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Safety and side effects of psychotropic medications

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Safety and side effects of psychotropic medications

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Editorial: Safety and side effects of psychotropic medications

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adverse drug reaction, adverse effects, mental disorders, mental health, psychiatry, psychopharmacology, real world evidence (RWE), tolerability

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

In the last few decades psychopharmacology has witnessed an incredible development in terms of efficacy, safety and number of options available for the treatment and management of major mental disorders (1, 2). The change of perspective from a therapy mainly centered on experience to the evidence-based medicine has represented a true Copernicus revolution in mental health, with the implication of providing concrete improvements on disease prognosis and patients' quality of life (3). Despite this, the tolerability profile of psychopharmacological therapy remains an area for improvement on which patients, caregivers, and health care providers agree (4, 5). To fill this gap, various strategies have been applied, which improve the quality of data available on adverse drug reactions (ADRs) related to psychiatric therapy (6–8). Notherless, much remains to be investigated about the systemic effects of psychoactive medicines, their pharmacokinetic and pharmacodynamic interactions, and the variability of these consequences in frail and special populations (9–13).

Therefore, in this Research Topic, we aimed to collect articles dealing with the safety and side effects of psychotropic medications in mental health. We welcomed all articles potentially able to add some elements of novelty and evidence on this sensitive topic.

Several papers focused on the role and safety of antipsychotic medications. Hakami et al. provided a retrospective cohort study investigating the antipsychotics-induced weight gain with metformin co-administration. Retrospectively screening 4,141 medical records of a psychiatric outpatient clinic, authors found a total of 395 patients' records, showing that the concomitant use of metformin was related to reduction in the weight gain tendency.

The paper by Yunusa et al. evaluated the hospitalizations related to serious ADRs associated to atypical antipsychotics (AAPs). In this cross-sectional analysis authors used the FDA Adverse Event Reporting System (FAERS) database (from 2004 to 2021) to examine disproportionality in reporting hospitalizations suspected to be associated with 12 AAPs. According to this analysis, patients taking clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone were more likely to report being hospitalized than users of other AAPs.

Following a similar research path, Peters et al. investigated the cumulative time spent in second generation antipsychotics (SGAs), antipsychotic polypharmacy, and clozapine in discharged patients affected by schizophrenia. Data from 2,997 patients with a minimum of 6 weeks medicated with SGAs were analyzed. Patients suffering from schizophrenia accumulated

44 months in SGA monotherapy, 4 months in polypharmacy, 11 months in medication gaps, and 17 days in clozapine over a 5-year period.

Zhu et al. reported data about 378 long-term hospitalized patients diagnosticated with schizophrenia analyzing the factors influencing comorbid type 2 diabetes mellitus (T2DM) on prolactin levels in their long-term stay in hospital. Surprisingly, compared with patients without T2DM, the patients in the T2DM subgroup had lower prolactin levels and rather severe psychiatric symptoms, with aripiprazole as a protective factor for hyperprolactinemia in long-term hospitalized patients, and female gender representing a risk factor.

The study by Akbarzadeh, Niksun et al. investigated the relevant hypothesis of inflammatory processes in central nervous system in bipolar disorder, through the co-administration of curcumin, with anti-inflammatory effects, and sodium valproate. However, the results of this randomized double-blind trial study did not identify any specific clinical advantages in the group taking curcumin compared to the placebo harm, reducing the weight that this option can play in the management of the tolerability of drug therapy.

One of the included papers in our Research Topic reported a case report describing neutropenia after the coadministration of clozapine and nirmatrelvir-ritonavir in a patient with SARS-CoV-2 infection, adding a literature review on the topic (Liu et al.). Indeed, the risk of neutropenia may increase during SARS-CoV-2 infection and co-administration of clozapine and the antiviral drug paxlovid. Thus, the white blood cell count and absolute neutrophil count should be closely monitored in this specific group of patients.

The paper by Khazaie et al. presented a systematic review and meta-analysis on randomized, double-blind, placebo-controlled trials on suvorexant and lemborexant, dual orexin receptor antagonists for treatment of insomnia. The study includes eight articles (five for suvorexant and three for lemborexant) evaluating diary measures, rating scales, polysomnography results, treatment discontinuation, and ADRs. Overall, efficacy favorably differs in both suvorexant and lemborexant groups compared to placebo. Safety profile did not differ significantly except for somnolence, excessive daytime sleepiness and nightmare in the treatment groups, but without severe ADRs reported. Authors conclude that suvorexant and lemborexant are efficacious and safe agents for insomnia treatment.

The last two papers describe peculiar case reports. The first one, by Akbarzadeh, Behravan et al., portrayed a case of citalopram-induced sleep bruxism in a 9-month-old female breastfed infant whose mother recently used citaliporm (10 mg per day) for her anxiety disorder. Then, patient's bruxism symptoms disappeared following the citalopram discontinuation by her mother.

The other case is reported by Shi et al., describing the treatment of psychiatric symptoms in a 41-year-old male patient suffering from pituitary adenoma with acromegaly since 8 years, more recently associated to untypical neuropsychiatric disturbances. Indeed, he developed an acute psychotic episode, such as to require hospitalization and good response and tolerability to aripiprazole.

All papers described in this Editorial explore several safety and tolerability aspects of medications in mental health. Considering the large utilization of such category and the relative paucity of evidence available about their long-term consequences (14), the articles gathered in this Research Topic shed some light on the clinical implications of the pharmacological approach throughout a wide range of different settings, conditions and samples.

Although research on psychopharmacology has already produced a large amount of data on many aspects (15, 16), we believe that the clinical framework offered in these articles provides a practical and original point of view that could lead to a more targeted and specific use of forces and resources, arousing the curiosity of clinicians and researchers.

Considering the psychopharmacological trends described in the included papers, we highlight the urgent need to deepen psychotropic drugs-related ADRs. The results collected in this Research Topic do not discourage the prescription of psychotropic drugs, but rather aim to promote their conscious use.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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ORIGINAL RESEARCH
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The Association Between Antipsychotics and Weight Gain and the Potential Role of Metformin Concomitant Use: A Retrospective Cohort Study

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Background: Obesity and its complications are associated with several adverse effects that may cause a serious impact on health. Antipsychotics-induced weight gain (AIWG) is one of the major, yet often neglected side effects of first and second generations antipsychotics. Importantly, several researches have shown metformin to be effective in managing weight gain especially, with AIWG. This study investigated the effect of antipsychotics use on weight gain and the theory of metformin concomitant use on the prevention of AIWG.

