq$6 points or a percentage reduction of the initial score $\geq$75%, CGI-I score $\leq$2 points, a percentage reduction in the initial score of CDRS-R $\geq$ 50%, and CORS cutoff scores $\leq$3 points were defined as clinical response.

The risk of bias assessment is shown in Tables 2, 3. The quality of the cohort and case-control studies evaluated by NOS was 7 or above, indicating a low risk of bias. Five prognosis studies were assessed by QUIPS, three studies were at a low or middle risk of bias, and two studied were considered a high risk of bias since it did not appropriately account for important confounding factors.

3.3. Clinical efficacy

3.3.1. Clinical response (Dichotomous)

Five studies provided the correlation between clinical response or nonresponse and plasma CIT concentration. Three case-control studies (22, 24, 25) concluded that there was no correlation between plasma CIT concentration and clinical response. One cohort study (21) revealed that, compared to patients with below 53 ng/mL of plasma CIT concentration, patients with above 53 ng/mL ($N = 19$, 35%) showed a significantly higher clinical response rate at day 35 (53 vs. 17%, $P = 0.01$). One prognosis study (27) reported that, compared with patients with lower concentrations, patients with

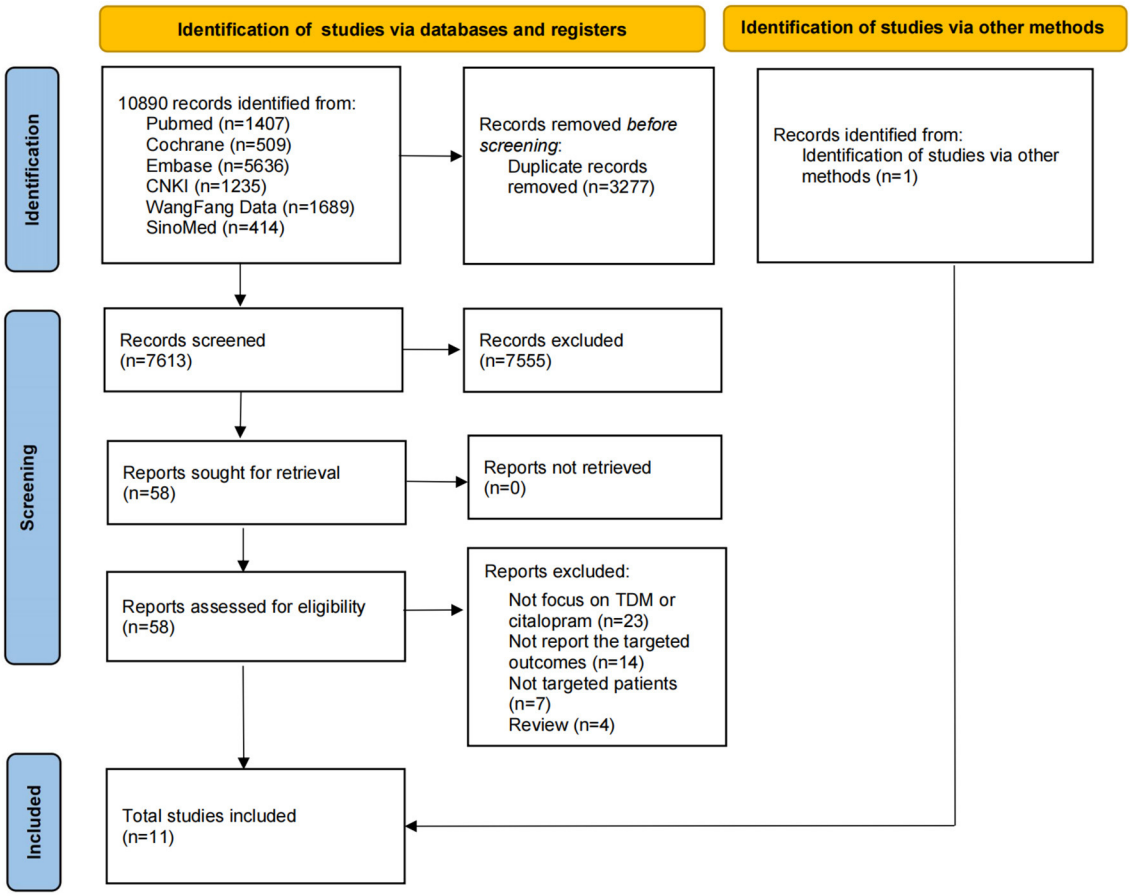

FIGURE 1
The PRISMA 2020 flow diagram of study selection for the systematic review.

plasma CIT concentrations equal to or greater than the geometric mean value showed a higher rate of response (76.5 vs. 30.0%, $P = 0.04$).

3.3.2. Improvement of scale scores (Continuous)

Six studies provided the relationship between the clinical assessments and plasma CIT concentration. One study (20) revealed that, compared to the low CIT concentration (<50 ng/mL) group, patients above 50 ng/mL showed a better percent reduction in HAMD score ($P \leq 0.019$) and a lower mean HAMD score ($P \leq 0.018$). Nevertheless, the other five studies (17–19, 23, 26) concluded that there was no correlation between clinical assessments and plasma CIT concentration.

Regarding the plasma concentration of the major metabolite N-desmethylcitalopram (NDCIT), one study (26) suggested that the high concentration (>73.25 ng/mL) group showed a more significant reduction in HDRS scores than the expected concentration (42.75–73.25 ng/mL) and the low concentration (<42.75 ng/mL) groups ($P = 0.002$). Regarding the concentrations of CIT and NDCIT, the findings are consistent with the above findings ($P = 0.003$).

3.4. Clinical safety

Three studies (20, 21, 26) reported the association of plasma CIT concentration and clinical safety, and most ADEs were rated as either mild or moderate. One study (20) revealed that the ADEs rate was significantly higher in the low CIT concentration (<50 ng/mL) group than in the high CIT concentration (>50 ng/mL) group ($\chi^2 = 7.7$, $P = 0.02$). One study (21) reported that mild or moderate ADEs occurred in 22 and 11%, respectively, in the high group and 44 and 21%, respectively, in the low group, but the detailed P value was not provided. Another study (26) showed that dry mouth, nausea, constipation, palpitation, dizziness and other ADEs occurred during CIT therapy, but there was no significant difference between the different concentration groups.

3.5. Cost-related outcomes

Only one study (20) reported cost-related outcomes but not direct medical expenses. Patients in the high CIT concentration group (≥50 ng/mL) had a 3-week shorter duration of hospitalization than patients in the low CIT group.

TABLE 1 Main characteristics of the studies included.

Study ID	Country	Study design	Disease	Diagnostic criteria	Rating scale	Age(y), median (range)	Outcome	Number of patients (F/M)	Therapy duration (weeks)	Plasma samples collection	Clinical efficacy outcomes measure	Correlation of efficacy to CIT Levels (ng/mL)	Correlation of Safety to CIT Levels (ng/mL)
Ozbey et al. (26)	Turkey	Cohort	MDD	DSM-IV	HDRS	37 (18–65)	Efficacy, safety	46(9/37)	6	ss	HDRS	No correlation	**ADE-rate:** $C(CIT)_{Low-expected}$ vs. $C(CIT)_{High}$: $P > 0.05$[b]
Haji et al. (21)[a]	Germany	Cohort	MDD (HAMD-17 ≥ 14)	ICD-10	HAMD-17	49	Efficacy, safety	55(28/27)	5	ss	HAMD	**Clinical response rate:** C(CIT) > 53.0 vs. C(CIT) < 53.0: 53 vs. 17%, $P = 0.01$	**1. Mild-ADE rate:** C(CIT) < 53.0 vs. C(CIT) > 53.0: 44 vs. 22%, the *P* value is not reported. **2. Moderate-ADE rate:** C(CIT) < 53.0 vs. C(CIT) > 53.0: 21 vs. 11%, the *P* value is not reported.
Haji et al. (20)[a]	Germany	Cohort	MDD (HAMD-17 ≥ 14)	ICD-10	HAMD-17	49	Efficacy, Safety, Cost-related outcomes	55(28/27)	5	ss	HAMD	**1. HAMD reduction percentage:** C(CIT)>50.0 vs. C(CIT) < 50.0: $P \leq 0.019$ **2. Mean HAMD**: C(CIT) > 50.0 vs. C(CIT) < 50.0: $P \leq 0.018$ **3. Mean duration hospitalization:** C(CIT) > 50.0 vs. C(CIT)< 50.0: $p = 0.033$	**ADE rate:** C(CIT) < 50.0 vs. C(CIT) > 50.0: $P = 0.02$
Sakolsky et al. (27)	USA	Prognosis	MDD	NR	CGI-S CDRS-R	12–18	Efficacy	27	6	ss	CGI-I CDRS-R	**Clinical response rate:** C(CIT) ≥ GM vs. C(CIT) < GM: 76.5 vs. 30.0%, $P = 0.04$	NR
Nikisch et al. (19)	Germany	Prognosis	MDD (HAMD-21 > 20)	DSM-IV	HAMD-21	19–55	Efficacy	22(13/9)	4	ss	HAMD	No correlation	NR
Amey et al. (24)	Switzerland	Case–control	MDD (HDRS-21 > 18)	DSM-III	HDRS-21	77.1 (67–88)	Efficacy	14(10/4)	4	ss	HDRS	No correlation	NR
Montgomery et al. (23)	UK	Prognosis	MDD (MADRS > 22)	DSM-Ill-R	MADRS	18–70	Efficacy	207(72/135)	12	ss	MADRS	No correlation	NR

(Continued)

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TABLE 1 (Continued)

Study ID	Country	Study design	Disease	Diagnostic criteria	Rating scale	Age(y), median (range)	Outcome	Number of patients (F/M)	Therapy duration (weeks)	Plasma samples collection	Clinical efficacy outcomes measure	Correlation of efficacy to CIT Levels (ng/mL)	Correlation of Safety to CIT Levels (ng/mL)
Dufour et al. (17)	France	Prognosis	Patients with depression	NR	MADRS	49.3 (29–79)	Efficacy	21(15/6)	4–6	ss	MADRS	No correlation	NR
Bouchard et al. (25)	France	Case–control	Patients with depression (MADRS > 15)	DSM-III	MADRS	44.7 (20–76)	Efficacy	46	6	ss	MADRS	No correlation	NR
Bjerkenstedt et al. (18)	Sweden	Prognosis	Patients with depression	Newcastle Scale II-71	MADRS	25–67	Efficacy	26(19/7)	4	ss	MADRS	No correlation	NR
Pedersen et al. (22)	Denmark	Case–control	Patients with depression (CORS > 5)	Newcastle Scale	CORS	18–60	Efficacy	19	4–6	ss	CORS	No correlation	NR

[a]The two studies included the same population but reported different outcomes. ss, steady state concentration; MDD, Major depressive disorder; NR, Not reported; ADE, Adverse drug events. [b]ADEs included dry mouth, nausea, constipation, palpitation, dizziness, increased perspiration, itching, headache, tremor, blurred vision, difficulty sleeping, sleeping too much, loss of sexual desire, and poor concentration. HAMD/HDRS, Hamilton Depression Scale; CDRS-R, Children's Depression Rating Scale Revised; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Asberg Depression Rating Scale; CORS, Cronholm-Ottosson Depression Rating Scale; GM, geometric mean. Definition of clinical response (dichotomous): (i) a percentage reduction in the initial HAMD/HDRS score ≥50%, (ii) MADRS cutoff scores ≤6 points or a percentage reduction in the initial score ≥75%, (iii) CORS cutoff scores ≤3 points, (iv) CGI-I score ≤2 points, and (v) a percentage reduction in the initial score of CDRS-R ≥ 50%.

4. Discussion

In the field of psychopharmacotherapy, TDM has been reported to not only improve efficacy and safety but also identify medication adherence issues (28, 29). Thus, TDM is considered a valid tool to improve patient outcomes and save healthcare costs in the treatment of depression. The latest clinical guidelines and expert consensus recommended the concentration ranges of CIT at the first recommendation level (4), while we found that the association of TDM-guided CIT concentration-efficacy was not particularly clear in actual clinical practice. Therefore, we paid more attention to the relationship between plasma CIT concentration and treatment outcomes in patients with depression in the present study.

4.1. Overall findings and trends

This review revealed four important findings. First, a definite correlation between plasma concentration and clinical efficacy cannot be drawn from inconsistent findings. However, limited studies have supported that the clinical efficacy of patients with plasma CIT concentrations above 50 or 53 ng/mL was better than that of patients with plasma CIT concentrations below 50 or 53 ng/mL. Second, a definite correlation between plasma concentration and clinical safety cannot be drawn in this review. More ADEs appeared to be associated with lower concentrations, but this result is not convincing from the perspective of pharmacokinetics/pharmacodynamics. From the perspective of long-term medication, considering the large utilization of CIT and the evidence gap, CIT-related safety should be paid more attention to (30). Third, with regard to the therapeutic range of CIT (50–110 ng/mL) recommended by clinical guidelines and expert consensus, no evidence was found on the upper limit of concentration. Finally, there is still a lack of evidence on the benefit of CIT TDM in medication adherence and cost savings.

4.2. Potential mechanisms and comparison with previous studies

Imaging studies have shown that concentrations of CIT correlate with serotonin transporter (5-HTT) occupancy (31). The study used [^{11}C]N,N-Dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([^{11}C]DASB) positron emission tomography to measure occupancies of SSRIs at minimum therapeutic doses. For SSRIs, as the dose (or plasma level) increased, the occupancy increased non-linearly, with a plateau for higher doses. It was assumed for SSRIs that 80% occupancy of 5-HTT should be attained for maximal clinical improvement. With regard to CIT, this requires serum concentrations of 50 ng/mL or higher (31), which corresponds to the findings in the present review. However, there were no consistent results between the included studies regarding efficacy and concentration. When interpreting results on concentration-efficacy association, heterogeneity between studies needs to be fully considered. Some factors, such as depression status, different scales and cutoff scores, cognitive

TABLE 2 Quality assessment of the cohort and case–control studies.

Study ID	Selection				Comparability	Exposure/Outcome			Score
	1	2	3	4	5[#]	6	7	8	
Ozbey et al. (26)[a]	*	*	*		**	*	*	*	8
Haji et al. (21)[a]	*	*	*		**	*	*	*	8
Haji et al. (20)[a]	*	*	*		*	*	*	*	7
Amey et al. (24)[b]	*	*	*		*	*	*	*	7
Bouchard et al. (25)[b]	*	*	*		**	*	*		7
Pedersen et al. (22)[b]	*	*	*		*	*	*	*	7

[a]Cohort studies: 1. Representativeness of the exposed cohort; 2. Selection of the nonexposed cohort; 3. Ascertainment of exposure; 4. Demonstration that the outcome of interest was not present at the start of the study; 5. Comparability of cohorts on the basis of the design or analysis; 6. Assessment of outcome; 7. Was follow-up long enough for outcomes to occur; 8. Adequacy of follow-up of cohorts. [b]Case–control studies: 1. Is the case definition adequate? 2. Representativeness of the cases; 3. Selection of Controls; 4. Definition of Controls; 5. Comparability of cases and controls on the basis of the design or analysis; 6. Ascertainment of exposure; 7. Same method of ascertainment for cases and controls; 8. Nonresponse rate. [#]There can be a maximum of two points*. ** Indicates that both the most important confounding factors (e.g., age) and other confounding factors were controlled.

TABLE 3 Quality assessment of the prognosis studies.

Study ID	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall
Sakolsky et al. (27)	L	H	L	L	M	L	4 L+1 M+1 H
Nikisch et al. (19)	M	L	L	L	M	L	4 L+2 M
Montgomery et al. (23)	L	L	L	L	M	M	4 L+2 M
Dufour et al. (17)	M	M	L	L	L	M	3 L+3 M
Bjerkenstedt et al. (18)	M	M	L	L	H	M	2 L+3 M+1 H

L, Low risk of bias; M, Medium risk of bias; H, High risk of bias.

status, and medication compliance, might have implications for the interpretation of the overall results.

It has been reported that neuropsychopharmacological drugs tend to exhibit two opposite directions of effect across their respective ranges of concentrations. In lower concentration ranges, there seems to be a positive direction of effect, increasing efficacy with increasing concentrations. In contrast, in higher concentration ranges, a negative direction could be observed, indicating a decline in efficacy with increasing concentrations (12). However, we did not find any data on the upper cut-off value of CIT concentrations in this study, although the recommended therapeutic reference range of CIT is 50–110 ng/mL by AGNP (4).

CIT is predominantly eliminated by cytochrome P450 (CYP)-catalyzed oxidation in the liver. CIT is partially N-demethylated to desmethylcitalopram (DCIT) by CYP2C19 and CYP3A4, and DCIT is further N-demethylated to NDCIT by CYP2D6 (32). In our review, the plasma levels of DCIT or NDCIT were also measured in six studies (17, 19, 22–24, 26), but only one study showed that the concentrations of NDCIT or CIT and NDCIT may be associated with the improvement in HDRS scores. According to previous consensus, the concentrations of DCIT and NDCIT are 30–50% and 5–10%, respectively, and the two metabolites are not active and are thought not to contribute to antidepressant activity (32).

Although TDM has been considered to identify medication adherence issues in psychopharmacotherapy, the role of conducting TDM in CIT medication adherence was not reported in any study included. Regarding the cost-related outcomes, only one indirect study (20) revealed that high concentrations (≥50 ng/mL) of CIT would help to shorten the hospitalization duration, but it did not provide other details or direct cost data. Since there are multiple potential factors contributing to longer hospital stays (e.g., patient insurance, hospital policy, funding, etc.), the results of this study need to be interpreted with caution. Additionally, one previous study reported that the TDM of SSRIs has the potential to reduce drug costs in elderly patients with depression (33). Based on the above considerations, higher quality studies are needed to validate the economic benefit of CIT TDM.

As the associations between concentration and clinical effects of antidepressants have become a wide clinical concern, some reviews have been published earlier. One systematic review published in 2022 (12) focused on the association between the concentration and clinical effect of antidepressants, which were divided into several categories such as SSRI, tricyclic antidepressants (TCA), tetracyclic antidepressants (Tetra-CA), and selective serotonin-noradrenaline reuptake-inhibitors (SSNRI), but did not provide detailed information on CIT or escitalopram to guide clinical

practice. From the perspective of review findings, both the previous review and our present review reported that research on the association between the concentration and clinical effect of antidepressants has yielded ambiguous results. Another systematic review published in 2020 (6) discussed a concentration-effect relationship for 11 psychotropic drugs in children and adolescents and found that the evidence is sparse and therapeutic reference ranges are generally not evaluated or reported.

4.3. Limitations

Several limitations should be considered in our review. First, the data were derived from studies with different study designs, efficacy assessments and outcome definitions. The substantial heterogeneity among the studies remained largely unexplained and thus may contribute to discrepancies in evaluation results. In addition, methodological shortcomings in primary studies might systematically influence the relationship between the variables. Second, the analysis relied on a limited number of original studies, and the sample size included in these selected studies was insufficient. Third, due to the substantial heterogeneity or the limited number of studies, meta-analyses could not be performed to draw more definitive conclusions. The aforementioned limitations warrant future larger validation studies of the association between plasma concentrations and treatment outcomes of CIT in patients with depression.