Methods: A retrospective cohort review of the medical records of patients from the psychiatry outpatient clinics in the King Abdulaziz Medical city, a tertiary hospital in Jeddah from May 2016 to August 2021. The population of patients in Psychiatry section was 4,141. The sampling technique was a non-random consecutive sampling technique. Moreover, the included patients' records were divided to group 1 (patients on antipsychotics) and group 2 (patients using antipsychotics with Metformin).

Results: According to the study criteria, 395 patients' records were included. A total of 309 (78%) patients were using antipsychotics without metformin, which in this study were depicted as group 1. In addition, a total of 86 (22%) were using antipsychotics with metformin, which in this study were assigned as group 2. Out of Group 1 patients (n = 309), only 67 patients experienced weight loss (21.68%), 43 remained with no weight change (13.92%), and 199 experienced weight gain (64.4%). Out of Group 2 patients (n = 86), 35 patients experienced weight loss (40.7%), 18 patients remained with no weight change (20.93%), and 33 experienced weight gain (38.37%). In addition,

group 1 had a mean weight change of 2.5 kg, whereas group 2 had a mean weight change of −0.04 kg.

Conclusion: Statistical analysis revealed that patients on antipsychotics alone experienced weight gain, whereas the concomitant use of metformin showed reduction in the weight gain tendency. Thus, study outcomes indicate that concomitant use of metformin with antipsychotics might significantly reduce the AIWG.

Keywords: antipsychotics, weight gain, weight loss, metformin, obesity

INTRODUCTION

In the past few decades, the prevalence of obesity has significantly increased in Saudi Arabia (1). Furthermore, obesity leads to the detrimental effects of metabolic syndrome such as cardiovascular diseases and type II diabetes mellitus (DM) (2). There are many factors that contribute to obesity, including the use of some antipsychotic drugs such as *olanzapine* and *clozapine* (3).

Antipsychotics, also known as neuroleptics, are majorly used to treat psychosis and mainly schizophrenia (3). The mechanism of antipsychotics-induced weight gain (AIWG) is generally hypothesized by the alteration of glucose metabolism and increasing cholesterol and triglyceride levels. Thus, increase the chance of insulin resistance and may cause arterial hypertension disposing to metabolic syndrome (4–6). Specifically, antipsychotics affect neuropeptides linked with appetite control and energy metabolism such as leptin, adiponectin, and ghrelin (3, 5). Changes in these neuropeptides' levels have shown a direct impact on weight gain hence increasing the release of triglycerides and Very Low-Density Lipoprotein (VLDL) (5, 6).

First generation (typical) antipsychotics mainly act upon the antagonism D2 receptor and serotonin (5HT) to a lesser extent which commonly lead to extra-pyramidal symptoms and tardive dyskinesia as adverse effects of these drugs. Second generation (atypical) antipsychotics mainly block serotonin (5-HT) and norepinephrine (α1 and α2). Atypical antipsychotics also show a reduction in extra-pyramidal symptoms compared to typical antipsychotics because of lower affinity to D2 receptor antagonism thus portraying more metabolic rather than neurologic side effects (7). One of the causes of Antipsychotics-induced weight gain (AIWG) is increased food intake (8). Besides antipsychotics, there are other lifestyle factors that may be attributed to the weight gain in psychiatric patients. For example, paranoia or hospitalization of patients with schizophrenia may force them to be isolated in a sedentary lifestyle (9).

Evidence have shown that the rate of weight gain is high during the first 6 months of antipsychotics treatment establishment and progress throughout the treatment period (10). Also, reports have determined that *clozapine* and *olanzapine* are associated with a high risk of weight gain, whereas the antipsychotics associated with a low risk of weight gain are *aripiprazole*, *lurasidone*, and *ziprasidone* (11, 12). The role of antidiabetic drugs in the management of AIWG has been introduced in several studies. *Metformin* improves the action of insulin in the liver which leads to decreased hepatic glucose production, increases peripheral utilization, and decreases appetite (13, 14). Moreover, *Metformin* reported that it can decrease antipsychotic-induced weight gain by decreasing insulin resistance and appetite (15). Previous report demonstrated that using *metformin* reduced body weight, body mass index (BMI), and insulin resistance index (IRI) (15). The insulin resistance can increase with continuous weight gain and with the chronic use of antipsychotics medications. Despite the notion that using antidiabetic drugs is suggested to decrease the weight gain following antipsychotic use, some antipsychotic medications have been linked to a more favorable weight effect. For example, in schizophrenic patients, the use of alternative medications such as *aripiprazole* can have a low risk of increasing weight (16, 17).

The prevalence rate of DM is alarmingly increasing worldwide (18). Moreover, one-fourth of the adult population of Saudi Arabia is affected by DM. This number is predicted to rise to more than double by the year 2030 (19). Moreover, the effect of antipsychotics on weight gain is not well-studied in Saudi Arabia. In addition, the literature review revealed that only few studies in the region have investigated the effect of metformin concomitant use on antipsychotic induced weight gain (20). This study aims to investigate the effect of antipsychotics on the weight gain, and the effect of Metformin in counteracting AIWG in patients from National Guard Health Affairs (NGHA) in Jeddah, Saudi Arabia.

MATERIALS AND METHODS

Ethical Approval

This study was approved by King Abdullah International Medical Research Center (KAIMRC) institutional review board (study number: SP21J/112/03).