4.4. Recommendation for clinical practice

In light of the findings in this study, the association of CIT plasma concentration and treatment outcomes in patients with depression remains inconclusive. From a clinician or pharmacist's point of view, we propose some suggestions on the clinical implementation of CIT TDM. First, for patients with satisfactory response and stable condition after CIT treatment, it is not recommended to carry out TDM routinely. In the case of insufficient clinical improvement, CIT TDM could be carried out, and the dose should be optimized to achieve a concentration above 50 or 53 ng/mL. Usually, the corresponding dose range to achieve this goal is 20 to 40 mg per day with a median level of 30 mg (21). Second, TDM may be useful under some certain conditions, such as patients with pregnancy, elderly patients, patients with liver impairment, and patients taking other medications that may interact with CIT. Third, given the lack of evidence on the upper limit of TDM from a safety perspective, concentration monitoring might offer some information on the ADE etiology only in the presence of ADEs. Last but not least, we would like to encourage clinicians or pharmacists to accumulate real-world evidence of the clinical or economic benefit of TDM in their clinical practice.

5. Conclusion

In summary, a definite correlation between plasma concentration and clinical or cost-related outcomes cannot be drawn from current findings, whereas a tendency toward improved efficacy in patients with plasma CIT concentrations above 50 or 53 ng/mL was suggestive. Therefore, we recommend that TDM for CIT be considered under certain conditions, such as patients who are pregnant, elderly patients, patients with liver impairment, patients taking other medications that may interact with CIT, and patients with insufficient clinical improvement.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RZ and ZS conceived and designed the study. NX and ZS collected and analyzed the data and performed the statistical analysis and wrote the article. NX and DJ prepared the pictures and tables. RZ provided suggestions and participated in the revision of the article. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Hospitalisations related to administration errors of psychotropic drugs: a nationwide retrospective study between 1998 and 2019 in Australia

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Objectives: Medication administration error occurs when there is a discrepancy between what the patient received or was planned to receive and what the doctor originally intended. The aim of this study was to examine the trends in hospitalisation related to administration errors of psychotropic drugs in Australia.

Materials and Methods: This was a secular trend analysis study that examined the hospitalisation pattern for medication administration errors of psychotropic drugs in Australia between 1998 and 2019. Data on medication administration errors of psychotropic drugs was obtained from The National Hospital Morbidity Database. We analysed the variation in hospitalisation rates using the Pearson chi-square test for independence.

Results: Hospitalisation rates related to administration errors of psychotropic drugs increased by 8.3% [from 36.22 (95% CI 35.36—37.08) in 1998 to 39.21 (95% CI 38.44—39.98) in 2019 per 100,000 persons, $p < 0.05$]. Overnight-stay hospital admission patients accounted for 70.3% of the total number of episodes. Rates of same-day hospitalisation increased by 12.3% [from 10.35 (95% CI 9.90—10.81) in 1998 to 11.63 (95% CI 11.21—12.05) in 2019 per 100,000 persons]. Rates of overnight-stay hospital admission increased by 1.8% [from 25.86 (95% CI 25.13—26.59) in 1998 to 26.34 (95% CI 25.71—26.97) in 2019 per 100,000 persons]. Other and unspecified antidepressants (selective serotonin and norepinephrine reuptake inhibitors) were the most common reason for hospitalisation accounting for 36.6% of the total number of hospitalisation episodes. Females accounted for 111,029 hospitalisation episodes, representing 63.2% of all hospitalisation episodes. The age group 20–39 years accounted for nearly half (48.6%) of the total number of episodes.

Conclusion: Psychotropic drug administration error is a regular cause of hospitalization in Australia. Hospitalizations usually required overnight stays. The majority of hospitalizations were in persons aged 20–39 years, which is concerning and warrants further investigation. Future studies should examine the risk factors for hospitalization related to psychiatric drug administration errors.

KEYWORDS

admission, Australia, hospitalisation, medication, psychotropic, poisoning, administration error

Introduction

Any error made when prescribing, dispensing, or administering a medication is referred to as a medication error. The definition of a medication administration error (MAE) is any deviation between what the patient received or was supposed to receive and what the doctor intended when the order was placed (Zed et al., 2008). MAE arises when there is a difference between the medicine obtained by the patient and the desired drug therapy (Williams et al., 2007). According to the ICD system MAEs include poisoning by, adverse effect of, and underdosing of medications (International Classification of Diseases, 2023). Drug poisoning is potentially one of the major drug-related problems and the primary reason for patient admission to critical care units and emergency departments worldwide (Kurdil, 2021). It is the main cause of non-traumatic coma among patients under the age of 35 admitted to the emergency department (Demİrel, 2010). In developed countries, the yearly poisoning incidence rate ranges from 0.02% to 0.93%, and this rate is increasing globally (Özayar et al., 2011).

Worldwide, acute poisoning is a prominent cause of mortality and morbidity and a frequent reason for hospital admissions and emergency service visits (Jesslin et al., 2010; Rutto et al., 2012; Maheswari et al., 2016). Besides, the most frequent global reason for acute poisoning is drug overdose. Poisoning by psychotropic drugs, including benzodiazepines, antidepressants, and antipsychotics is the most common method by which individuals attempt suicide (Moens et al., 1989; Kim et al., 2015; Mowry et al., 2015). The toxicity of psychotropic medicines varies greatly, ranging from acute to chronic (Bickel, 1986). Although the real impact of psychotropic medications differs across countries, it is typically a severe health issue requiring an urgent attention (Kinoshita et al., 2015).

Women are approximately twice as likely to suffer from mood and anxiety disorders, while men are approximately four times more likely to suffer from substance-use and impulsive disorders (Offord et al., 1996; Seedat et al., 2009). The gender-based difference in the prevalence of psychiatric disorders itself contributes to the difference in the utilization of psychotropic medications and ultimately their associated MAEs. A previous study in the United Kingdom (United Kingdom) reported that the hospitalization rate for psychotropic drug poisoning increased in England and Wales by 20.0% between the periods from 1999 to 2020 (Al-Daghastani and Naser, 2022). In Australia, intentional self-poisoning with psychotropic, anti-parkinsonism, sedative-hypnotic, and anti-epileptic drugs was the most frequent form of self-harm leading to hospital admissions between 2008/2009 and 2020/2021, accounting for 40% of intentional self-harm hospital admissions in 2020/2021 (Australian Institute of Health and Welfare, 2022a). Given the risks associated with psychotropic drug use and poisoning, it is crucial to identify the patterns of hospitals admissions due to administration errors relevant to these agents. This will help understanding the extent of the problem and to advise strategies for reducing and preventing patient harm. Therefore, this study aimed to examine the trends of hospitalisation related to administration errors of psychotropic drugs in Australia.

Material and methods

Study design

This was a secular trend analysis study that examined the hospitalisation pattern for medication administration errors of psychotropic drugs in Australia between 1998 and 2019.

Data sources

National hospital morbidity database

The National Hospital Data Collection (NHDC) covers the National Hospital Morbidity Database (NHMD). The Australian Institute of Health and Welfare (AIHW) maintains several key national hospital databases, which are included in the NHDC (Australian Institute of Health and Welfare, 2022b). The NHMD, an online database, receives data from Australia's state and territory health authorities (Australian Institute of Health and Welfare, 2022c). The data gathered at the NHMD is made up of sets of episode-level information from morbidity data collection systems of patients admitted to private and public hospitals in Australia. The data are based on the NMDS for admitted patient care and contain information on the patients' diagnoses, external sources of injury and poisoning, length of hospital stays, treatments received, and demographics. The goal of NMDS for admitted patient care is to collect data on the treatment offered to hospitalized patients in Australian hospitals. The NMDS includes episodes of care for individuals admitted to hospitals from all alcohol and drug treatment facilities, independent day hospitals, and private and public mental and acute hospitals. Using the ICD-10, we identified hospitalization events related to all medication administration errors of psychotropic drugs (T43). The data included in this study are for patients who were primarily admitted to hospitals due to medication administration errors of psychotropic drugs (poisoning by, adverse effect of and underdosing of medications). Same-day hospitalisation is defined as "a day during which a person admitted as an inpatient is confined to a bed and in which the patient stays overnight in a hospital". Overnight-stay admitted care is defined as "the care provided for a minimum of one night, to a patient who is admitted to and separated from the hospital on different dates". Differentiating whether a patient will require an overnight stay or will be admitted on the same day is essential for the development of appropriate treatment plans. Longer hospital visits may necessitate additional assessments, interventions, and monitoring, whereas same-day admissions may be subject to specific care protocols or post-procedure instructions.

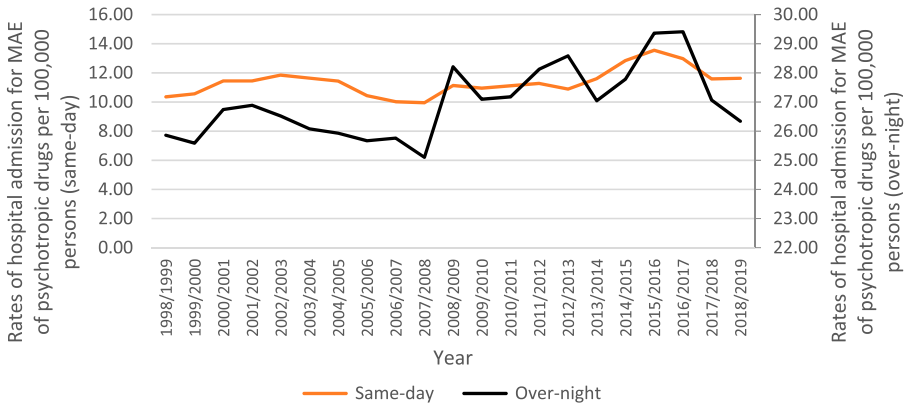

FIGURE 1
Rates of same-day and overnight-stay patients hospital admission in Australia between 1998 and 2019.

Australian Bureau of Statistics

Mid-year population data between 1998 and 2019 was collected from The Australian Bureau of Statistics (ABS) (Australian Bureau of Statistics, 2022a). Between 1998 and 2016, data on the population were collected using the historical population (Australian Institute of Health and Welfare, 2022d). Between 2017 and 2019, population data were collected utilizing national, state, and territorial populations (Australian Bureau of Statistics, 2016).

Study population

From 1998 to 2019, data on all private and public hospitalizations in Australia were collected for this study (Australian Bureau of Statistics, 2022b).

Statistical analysis

SPSS version 27 (IBM Corp, Armonk, NY, United States) was used for all analyses. Hospitalisation rates with 95% CIs were determined by dividing hospitalisation episodes by the mid-year population. Pearson chi-square test for independence was used to analyse the variation in hospitalisation rates between 1998 and 2019. The confidence interval was estimated using the following equation for the population proportion: $\hat{p}$ +/− z*($\hat{p}$(1 − $\hat{p}$)/n)0.5.

Results

Administration errors of psychotropic drugs hospitalisation

Between 1998 and 2019, there were 176,925 episodes of hospitalisation for administration errors of psychotropic drugs reported in Australia. The total yearly number of hospitalisation episodes increased by 45.8% from 6,813 in 1998 to 9,935 in 2019, representing an increase in hospitalisation rate of 8.3% [from 36.22 (95% CI 35.36—37.08) in 1998 to 39.21 (95% CI 38.44—39.98) in 2019 per 100,000 persons, $p < 0.05$].

A total of 70.3% of all hospitalization episodes involved patients admitted for an overnight stay, while 29.7% involved same-day admissions. Rates of same-day hospitalisation increased by 12.3% [from 10.35 (95%CI 9.90—10.81) in 1998 to 11.63 (95%CI 11.21—12.05) in 2019 per 100,000 persons]. Rates of overnight-stay hospital admission increased by 1.8% [from 25.86 (95%CI 25.13—26.59) in 1998 to 26.34 (95%CI 25.71—26.97) in 2019 per 100,000 persons] (Figure 1).

Other and unspecified antidepressants (selective serotonin and norepinephrine reuptake inhibitors) were the most common reason for administration errors of psychotropic drugs hospitalisation accounting for 36.6% of the total number, followed by other and unspecified antipsychotics and neuroleptics with 29.3%, psychostimulants with potential for use disorder with 11.6%, tricyclic and tetracyclic antidepressants with 11.2%, and phenothiazine antipsychotics and neuroleptics with 9.4% (Table 1).

Trends of hospitalisation (based on indication)

During the study period, administration errors of psychotropic drugs hospitalisation rate for other and unspecified antipsychotics and neuroleptics rose considerably by 361.6%. Moreover, hospitalisation rate for psychostimulants with potential for use disorder increased by 73.3%. However, hospitalisation rate for other psychotropic drugs, unspecified, butyrophenone and thioxanthene neuroleptics, monoamine-oxidase-inhibitor antidepressants, phenothiazine antipsychotics and neuroleptics, other and unspecified antidepressants, and tricyclic and tetracyclic antidepressants decreased by 100.0%, 100.0%, 79.6%, 72.4%, 65.6%, 23.4%, and 8.8%, respectively (Table 2; Supplementary Figure S1).

TABLE 1 Percentage of hospitalisation from total number of hospitalisation episodes per ICD code.

ICD code	Description	Percentage from total number of hospitalisation episodes (%)
T43.0	"Tricyclic and tetracyclic antidepressants"	11.2
T43.1	"Monoamine-oxidase-inhibitor antidepressants"	0.7
T43.2	"Other and unspecified antidepressants (selective serotonin and norepinephrine reuptake inhibitors)"	36.6
T43.3	"Phenothiazine antipsychotics and neuroleptics"	9.4
T43.4	"Butyrophenone and thioxanthene neuroleptics"	0.7
T43.5	"Other and unspecified antipsychotics and neuroleptics"	29.3
T43.6	"Psychostimulants with potential for use disorder"	11.6
T43.8	"Other psychotropic drugs, not elsewhere classified"	0.5
T43.9	"Psychotropic drug, unspecified"	0.1

TABLE 2 Percentage change in the hospitalisation rates from 1998—2019 in Australia.

Poisonings	Hospitalisation rate in 1998 per 100,000 persons (95% CI)	Hospitalisation rate in 2019 per 100,000 persons (95% CI)	Percentage change from 1998—2019 (%)
"Tricyclic and tetracyclic antidepressants"	3.69 (3.41—3.96)	3.37 (3.14—3.59)	−8.8
"Monoamine-oxidase-inhibitor antidepressants"	0.41 (0.32—0.51)	0.11 (0.07—0.16)	−72.4
"Other and unspecified antidepressants (selective serotonin and norepinephrine reuptake inhibitors)"	16.61 (16.03—17.19)	12.73 (12.29—13.17)	−23.4
"Phenothiazine antipsychotics and neuroleptics"	7.53 (7.13—7.92)	2.59 (2.39—2.79)	−65.6
"Butyrophenone and thioxanthene neuroleptics"	0.64 (0.52—0.75)	0.13 (0.09—0.17)	−79.6
"Other and unspecified antipsychotics and neuroleptics"	3.20 (2.94—3.46)	14.77 (14.30—15.24)	361.6
"Psychostimulants with potential for use disorder"	3.17 (2.92—3.43)	5.50 (5.21—5.79)	73.3
"Other psychotropic drugs, not elsewhere classified"	0.88 (0.75—1.02)	0.00 (0.00—0.00)	−100.0
"Psychotropic drug, unspecified"	0.08 (0.04—0.12)	0.00 (0.00—0.00)	−100.0

Trends in hospitalisation stratified by gender

Females accounted for 111,029 hospitalisation episodes, representing 63.2% of all hospitalisation episodes, with a mean number of 5,287 episodes per year. Hospitalisation rate among females increased by 10.3% [from 44.02 (95% CI 42.69—45.36) in 1998 to 48.55 (95% CI 47.34—49.76) in 2019 per 100,000 persons]. Hospitalisation rate among males decreased by 3.8% [from 28.30 (95% CI 27.22—29.38) in 1998 to 27.21 (95% CI 26.30—28.12) in 2019 per 100,000 persons] (Supplementary Figure S2).

Trends in hospitalisation stratified by age group

As per age group differences in hospitalisation episodes, the persons aged 20–39 years accounted for 48.6% of the total number of episodes, followed by the group aged 40–59 years with 26.9%, the age group below 20 years with 19.5%, the age group 60–74 years with 3.7%, and then the age group 75 years and above with 1.3%. The highest increase in the hospitalisation rate was observed among patients aged below 20 years. On the other hand, the hospitalisation rate among patients aged 20–39 years decreased by 10.5%, Table 3.

TABLE 3 Percentage change in hospitalisation rate stratified by age.

Age group	Hospitalisation rate in 1998 per 100,000 persons (95% CI)	Hospitalisation rate in 2019 per 100,000 persons (95% CI)	Percentage change (%)
Below 20 years	20.35 (95%CI 19.13—21.58)	32.74 (95%CI 31.32—34.16)	60.9
20–39 years	66.41 (95%CI 64.28—68.53)	59.42 (95%CI 57.65—61.19)	−10.5
40–59 years	35.47 (95%CI 33.80—37.15)	40.03 (95%CI 38.48—41.59)	12.9
60–74 years	9.30 (95%CI 7.98—10.62)	14.19 (95%CI 12.98—15.41)	52.6
75 years and above	8.32 (95%CI 6.55—10.09)	9.31 (95%CI 7.88—10.74)	11.9

The trends of hospitalisation rate stratified by age group is presented in Supplementary Figure S3.

Trends in hospitalisation stratified by indication and gender

The preponderance of MAE of psychotropic drugs, not elsewhere classified hospital admission rates were higher among females compared to males, that include the following: tricyclic and tetracyclic antidepressants, monoamine-oxidase-inhibitor antidepressants, other and unspecified antidepressants, phenothiazine antipsychotics and neuroleptics, butyrophenone and thioxanthene neuroleptics, and other and unspecified antipsychotics and neuroleptics (Supplementary Figure S1). Still, MAE of psychotropic drugs, not elsewhere classified hospital admission rates for psychostimulants with potential for use disorder, other psychotropic drugs, not elsewhere classified, and psychotropic drug, unspecified were higher among males compared to females (Supplementary Figure S4).

Trends in hospitalisation stratified by indication and age

All MAE of psychotropic drugs, not elsewhere classified-related hospital admission rates were more common among the age group 20–39 years (Supplementary Figure S5).

Discussion

To our knowledge, this is the first study to utilise a nationwide database in Australia to describe the patterns of hospital admission due to psychotropic drug administration errors. Results from the current study showed that hospitalisation rate for administration errors of psychotropic drugs has increased in Australia by 8.3% during the periods from 1998 to 2019, with an annual growth of 45.8%. One explanation for this growth could be the rise in mental illnesses and hence psychotropic prescribing practices in Australia (Wallis et al., 2021; Pai et al., 2022) and worldwide (Rani et al., 2008; Lao et al., 2017). Regardless, this increase imposes an urgent attention to be explored and monitored to prevent future patient harm and reduce costs (Suh et al., 2000; Leendertse et al., 2011). It is estimated that approximately 44% of Australians aged 16–85 have experienced a mental disorder at some point in their lives, with 21% having experienced a mental disorder in the preceding 12 months 17% of Australians suffer from anxiety disorders, followed by 8% with affective disorders and 3% with substance use disorders (Australian Institute of Health and Welfare, 2023). In addition, a recent study in Australia by Bartholomaeus et al. found that between 2009 and 2019, psychological therapy claims and GP mental health treatments increased by 167.4% and 85.4%, respectively (Bartholomaeus et al., 2023).

In line with results from the current study, a study in the United Kingdom showed that the hospital admission rate due to MAE of psychotropic medications increased by 19.9% over 21 years' study period (Al-Daghastani and Naser, 2022). Similar growth in the recorded number of administration errors of psychotropic drugs was reported in the United States by Vargas et al. (2020). On the other hand, a higher increase was noted in the United States of America in 2010 by Coben et al. (2010), where approximately a two-third (65%) increase in hospitalisation rate was reported. This higher increase can be related to the broader scheme of drugs used in Coben's study which also included opioids and sedatives. In the current study, the overnight-stay administration errors of psychotropic drugs hospital admission patients accounted for most hospitalisation episodes (70.3%) as compared to one-third of the episodes that were for same day patients. This indicates the seriousness of adverse effects caused by these agents (Bickel, 1986; Kinoshita et al., 2015; Chan, 2019).

The most common cause of administration errors of psychotropic drugs that lead to hospital admission in the current study was MAE of other and unspecified antidepressants, which accounted for 36.6% of the total number of hospitalisation episodes. This was followed by other and unspecified antipsychotics and neuroleptics, psychostimulants with potential for use disorder, tricyclic and tetracyclic antidepressants, and phenothiazine antipsychotics and neuroleptics which accounted for 29.3%, 11.6%, 11.2% and 9.4%, respectively. These finding were consistent to the study in the United Kingdom where the main cause of increased hospital admission was mainly caused by unspecified poisoning with antidepressants which accounted for 48.9%, followed by MAE of tricyclic and tetracyclic antidepressants, and unspecified poisoning with antipsychotics and neuroleptics which accounted for 20.9% and 13.4%, respectively (Al-Daghastani and Naser, 2022). Although overdosing on tricyclic and tetracyclic antidepressants can be hazardous, the percentage

of hospital admissions due to these agents were less in the current study in comparison to the study in the United Kingdom. This can be related to the fact that these agents are not recommended as first-line treatment. In addition, prescribing practices in Australia showed that only 25% of patients are prescribed these agents as compared to 52% of antidepressant prescriptions which where the less toxic agents in overdose SSRIs were chosen as first-line agents (Malhi et al., 2022).

With regards to gender, females were responsible for the majority of hospitalisation episodes (63.2%) in the current study. Females' hospital admission rate has increased by 10.3% while hospital admission rates among males have decreased by 3.8% over the years between 1998 and 2019. In this context, studies in the literature have clearly documented that females are more likely than males to be poisoned by psychotropic drugs (Vargas et al., 2020). This could be explained by the higher prevalence of psychiatric disorders (e.g., depression and anxiety) among female patients as compared to the males and hence receiving a higher number of psychotropic prescriptions (Boyd et al., 2015). In an Australian study by Malhi et al. (2022), antidepressants prescribing patterns were investigated between the years of 3,013 and 2019 and it was found that more than half of the study sample (56%) were female patients.

The age range 20–39 years in the current study accounted for almost half (48.6%) of the total number of hospitalization episodes, followed by the age group 40–59 years with 26.9%. On the other hand, children and younger adults (below age of 20 years) showed a lower admission rate of 19.5%. This could be explained in part by the higher usage of psychotropic medications among older age groups (Malhi et al., 2022), adding to the fact that children and adolescents more likely to be poisoned by over-the-counter medications as compared to prescription medications (Huynh et al., 2018).

In the current study, the overnight-stay administration errors of psychotropic drugs hospital admission patients accounted for most hospitalisation episodes (70.3%) as compared to one-third of the episodes that were for same day patients. However, future research would be beneficial to investigate the risk factors for longer hospital stay. With regards to age groups, future studies might include investigating the prevalence trends of different classes of psychotropics per each age group. Exploring rate of admission due to psychotropic poisoning based on diagnosed conditions is another point to be considered by future studies.

To the best of our knowledge, this is the first study to examine the trends of hospitalisation related to administration errors of psychotropic drugs in Australia. Our study was not restricted to a specific age group or gender which increase the generalisability of our findings. At the same time, this study has limitations. The data used in this study was on the population level not on the individual level of the patients which restricted our ability to identify risk factors that might have influenced our estimated hospitalisation rate. Our hospitalisation rate estimates include re-admission episodes, which might have led to an overestimation. Therefore, our findings should be interpreted carefully.

In conclusion, psychotropic drugs administration errors are common reason for hospitalization in Australia. Most hospitalisation episodes required an overnight stay. The majority of hospitalizations were in persons aged 20–39 years, which is an alarming result that requires additional investigation. Future studies should examine the risk factors for hospitalization related to psychiatric medication poisoning.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://meteor.aihw.gov.au/content/394352.

Ethics statement

This study used de-identified data and was considered exempt from human protection oversight by the institutional review board.

Author contributions

Supervision: FA and AN; Conception: FA and AN; Methodology: FA and AN; Investigation: FA, AN, ZA, and RO-A; Formal analysis: AN; Visualization: FA and AN; Writing—original draft: FA and AN; Project administration: FA and AN; Software: AN; Writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer OA declared a past co-authorship with the authors AN and ZA to the handling editor.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1149500/full#supplementary-material

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Association of the use of psychotropic drugs with hospitalization, cardiovascular events, and mortality in patients with type 2 diabetes: a propensity score-matched cohort study

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Background: Use of psychotropic drugs (PD) may be associated with impairment of physical function. However, few studies have assessed the impact of PD on health outcomes in patients with type 2 diabetes. This study aimed to examine the associations between psychotropic drug use and handgrip strength (HGS) and between the use of PD and hospitalization in patients with type 2 diabetes.

Methods: From April 2013 to December 2015, we conducted a retrospective cohort study in patients with type 2 diabetes at the National Center for Global Health and Medicine Kohnodai Hospital. Patients aged 20 years and over who can measure HGS were included. All participants received nutritional guidance regarding diet therapy for type 2 diabetes at baseline. Nonpsychotropic drug users were matched one-to-one with the PD users using propensity score matching method with respect to their baseline covariates. The differences in HGS and the number of patients who had hospitalizations during the study period were examined. By Cox proportional hazard regression analysis, the association between the use of PD and repeated hospitalizations was estimated.

Results: A total of 1,282 patients were enrolled and followed up for 2.36 $\pm$ 0.73 years. In the propensity score matching cohort, HGS was significantly lower ($p = 0.006$) in PD users than non-PD users. PD users had more hospitalizations than non-PD users. Cox proportional hazard regression analysis confirmed the association of repeated hospitalizations with the use of PD (hazard ratio = 2.138; 95% confidence interval, 1.144–3.995, $p = 0.017$)). In addition, HGS was significantly and inversely correlated with the number of hospitalizations ($r = -0.143$, $p = 0.013$).

Conclusions: The use of PD could increase the risk of repeated hospitalizations. Skeletal muscle may play a role in reducing the risk of hospitalization in patients who are treated with PD.

KEYWORDS

psychotropic drugs, type 2 diabetes, hospitalization, handgrip strength, skeletal muscle, psychiatric comorbidity

1 Introduction

Patients with diabetes mellitus may suffer from psychological disorders, such as depression, anxiety, eating disorders, and schizophrenia (1). Although the definition of psychological disorders/syndromes in patients with diabetes varies across clinical studies, ranging from self-reported symptoms to using formal diagnostic criteria such as Diagnostic and Statistical Manual of Mental Disorders, interventions for psychological problems in patients with diabetes result in an improvement in the management of diabetes (1). Chronic insomnia with a sleep duration ≤ 5 h has been associated with an increased risk of diabetes (2). A meta-analysis showed that depression was associated with a 60% increase in the risk of development of type 2 diabetes (3). The prevalence of type 2 diabetes is 10% in patients with schizophrenia, and the relative risk of developing diabetes is 2.5 times higher in patients with schizophrenia than that in the general population (4). Therefore, clinicians should pay attention to such psychiatric comorbidities in patients with diabetes.

Antipsychotic drugs probably increase the risk of diabetes (5, 6) through causing obesity (7) and a reduced insulin sensitivity (8). Furthermore, although psychotropic drugs (PD) are widely used even in the absence of a confirmed diagnosis of psychiatric disorders, epidemiological studies have shown that antipsychotic drug use is associated with an increased mortality risk in patients with Parkinson's disease (9) and Alzheimer's (10). In addition, high-dose benzodiazepines use has a dose–response relationship with mortality in patients with schizophrenia (11); similarly, antipsychotic drug use in combination with benzodiazepines is associated with an increased risk of mortality in patients with dementia (12). Furthermore, a systematic review and meta-analysis has shown that antipsychotics, antidepressants, and benzodiazepines were consistently associated with a higher risk of falls (13). On the other hand, the relationship between the use of benzodiazepines, antidepressants, and antipsychotics and serious diseases, such as pneumonia, cancer and cardiovascular (CV) disease is controversial (14–18). In the literature, few studies have assessed the impact of PD on such health outcomes in patients with type 2 diabetes.

Generally, patients with type 2 diabetes have a lower energy expenditure, physical activity duration (19), and muscle strength (20, 21) than healthy individuals. Recently, we showed that handgrip strength (HGS), which is a simple and cost-effective method for evaluating muscle strength, predicts hospitalization, occurrence of CV events, and death among Japanese patients with type 2 diabetes (22). van Milligen et al. reported that women with depression and anxiety disorder had lower HGS compared with healthy controls (23). Antipsychotic drugs also decrease physical activity, whole body balance, and cardiorespiratory endurance (24). We hypothesize that PD, including benzodiazepine, antidepressant, and antipsychotic use, is associated with impairment of physical function such as HGS and subsequently leads to an increased risk of hospitalization. Thus, in this study, we examined the association of PD use with HGS and deaths, CV events, and hospitalization in patients with type 2 diabetes.

2 Materials and methods

2.1 Study design and subjects

We conducted a retrospective cohort study in patients with type 2 diabetes who were treated at the National Center for Global Health and Medicine Kohnodai Hospital between April 2013 and December 2015. Baseline is the date on which each patient's data, such as medical history, anthropometric, physiological, and biochemical data, were collected. A total of 1,327 individuals aged >20 years with type 2 diabetes whose medical history, i.e., regular treatment with benzodiazepines, antidepressants, and antipsychotics, was collected at first examination were eligible for inclusion in our analyses. Patients aged <20 years (n = 2) with type 1 diabetes (n = 16) and without medication information (n = 24) were ineligible for inclusion. Additionally, patients whose HGS could not be measured because of disabilities, such as cerebral infarction sequelae (n = 3), were also excluded (Figure 1). The PD patient group was defined as follows (1): Patients who were prescribed at least one PD (benzodiazepines, antidepressants, and antipsychotics) at the first examination during the study period; (2) Patients who continuously received PD and confirmed medication adherence during the study period. Patients who were not prescribed PD at the start of follow-up did not receive any new PD during the course of the study.

The study protocol was approved by the Medical Ethics Committee of the National Center for Global Health and Medicine (Reference No. NCGM-G-002052), and the study was performed in accordance with the Declaration of Helsinki.

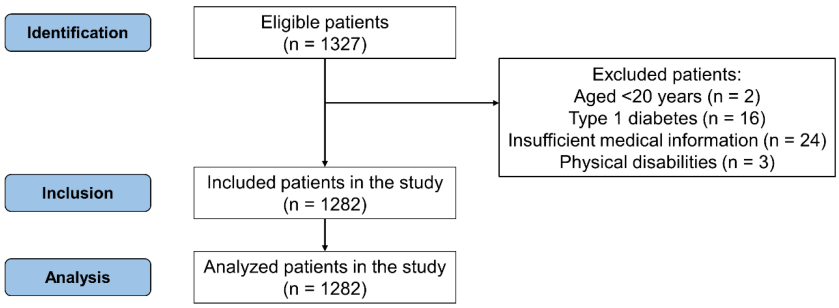

FIGURE 1
STROBE flow chart.

2.2 Study procedures

At the first clinical visit, patients were instructed to consume a calorie-restricted diet of 25–30 kcal/kg (ideal body weight) each day by certified nutritional educators as diet therapy for diabetes and to continue the diet during the study period. The dietary adherence of patients was confirmed on every consultation day on a monthly basis. All patients were evaluated and followed up until death or at the end of follow-up in May 2016. At the end of the follow-up, the information on hospitalization was collected from medical record review. Next, the number of hospitalizations was calculated in all subjects, and hospitalization for two or more times was defined as repeated hospitalization. In other words, repeated hospitalization refers to any hospitalization that occurred after the initial hospitalization during the study period.

2.3 Anthropometric and physiological measurements

Participants' height was measured using a rigid stadiometer (TTM stadiometer; Tsutsumi Co., Ltd., Tokyo, Japan). Their weights were measured using calibrated scales (AD-6107NW; A&D Medical Co., Ltd., Tokyo, Japan). Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the body height in meters. Waist circumference was measured with the participant in a standing position at the level of the umbilicus at the end of exhalation. HGS was measured twice using a Smedley analog hand dynamometer (No. 04125; MIS, Tokyo, Japan) using both hands in a standing position. We used the average HGS in kilograms in our final analyses. Blood pressure was measured with the participant in a seated position using an automatic sphygmomanometer (HBP-9020; Omron Co., Ltd, Tokyo, Japan).

2.4 History taking and physical activity assessment

To collect participants' baseline characteristics, trained technicians at the Clinical Research Center of the National Center for Global Health and Medicine at Kohnodai Hospital asked participants at the outpatient clinic about their physical activity levels, smoking and drinking habits, sleep duration, and medication use. The Brinkman index (number of cigarettes per day multiplied by the number of years) was calculated to quantify patients' smoking habits (25). Using patients' regular exercise habits, we calculated the exercise time per day based on exercise sessions per day × exercise duration per session.

2.5 Blood assessments

Blood samples were taken from the antecubital vein at the enrolment when HGS was measured. We measured plasma hemoglobin A1c (HbA1c) by high-performance liquid chromatography (HA-8180; Arkray, Tokyo, Japan). We calculated estimated glomerular filtration rate (eGFR) using the revised equation adjusted for the Japanese population (26).

2.6 Sample size

Sample size calculation was performed using G*Power (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). Our sample size had sufficient power to detect statistical significance (Supplementary File).

2.7 Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD). Categorical variables were expressed as numbers and patient groups compared using $\chi 2$ test. Student's t test or the Mann–Whitney test, depending on whether the variables followed normal or nonnormal distribution, was performed to detect significant differences between patients treated with PD and those treated without PD, as appropriate. Additionally, the relationship between the number of hospitalizations and HGS (in kilograms) was assessed using Spearman's rank correlation coefficient. We also compared patient outcomes i.e., hospitalizations, CV events, and deaths for patients treated with and without PD before and after propensity score matching using χ^2 tests.

A propensity score-matched analysis was performed to balance the characteristics of subjects at baseline between groups. Covariates were age, gender, BMI, alcohol consumption, exercise time, sleep duration, systolic blood pressure, and HbA1c levels. Based on the propensity score, PD users were matched to non-PD users by the nearest neighbor matching that is based on the greedy matching algorithm at a 1:1 ratio to create a propensity score-matched cohort (27). Subjects were matched based on the logit of the propensity score using a caliper width of 0.2 of SD. Standardized differences in each variable were calculated to confirm the balance between groups. In addition, the c-statistic for evaluating the goodness of fit was calculated. Subjects were then compared based on number of hospitalizations, CV events, and deaths.

Subsequently, Cox proportional hazard regression analysis was performed to assess the independent associations of mortality, CV events, and hospitalization with the use of PD in propensity score matched cohorts. Furthermore, multiple regression analysis was performed to assess relationship between hospitalization and HGS and use of PD.

P values of <0.05 determined by performing a two-sided test were considered statistically significance. Statistical analyses were performed using SPSS version 25 (IBM Co., Ltd., Chicago, IL).

3 Results

3.1 Participant characteristics prior to propensity score matching

This study enrolled 1,282 patients (709 men and 573 women) with type 2 diabetes. Of these, 379 (29.6%) patients were treated with PD, whereas 903 (70.4%) patients did not receive PD. A total of 314 patients (24.5%) received benzodiazepines, antidepressants, and/or antipsychotics; 175 (13.7%) received benzodiazepines; 93 (7.3%) received antidepressants; and 168 received antipsychotics (13.1%). The mean age and BMI of patients treated with PD were 60.1 ± 14.4) years and 26.9 ± 6 kg/m2, respectively. Patients with PD consume more alcohol (14.5 ± 26.7 g/day), engage in less exercise (9.5 ± 33.1 min/day), and sleep longer (7.8 ± 2.1 hours) compared to patients without PD. Additionally, patients with PD had lower systolic blood pressure (129.2 ± 18.5 mmHg), HbA1c levels (7.1 ± 1.4%), and HGS (22.3 ± 9.7 kg) compared to those without PD. Patients' characteristics are listed in Supplementary Table 1.

Age, duration since diagnosis of diabetes, alcohol consumption, exercise time, systolic blood pressure, HbA1c, and HGS were lower in patients treated with PD than in those treated without PD. In contrast, BMI, sleep duration, and eGFR were higher in patients treated with PD. Patient groups did not differ by smoking status and diastolic blood pressure.

3.2 Participant characteristics after propensity score matching

After a propensity score-matched analysis, two groups of 254 well-matched patients were generated. The c-statistic was 0.717 (95% confidence interval [CI], 0.683–0.750), suggesting that the performance of the propensity score-matched model was acceptable. Of these, 76 patients (29.9%) received benzodiazepines only; 27 patients (10.6%) received antidepressants only; and 44 patients received antipsychotics (17.3%) only. Patient's characteristics at baseline were balanced (Table 1); however, HGS was still lower in patients treated with PD that in those treated without PD.

TABLE 1 Characteristics of patients with or without psychotropic drugs in the matched cohort.