Design and Setting

This is a retrospective cohort study that examined the medical records of patients who received antipsychotic medications in the psychiatric section in National Guard Health Affairs (NGHA), a tertiary hospital, in King Abdulaziz Medical City in Jeddah (KAMC-J), from May 2016 to August 2021. The sampling technique was a non-probability consecutive sampling technique and the patients were divided into two groups. The first group included patients on antipsychotic medications only, and the second group was patients taking antipsychotics with metformin. Then using the hospital information system (BestCare), patients' data were collected according to the variables in the data collection sheet. These variables include, gender, age, weight

measurements, weight recording interval, and the name of antipsychotic medications were recorded for each patient. Following the data collection phase, data were initially encoded within an excel sheet to identify any missing data. The initial number of patients examined in the study was 4,141 patients. The inclusion criteria consist of patients using antipsychotics (group 1) and patients using antipsychotics with metformin (group 2). The exclusion criteria consist of physically disabled patients, hormonal disorders causing weight fluctuations such as thyroid disorders, patients below the age of 20, loss of follow up after prescribing antipsychotics, patients diagnosed with any type of cancer, any patients using antipsychotics without a weight record, pregnancy, and patients with a history of bariatric surgery. The total sample size after exclusion criteria is shown in **Figure 1**. The sample size was calculated by Openepi website version 3 using the confidence interval of 95%, and a power of study 80%. According to de Silva et al. (21) and de silva et al. (15), the first group who used antipsychotics alone had a mean of –1.56 kg with a standard deviation of 4.29 (15, 21). On the other hand, the second group who used antipsychotics with metformin had a mean weight gain of 1 kg, and the standard deviation was 2.69. Since the ratio of group 2/group 1 is 1.06, the required minimum sample size is 30 and 32, or groups 1 and 2, respectively. However, since this study is a consecutive study, all the patients who met the inclusion criteria and did not meet the exclusion criteria were involved in the study with numbers of 309 and 86 for group 1 and group 2, respectively.

Data Analysis

The applications used in this study are J Macintosh Project (JMP) pro 15.2.0 and IBM Statistical Package for the Social Sciences (SPSS) statistics 28.0.1.1 (14). Regarding the descriptive categorical data, which are gender, age, weight interval, diagnosis, name of the antipsychotic drug, and metformin usage, were depicted by using frequency and percentages. The dependent factor of this study is the weight difference between "before using

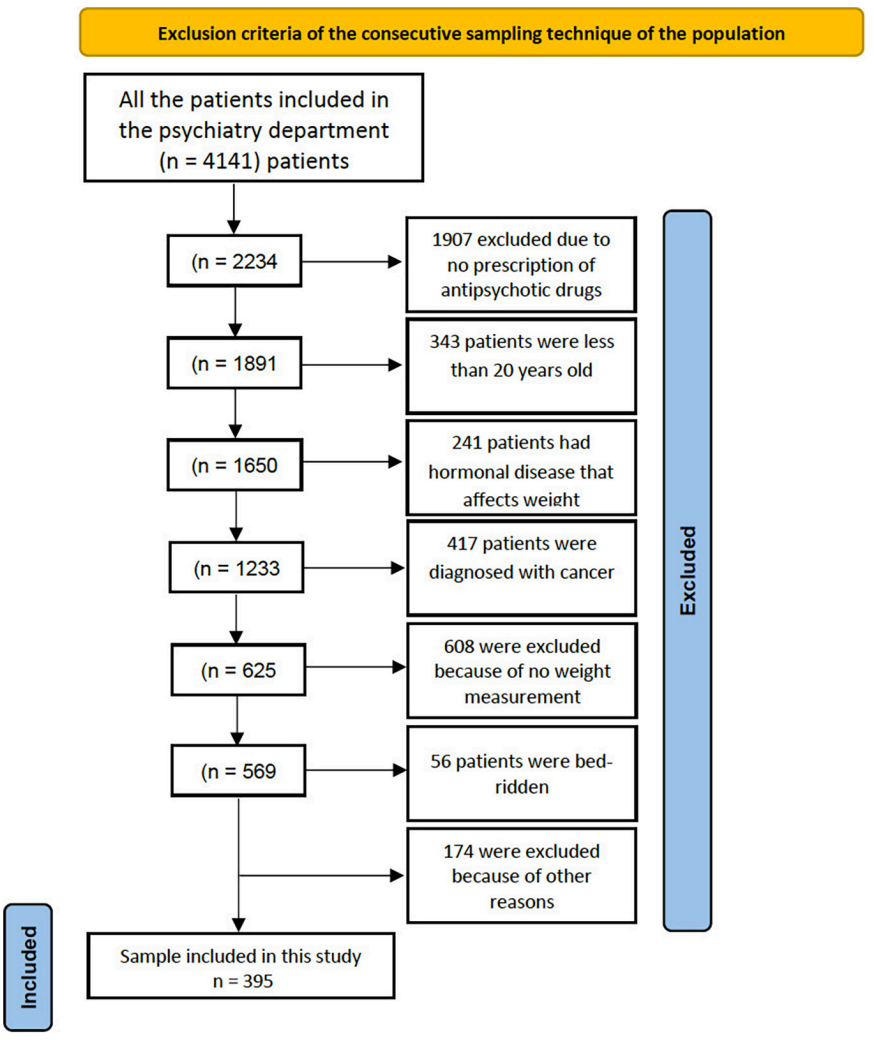

FIGURE 1 | Illustrates the entire population on which inclusion and exclusion criteria were applied. The population included 4,141 patients. The authors went through each individual patient in BestCare system to match the criteria and only 395 patients out of the population met the criteria.

antipsychotics" and "after using antipsychotics" in both group 1 and group 2. The weight difference was depicted numerically by the mean and standard deviation and categorically by three categories which are "increased weight, "no difference in weight," and "decreased weight." For the univariable inferential statistics, parametric data were depicted by chi-square, *T*-test, and one-way ANOVA. Non-parametric inferential statistics are depicted by Mann–Whitney U test, Wilcoxon signed-rank test, and Kruskal–Wallis test. Regarding multivariable inferential statistics, binary logistic regression model was used for comparing different variables. *P*-values less than 0.05 were considered statistically significant.