Characteristics	With psychotropic drugs	Without psychotropic drugs	p	Standardized difference
N	254	254	–	–
Age (years)	60.1 (14.1)	59.7 (14.9)	0.79	0.024
Gender (male/female)	129/125	129/125	1	<0.001
BMI (kg/m^2)	26.3 (5.9)	26.4 (6.2)	0.84	0.018
Duration of diabetes (years)	10.5 (10.5)	9.3 (10.3)	0.21	0.112
Smoking habits (Brinkman index)	298.5 (441.1)	287.1 (557.1)	0.8	0.023
Drinking habits (g/day in ethanol consumption)	17.6 (30.2)	19.2 (31.2)	0.54	0.055
Exercise time (min/day)	9.5 (36.2)	8.6 (26.1)	0.75	0.028
Sleep duration (h)	7.5 (2.1)	7.5 (1.7)	0.98	0.003
Systolic blood pressure (mmHg)	130.4 (17.7)	131.1 (21.2)	0.68	0.036
Diastolic blood pressure (mmHg)	74 (13.6)	74.8 (14.4)	0.53	0.056
HbA1c (%)	7.4 (1.6)	7.4 (1.6)	0.96	0.005
eGFR (mL/min/1.73m^2)	76.1 (22.3)	76 (23.9)	0.98	0.003
Handgrip strength (kg)	22.7 (9.3)	25.1 (10.2)	0.006	0.243

Data are represented as the mean value (SD) except for the number of subjects and sex. BMI, body mass index; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

3.3 Patient outcomes

During a mean follow-up of 861 ± 265 days, 9 patients (1.8%) died, 4 (0.8%) experienced CV events, and 336 (66.1%) were admitted to our hospital in the matched cohort. All deceased patients had one or more hospitalizations during the study period. Among the PD group, 6 patients died, one experienced CV events and 119 were admitted. The total number of hospitalizations was 482. Of these, 185 (38.4%) were in the Diabetes and Endocrinology ward, 81 (16.8%) were in the Surgery ward, 55 (11.4%) were in the Internal Medicine ward, 34 (7.1%) were in the Hepatology ward, 27 (5.6%) were in the Gastroenterology ward, 24 (5.0%) were in the Ophthalmology ward, and 40 (8.3%) were in the Psychiatry ward. No significant difference in hospitalization was observed between groups; however, the number of patients treated with PD who were admitted to our hospital more than once was significantly higher than those treated without PD (Table 2).

Moreover, Cox proportional hazard regression analysis confirmed the association of repeated hospitalizations (three or more times) with the use of PD (hazard ratio [HR] = 2.138; 95% CI, 1.144–3.995, p = 0.017), while there are no significant associations between the use of PD and all-cause mortality and CV events (Table 3).

There is a negative correlation between HGS and the number of hospitalizations (r = −0.143, p = 0.013) (Figure 2). Furthermore, multiple regression analysis identified a positive association between repeated hospitalizations (three or more times) and the use of PD (β = 0.119, p = 0.007) (Table 4).

4 Discussion

The main aim of this study was to examine the association of PD use with HGS and hospitalization in patients with type 2 diabetes. We demonstrated that PD users had lower HGS and more hospitalizations in a type 2 diabetes population than non-PD users. To the best of our knowledge, this study is the first to demonstrate that patients with type 2 diabetes receiving PD have decreased HGS, and such medication is associated with repeated hospitalizations in patients with type 2 diabetes.

No significant association between the use of PD and all-cause mortality was observed in this study; however, hospitalization and death share a commonality in indicating a decline in physical function. The average number of hospitalizations was higher in deceased patients than in surviving patients (3.44 ± 4.1 times vs. 0.88 ± 1.78 times, p <0.001 by Mann-Whitney U test). The number of repeated hospitalizations was also higher in deceased patients than in surviving patients (two or more times; p = 0.001; three or more times; p = 0.006 by χ^2 test). In this study, six out of nine deceased patients were treated with PD, suggesting that the inappropriate use of PD could cause serious harm to physical health.

4.1 Psychotropic drugs and skeletal muscle

Cross-sectional studies have shown that female patients with depressive or anxiety disorders had lower HGS (23) and patients with schizophrenia have more impairments in muscular strength, endurance, and flexibility compared with healthy controls (28). In addition, higher antipsychotic dosages were associated with poor physical function (28), and benzodiazepines were found to increase the risk of fall by muscle relaxant effect in older adults (29). The findings of previous studies suggest that psychotropic medication decreases muscle strength and physical fitness.

Although the causal relationship between physical function and psychotropic medication is unknown, benzodiazepines, antidepressants, and antipsychotics may induce muscle weakness and increase the risk of hospitalization. Recently, Sandvik et al. (30) reported that the use of PD was significantly associated with reduced handgrip strength in older hospitalized patients.

We cannot reveal the mechanism underlying the unfavorable impact of PD on muscle strength and physical function based on the findings of this study alone; however, PDs have the possibility of damaging skeletal muscle. PDs have a variety of adverse health effects, such as dizziness, drowsiness, unconsciousness, fatigue, and sleep disturbances. In addition, benzodiazepines are well known as having skeletal muscle relaxant effects (31). Although the underlying mechanism is unclear, use of antipsychotics is associated with the elevation of creatinine kinase and rhabdomyolysis (32). Furthermore, a benzodiazepine, namely, diazepam that enhances the activity of the $GABA_A$ receptors increases muscle sympathetic nerve activity and blood pressure during handgrip exercise in humans (33). Sympathetic nerve and arterial blood pressure responses to exercise is exaggerated in type 2 diabetes (34); thus, patients with type 2 diabetes might be prone to adverse effects of benzodiazepines. Such sympathetic nervous

TABLE 2 Comparison of health outcomes between patients with or without psychotropic drugs in the full and matched cohorts.

	Full cohort			Propensity score matched cohort		
Outcomes	With psychotropic drugs	Without psychotropic drugs	p	With psychotropic drugs	Without psychotropic drugs	p
Hospitalizations	168	389	0.71	119	117	0.93
Repeated hospitalizations	75	149	0.17	54	36	0.048
Cardiovascular events	2	12	0.25	1	3	0.62
Deaths	8	12	0.33	6	3	0.50

TABLE 3 Cox proportional hazard regression analysis for evaluating the associations of the use of psychotropic drugs with all-cause mortality, cardiovascular events, hospitalization, and repeated hospitalizations in patients with type 2 diabetes.

	All-cause mortality			CV events			Hospitalization (once)			Repeated hospitalization (two or more times)			Repeated hospitalization (three or more times)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Use of PD	1.814	0.452–7.277	0.4	0.93	0.72–1.2	0.58	0.31	0.032–3.005	0.31	1.366	0.896–2.083	0.15	2.138	1.144–3.995	0.017

CV, cardiovascular disease; HR, hazard ratio; CI, confidence interval; PD, psychotropic drugs.

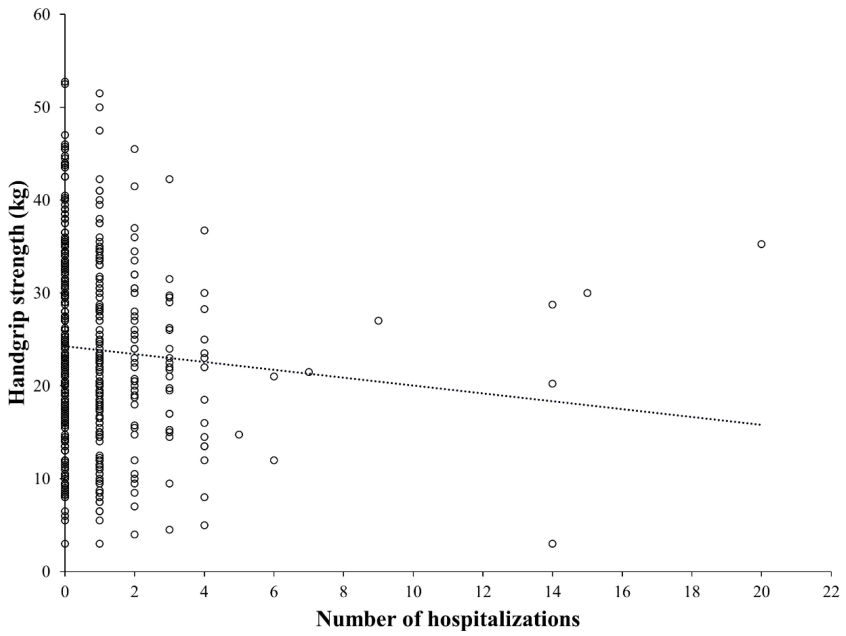

FIGURE 2
Correlation coefficient between handgrip strength and number of hospitalizations.

TABLE 4 Multiple regression analysis for evaluating the associations of the use of psychotropic drugs with hospitalization and repeated hospitalizations in patients with type 2 diabetes.

	Hospitalization (once)		Repeated hospitalizations (two or more times)		Repeated hospitalizations (three or more times)	
	β	p	β	p	β	p
Psychotropic drugs	−0.01	0.82	0.083	0.062	0.119	0.007
Handgrip strength	−0.15	0.001	−0.079	0.078	−0.082	0.065

dysfunction decreases skeletal muscle blood flow, which might cause muscle weakness (35).

4.2 Hospitalization due to the use of psychotropic drugs

To emphasize, few studies have examined the association between PD and hospitalization in patients with diabetes. An observational cohort study in a nursing facility reported that psychotropic and psychoactive drugs were associated with an increase in the rate of hospitalization; however, the reasons for hospitalization were various, and how such drugs affect the risk of hospitalization was not clarified (36). However, hypoglycemia may also be associated with reduced physical fitness, which results in the increased risk of hospitalization in patients with PD. Indeed, the use of antipsychotics is significantly associated with an increased risk of hypoglycemia in older adults (37). Severe hypoglycemia is strongly associated with all-cause mortality (HR = 2.69; 95% CI, 1.97 to 3.67), cardiovascular mortality (HR = 2.68; 95% CI, 1.72 to 4.19), and other health outcomes, including cancer and

respiratory and digestive diseases (38). Ogama et al. (39) reported that glucose fluctuations were independently and significantly associated with low HGS and muscle mass after adjusting for HbA1c levels. Ørngreen et al. (40) showed that decreased muscle mass could increase the risk of hypoglycemia in patients with neuromuscular disease. Skeletal muscle is an important source of gluconeogenesis in the fasting state and plays a crucial role in the regulation of glucose homeostasis (41). In this study, patients with PD might have experienced hypoglycemia due to decreased muscle fitness, resulting in some impairment of physical function and hospitalizations. However, we did not investigate whether study participants experienced hypoglycemia during the study period. Therefore, further investigations are warranted.

4.3 Limitations

Some limitations need to be addressed in the present study. First, we enrolled subjects who regularly received psychotropic medications; however, we did not investigate whether they were diagnosed with mental disorders, such as schizophrenia, depression, bipolar, and anxiety disorder. Thus, our findings cannot refer to the association of mental disorders with hospitalization in patients with type 2 diabetes. However, the number of patients admitted to the psychiatric ward was small (n = 16) during the 3-year follow-up, suggesting that the number of patients with severe mental disorders was relatively few in this study cohort. However, this issue is the most critical when assessing the effect of PD other than the mental illness itself. Further studies which examine the relationship of health outcomes with the use of PD and the existence of mental disorders separately are required. Second, the matched cohort is limited by small sample size and relatively short follow-up period to identify the significant difference in CV events and deaths between groups and limited generalizability. Considering that psychiatric disorders are common in patients with diabetes (42), multi-institutional or population-based studies may be required to obtain a larger cohort. Third, we did not investigate detailed causes of hospitalizations (e.g., name of disease, severity of disease); therefore, how the use of PD was associated with hospitalization is unknown. Finally, we grouped benzodiazepines, antidepressants, and antipsychotics together as PD in this study; however, each drug class should be investigated separately in future studies. Each drug has different physical and mental effects depending on the type of drug. Not all PDs, but second-generation antipsychotics, cause weight gain and reduce insulin sensitivity and glucose tolerance, which may lead to the development of type 2 diabetes (43). Antidepressants may exert a cardioprotective effect and reduce the risk of CV events (18). In this study, 27 patients took only antidepressants, which could have possibly affected the study results. Despite these limitations, our findings suggest that the use of PD leads to unfavorable health outcomes in patients with type 2 diabetes.

4.4 Suggestions for future studies

Randomized controlled trials (RCTs) are considered the gold standard in evidence-based medicine research. However, there are situations where conducting such trials may not be feasible or ethical, necessitating the reliance on observational studies. It is unethical to investigate the effects of PD on hard endpoints, such as death or CV events, in patients who require medication through RCTs. In this context, propensity score matching, as used in this study, is a practical method for estimating causal effects in observational studies (44). Nevertheless, there may still be unknown and unmeasured confounding factors, despite the use of appropriate methods. Therefore, future studies should incorporate additional information about study participants, including the presence or absence of mental disorders, detailed disease conditions, educational level, socioeconomic status, and genetic information. For instance, pharmacogenetic variants have a significant impact on the metabolism of PD, and genetic testing is considered crucial in determining whether the use of PD is toxic or therapeutic for patients (45). Furthermore, the interactions between PDs should also be taken into account, as a high number of PD interactions can result in severe health issues in clinical practice (46). Ideally, researchers should examine both the individual and interaction effects of PD on health outcomes. Well-designed future studies of this nature are warranted.

In conclusion, the use of PD could increase the risk of repeated hospitalizations in patients with type 2 diabetes. An increase skeletal muscle strength may reduce the risk of hospitalization in patients treated with PD. Our findings suggest that clinicians should judiciously prescribe PD to patients with type 2 diabetes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Medical Ethics Committee of the National Center for Global Health and Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HH conducted the study, performed data analyses, drafted and revised the manuscript. HY critically reviewed the manuscript and the scientific interpretations of study results. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcdhc.2023.1181998/full#supplementary-material

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Cardiovascular adverse reactions associated with escitalopram in patients with underlying cardiovascular diseases: a systematic review and meta-analysis

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Background: Despite the anticipated efficacy of escitalopram in treating depression and anxiety in individuals with preexisting cardiovascular conditions, persistent concerns regarding its adverse effects have emerged. In this systematic review, we aimed to evaluate the cardiovascular safety profile of escitalopram compared with that of placebo in patients with underlying cardiovascular disease.

Methods: We used a predefined search strategy in PubMed, Cochrane Central Register of Controlled Trials, Embase, International Clinical Trials Registry Platform, and ClinicalTrials.gov to identify studies evaluating adverse cardiovascular reactions to escitalopram in patients with underlying cardiovascular disease. Randomized controlled trials (RCTs) that provided results on cardiovascular safety outcomes were included. Two independent reviewers screened the abstracts and full texts of the individual studies. The risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: The primary outcomes were the frequency of major adverse cardiovascular events (MACE), QTc prolongation, and discontinuation of study medication. We identified 5 RCTs with 773 participants who met the inclusion criteria. Escitalopram was not associated with significantly increased risk of MACE (risk ratio [RR] = 1.85; 95% confidence interval [CI] 0.80 to 4.26; I^2 0%; 5 RCTs; n = 773, moderate certainty of evidence), discontinuation of study medication (RR = 1.03; 95% CI 0.84–1.26; I^2 0%; 5 RCTs; n = 773, low certainty of evidence), and QTc prolongation (RR = 1.20; 95% CI 0.76–1.90; I^2 0%; 4 RCTs; n = 646, low certainty of evidence).

Conclusion: Escitalopram does not significantly increase the risk of cardiovascular adverse reactions compared with placebo in patients with underlying cardiovascular disease. However, the presence of wide CIs and the limited number

of included studies highlight the need for further studies with larger sample sizes to enhance the precision and reliability of these findings.

Systematic review registration: International Prospective Register of Systematic Reviews [CRD42022298181].

KEYWORDS

escitalopram, cardiovascular disease, major adverse cardiovascular events, systematic review, meta-analysis

1. Introduction

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for the treatment of psychiatric disorders such as major depressive, generalized anxiety, and obsessive-compulsive disorders (1). It was introduced in US market in 2002 and became available in a generic form in 2012 (1, 2). Its cost has significantly decreased since it became generic, resulting in increased global availability and improved cost-effectiveness. According to data from 2020, escitalopram is ranked the 15th most commonly prescribed medication in the United States (2).

Although escitalopram has been widely used and is generally considered safe, concerns have emerged regarding its potential for adverse cardiovascular reactions, specifically QT interval prolongation and risk of torsade de pointes. In 2011, the United Kingdom Medicines and Healthcare products Regulatory Agency issued a safety warnings highlighting the increased risk of QTc prolongation and cardiac outcomes associated with the use of escitalopram (3). An *in vitro* study demonstrated that escitalopram had the potential to delay ventricular repolarization, prolong QT intervals, and increase the risk of torsade de pointes by directly blocking potassium-hERG channels in cardiomyocytes (4). Additionally, a randomized controlled trial (RCT) conducted in 2016 indicated that the use of escitalopram might increase the risk of QTc prolongation in healthy human volunteers, leading to potentially fatal arrhythmias (5).

Furthermore, there have been reports indicating that depression and anxiety may be independently associated with poor prognoses in patients with cardiovascular diseases. Anxiety is associated with the onset and progression of cardiac disease and adverse cardiovascular outcomes, including mortality (6). Similarly, depression is associated with increased mortality, excess disability, higher health care costs, and reduced quality of life in patients with cardiovascular diseases (7). Despite the anticipated efficacy of escitalopram in the treatment of depression and anxiety in individuals with preexisting cardiovascular conditions, there are ongoing concerns regarding its potential adverse effects. Nevertheless, currently, there is a lack of comprehensive systematic reviews and meta-analyses specifically examining the risk-benefit balance assessment of escitalopram administration across all indications for patients with underlying cardiovascular diseases.

Thus, this systematic review and meta-analysis aimed to evaluate the risk-benefit balance of escitalopram treatment in patients with underlying cardiovascular disease. This assessment included quantification of the frequency and severity of adverse cardiovascular reactions and evaluation of the improvement of depressive or anxiety symptoms associated with escitalopram administration compared to those after using placebo in RCTs, particularly within the subgroup of patients with pre-existing cardiovascular diseases. By examining the available evidence, we aimed to provide a comprehensive and up-to-date evaluation of the cardiovascular safety profile and the impact on depressive or anxiety symptoms in individuals with underlying cardiovascular diseases who would benefit from escitalopram treatment. This evaluation may support clinical decision-making regarding the prescription of escitalopram for individuals experiencing anxiety or depressive symptoms within this specific patient population, potentially improving overall patient outcomes.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42022298181).

2.1. Inclusion and exclusion criteria

Placebo-controlled RCTs involving participants diagnosed with underlying heart disease by healthcare professionals, regardless of underlying psychiatric disorders, were included. No restrictions were imposed on age, sex, ethnicity, or language. The intervention included escitalopram monotherapy, with no limitations on dose, frequency, or treatment duration. Patients taking cardiovascular medication such as antiplatelets, anticoagulants, and beta-blockers were included because they were necessary for the treatment of underlying cardiovascular disease. Interventions involving other antidepressants, antipsychotics, or electroconvulsive therapies were excluded.

2.2. Outcomes

The primary outcomes were major adverse cardiovascular events (MACE), QTc prolongation, and discontinuation of study medication. MACE was defined as a composite of all-cause mortality, myocardial infarction (MI), and percutaneous coronary intervention (9). The secondary outcomes were all-cause mortality, cardiac death, nonfatal MI, all-cause hospitalization, acute coronary syndrome, congestive heart failure, arrhythmia, chest pain, palpitation, hypertension, hypotension, syncope, depressive symptoms, and anxiety symptoms.

2.3. Search methods

We performed a comprehensive literature search on PubMed (02/12/2022), Cochrane Central Register of Controlled Trials (02/23/2022), Embase (12/16/2021), World Health Organization International Clinical Trials Registry Platform (02/23/2022), and ClinicalTrials.gov (02/23/2022) to identify relevant studies. We applied no search restrictions on the date, language, or publication status. The search strategy for each database is included in the Supplementary Table S1.