RESULTS

A total of 395 patients who visited the psychiatry clinic in NGHA during the period of May 2016 to August 2021 met the inclusion criteria of the study. Regarding the weight interval, patients were divided into four groups according to the weight measurement, which are 1–3 months, 4–6 months, 7–9 months, and 10–12 months. The most common weight intervals were in both group 3–6 months and 9–12 months with a number of 111 patients (23%) each. In addition, a total of 105 patients (27%) were between 30 and 39 years age category. Moreover, around 62% of the patients included in the study were males. Regarding the medications reported in the study, 118 (30%) of the patients used quetiapine as one of the main options in the management plan for their psychiatric condition. Importantly, 104 (27%) of the sample in the study were reported as patients with depressive disorders. Patients' demographic characteristics are illustrated in **Table 1**.

TABLE 1 | Patient demographic characteristics, medical conditions, and antipsychotics.

Parameter	Values
Age (*n* = 395)	
20–29	73 (18%)
30–39	105 (27%)
40–49	97 (25%)
50–59	62 (16%)
60–69	34 (9%)
>70	24 (6%)
Gender (*n* = 395)	
Male	244 (62%)
Female	151 (38%)
Group (*n* = 395)	
Group 1 (antipsychotic)	309 (78%)
Group 2 (antipsychotic with metformin)	86 (22%)
Weight recording interval (*n* = 395)	
Low (0–3 months)	89 (23%)
Middle (3–6 months)	111 (28%)
High (6–9 months)	84 (21%)
Very high (9–12 months)	111 (28%)
Medical psychiatric condition (*n* = 392)	
Depressive disorders*	104 (27%)
Bipolar disorder	54 (14%)
Psychotic disorders**	54 (14%)
Prescribed for non-psychiatric disease	30 (8%)
Anxiety disorders***	29 (7%)
Mixed anxiety and depression	9 (2%)
Obsessive-compulsive disorder	7 (2%)
Substance misuse	4 (1%)
Post-traumatic stress disorder	3 (1%)
Autism	3 (1%)
Personality disorder	2 (1%)
Somatic disorder	2 (1%)
Pseudodementia	1 (0%)
Insomnia	1 (0%)
Attention deficit hyperactivity disorder	1 (0%)
Multiconditions of two or more of the above diagnosis	88 (22%)
Antipsychotics (*n* = 395)	
Quetiapine	118 (30%)
Olanzapine	87 (22%)
Risperidone	42 (11%)
Aripiprazole	37 (9%)
Sulpiride	30 (8%)
Trifluoperazin	15 (4%)
Haloperidol	5 (1%)
Multidrug combination of two or more of the above medications	61 (15%)

**Depressive Disorders: Major Depressive Disorder and its subtypes (MDD), Depressive neurosis, Postpartum Depression.*
***Psychotic Disorders: Schizophrenia, Schizoaffective Disorder.*
****Anxiety Disorders: Generalized Anxiety Disorder (GAD), Agoraphobia, Claustrophobia, Panic Disorder, Social Phobia.*

The statistical analysis revealed that group 1 patients had a mean weight change of +2.5 kg (95% CI = 1.94–3.06), whereas group 2 patients had a mean weight change of −0.04 kg (95% CI = −1.09 to 1.02) as illustrated in **Table 2**. Out of 309 patients in group 1, 67 (21.68%) patients experienced weight loss, 43 (13.92%), remained with no weight change, and 199 (64.4%) experienced weight gain. Out of 86 patients of group 2, 35 (40.7%) patients experienced weight loss, 18 (20.93%) patients remained with no weight change, and 33 (38.37%) experienced weight gain as illustrated in **Figure 2**. Importantly, statistical analysis showed no significant association between metformin usage and change of weight interval.

There is no significant association between gender and weight difference either in quantitative data or qualitative univariable analysis. However, a significant difference was reported between gender and metformin usage as illustrated in **Figure 3**. Thus, statistical analysis revealed that female patients on metformin with antipsychotics counted as 41 out of 154 (27.15%), whereas only 45 out of 244 (18.44%) of male patients had a metformin concomitant used with antipsychotics.

Regarding the age variable, a total of 50 out of 73 (68.49%) patients in the 20–29 years age group had an average weight increase of +4.66 kg (95% CI 3.54–5.78). In contrast, the least affected group with weight gain were geriatric patients aged 60–69 with 11 patients out of 34 (32.35%) with decreased weight, and the mean of weight difference in this group is +0.15 kg (95% CI −1.5 to 1.79) as illustrated in **Table 3**. Moreover, the study outcomes revealed that metformin was prescribed more in elderly population as compared to other age groups. Of note,

TABLE 2 | Comparison between mean of weight change between antipsychotics alone vs. antipsychotics with metformin.

Variable	Antipsychotics use alone (*n* = 310)	Antipsychotics use with metformin (*n* = 89)	Significance
Mean	2.5 kg	−0.04 kg	$P < 0.0001$
Standard deviation (SD)	0.28	0.54	
95% CI	1.94–3.06 kg	−1.09 to 1.02 kg	

18 out of 34 (52.94%) and 12 out of 24 (50%) of patients were reported to use metformin with antipsychotics in the following age groups, 60–69 years and more than 70 years, respectively. However, only 3 patients out of 73 (4.11%) in the 20–29 group were reported to use metformin with antipsychotics, the data illustrated in **Figure 4**. Importantly, statistical analysis revealed no significant association between age and weight interval. There was no significant association between group 1 patients and weight interval in qualitative nor quantitative analysis.

In the binary logistic regression model, the independent variables were the usage of metformin, gender, age, and weight interval. The two dependent variables were decrease/no change in weight, and the other variable was increase in weight. Patients who used antipsychotics alone had an odds ratio of 2.35 to develop weight gain in comparison to patients who used antipsychotics with metformin. In addition, 20–29-year-old patients had a 3.46 odds ratio to develop weight gain in

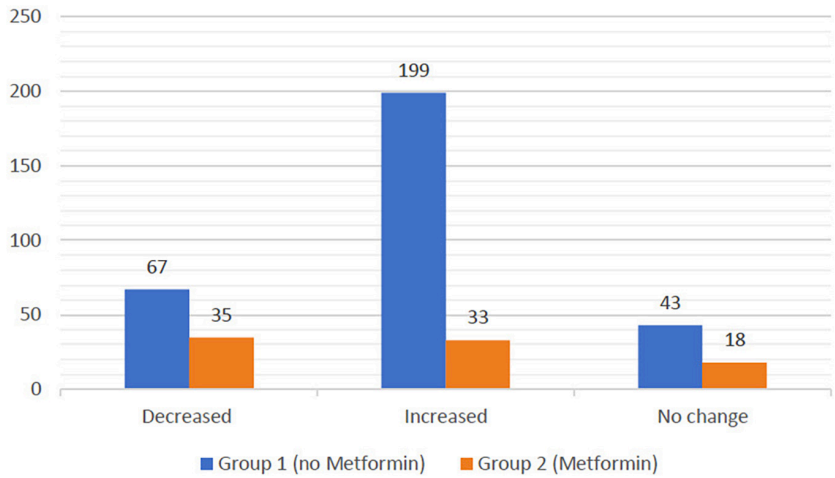

FIGURE 2 | Represents the weight difference among group 1 and group 2 patients categorically. Group 1 revealed increase in the weight with 199 participants, whereas group 2 depicted much less weight gain with 33 participants only. In addition, 67 participants from group 1 have shown weight reduction in contrast to 35 participants from group 2. Importantly, only 43 and 18 participants from both group 1 and group 2 revealed no weight change during the study.

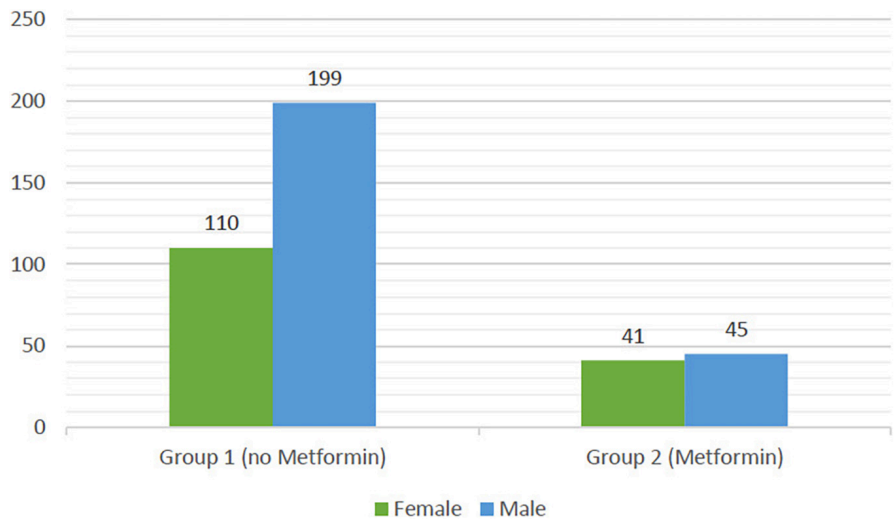

FIGURE 3 | Illustrates the difference between male and female participants in metformin concomitant use. The 199 male participants formed the majority of group 1 vs. the 110 female participants. In group 2 the number of participants showed some similarities with 45 male and 41 female participants.

TABLE 3 | Changes in the Participants' body weight.

Age group	Mean weight difference (kg)	95% CI	Standard deviation (SD)	Significance
20–29	4.66	3.54–5.78	0.57	$P < 0.0001$
30–39	2.59	1.66–3.51	0.48	
40–49	0.95	−0.01 to 1.92	0.50	
50–59	0.78	−0.41 to 1.98	0.62	
60–69	0.15	−1.49 to 1.78	0.84	
≥70	0.35	−1.59 to 2.31	0.99	

comparison to patients who aged ≥70 years. Similarly, patients in the 30–39-year-old age group had a 3.58 odds ratio to develop weight gain in comparison to ≥70-year-old patients. The other age group categories which are 40–49, 50–59, and 60–69 have no difference regarding weight in comparison to ≥70-year-old patients. Gender and weight interval also have no significant difference on weight in binary regression model using the aforementioned variables.

DISCUSSION

Antipsychotics are used for a wide spectrum of mental illnesses. As they are used chronically, the side effects of these medications can cause an impact on the patients' health. AIWG is considered one of the most prominent side effects of these drugs which can lead to the detrimental effects of metabolic syndrome. This study aims to measure the effects of antipsychotics with and without the concomitant use of metformin on body weight. The study outcomes revealed that patients in the metformin and antipsychotics group had less tendency to gain weight when compared to patients in the antipsychotics group.

In this study, we investigated the effect of metformin in reducing the AIWG. The statistical analysis reported that metformin concomitant use caused a significant reduction in the AIWG with a mean change of −0.04 kg as compared to a mean increase of 2.5 kg in patients in the antipsychotics group. These quantitative results are in line with the existing evidence that metformin is effective in controlling AIWG. A meta-analysis conducted by de Silva et al. (15) reported similar findings from several clinical studies where metformin effectively reduced the AIWG. Armen et al. reported that patients treated with metformin had a mean weight gain of 0.83 kg, while the placebo group had a mean weight gain of 2.2 kg (20). Regarding the qualitative results in our study, only 21.68% of patients in the antipsychotics group experienced weight loss as compared to 40.7% of patients who used antipsychotics and metformin. In addition, Wang et al. study reported that 7% of those using antipsychotics without metformin lost weight as compared to 40.7% of patients using metformin (22). In our study, only 38.37% of the patients in the metformin treated group experienced weight gain as compared to 64.4% of those in the antipsychotics group. Wu et al. concluded that 16.7% of patients in the metformin-treated group gained more than 7% of their body weight, as compared to 63.13% in the placebo group (23). These results are in the same line with this study outcome. However, some variability might be addressed in the previous randomized controlled trial by Wu et al., where it was reported that 16.7% in the metformin treated group gained weight compared to 38.37% in our study. We can attribute these differences to the fact that our study was a retrospective cohort study, which justifies, to some extent, the mild inconsistency with other studies.