2.4. Selection of studies and data extraction

The search results that met the inclusion criteria were extracted from the databases and systematically managed using the review management software, Rayyan (10). Within the program, duplicate entries were identified and excluded. Two authors independently assessed the titles and abstracts of the identified references; if considered relevant by at least one author, they were included in the second screening phase. We obtained and reviewed the full texts of the included studies using the same criteria applied in the first screening process. We included studies for which both reviewers agreed upon. In cases of disagreement, we consulted a third author to make a final decision. We conducted data extraction using the same approach used in the second screening process. We contacted the authors of the studies to obtain additional data or clarifications, if necessary.

2.5. Measurement of outcomes

We used a Mantel-Haenszel random-effects model to estimate the risk ratios (RRs) with their corresponding 95% confidence intervals (CIs) for dichotomous variables. For continuous variables, we calculated the standardized mean differences (SMDs) with their corresponding 95% CIs using inverse variance weighting.

2.6. Assessment of risk of bias

We assessed the risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (Figures 1, 2) (11). The risk-of-bias tool evaluates the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of reported results. We assigned each domain a rating of low risk of bias, some concerns, or high risk of bias.

2.7. Analysis

Heterogeneity was assessed using the I^2 statistic, with interpretation based on the Cochrane Handbook for Systematic Reviews of Interventions (0–40% may not be important; 30–60% may indicate moderate heterogeneity; 50–90% may indicate substantial heterogeneity; and 75–100% may indicate considerable heterogeneity) (12). If significant heterogeneity was observed, the source was further investigated. Specifically, sensitivity analysis was performed to assess the robustness of the results by excluding low-quality studies and studies with small sample sizes. Subgroup analysis was performed based on the proportion of female participants per trial, types of underlying cardiovascular diseases, and comorbid psychiatric disorders as potential moderators to examine potential heterogeneity and inconsistencies across the included studies based on participant characteristics. Statistical analyses were performed using the Review Manager software (version 5.4.1; Cochrane Collaboration).

The certainty of evidence for the primary outcomes was evaluated according to the Grading of Recommendations, Assessment, Development, and Evaluation rating (Supplementary Figure S12) (13).

3. Results

3.1. General description

A total of 4,160 records were identified in the literature search process. After removing duplicates, two independent researchers reviewed 3,547 titles and abstracts. In the case of any disagreements between the researchers, a third reviewer was consulted for resolution. Following a thorough examination, a consensus was reached, resulting in 144 potentially relevant records. These 144 records were subjected to a comprehensive full-text review. Ultimately, five studies met the eligibility criteria and were included in this systematic review, which included 43 records of relevant data. The entire process is shown in Figure 3, the PRISMA flowchart.

3.2. Characteristics of included studies

Table 1 summarizes the key characteristics of the included studies. All studies met the inclusion criteria and were RCTs conducted using a parallel-group design. Among these studies, one was a three-arm trial (14), whereas the others were two-arm trials. The mean sample size per arm was 75, with a range of 15–151 participants. The studies were conducted in various regions, with two participants recruited from North America (15, 16), one from South

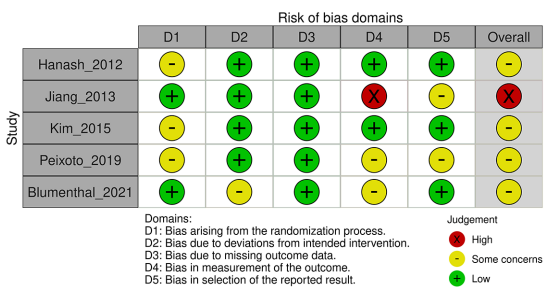

FIGURE 1
Risk of bias for major adverse cardiovascular events, discontinuation of study medication, and mortality according to version 2 of the Cochrane risk-of-bias tool.

America (14), one from Europe (17), and one from Asia (18). The proportion of female participants across the included studies ranged from 20.5 to 76.7%. The mean age of the participants varied from 57.2 to 64.8 years.

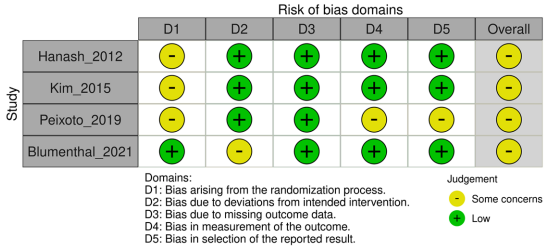

FIGURE 2
Risk of bias for QTc prolongation according to version 2 of the Cochrane risk-of-bias tool.

Regarding baseline cardiologic conditions, the left ventricular ejection fraction at baseline was 61.3% (18). For heart failure risk stratification, two studies used the New York Heart Association (NYHA) classification at baseline, yielding the following results: NYHA class I was reported in 92.9% (15) and 57.7% (17), whereas NYHA class II or III was observed in 7.1% (15) and 42.3% (17) of the participants. One of the studies excluded patients with an ejection fraction of <30% or decompensated heart failure, pacemaker dependence, or resting blood pressure of >200/120 mmHg (16). Similarly, another study excluded patients with congestive heart failure, chronic renal failure and/or acute myocardial infarction, and secondary hypertension (14).

3.3. Risk of bias

3.3.1. Bias arising from the randomization process

Three studies did not provide information on the allocation sequence concealment. However, two studies used block randomization (15) and sealed envelopes (16).

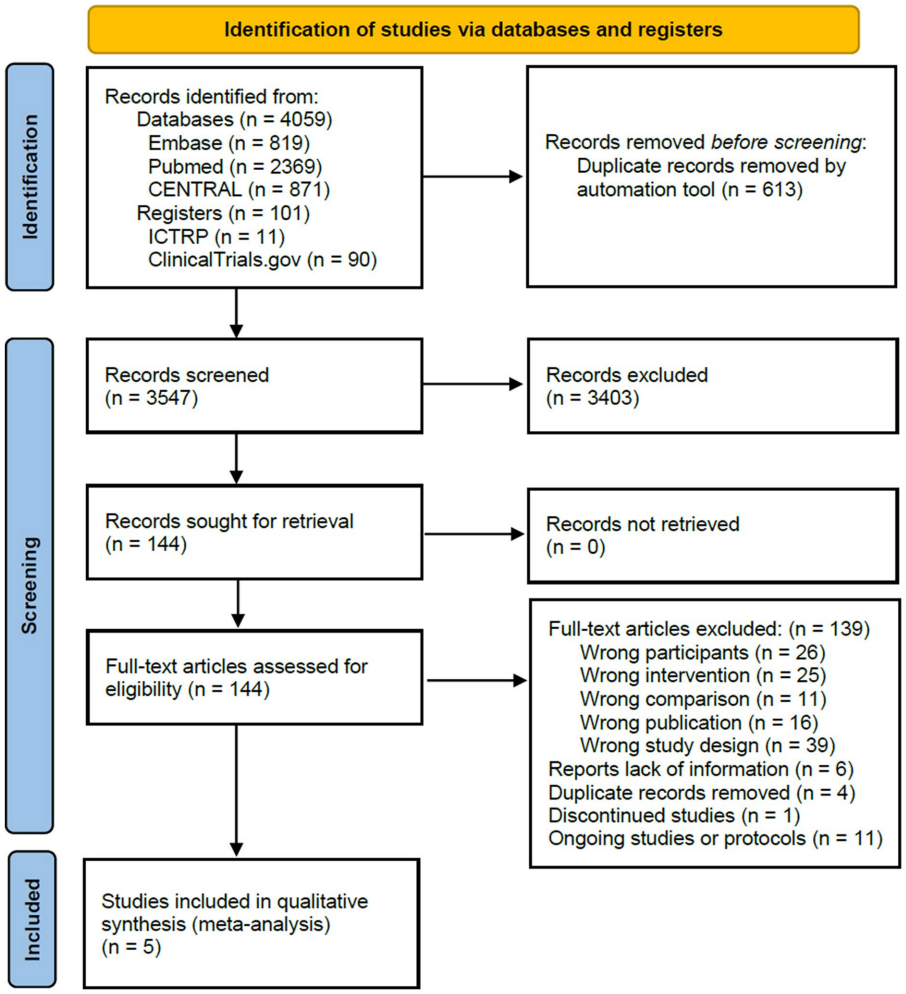

FIGURE 3
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of included studies.

TABLE 1 Characteristics of the included studies.

Author; year; citation; country; study design	*N*	Age mean ± SD	% female	Underlying cardiovascular disease	Comorbid psychiatric disorders	Intervention	Comparator	Time point for follow-up (weeks)	Dose of escitalopram (mg/day)
Peixoto et al. (14); South America; RCT	30	57.2 ± 6.65	76.7	Hypertension	Depressive disorder	Escitalopram	Passive placebo	8	Flexible doses of 10–20
Jiang et al. (15); North America; RCT	127	64.0 ± 10.7	20.5	Ischemic heart disease	None	Escitalopram	Passive placebo	6	Began at 5, with titration to 20 in 3 weeks
Blumenthal et al. (16); North America; RCT	128	64.6 ± 9.6	28.9	Ischemic heart disease	Anxiety disorder	Escitalopram Exercise	Passive placebo	12	Flexible doses of 10–20
Hanash et al. (17); Europe; RCT	240	64.8 ± 12.1	36.9	Ischemic heart disease	None	Escitalopram	Passive placebo	52	10
Kim et al. (18); Asia; RCT	300	59.3 ± 10.8	40.0	Ischemic heart disease	Depressive disorder	Escitalopram	Passive placebo	24	Flexible doses of 5–20

3.3.2. Bias due to deviations from intended interventions

Four studies were conducted using a double-blind design, in which both participants and outcome assessors were blinded of the treatment assignments. The percentage of dropouts was balanced between arms. In one study, the intervention involved exercise (16), which meant that participants were aware of their treatment assignments. As a result, there is the potential for deviations to arise owing to trial contexts. However, notably, the percentage of dropouts was balanced among the arms, which suggests that these deviations do not have a significant effect on the study outcomes.

3.3.3. Bias due to missing outcome data

In three of the studies, the percentage of missing outcome data exceeded 5%, but was balanced between each study arm (15, 17, 18). Although this suggests that the results are unlikely to be biased because of missing data, a high percentage of missing data may still affect the overall certainty of the evidence. Reasons for dropping out included lost to follow-up, withdrawing consent, experiencing adverse events, violating the study protocol, or lack of efficacy. In two other studies, the percentage of missing outcome data was <5% (14, 16).

3.3.4. Bias in measurement of the outcomes

The primary outcome was assessed using the incidence of MACE, QTc prolongation, and discontinuation of study medication. In three of the included studies (14–16), blinding of the outcome assessor to the treatment allocation was compromised in relation to both MACE and discontinuation of study medication. Moreover, in one of these studies (15), it remained uncertain whether knowledge of the intervention influenced the obtained results. Furthermore, in one of the studies (14) assessing QTc prolongation, the outcome assessor was not blinded to the treatment allocation.

3.3.5. Bias in selection of the reported result

All included studies were conducted in accordance with pre-specified protocols. In two studies, it was unclear whether the reported results were selected from multiple analyses of data or outcome measurements (14, 15).

3.4. Primary outcomes

3.4.1. Major adverse cardiovascular events

As illustrated in Figure 4, the risk of MACE was not significantly different between the escitalopram and placebo groups, as the 95% CI included 1 (RR = 1.85; 95% CI 0.80–4.26; 5 studies; 773 patients). Although an RR of 1.85 suggests a slightly higher risk of MACE in the escitalopram group, a CI that includes 1 indicates that the results are not statistically significant. The absence of heterogeneity among the studies reinforced the consistency of the findings ($I^2 = 0\%$; $\text{Tau}^2 = 0.00$).

The sensitivity analysis, excluding studies with a high risk of bias (RR = 1.79; 95% CI 0.75–4.24; 4 studies; 646 patients) or small sample sizes (RR = 1.79; 95% CI 0.75–4.24; 2 studies; 540 patients), did not result in a significant change to the risk of MACE between the escitalopram and placebo groups (Supplementary Figures S1, S2). Similarly, subgroup analysis examining the effects based on the types of underlying cardiovascular diseases and comorbid psychiatric disorders did not yield significant alterations in the risk of MACE between the escitalopram and

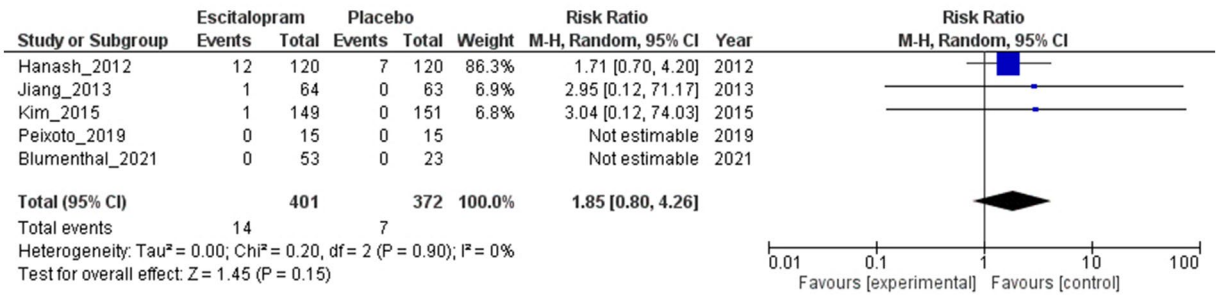

FIGURE 4
Escitalopram vs. placebo, major adverse cardiovascular events.

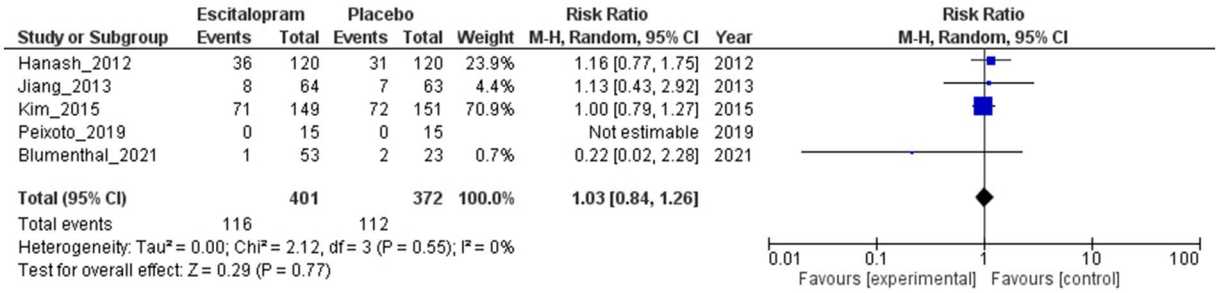

FIGURE 5
Escitalopram vs. placebo, discontinuation of study medication.

placebo groups (Supplementary Figures S3, S4). A subgroup analysis based on the proportion of female participants per trial could not be performed because of insufficient data availability.

3.4.2. Discontinuation of study medication

The results presented in Figure 5 indicated no statistically significant difference in the risk of discontinuation of study medication between the escitalopram- and placebo-treated groups. The RR was 1.03 (95% CI 0.84–1.26; 5 studies; 773 patients), indicating a slightly higher risk of discontinuation of study medication in the escitalopram group than in the placebo group, but this difference did not reach statistical significance as the 95% CI included the null value of 1.0. No heterogeneity was observed among the studies indicating consistency in the results ($I^2 = 0\%$; $\text{Tau}^2 = 0.00$).

The sensitivity analysis, excluding studies with a high risk of bias (RR = 1.03; 95% CI 0.83–1.28; 4 studies; 646 patients) or small sample sizes (RR = 1.04; 95% CI 0.85–1.27; 2 studies; 540 patients), did not result in a significant change to the risk of discontinuation of study medication between the escitalopram and placebo groups (Supplementary Figures S5, S6). Similarly, a subgroup analysis examining the effects based on the types of underlying cardiovascular diseases and comorbid psychiatric disorders did not yield significant alterations in the risk of discontinuation of the study medication between the escitalopram and placebo groups (Supplementary Figures S7, S8). A subgroup analysis based on the proportion of female participants per trial could not be performed because of insufficient data availability.

3.4.3. QTc prolongation

Figure 6 shows the results of the RR analysis of QTc prolongation in patients treated with escitalopram and placebo. The RR was 1.20 (95% CI 0.76–1.90; 4 studies; 646 patients), suggesting a slightly higher risk of QTc prolongation in the escitalopram group than in the placebo group, but the difference was not statistically significant as the 95% CI included the null value of 1.0. No heterogeneity was observed among the studies ($I^2 = 0\%$; $\text{Tau}^2 = 0.00$), indicating consistency of the findings.

The sensitivity analysis, excluding studies with small sample sizes (RR = 1.20; 95% CI 0.76 to 1.90; 2 studies; 540 patients) did not result in a significant change to the risk of QTc prolongation between the escitalopram and placebo groups (Supplementary Figure S9). However, a sensitivity analysis excluding studies with a high risk of bias could not be performed because all included studies were found to have a moderate risk of bias. Subgroup analyses examining the effects of the types of underlying cardiovascular diseases and comorbid psychiatric disorders did not yield significant alterations in the risk of QTc prolongation between the escitalopram and placebo groups (Supplementary Figures S10, S11). A subgroup analysis based on the proportion of female participants per trial could not be performed because of insufficient data availability.

3.5. Secondary outcomes

3.5.1. Mortality

Figure 7 illustrates the outcomes of the RR analysis, which assessed mortality in patients administered escitalopram compared with those who received a placebo. The RR estimate was 1.64 (95% CI 0.52 to 5.21; 5 studies; 773 patients). This finding suggests a slightly elevated risk of mortality in the escitalopram group. However, this result was not statistically significant because the 95% CI

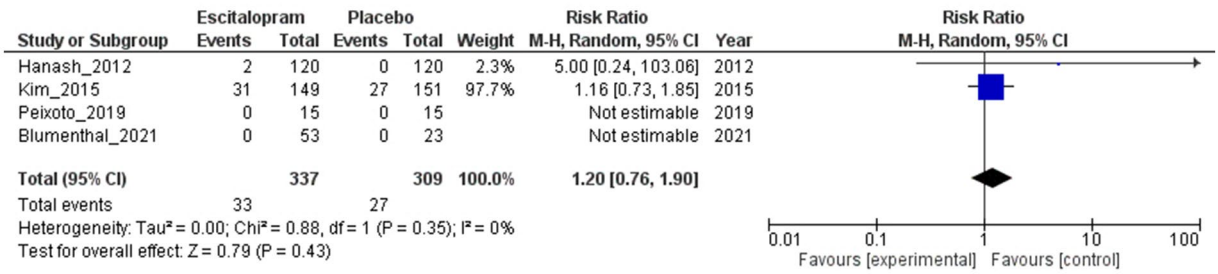

FIGURE 6
Escitalopram vs. placebo, QTc prolongation.