Regarding the association between gender and weight, a study conducted by Lee et al. (24) suggested that female patients marginally have more weight gain than males. However, in

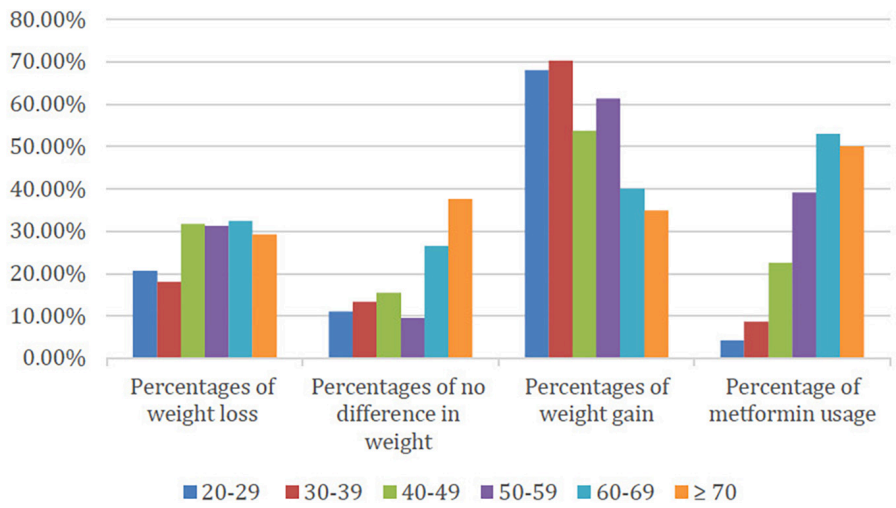

FIGURE 4 | Demonstrates the changes in body weight and metformin use in different age groups of the participants. Weight loss was more prominent in the age groups of 40 and above (approximately 30% reduction). No weight changes were most common among the two oldest age groups (60–69 and ≥70) with frequencies of 26.47 and 37.50%, respectively. The youngest two age groups (20–29 and 30–39) showed the highest frequency of weight gain of 68.06 and 70.30%, respectively. The percentage of concomitant metformin use increased throughout the age groups with the youngest having the least frequency and the two oldest age groups (60–69 and ≥70) reported the highest frequencies of 52.94 and 50%, respectively.

this study, statistical analysis revealed no significant difference between gender and weight change. Importantly, the study outcomes exhibited that female patients appeared to take metformin with antipsychotics more than males even though there was no significant difference regarding weight and gender. The elevated proportion of females taking metformin with antipsychotics can be explained by some other indications for metformin use such as polycystic ovary syndrome as one of the obesity's complications in females (16, 25).

The weight gain between different age groups is found to be elevated among the youngest group (20–29 years) and lowest among the group of 60–69 years old. This significance regarding AIWG in different age groups might be related to the use of Metformin since the concomitant use of metformin with antipsychotics was higher in the oldest (≥70 years) group as compared to the youngest age group (20–29 years). In similar line with this outcome, studies conducted by M. Dayabandara et al. and Lee S. Y. et al., reported that the amount of weight gain is highest in younger patients, then gradually decreased with the increase in age (5, 24). Little evidence supports our results on the increasing use of metformin among the oldest group of patients (≥70 years). However, we estimate that it could be due to comorbidities among elderly patients, namely type 2 diabetes. These results suggest paying more attention to weight gain among young patients.

Despite the current study outcomes, which suggest that there is no significant difference among various antipsychotics monotherapy, several reports revealed that antipsychotics, such as clozapine, olanzapine, and quetiapine can cause AIWG as side effects more than other antipsychotics (26–28). However, the mechanism by which these medications induce weight gain is not fully understood (29). On the other hand, there is also sufficient research that aripiprazole is one of the least weight gain inducing antipsychotics. Another study suggested that aripiprazole had significantly less impact on weight gain as compared to different antipsychotic drugs (12). Another research also demonstrated that aripiprazole may have an effect on its own reducing AIWG as an add-on treatment without the use of Metformin (5). These results support that there is a difference in weight between different antipsychotics, so if a patient with a psychiatric disease has obesity, a physician should consider antipsychotics with a minimum weight increase such as aripiprazole instead of medications that have a high impact on weight such as olanzapine or clozapine. However, as previously mentioned, this study concluded that there is no significant difference among different drugs which may be attributed to the presences of confounding factors, such as unequal distribution of Metformin usage or unequal distribution of patients' numbers. In addition, statistical analysis revealed no significant difference between different weight intervals. In contrast to our outcomes, another study revealed that weight gain was increased in patients using antipsychotics for 6 months (3.5 kg), whereas in 3 months, the weight increased was only 2 kg from baseline (30).

By using a binary logistic regression model with the outcome of decrease/no change in weight and increase in weight, the independent variables of metformin usage, gender, age, and weight interval. Gender and weight interval outcomes are similar to the univariable analysis done in this study, which revealed that these two variables have no significant difference in weight. Also similar to the uni-variable analysis, usage of Metformin can significantly improve the weight since using antipsychotics alone is associated with increasing the weight gain by 2.35-folds. Also, in the binary logistic regression model, the highest age group who had weight gain are patients who are 20–29 years old. This is a dissimilarity of our univariable results which mention that the highest weight gain is in patients who are aged 20–29. These findings are clinically significant in guiding physicians to select the appropriate regimen for an acceptable duration, given that AIWG can be avoided or minimized using the previous results.

LIMITATIONS AND FUTURE DIRECTIONS

One of the limitations of this study is the retrospective design for measuring the desired outcomes. Prospective studies are more accurate in portraying the effect of antipsychotics due to privilege of selecting the participants and ability to reduce the confounding factors. Thus, future studies are guaranteed to prospectively measure the outcomes of antipsychotics and metformin concomitant use on AIWG. Even though this study excluded some conditions that cause weight fluctuations as mentioned in the methods section, many confounding factors such as patients with polypharmacy, lifestyle, physical activity, diet, and other comorbidities may cause weight changes were not measured. Also, some participants underwent some changes in their treatment regimen which in turn may have affected the duration of the medication used. To the best of our knowledge, the research in this field is not well-established in the Kingdom of Saudi Arabia; thus, additional prospective and multi-center studies should be implemented. Moreover, further studies are required to investigate the impact of AIWG on different age groups. Furthermore, additional research is necessary to demonstrate the potential role of other medications such as statins or incretin mimetics on reducing the AIWG (31).

CONCLUSION

Statistically significant data displayed that antipsychotic drugs can cause weight gain among patients and if paired with metformin, it can reduce these effects or even cause weight loss. As weight gain has many side effects, it is important for psychiatrists to educate their patients about these side effects and suggest the appropriate modifications to their treatment regimen to prevent these effects.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the patients' data are utilized for the research purpose, and the datasets are not publicly available since it

contains personal information regarding the patients. Requests to access these datasets should be directed to AH, hakamia@ksau-hs.edu.sa.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the King Abdullah International Medical Research Center (KAIMRC) Institutional review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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BRIEF RESEARCH REPORT
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Comparative Safety Signal Assessment of Hospitalization Associated With the Use of Atypical Antipsychotics

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Background: Persons with symptoms of psychosis receiving treatment with atypical antipsychotics (AAPs) can experience serious adverse events (AEs) requiring admission to the hospital. The comparative likelihood of AE-related hospitalization following the use of all AAPs has not been fully characterized. Therefore, we evaluated the safety signals of hospitalizations associated with the use of AAPs.

Methods: We conducted a cross-sectional analysis using the FDA Adverse Event Reporting System (FAERS) database (from January 1, 2004, to December 31, 2021) to examine disproportionality in reporting hospitalizations suspected to be associated with 12 AAPs (aripiprazole, asenapine, brexpiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, and pimavanserin, quetiapine, risperidone, and ziprasidone). Hospitalization in the FAERs database is an outcome that is recorded as a result of an AE occurring at any drug dose. We estimated reporting odds ratios (RORs) by comparing the odds of hospitalization occurring with a particular AAP to the odds of its occurrence with other drugs. In addition, we considered the presence of a significant safety signal when the lower limit of the 95% confidence interval (CI) of the ROR is >1.

Results: A total of 204,287 cases of hospitalizations were reported to the FDA for individuals treated with AAPs. There were significant safety signals of hospitalization associated with using clozapine (ROR, 2.88; 95% CI, 2.84–2.92), olanzapine (ROR, 2.61; 95% CI, 2.57–2.64), quetiapine (ROR, 1.87; 95% CI, 1.85–1.89), risperidone (ROR, 1.41; 95% CI, 1.39–1.43), aripiprazole (ROR, 1.34; 95% CI, 1.32–1.35), and ziprasidone (ROR, 1.14; 95% CI, 1.10–1.18). However, no hospitalization-related safety signals were observed with the use of paliperidone, pimavanserin, iloperidone, asenapine, lurasidone, and brexpiprazole. The ROR estimates were numerically higher among older adults than younger adults.

Conclusions: This cross-sectional assessment of data from FAERs (2004–2021) suggested that users of clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone were more likely to report being hospitalized than users of other AAPs. Given that the FAERs database

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only contains spontaneous reports of AEs experienced by persons exposed to a drug but without information on exposed persons who did not have an event, a cohort study comparing hospitalizations among new users of individual AAPs against each other is needed to delineate these safety signals further.

Keywords: antipsychotic medication, hospitalization, FAERS database, signal detection, atypical antipsychotics

INTRODUCTION

In patients with psychotic disorders, treatment with antipsychotic (AP) medications entails a trade-off between improving psychotic symptoms and the potential risk of adverse health outcomes requiring hospitalization (1–5). Conditions such as schizophrenia, bipolar disorder, depression, dementia, and Parkinson's disease (PD) may present with psychotic symptoms that require treatment with APs (6, 7). In these patients, hospitalization can occur due to serious adverse events (AEs) associated with AP use (4, 8–10). For example, persons treated with clozapine can experience seizures, myocarditis, pneumonia, and lifethreatening agranulocytosis and may need to be hospitalized for treatment (1, 3, 4, 11, 12). Also, persons with a clinical indication for long-term AP use who do not adhere to their medications can experience acute episodes that may necessitate admission to the hospital (13–16). Specifically, due to their relatively more favorable side effect profiles, atypical APs (AAPs) are generally preferred than typical (first-generation) APs, and they are increasingly used for a broad range of clinical indications in various psychotic disorders (17).

To help improve health outcomes and downstream expenses associated with admission to the hospital, it is crucial to compare individual AAPs and identify which among them are more likely to result in hospital admissions than others. Evidence suggests that first-generation APs were associated with a greater risk for hospitalization than AAPs (18). While there are some differences in efficacy between AAPs, their adverse effects are more different (19). Between 1989 and 2003, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were the only AAPs approved by the US Food and Drug Administration (FDA). Since 2004, the FDA has approved more than 5 AAPs for diverse indications. Although some AAPs are used off-label to treat psychotic symptoms, in situations where there is no strong scientific evidence, such use can lead to AEs, and, ultimately, hospitalization (20, 21). To our knowledge, no study examined the safety signal of all AAPs related to hospitalization. Therefore, this study evaluated hospitalizations reported to the FDA associated with AAP use.

METHODS

Data Source

We performed a cross-sectional analysis of hospitalization reports following treatment with AAPs using the publicly available data from the FDA Adverse Event Reporting System (FAERS) database. The FAERS database is a spontaneous reporting system for AEs and one of the primary tools for pharmacovigilance (22). Although the FAERs database also contains spontaneous reports data from outside the US, it is the largest and best-known national database for the surveillance of AE reports worldwide and reflects clinical practice realities. The study was exempt from ethical review because all analyzed datasets are de-identified and publicly available. In addition, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cross-sectional studies (23).