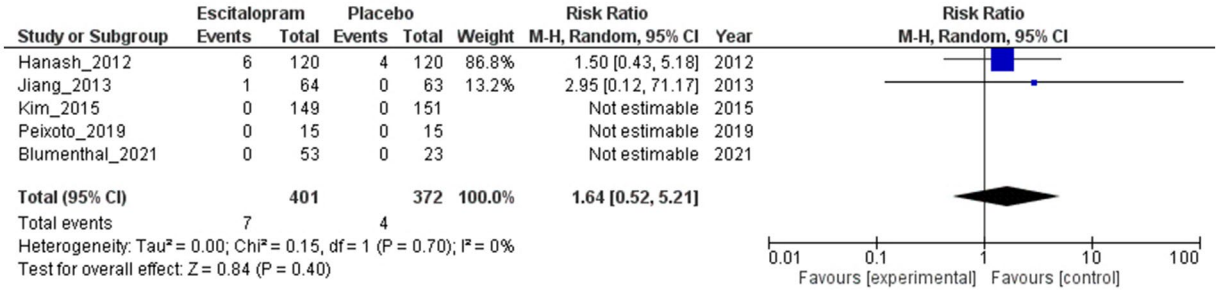

FIGURE 7
Escitalopram vs. placebo, mortality.

included the null value of 1.0. The analysis revealed no heterogeneity among the studies ($I^2 = 0\%$; $Tau^2 = 0.00$), indicating consistency in the results.

3.5.2. Cardiac death

Two studies evaluated the incidence of cardiac death after treatment. Neither study reported cardiac death (15, 18).

3.5.3. Nonfatal myocardial infarction

One study evaluated the occurrence of nonfatal MI after treatment. According to the study findings, no incidents of nonfatal MI were reported (16).

3.5.4. Acute coronary syndrome

Two studies assessed the incidence of acute coronary syndrome after treatment, and RR analysis was performed to compare the incidence between patients who received escitalopram and a placebo. Figure 8 presents the results of the RR for acute coronary syndrome between patients treated with escitalopram and a placebo. The RR was 1.14 (95% CI 0.34 to 3.76; 2 studies; 540 patients), suggesting a slightly higher risk of acute coronary syndrome in the escitalopram group than in the placebo group, but the difference was not statistically significant as the 95% CI includes the null value of 1.0. Moderate heterogeneity was observed between the studies indicating inconsistency in the results ($I^2 = 36\%$; $Tau^2 = 0.29$).

3.5.5. Depressive symptoms

Three studies assessed depressive symptoms after escitalopram treatment compared with placebo. Two studies used the Beck Depression Inventory (15, 16) and one study used the Montgomery-Asberg Depression Rating Scale (18) to assess the severity of depressive symptoms. An SMD analysis was performed to compare the severity of depressive symptoms between the two groups, and the results are shown in Figure 9. The analysis showed an estimated SMD of −0.29 (95% CI −0.65 to 0.08; 3 studies; 503 patients). However, substantial heterogeneity was observed among the studies indicating inconsistency in the results ($I^2 = 70\%$; $Tau^2 = 0.07$).

3.5.6. Anxiety symptoms

Three RCTs assessed anxiety symptoms after escitalopram treatment compared with placebo. The State–Trait Anxiety Inventory-State (15), Hamilton Anxiety Scale (16), and Hospital Anxiety and Depression Scale-Anxiety (18, 19) were used to assess the severity of the anxiety symptoms in each study. A meta-analysis using an SMD was performed to compare the severity of anxiety symptoms between the two groups, and the results are shown in Figure 10. The pooled analysis showed an estimated SMD of −0.45 (95% CI −0.89 to −0.00; 3 studies; 503 patients). Considerable heterogeneity was observed among the studies, indicating inconsistency in the results ($I^2 = 80\%$; $Tau^2 = 0.12$).

4. Discussion

4.1. Summary of main results

In this systematic review, we identified five RCTs with 773 participants, that evaluated the risk of MACE and discontinuation of study medication associated with the use of escitalopram in patients

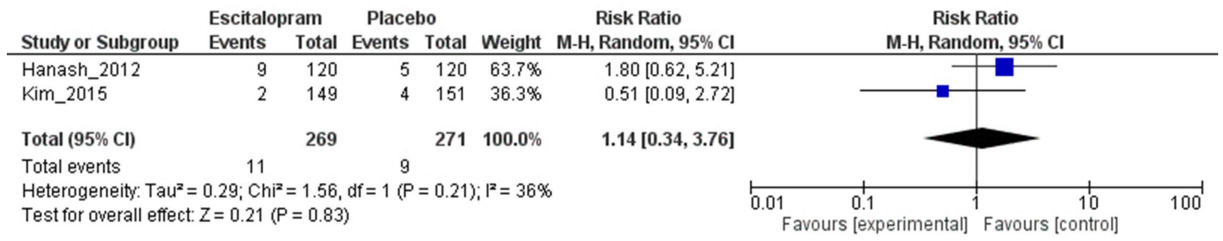

FIGURE 8
Escitalopram vs. placebo, acute coronary syndrome.

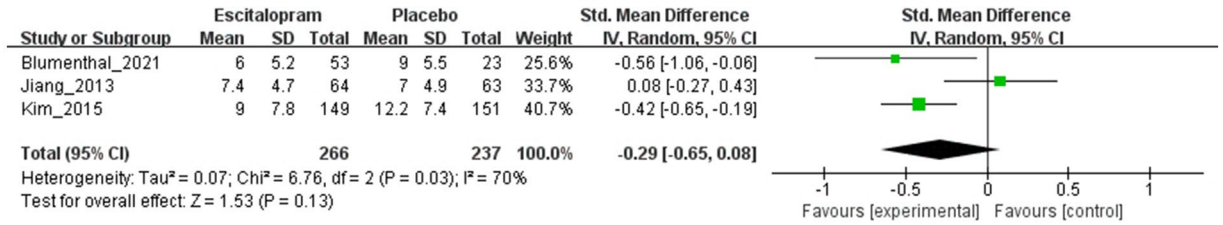

FIGURE 9
Escitalopram vs. placebo, post-treatment depressive symptoms.

with underlying heart disease. The moderate certainty of evidence indicated that the use of escitalopram did not significantly increase the risk of MACE compared with the placebo. However, caution is necessary because a wide CI implies considerable uncertainty in the estimate. Furthermore, the low certainty of evidence showed that the use of escitalopram did not significantly increase the risk of discontinuation of study medication compared with the placebo. These findings suggest that the rates of discontinuation of study medication are comparable between the two groups, implying that the use of escitalopram does not result in additional challenges regarding medication adherence.

Among these studies, four involving 646 participants specifically investigated the risk of QTc prolongation in patients with underlying heart diseases treated with escitalopram. The low certainty of evidence demonstrated that there was no significant increase in the risk of QTc prolongation when escitalopram was compared with the placebo. These results suggest that the risk of QTc prolongation is comparable between the two groups, indicating that escitalopram does not increase the risk of QTc prolongation in patients with underlying cardiovascular diseases. Heterogeneity was not observed in the primary outcomes.

Regarding secondary outcomes, escitalopram use in patients with underlying heart diseases did not significantly increase the risk of all-cause mortality or acute coronary syndrome. Two studies specifically evaluated the incidence of cardiac death and reported no cases of cardiac death. Additionally, a single study assessed the occurrence of nonfatal MI and found no reported incidents. These findings further support the notion that escitalopram does not increase the risk of adverse cardiovascular events leading to mortality.

Three studies assessed the effects of escitalopram treatment on depressive and anxiety symptoms compared with a placebo. In alignment with the findings from a previously published RCT in 2016 (20), conducted over an 18-month treatment period which reported no significant improvements in depressive symptoms when compared to a placebo among patients with chronic systolic heart failure and comorbid depression, our analysis revealed that escitalopram did not yield significant improvements in depressive symptoms when compared to a placebo among patients with underlying cardiovascular diseases. These consistent findings indicate the need for caution when considering the prescription of escitalopram within this specific patient population. However, a statistically significant trend toward reduced anxiety symptoms was identified in patients treated with escitalopram. These findings suggest that escitalopram may be effective in alleviating anxiety symptoms in patients with underlying cardiovascular diseases, highlighting the potential benefits of its use beyond cardiovascular safety. Nevertheless, the presence of substantial to considerable heterogeneity in post-treatment anxiety and depressive symptoms underscores the need to perform a meta-analysis that specifically focuses on individual psychiatric disorders to comprehensively evaluate the effects of escitalopram.

Based on the evidence obtained from this systematic review, the use of escitalopram in patients with underlying heart diseases does not significantly increase the risk of MACE, medication discontinuation, QTc prolongation, all-cause mortality, or acute coronary syndrome. The absence of observed heterogeneity in relation to the primary outcomes underscores the consistency and robustness of the findings and provides strong evidence for the cardiovascular safety of escitalopram in patients with underlying heart diseases. However, wide CIs in the estimates indicate a notable level of uncertainty, emphasizing the need for cautious interpretation of the results. Considering the relatively short follow-up duration of the included studies, which ranged from 6 to 52 weeks, additional studies with extended follow-up periods are required to improve evaluation, specifically concerning outcomes, such as MACE and overall

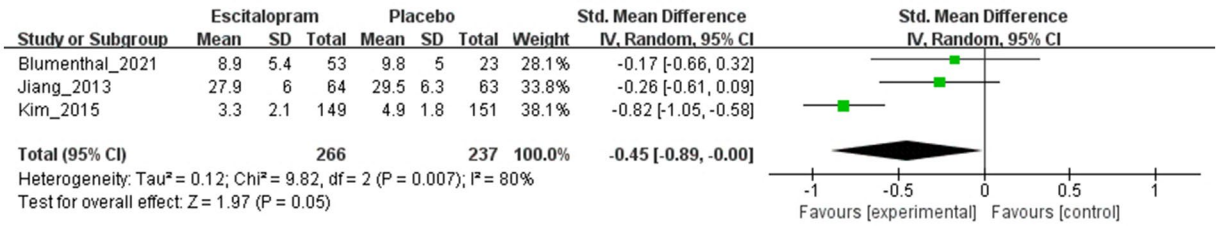

FIGURE 10
Escitalopram vs. placebo, post-treatment anxiety symptoms.

mortality. Overall, our findings indicate the potential safety of escitalopram in this patient population; however, additional studies are required to validate and strengthen these conclusions.

4.2. Overall completeness and applicability of evidence

We performed a meta-analysis based on our preregistered protocol to avoid selective reporting bias and ensure transparency. A literature search identified 3,547 records, which were subsequently screened and assessed for eligibility. The final analysis was performed using data from 43 records of five studies. The included studies were conducted in different regions including Asia, Europe, North America, and South America. This geographical diversity enhances the generalizability of our findings, allowing for a more comprehensive understanding of the topic across various populations.

The risk-of-bias assessment within the included studies revealed that some lacked adequate information on allocation sequence concealment, and there was uncertainty regarding the blinding of outcome assessors. These factors may introduce a potential risk of bias, although the studies utilized a double-blind design, and the percentage of dropouts was balanced between treatment arms. Although the effect of these biases is likely to be minimal, they should be acknowledged when interpreting the results.

The analysis of the SMD for depressive and anxiety symptoms across the included studies highlighted significant heterogeneity (15, 16, 18). In the context of depressive symptoms, a sensitivity analysis was performed, which excluded Jiang et al. study (Supplementary Figure S13) (15). This exclusion resulted in a reduction in the observed heterogeneity ($I^2 = 0\%$; $Tau^2 = 0.00$). and a statistically significant improvement in depressive symptoms (SMD −0.44; 95% CI −0.65 to −0.24; 2 studies; 376 patients). This analysis underscores the pivotal role of Jiang et al. study in driving the observed variability. Jiang et al. study reported no substantial improvement in depressive symptoms following escitalopram treatment, a contrast to the positive outcomes evident in both Kim et al. and Blumenthal et al. studies (16, 18), which indicated an amelioration of depressive symptoms after escitalopram administration. It is essential to acknowledge that Jiang et al. study had a shorter follow-up duration of 6 weeks than the other studies (12–24 weeks). Additionally, a distinguishing feature of Jiang et al. study was the absence of comorbid psychiatric disorders among participants, setting it apart from the other studies where participants exhibited comorbid depressive or anxiety disorders.

Shifting focus to the evaluation of anxiety symptoms, the inclusion of Kim et al. study introduced a source of heterogeneity into the analysis. The sensitivity analysis, involving the exclusion of Kim et al. study (18), yielded a reduction in the heterogeneity observed ($I^2 = 0\%$; $Tau^2 = 0.00$) (Supplementary Figure S14). Kim et al. study stood out because of its larger participant sample size and extended follow-up duration of 24 weeks. Their study included participants diagnosed with major depressive disorder as a comorbid psychiatric disorder, in contrast to the other studies that included participants either without comorbidities or with anxiety disorders. Additionally, the geographical diversity between Kim et al. study, conducted in Asia, and the other studies conducted in North America, adds an additional layer of complexity to the analysis. The potential influence of cultural, social, and environmental factors on treatment outcomes warrants consideration.

In light of the findings, it is important to interpret the results with caution. Although the analysis did not reveal a statistically significant reduction in depressive symptoms associated with escitalopram administration, it did demonstrate a statistically significant reduction in anxiety symptoms linked to escitalopram use. However, the heterogeneity observed can be attributed to a combination of factors, including variations in the study duration, participant characteristics, comorbid psychiatric conditions, and geographical locations. These factors should be weighed when interpreting and extrapolating the outcomes. The existence of diverse conditions among the study populations may have contributed to the observed heterogeneity, potentially impacting the treatment effects unveiled in the meta-analysis. Therefore, a comprehensive understanding of the multifaceted nature of the study populations is crucial when interpreting the results.

This systematic review has some limitations. The number of included studies was relatively small, and the sample sizes varied. The longest follow-up period in the included studies was 52 weeks. The primary and secondary outcomes of this systematic review did not include the risk of abnormal bleeding events. However, SSRI therapy may increase the risk of abnormal bleeding events (21). Additionally, there is evidence suggesting the risk of bleeding with concurrent use of SSRI and aspirin (hazard ratio 1.42; 95% CI 1.08–1.87) compared with aspirin monotherapy, which is commonly prescribed in patients with underlying cardiovascular disease (22). Consequently, the long-term safety and efficacy of escitalopram, as well as the risk of abnormal bleeding events in patients with underlying cardiovascular diseases remain unclear. These limitations indicate the need for caution when interpreting our findings and highlight the importance of further studies.

Despite these limitations, we conducted a comprehensive synthesis of the available evidence to provide valuable insights into the safety and potential benefits of escitalopram in patients with underlying heart diseases. These findings suggest that the use of escitalopram within a 52-week timeframe is relatively safe for managing depressive and anxiety symptoms in this patient population.

To address these limitations and provide more robust evidence, future studies should focus on larger sample sizes, longer follow-up periods, and examination of the impact of concurrent anticoagulant or antiplatelet therapy. This would allow for a more comprehensive assessment of the safety profile, long-term effects, and potential benefits of escitalopram in patients with underlying heart diseases.

4.3. Quality of the evidence

All included studies were RCTs conducted using a parallel-group design; one study was a three-arm trial, whereas the others were two-arm trials. The studies were conducted in various regions, and the proportion of female participants across the included studies ranged from 20.5 to 76.7%. The mean age of the participants varied from 57.2 to 64.8 years.

Three studies did not provide information on allocation sequence concealment, and three of the studies had a percentage of missing outcome data exceeding 5%. The primary outcome was assessed using the incidence of MACE, QTc prolongation, and discontinuation of study medication. In three of the studies, the outcome assessor was not blinded to the treatment allocation. In two of the studies, it was unclear whether the reported results were selected from multiple analyses of data or outcome measurements.

Based on these findings, the risk of MACE was comparable between the groups, suggesting that escitalopram does not increase the risk of MACE in patients with underlying heart diseases. However, a wide CI implied considerable uncertainty in the estimate, and the certainty of the evidence was moderate because of the imprecision of the results (Supplementary Figure S12). Furthermore, the results suggested no statistically significant difference in the risk of discontinuation of study medication and QTc prolongation between the groups treated with escitalopram and placebo, with the certainty of evidence being low owing to the imprecision and indirectness of the results (Supplementary Figure S12).

Although the included studies were RCTs conducted using a parallel-group design and the risk of bias was assessed and reported, the certainty of evidence in this systematic review was low to moderate owing to the imprecision and indirectness of the results and limitations in the methodology and reporting of some of the included studies.

4.4. Potential biases in the review process

The strengths of this systematic review include the rigorous methodology employed, which adhered to current methodological standards. The review involved a comprehensive and independent search of electronic databases, with data extraction, analysis, and risk of bias assessment performed by two authors. To ensure objectivity, two authors independently interpreted the risk of bias domains and minimized bias in the assessment process. Additionally, the review aimed to minimize selection and language bias by not imposing restrictions on age, sex, ethnicity, language, sample size, or geographic region during the review process.

However, our study only included published studies despite our efforts to screen unpublished trials based on our pre-planned search strategy. Moreover, our search strategy did not cover gray literature. This limitation introduces the potential for publication bias, which can lead to an overrepresentation of studies demonstrating favorable outcomes for escitalopram. Consequently, this may have introduced bias and influenced the overall findings of our review.

Our review exclusively included studies written in English; however, we did not impose language restrictions to prevent language bias. This limitation raises the possibility that a language bias may have influenced our results. Despite conducting a comprehensive literature search, it is possible that relevant studies in other languages were inadvertently missed.

4.5. Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the first systematic review to assess the safety and effectiveness of escitalopram in patients with underlying cardiovascular diseases. Our findings are consistent with those of a previously published systematic review in 2022 (23), which included 11 RCTs involving participants diagnosed with stroke, who were randomly assigned to receive either escitalopram or a placebo. No significant differences were observed in the cardiovascular adverse effects between patients with stroke receiving escitalopram and those assigned to the placebo group in this study. Our systematic review incorporated five RCTs involving participants diagnosed with either ischemic heart disease or hypertension, further bolstering the evidence for the cardiovascular safety of escitalopram across different types of underlying cardiovascular diseases. In addition, our analysis demonstrated a statistically significant reduction in anxiety symptoms associated with escitalopram.

In a recent systematic Cochrane review published in 2021 (24), which included 30 RCTs involving participants diagnosed with coronary artery disease and comorbid depressive disorder and incorporated various types of interventions, such as psychotherapy and pharmacotherapy, the review failed to provide systematic evidence regarding the cardiovascular safety of escitalopram. This limitation arises from the inclusion of only one trial (9, 18, 19, 25–28) that directly compared escitalopram with a placebo. In contrast, our systematic review, which also included the aforementioned trials (9, 18, 19, 25–28), provides substantial evidence supporting the safety of escitalopram in patients with underlying cardiovascular disease. This is attributed to our analysis of cardiac death outcomes, which were derived from one additional RCTs (15), and our assessment of overall mortality, which was based on five RCTs (14–18).

In a network meta-analysis of 15 RCTs (29) involving participants diagnosed with depressive disorder, and comparing the

cardiovascular safety of different SSRIs, escitalopram had significantly lower occurrence of cardiovascular side effects compared with paroxetine (odds ratio [OR] 0.37, 95% CI 0.14–0.77). Similarly, the findings indicated a lower risk of cardiovascular reactions to escitalopram compared with fluoxetine (OR 0.06, 95% CI 0.00 to 0.74). The authors concluded that treatment with escitalopram was associated with a lower risk of adverse cardiovascular reactions compared with other SSRIs. However, notably, the authors excluded patients with pre-existing cardiovascular diseases, which may have affected the evaluation of cardiovascular adverse reactions to escitalopram in patients with underlying cardiovascular diseases. Furthermore, the absence of a placebo group in this study made it challenging to quantify the risk of adverse reactions specifically attributed to escitalopram. To address these limitations, this systematic review employed a distinct approach. We exclusively included studies with designs involving placebo controls and patients diagnosed with underlying cardiovascular diseases. This deliberate methodology enabled us to accurately assess the risk of cardiovascular reactions relative to placebo in patients with underlying cardiovascular diseases. Consequently, our findings verified that escitalopram treatment was not associated with an increased risk of cardiovascular reactions in this patient population.

A prior comprehensive systematic review (30), which included six RCTs, six prospective studies, two cross-sectional studies, two pilot studies, one open-label study, and one secondary analysis involving participants diagnosed with heart failure and comorbid depressive disorder and incorporating various types of pharmacotherapy, including escitalopram, sertraline, and nefazodone, did not yield systematic evidence regarding the effectiveness and safety of escitalopram. This limitation arose from the fact that the findings were primarily based on one RCT (20) and two prospective studies (31, 32). The results of the RCT (20), which was excluded from our systematic review because of a lack of information about MACE and QTc prolongation, indicated that escitalopram treatment for a maximum of 24 months did not demonstrate a difference in depression severity compared with placebo, which aligns with the findings of our systematic review. However, our systematic review provided a more comprehensive and robust evaluation of the effect of escitalopram on depressive symptoms in this specific patient population. This is supported by our meta-analysis of these RCTs, which strengthens our conclusion regarding the effects of escitalopram on depressive symptoms.

In a prior meta-analysis (33), including two RCTs, two retrospective studies, and four prospective studies, participants diagnosed with heart failure were divided into antidepressant use and control groups for comparison. The findings revealed that the use of antidepressants was associated with an increased risk of all-cause mortality (RR 1.27; 95% CI 1.21–1.34) and cardiovascular mortality (RR 1.14; 95% CI 1.08–1.20). According to the 2021 European Society of Cardiology Guidelines on cardiovascular disease prevention in clinical practice, SSRIs are not recommended for patients with heart failure and major depression (34). Although we identified an RCT (20) that met our inclusion criteria and included patients with heart failure, it did not include the primary outcomes we targeted in our review, namely MACE and QT prolongation. Furthermore, the results of ongoing RCTs involving individuals with heart failure were not attainable for retrieval. Therefore, forthcoming RCTs focused on heart failure patients should incorporate assessments of MACE and QT prolongation. Caution is advised when applying our evidence to patients with heart failure, and further studies focusing specifically on this patient population are needed to make more precise recommendations.

In routine clinical practice, clinicians encounter a broad array of antidepressant options, necessitating substantial evidence to make optimal decisions for each patient. We anticipate that our findings will assume a pivotal role in guiding the prescription of escitalopram for individuals with underlying cardiovascular diseases experiencing anxiety or depressive symptoms. These results are expected to serve as a critical resource in shaping clinical guidelines and facilitating the collaborative decision-making process among patients, caregivers, and healthcare providers within everyday practice in this specific patient population. Future research endeavors should aim to expand upon our work by extending network meta-analysis techniques to integrate both aggregated and individual-patient data from clinical trials. This approach has the potential to predict personalized clinical outcomes, such as early treatment response or the occurrence of specific side effects.

5. Conclusion

Based on the available evidence from this systematic review, the use of escitalopram in patients with underlying heart diseases does not significantly increase the risk of MACE, discontinuation of study medication, or QTc prolongation compared with placebo. Additionally, escitalopram shows promise in reducing the severity of anxiety symptoms in this patient population. These results support the safe use of escitalopram as a treatment option for patients with underlying heart diseases. However, further studies are necessary to validate these findings and establish more robust evidence in this context. In each therapeutic attempt, the potential risks must be balanced against the benefits for the patient, considering the qualitative and quantitative effects of using a drug and the result to be expected if it is not administered.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

KK, HN, and HI conceptualized and designed the study. MK and YK developed the search strategies. KK, HN, HI, HA, SI, RS, TI, and MN independently screened the eligible studies. KK, HN, HI, HA, SI, and RS independently extracted the data from the included studies. KK performed the meta-analyses. HN and HI supervised all the phases of this review and resolved any disagreements to avoid errors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

HI has received honoraria for lectures from Otsuka Pharmaceutical and Viatris.

SI has received personal fees from Eisai, Janssen Pharmaceutical, Lundbeck, Meiji Seika Pharma, Otsuka Pharmaceutical, Sumitomo Pharma, and Takeda Pharmaceutical, and has received research/grant support from Eli Lilly.

IK has received honoraria from Boehringer Ingelheim, Eisai, Eli Lilly, Janssen Pharmaceutical, Meiji Seika Pharma, Mochida Pharmaceutical, Novartis Pharma, Otsuka Pharmaceutical, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, Tsumura, Viatris, and Yoshitomiyakuhin, and has received research/grant support from Asahi Kasei Pharma, Astellas, Daiichi Sankyo, Eisai, Eli Lilly, Mochida Pharmaceutical, Nihon Medi-Physics, Otsuka Pharmaceutical, Pfizer, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, and Tanabe Mitsubishi Pharma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1248397/full#supplementary-material

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Gender differences in spontaneous adverse event reports associated with zolpidem in South Korea, 2015–2019

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Study objectives: While zolpidem is considered as an example of a gender effect on drug response, there is insufficient evidence to reach a consensus. This study aimed to investigate gender differences in adverse events (AEs) of zolpidem.

Methods: We estimated the difference between the reporting odds ratios (RORs) calculated in gender subgroups for the AEs signals detected in data mining using 2015–2019 Korea voluntary adverse drug events reporting system (KAERS) data. Different reporting risk by gender was evaluated by using the log RORs being significantly different by gender at the 5% significance level and the 95% confidence intervals of the gender ROR.

Results: A total of 94 AE signals were detected. Among these, 35 signals showed significant disparities by gender at the 5% level or were detected only in one gender. When categorized by similarity of AEs, parasomnia including somnambulism and paroniria, and cardiovascular disorders including coronary thrombosis had higher reporting risks in women. Men were more likely to report cognitive disorders such as delirium, insomnia related disorders, and movement disorders. Among all AEs with gender differences in reporting risk, the difference in somnambulism was the most consistent and substantial.

Conclusion: For several AEs associated with zolpidem, gender-based reporting disparities were evident. Notably, women exhibited a higher susbeptibility to somnambulism, potentially serious adverse effects of zolpidem. This underscores the need for further investigation into the underlying factors influencing these gender-specific reporting patterns.

KEYWORDS

zolpidem, adverse event, gender difference, somnambulism, sleepwalking, voluntary adverse drug events reporting system

Abbreviations: ADR, adverse drug reaction; AE, Adverse event; ATC, Anatomical Therapeutic Chemical Classification System; BCPNN, Bayesian confidence propagation neural network; GABAA, γ-Aminobutyric acid type A; IC, Information component; IR, immediate release; KAERS, Korea voluntary adverse drug events reporting system; KIDS, Korea Institute of Drug Safety and Risk Management; MR, modified release; PRR, proportional reporting ratio; PT, preferred term; ROR, reporting odds ratio; WHO-ART, World Health Organization Adverse Reaction Terminology.

Introduction

Zolpidem is a major hypnotic agent that selectively targets the γ-aminobutyric acid type A (GABAA) receptor. Due to the short acting effect and general tolerability, it has been a preferred choice among prescribers and patients for treating insomnia (Olson, 2008). With the significant increase in the use of zolpidem, post-marketing studies and case reports have indicated rare but associated sleep-related complex behaviors, making it a key warning for this medication (Daley et al., 2011). Another specific issue for zolpidem is for its sex-related differences in pharmacokinetic and pharmacodynamic parameters leading to the US FDA issuing recommendations in 2013 to lower the initial dosage of Zolpidem for women (Communication FaDADS, 2023). For women, the FDA warned to reduce initial dosage of zolpidem to 5 mg of immediate release (IR) tablets, or 6.25 mg of modified release (MR) tablets (FDA FaDA, 2023).

However, there is an argument that these regulatory actions lack a confirmative clinical evidence (Greenblatt et al., 2000; Greenblatt et al., 2019; Yoon et al., 2021). According to a recent study evaluating gender effects on zolpidem through an analysis of data from an existing study, no gender-related difference in clinical efficacy or adverse reactions was demonstrated, although lower clearance of zolpidem in women than in men was apparent which could not be explained by body weight (Greenblatt et al., 2019). So far, no other country outside the United States, including Korea, has taken such a measure to reduce the initial dose of zolpidem in women.

Gender is rarely taken into account in the majority of mental health studies (Howard et al., 2017). For instance, a study found that less than 1% reported intention to analyze by gender among 768 trials of treatments for depression on ClinicalTrials.gov (Weinberger et al., 2010). Despite having several drawbacks, spontaneous adverse event (AE) reporting data is a valuable real-world data source for pharmacovigilance investigations (World Health Organization, 2002; Palleria et al., 2013). Even in research that used these data, gender was rarely taken into account and to our knowledge, no study using these data to examine the adverse effects of zolpidem focused on gender differences exists (BEN-HAMOU et al., 2011; Wong et al., 2017; Greenblatt et al., 2019).

As such, although zolpidem is cited as an example of a gender effect on drug response, there is no consensus in both regulatory authorities worldwide and healthcare professionals due to insufficient scientific evidence. This study aimed to explore gender differences in adverse effects related to zolpidem using Korea's voluntary adverse events reporting data.

Methods

Data source

The Korea Adverse Event Reporting System (KAERS) was retrospectively observed as the data source for the analysis, which covered the period between January 2015 and December 2019. The Korea Institute of Drug Safety and Risk Management (KIDS) established the automated AE reporting system known as KAERS in 2012. Both databases contain voluntarily submitted AE reports from consumers, healthcare professionals, 27 local pharmacovigilance centers, and marketing authorization holders, most of which are pharmaceutical firms. Reports from all types of reporters were included in the analysis. Each case contains data on the patient's age, sex, administration date of zolpidem, type, and symptom of AEs, and patient outcomes without identifying any particular individuals. The international drug monitoring program operated by the WHO-Uppsala Monitoring Center is compatible with the KAERS database. The Anatomical Therapeutic Chemical Classification System (ATC Code) was utilized to record the drug names, and the World Health Organization- Adverse Reaction Terminology (WHO-ART)'s preferred terms (PTs) were use to code the adverse events (AEs). The KIDS (https://open.drugsafe.or.kr/original/invitation.jsp) websites host the KAERS datasets (Shin et al., 2009; Joung et al., 2020a).

Exposure definition and data mining for signal detection

Exposure was defined as reported zolpidem use. Disproportionality analysis methods including proportional reporting ratios (PRR) (Evans et al., 2001), reporting odds ratios (ROR) (Rothman et al., 2004), and Information component (IC) of Bayesian confidence propagation neural network (BCPNN) (Norén et al., 2008) were used to identify adverse reaction signals of zolpidem in KAERS. Calculations of measures of disproportionality are primarily based on a two-by-two contingency table (van Puijenbroek et al., 2002). In brief, PRR is the proportion of AEs in zolpidem divided by the fraction of specific AEs in all other drugs, and the criteria for conforming to the signal are PRR ≥ 2, chi-square ≥ 4, and the number of cases with AEs ≥ 3, and the ROR The formula is (A/C)/(B/D), and the criteria for signal are ROR ≥ 2, chi-square ≥ 4, and the number of cases with AEs ≥ 3. The IC is the logarithmic value of the probability of using a certain drug multiplied by the probability of the occurrence of a specific AE if the use of that drug and the occurrence of the particular AE are independent of each other. The formula for the calculation of IC is and the criterion is when the lower limit of the 95% confidence interval is higher than 0. In this study, AEs that satisfied all three criteria (PRR, ROR, and IC) were defined as signals.

We investigated the ROR of adverse drug reactions (ADRs) grouped by ADR type, which can be difficult for reporters to distinguish due to their similarity, or can be grouped together by a common characteristic, such as parasomnia (Bjorvatn et al., 2010), which include both paroniria and somnambulism, and the cardiovascular disorder group, which includes eight diseases such as cardiac failure, heart disorder, and coronary thrombosis. Because the PTs are highly specific and in some cases, one PT may belong to a sub-group of another PT, making them not mutually exclusive, we considered it more rational to investigate the RORs by ADR category rather than individual ADRs of PT level.

Verification of gender differences and statistical analysis

To explore the gender differences, each analysis was performed separately by gender. The *t*-test and Chi-square test were applied for

continuous variables and categorical variables, respectively to examine the differences in the basic demographic and AE reporting data by gender. Serious AEs refers to any of the following: 1) death or a life-threatening condition, 2) hospitalization or prolongation of existing hospitalization, 3) persistent or significant disability/incapacity, 4) congenital anomaly/birth defect, 5) any other medically important condition that requires medical intervention, such as drug dependence or abuse, or a blood disorder, etc.

For each signal detected, we calculated the frequency and ROR with 95% confidence intervals for each gender subgroup. The difference between the two odds ratios was estimated as the difference between the logarithms of the two RORs. We evaluated different reporting risks by gender using the log reporting odds ratios (RORs), with statistical significance determined at the 5% level, and the 95% confidence intervals of the gender ROR were also considered.

In a secondary analysis, we defined control group as patients exposed to benzodiazepine anxiolytic/hypnotic drugs, then the RORs were calculated. We expected the size (ROR) of signals detected in this analysis to generally be smaller than those in the primary analysis due to the similar mechanisms of action on the nervous system. Therefore, the number of signals detected was anticipated to decrease significantly. However, if we detected gender differences in the signals and reporting risk in this analysis, it would support the robustness of the primary study results. Benzodiazepine derivatives included all drugs in the WHO ATC N05BA category.

In another secondary analysis, RORs were calculated by gender for ADR categories only for suspected drugs. In KAERS, "suspected drugs" are drugs suspected to have caused the adverse reaction in question, while other drugs are classified as "concomitant drugs."

All data were analyzed using the SAS statistical application program (Version 9.4, SAS Institute Inc., NC, United States).

Results

The dataset consisted of 1,016,161 reports, with 599,311 reports from women and 416,850 from men. The number of drug-adverse event combinations was 3,524,587, with 11,341 AE reports associated with zolpidem, 5,791 occurring in women and 5,550 in men. In the reports containing zolpidem, 476 types of AEs were observed in women, and 468 in men. Out of the 2,442 reports that provided information on the daily dosage of zolpidem, there was no significant difference between women and men in the administered dosage, which was 8.55 and 8.54 mg, respectively. Among all reports, the proportion of serious AEs was lower in women than in men (7.37% vs. 10.28%), while the proportion of serious AEs associated with zolpidem use was similar between women and men (25.20% vs. 24.49%). The majority of reporters (96.49%) were healthcare professionals, such as doctors, pharmacists, and nurses (Table 1).

In total, 94 PT signals were detected. Supplementary Table S1 presents all signals detected in the overall population, their number of cases in zolpidem users, and the RORs (95% CI) by gender. Delirium was the most frequently reported AE, with 333 and 691 cases in women and men, respectively. Out of the 94 PTs, 14 PTs exhibited differences in ROR at the 5% significance level between men and women, with AE reports present in both genders. These PTs are presented in Table 2. Of these, somnambulism had a significantly higher ROR in women than in men, with non-overlapping 95% CIs and a much higher frequency of reporting in women (42 out of a total of 56 reports) compared to men. PTs for which the ROR was higher in men than in women included delirium, hyperkinesia, anxiety, and depression.

Table 3 presents the PTs that are reported only in one gender. Anal ulcer had the highest reporting frequency with an ROR (95% CI) of 13.82 (7.74–24.68) in women. Tolerance was reported only in women, with a very high ROR of 54.81 (22.06–136.2) in women. Hepatic cirrhosis (nine cases) and vein varicose (seven cases) were reported only in men.

When the PTs were categorized as shown in Table 4, there were gender differences in six out of the 11 categories. Parasomnia, speech disorders, and cardiovascular disorders had higher RORs in women, while insomnia-related disorders, cognitive disorders, and movement disorders (marginally significant, $p = 0.057$) had higher RORs in men. Parasomnia showed the largest gender difference, with a higher ROR in women than in men (Table 5).

In a secondary analysis that limited the non-exposed control group to users of benzodiazepine derivatives, six AEs including cardiac failure and somnambulism were particularly higher in women, while insomnia and delirium had higher reporting risk in men. Cardiac failure was the most prominent PT level AE with predominance in women (difference in log ORs = 1.78, p value = 0.001). Somnambulism had the highest ROR among both genders, with higher reporting risk in women (difference in log ORs = 0.85, p value = 0.015) (Table 6). In the other secondary analysis focusing only on suspect cases, gender differences in AE categories were also found to be significant in parasomnia (difference in log ORs = 1.12, p value < 0.001) and cognitive disorders (difference in log ORs = −0.32, p value < 0.001) (Table 7).

Discussion

This study aimed to investigate gender differences in AEs associated with zolpidem using voluntary AE reporting data in Korea. Due to potential differences in reporting behavior of adverse drug reactions between genders (Mosnier-Pudar et al., 2009; Holm et al., 2017), and the possibility of different numbers of zolpidem users between genders (Joung et al., 2020b), we estimated the difference between the RORs calculated in gender subgroups, rather than comparing reporting frequencies or rates. Our findings showed a similar AE signal in zolpidem users as previous studies, with most AEs related to the central nervous system. Compared to a previous study using the 1988–2015 KAERS data in 2018, our study detected significantly more signals (94 vs. 59) due to the establishment of a voluntary adverse drug events reporting system through the internet by the Korea Institute of Drug Safety and Risk Management in 2012 (Han et al., 2018).

TABLE 1 Characteristics of zolpidem users whose adverse events were reported and their reports to the Korea Adverse Event Reporting System (KAERS), 2015–2019.

	Overall	Women	Men	*p* value
Age				<0.0001
Mean (SD)	54.14 (18.92)	53.84 (18.41)	54.56 (19.65)	
0–19	56,655 (5.58)	25,948 (4.33)	30,707 (7.37)	
20–39	159,198 (15.67)	105,485 (17.6)	53,713 (12.89)	
40–64	471,060 (46.36)	284,191 (47.42)	186,869 (44.83)	
≥65	329,248 (32.4)	183,687 (30.65)	145,561 (34.92)	
Number of reports	1,016,161 (100.0)	599,311 (59.0)	416,850 (41.0%)	<0.001
2015	165,973 (16.33)	95,675 (15.96)	70,298 (16.86)	
2016	195,773 (19.27)	115,672 (19.3)	80,101 (19.22)	
2017	219,073 (21.56)	129,762 (21.65)	89,311 (21.43)	
2018	218,250 (21.48)	129,092 (21.54)	89,158 (21.39)	
2019	217,092 (21.36)	129,110 (21.54)	87,982 (21.11)	
Number of AE types found in the reports containing zolpidem	621	476	468	<0.001
Number of AE types found in the reports containing all drugs other than zolpidem	1736	2024	1,518	
Average prescribed amount per dose, mg (SD)	8.54 (2.79)	8.55 (2.38)	8.54 (2.78)	>0.05
	N = 2,442	N = 1,222	N = 1,220	
Type of reporter				>0.05
Physician, Pharmacist, Nurse	10,563 (96.49)	5,374 (96.31)	5,189 (96.60)	
Consumer	289 (2.64)	165 (2.96)	124 (2.31)	
Others (other medical professional, lawyer)	95 (0.87)	41 (0.73)	54 (1.01)	
Serious adverse events (n, %)	2,838 (25.02)	1,479 (25.54)	1,359 (24.49)	>0.05
Death or life threatening (n, %)	258 (2.27)	103 (1.78)	155 (2.79)	<0.001
Suspected AEs	228	189	158	>0.05

Abbreviations: AE, adverse event; SD, standard deviation.

When comparing by gender, we found that the distribution of AEs was different, with 38% of AEs in PT level (36 out of 94) having different reporting risks by gender. Somnambulism had a significantly higher ROR in women than in men, while delirium, hyperkinesia, anxiety, and depression were higher in men. Categorizing PTs according to the similarity of AEs revealed that parasomnia and cardiovascular disorders had a higher risk of reporting in women, while insomnia related disorders, cognitive disorders, and movement disorders (marginally, $p = 0.057$) were dominant in men. Parasomnia had the largest gender difference in ROR among all PT-level AEs.

Somnambulance

Complex sleep behaviors, which are mainly induced by non-benzodiazepine hypnotics, are not clearly defined in terms of the types of behaviors involved, but common examples include sleep walking, sleep-related eating, sleep conversations, sleep sex, and driving (Harbourt et al., 2020). Although complex sleep behaviors are rare, identifying its risk factors is essential from a medical and public health perspective, as they can result in serious consequences such as self-harm, falls, attacks on others, or even criminal acts (Daley et al., 2011).

While, the WHO-ART classification may not be sufficient in identifying the specific symptoms of complex sleep behaviors, as it only lists somnambulism (sleepwalking) as a symptom, this study found that somnambulism was reported three times more frequently in women than in men, and had the largest gender difference in ROR among all PT-level AEs. Although there is limited research on whether the risk of complex sleep behaviors due to zolpidem is related to gender, previous case reports and a systematic review are consistent with our findings, suggesting that women may be more at risk (Dolder and Nelson, 2008; Cubała and Gabrielsson, 2014; Stallman et al., 2018). However, a case-control study in nonpsychotic patients (Chen et al., 2013) and a cross-sectional

TABLE 2 Adverse events signals of zolpidem reported in both men and women, with significant gender differences in ROR.

No	Adverse event	Women		Men		Difference[a]	*p* value
		No. of cases	ROR[a] (95% CI)	No. of cases	ROR (95% CI)		
1	Thrombosis coronary	4	12.34 (4.71–32.34)	1	1.02 (0.14–7.10)	2.51	0.026
2	Respiratory depression	3	8.93 (2.92–27.31)	2	1.39 (0.35–5.54)	1.86	0.043
3	Neuralgia	11	5.19 (2.89–9.34)	2	1.11 (0.28–4.44)	1.54	0.046
4	Infusion site reaction	10	3.37 (1.82–6.25)	3	0.89 (0.29–2.77)	1.33	0.045
5	Psychosis	7	27.90 (13.68–56.9)	4	7.56 (2.87–19.89)	1.31	0.042
6	Somnambulism	42	150.85 (117.06–194.39)	14	64.52 (40.23–103.48)	0.85	0.015
7	Speech disorder	21	7.18 (4.7–10.98)	14	3.44 (2.05–5.80)	0.73	0.035
8	Delirium	333	55.88 (50.39–61.97)	691	67.70 (62.92–72.84)	−0.19	0.010
9	Insomnia	309	4.16 (3.71–4.66)	253	5.17 (4.56–5.86)	−0.22	0.013
10	Hyperkinesia	52	17.31 (13.26–22.60)	95	29.57 (24.38–35.87)	−0.53	0.003
11	Anxiety	47	3.47 (2.61–4.61)	71	5.90 (4.68–7.44)	−0.54	0.005
12	Depression	24	2.37 (1.59–3.53)	37	5.09 (3.70–7.02)	−0.77	0.004
13	Aggressive reaction	2	1.90 (0.48–7.56)	11	8.66 (4.84–15.51)	−1.52	0.049
14	Inappropriate schedule of drug administration	1	0.47 (0.07–3.31)	8	3.81 (1.91–7.58)	−2.10	0.048

Abbreviations: ROR, reporting odds ratio; 95% CI, 95% confidence interval.
[a]The difference was calculated by subtracting the log odds ratios in men from the log odds ratio in women.

study in psychiatric outpatients (Chen et al., 2014) found that sex was not associated with the risk of complex sleep behaviors.

Although these examples are exceptional, a review of post-2000 literature has demonstrated that out of five cases of homicide related to zolpidem use among patients with mood or anxiety disorders (Westermeyer and Carr, 2020), three were committed by women and two by men (Daley et al., 2011; Paradis et al., 2012; Edinoff et al., 2021). To our knowledge, this study is the first to confirm, through a large-scale voluntary reporting system, that zolpidem-related somnambulism is more commonly reported in women. The sex differences in reporting somnambulism were consistently observed in both secondary investigations, which supports the robustness of the findings.

Cardiovascular disorder

There have been several studies on the association between zolpidem use and cardiovascular or cerebrovascular risks (Huang et al., 2013; Lee et al., 2014; Hu et al., 2022), but the results are inconsistent, and no research appear to have taken gender into consideration. Some studies have found an increased risk of adverse cardiovascular events, such as atrial fibrillation (Hu et al., 2022) and stroke (Huang et al., 2013; Lee et al., 2014) in zolpidem users, while other studies have reported a decreased risk of stroke (Zhu et al., 2016) or cardiovascular risk (Kim et al., 2018). Currently, the drug label in the US includes rare cardiovascular adverse effects such as arrhythmia, myocardial infarction, and hypertension (DAILYMED, 2023), while Korea and the United Kingdom do not list any significant cardiovascular-related adverse effect (Center KPI, 2023; Electronic Medicines Compendium, 2023).

In our study, a total of 68 cases of cardiovascular AEs associated with zolpidem were reported, of which 42 cases were reported in women, and the gender difference in log ROR was significant at 0.62. Besides, although the frequencies were low, signals of coronary thrombosis and myocarditis were detected only in women. In the secondary analysis, which set users of benzodiazepine anxiolytics/hypnotics as the non-exposed control group, heart failure showed the largest gender difference in ROR which is in line with the primary analysis. On the contrary, only two cases of cardiovascular disorders were reported in the secondary analysis II, which focused on suspected cases only. This is most likely because the reporter was unsure whether the cardiovascular reactions were caused by the adverse effects of zolpidem and did not mark them as suspected drug reactions. The estimates from voluntary AE reports do not allow for the confirmation of causality or association. Additionally, insomnia itself is known to be a risk factor for heart failure or myocardial infarction (Sofi et al., 2014; Javaheri and Redline, 2017). Due to the inherent limitations of the data source, our results do not provide conclusive evidence on the relationship between zolpidem and cardiovascular disease and, if present, whether women are at higher risk of zolpidem-related cardiovascular disease. This results support the need for future research to test the hypotheses.

TABLE 3 Adverse events signals reported only one gender among zolpidem users.

No.	Preferred term	Women		Men	
		No. of cases	ROR (95% CI)	No. of cases	ROR (95% CI)
1	Anal ulcer	11	13.82 (7.74–24.68)	0	-
2	Lactation non-puerperal	7	3.23 (1.54–6.75)	0	-
3	Bowel motility disorder	7	11.76 (5.67–24.37)	0	-
4	Amenorrhoea	6	4.59 (2.07–10.16)	0	-
5	Atherosclerosis	4	8.46 (3.21–22.28)	0	-
6	Myocarditis	4	9.26 (3.52–24.36)	0	-
7	Tolerance	4	54.81 (22.06–136.2)	0	-
8	Leukaemia lymphocytic	3	8.63 (2.82–26.41)	0	-
9	Varicella	3	22.34 (7.46–66.88)	0	-
10	Wound dehiscence	3	10.27 (3.37–31.34)	0	-
11	Pain axillary	3	8.22 (2.69–25.15)	0	-
12	Hepatic cirrhosis	0	-	9	7.1 (3.72–13.55)
13	Acrodynia	0	-	7	13.91 (6.75–28.67)
14	Vein varicose	0	-	6	4.59 (2.07–10.15)
15	Skin depigmentation	0	-	4	10.32 (3.94–27.02)
16	Oculomotor nerve paralysis	0	-	4	13.63 (5.23–35.49)
17	Hepatitis cholestatic	0	-	4	14.72 (5.66–38.26)
18	Artery malformation	0	-	4	9.05 (3.45–23.75)
19	Retinal detachment	0	-	4	3.49 (1.32–9.25)
20	Decubitus ulcer	0	-	4	4.7 (1.78–12.42)
21	Haemangioma acquired	0	-	3	8.04 (2.63–24.53)

Abbreviations: ROR, reporting odds ratio; 95% CI, 95% confidence interval.

TABLE 4 Adverse event categories of interest and preferred terms defining cases.

	Category	Preferred terms included
1	Cognitive disorders	Delirium, amnesia, dementia, cognitive disorders, stupor
2	Insomnia related disorders	Sleep disorder, insomnia
3	Parasomnia	Somnambulism, paroniria
4	Speech disorders	Aphasia, speech disorder, communication disorder
5	Cardiovascular disorders	Cardiac failure, heart disorder, cardiomyopathy, myocarditis, thrombosis coronary, tachycardia supraventricular, tachycardia ventricular, ECG abnormal specific
6	Movement disorders	Extrapyramidal disorder, dyskinesia, gait abnormal, hemiparesis, hyperkinesia
7	Misuse	Inappropriate schedule of drug administration, medication error related problems, drug abuse, drug dependence, tolerance
8	Unexpected or increased response	Unexpected therapeutic effect, therapeutic response increased
9	Ocular disorders	Oculogyric crisis, oculomotor nerve paralysis, diplopia, xerophthalinia, retinal detachment
10	Dental disorders	Toothache, peridontal disorder
11	Otitis	Otitis externa, otitis media chronic

TABLE 5 Frequencies of categorized adverse events by gender, and its difference of women to men.

No.	Category	Women		Men		Difference[a]	*p* value
		No. of cases	ROR (95% CI)	No. of cases	ROR (95% CI)		
1	Parasomnia	73	70.28 (51.93–86.78)	32	31.25 (22.48–43.45)	0.81	0.004
2	Speech disorders	29	7.21 (5.03–10.35)	21	3.75 (2.45–5.74)	0.65	0.021
3	Cardiovascular disorders	42	3.65 (2.70–4.94)	26	1.97 (1.34–2.90)	0.62	0.010
4	Insomnia related disorders	351	4.50 (4.05–5.01)	302	5.82 (5.19–6.53)	−0.26	0.002
5	Cognitive disorders	468	24.50 (22.35–26.86)	841	37.34 (34.81–40.05)	−0.42	<0.001
6	Movement disorders	89	7.41 (6.02–9.12)	133	9.68 (8.17–11.46)	−0.27	0.057
7	Dental disorders	7	2.95 (1.41–6.16)	9	2.45 (1.28–4.69)	−2.67	>0.05
8	Otitis	5	3.71 (1.55–8.87)	3	2.75 (0.89–8.50)	−0.30	>0.05
9	Ocular disorders	18	3.49 (2.21–5.53)	12	2.15 (1.22–3.78)	−0.48	>0.05
10	Misuse	28	8.46 (5.86–12.21)	26	8.24 (5.64–12.05)	0.026	>0.05
11	Unexpected or increased response	7	6.85 (3.29–14.28)	3	8.36 (2.74–25.51)	−0.20	>0.05

Abbreviations: ROR, reporting odds ratio; 95% CI, 95% confidence interval.
[a]The difference was calculated by subtracting the log odds ratios in men from the log odds ratio in women.

TABLE 6 Secondary analysis I: frequencies of categorized adverse events by gender and its difference of women to men when non-exposed control group was confined as benzodiazepine derivate users.

No.	Adverse event	Women		Men		Difference[a]	*p* value
		No. of cases	ROR (95% CI)	No. of cases	ROR (95% CI)		
1	Cardiac failure	28	3.23 (2.23–4.68)	4	0.54 (0.20–1.45)	1.78	0.001
2	Neuralgia	11	5.19 (2.89–9.34)	2	1.11 (0.28–4.44)	1.54	0.046
3	Infusion site reaction	10	3.37 (1.82–6.25)	3	0.89 (0.29–2.77)	1.33	0.045
4	Hypoproteinaemia	12	2.49 (1.41–4.37)	7	0.75 (0.36–1.56)	1.20	0.012
5	Somnambulism	42	150.85 (117.06–194.39)	14	64.52 (40.23–103.48)	0.85	0.015
6	Paroniria	31	40.41 (28.93–56.43)	18	22.23 (14.24–34.70)	0.60	0.054
7	Delirium	333	55.88 (50.39–64.97)	691	67.70 (62.92–72.84)	−0.19	0.010
8	Insomnia	309	4.16 (3.71–4.66)	253	5.17 (4.56–5.86)	−0.22	0.013

Abbreviations: ROR, reporting odds ratio; 95% CI, 95% confidence interval.
[a]The difference was calculated by subtracting the log odds ratios in men from the log odds ratio in women.

TABLE 7 Secondary analysis II: frequencies of categorized adverse events by gender, and its difference of women to men only for the suspected cases.

No.	Category	Women		Men		Difference[a]	*p* value
		No. of cases	ROR (95% CI)	No. of cases	ROR (95% CI)		
1	Parasomnia	72	152.24 (123.37–187.55)	32	49.45 (35.64–68.62)	1.12	<0.001
2	Cognitive disorders	389	146.40 (132.44–161.84)	746	202.48 (187.00–219.25)	−0.32	<0.001
3	Insomnia related disorders	119	3.75 (3.12–4.51)	92	4.82 (3.92–5.93)	−0.25	0.078
4	Cardiovascular disorders	1	0.63 (0.09–4.50)	1	0.51 (0.07–3.64)	0.21	0.88
5	Speech disorders	14	8.89 (5.28–14.98)	15	8.53 (5.17–14.10)	0.04	0.91

Abbreviations: ROR, reporting odds ratio; 95% CI, 95% confidence interval.
[a]The difference was calculated by subtracting the log odds ratios in men from the log odds ratio in women.

Hyperkinesia, insomnia, and movement disorder

In our study, men were more likely to report insomnia, hyperkinesia, or aggressive reaction than women. Although the frequency and size of the difference are varied, these AEs seem to share a common possibility of being related to a rebound effect from zolpidem with a short half-life (Denise and Bocca, 2003; Ebert et al., 2006). While the rebound symptoms of non-benzodiazepine hypnotics are well established (Voshaar et al., 2004; Ebert et al., 2006), studies on gender difference is limited. In the *post hoc* clinical trial of chronic nightly zolpidem, there was no gender difference in rebound insomnia, which differed from the results of our study (Roehrs and Roth, 2016). Movement disorders, including hyperkinesia and extrapyramidal disorders, also showed a higher ROR in men. Future research is needed to determine whether men are at greater risk for these neurocognitive disorders.

In case of cognitive disorders or delirium, both primary and two secondary studies showed higher reporting risk in men. To determine whether there are gender-specific vulnerabilities in the cognitive function issues brought on by zolpidem use, more research may be required.

Strengths and limitations

To our knowledge, this study is the first to investigate overall gender differences in the risk of reporting AEs of zolpidem using national voluntary AE reporting data. The use of vast amounts of national data over the last 5 years would have yielded reliable findings. Second, by comparing the RORs that were not dependent on the size of drug use and reporting behavior for each gender, we were able to make a reasonable comparison of gender differences in reporting risk. A number of studies have shown a higher frequency or rate of AEs reported in women (Lucca et al., 2017; de Vries et al., 2019). However, gender differences in the scale of drug users were not taken into account (Yu et al., 2016), and even if it is considered as the denominator, reporting behavior is regarded as gender-dependent. A study indicated that healthcare professionals more frequently reported AEs for women. Conversely, serious reports were more frequently reported for men, which was also supported by our findings (Holm et al., 2017).

Our study has several limitations. First, owing to the inherent limitations of data source and the signal detection methodology, causal inferences were not possible. This study underscores the need for future research to investigate potential factors such as concomitant medications, comorbidities, pharmacokinetics, dose variability, and alcohol intake that may contribute to gender disparities in adverse effects. Secondly, the data quality is inconsistent and underreporting is prevalent, especially concerning AEs like complex sleep behaviors, where concerns about discontinuing prescriptions or embarrassment may lead to underreporting. Thirdly, although the average daily prescription dose was similar for each gender, it remains unknown whether the dose variability affects the individual AEs signal discrepancies by gender. Furthermore, only 2,442 out of 11,341 reports contained dose information. Lastly, using data limited to Korean population makes it challenging to directly compare with studies involving other populations, particularly regarding genetic diversity and pharmacogenetics.

Conclusion

The analysis of real-world data showed that reporting of AEs among zolpidem users was different by gender. This gender imbalance was pronounced in some of AEs such as parasomnia including somnambulism and cardiovascular disorders which is dominant in women, while cognitive disorders and insomnia are more frequent in men. Specifically, women demonstrated a greater vulnerability to somnambulism, which is a potentially severe adverse effect of zolpidem. The results support the need for more comprehensive clinical research on gender differences related to zolpidem in the future.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://open.drugsafe.or.kr/original/invitation.jsp.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) of CHA University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

K-IJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1256245/full#supplementary-material

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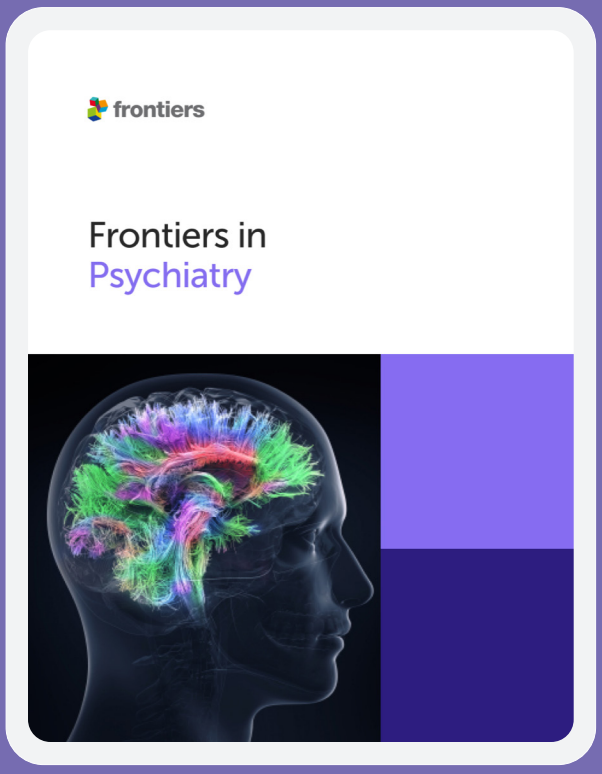

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