Primary and Subgroup Analyses

We retrieved spontaneous reports (from January 1, 2004, to December 31, 2021) of hospitalizations following the use of 12 different AAPs (aripiprazole, asenapine, brexpiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, and pimavanserin, quetiapine, risperidone, and ziprasidone) from the FEARs database. Within the FAERs database, hospitalization is an outcome that is recorded as a result of an AE occurring at any drug dose. To evaluate safety signals, we examined the disproportionality in reporting hospitalizations suspected to be associated with AAP use. We estimated reporting odds ratios (RORs) by comparing the odds of hospitalization occurring with a particular AAP to the odds of its occurrence with other drugs, representing standard practice for the safety signal quantitative analyses of data in spontaneous AE reporting in similar databases (24). RORs were estimated because Rothman et al. established that estimating ROR in databases such as the FAERs is advantageous over the proportional reporting ratio (PRR), given that it estimates a relative risk (24). We considered the presence of a significant safety signal when the lower limit of the 95% confidence interval (CI) of the ROR is >1 (25). The 95% CI indicates the precision of the ROR estimate. Furthermore, to examine the influence of patient demographic variables available in the FAERs database that may likely explain a potential relationship between hospitalization and AAP use, we conducted subgroup analyses by age [older adults (65 years or older) vs. younger adults (<65 years)] and sex (male vs. female). We used SAS, version 9.4, to perform all analyses.

RESULTS

Primary Findings

A total of 204,287 hospitalization cases were reported to the FDA for patients treated with AAPs (**Table 1**). There were significant safety signals associated with the use of clozapine (ROR, 2.88; 95% CI, 2.84–2.92), olanzapine (ROR, 2.61; 95% CI, 2.57–2.64), quetiapine (ROR, 1.87; 95% CI, 1.85–1.89), risperidone (ROR, 1.41; 95% CI, 1.39–1.43), aripiprazole (ROR, 1.34; 95%

TABLE 1 | Safety signals of hospitalization associated with atypical antipsychotics use.

AAP	AE reports with AAP (n = 642,578)	No. of hospitalizations (n = 204,287)	ROR	LL 95% CI	UL 95% CI
Aripiprazole	98,129	27,119	1.34	1.32	1.35
Asenapine	8,367	1,392	0.70	0.66	0.74
Brexpiprazole	9,804	861	0.34	0.31	0.36
Clozapine	84,242	37,892	2.88	2.84	2.92
Iloperidone	1,246	210	0.71	0.61	0.82
Lurasidone	17,424	2,511	0.59	0.56	0.61
Olanzapine	80,520	34,286	2.61	2.57	2.64
Paliperidone	41,765	8,081	0.84	0.82	0.86
Pimavanserin	23,438	4,034	0.73	0.70	0.75
Quetiapine	148,278	51,525	1.87	1.85	1.89
Risperidone	110,206	31,659	1.41	1.39	1.43
Ziprasidone	19,159	4,717	1.14	1.10	1.18

AE, adverse event; AAP, atypical antipsychotic; CI, confidence interval; LL, lower limit; UL, upper limit; ROR, reporting odds ratio.
A safety signal is present when the 95% confidence interval of the ROR is >1.

CI, 1.32–1.35), and ziprasidone (ROR, 1.14; 95% CI, 1.10–1.18). There were no significant safety signals associated with using paliperidone (ROR, 0.84; 95% CI, 0.82–0.86), pimavanserin (ROR, 0.73; 95% CI, 0.70–0.75), iloperidone (ROR, 0.71; 95% CI, 0.61–0.82), asenapine (ROR, 0.70; 95% CI, 0.66–0.74), lurasidone (ROR, 0.59; 95% CI, 0.56–0.61), and brexpiprazole (ROR, 0.34; 95% CI, 0.31–0.36).

Subgroup Findings

Clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone showed a consistent association with hospitalization across all subgroups (**Figure 1**). Among a subgroup of persons 65 years or older, we observed a significant safety signal for asenapine (ROR, 2.37; 95% CI, 1.91–2.95) and paliperidone (ROR, 2.16; 95% CI, 1.90–2.45)**.** Furthermore, the estimates of hospitalization-related RORs were generally numerically higher for all AAPs among older adults than younger adults. The study also found that the reporting odds of hospitalization were significantly greater among female users of paliperidone (ROR, 1.08; 95% CI, 1.03–1.12) vs. other drugs but not among males.

DISCUSSION

In this cross-sectional evaluation of data from FAERs (2004–2021), we found significant safety signals related to hospitalization reports following the use of clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone but not with paliperidone, pimavanserin, iloperidone, asenapine, lurasidone, and brexpiprazole. We also observed that asenapine and paliperidone were significantly associated with hospitalization among older adults. In addition, older adults generally had numerically higher ROR estimates for all AAPs than younger adults. Finally, the study found a hospitalization-related safety signal among female users of paliperidone but not in males.

While this study was not designed to assess the specific causes of increased hospitalization, prior research found that hospitalization following the use of AAPs is driven by several known risk factors such as age, sex, drug formulation [e.g., oral vs. long-acting injectable (LAI)], non-adherence, and living in a supervised setting (15). The current study found that older adults generally had higher RORs of hospitalization than younger adults partly because AAPs are associated with potentially serious AEs in vulnerable older adults due to age-related reduction in the ability to metabolize and excrete drugs (26). The ROR estimate for olanzapine in persons 65 years or older was almost twice that of individuals younger than 65. This remarkable difference is likely because, as a previous study demonstrated, the systemic exposure to olanzapine increases by age (27). When older adults are exposed to higher plasma concentrations of olanzapine, they can experience olanzapine-related AEs, which may necessitate being hospitalized for treatment. In addition, the study observed a significant safety signal among persons aged 65 years or above and among female users of paliperidone. These observations might be because female patients aged 65 years and above are more likely to be exposed to a higher plasma concentration of paliperidone, resulting in more AE-related hospitalizations than males (28, 29). Thus, cautious dosing when prescribing paliperidone to older females is needed (28).

The numerically higher RORs among users of olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone than lurasidone users found in this study are consistent with the results of previous cohort studies (30–33). However, while these studies were conducted in patients with schizophrenia and bipolar disorder, the FAERs data used in this study cannot accurately distinguish between the indications of various AAPs; hence we could not conduct analysis by underlying diagnoses. In addition, a retrospective cohort study of older adults with PD by Hwang et al. reported that pimavanserin was associated with an increased risk of 30-day hospitalization compared to non-use (34). However, the study did not compare hospitalizations related to other AAPs. Therefore, the implication of its findings was thought to be limited by confounding with indication due to the lack of an active comparator (34–38). Given our study's findings of hospitalization safety signals related to commonly used off-label AAPs such as quetiapine, olanzapine, risperidone,

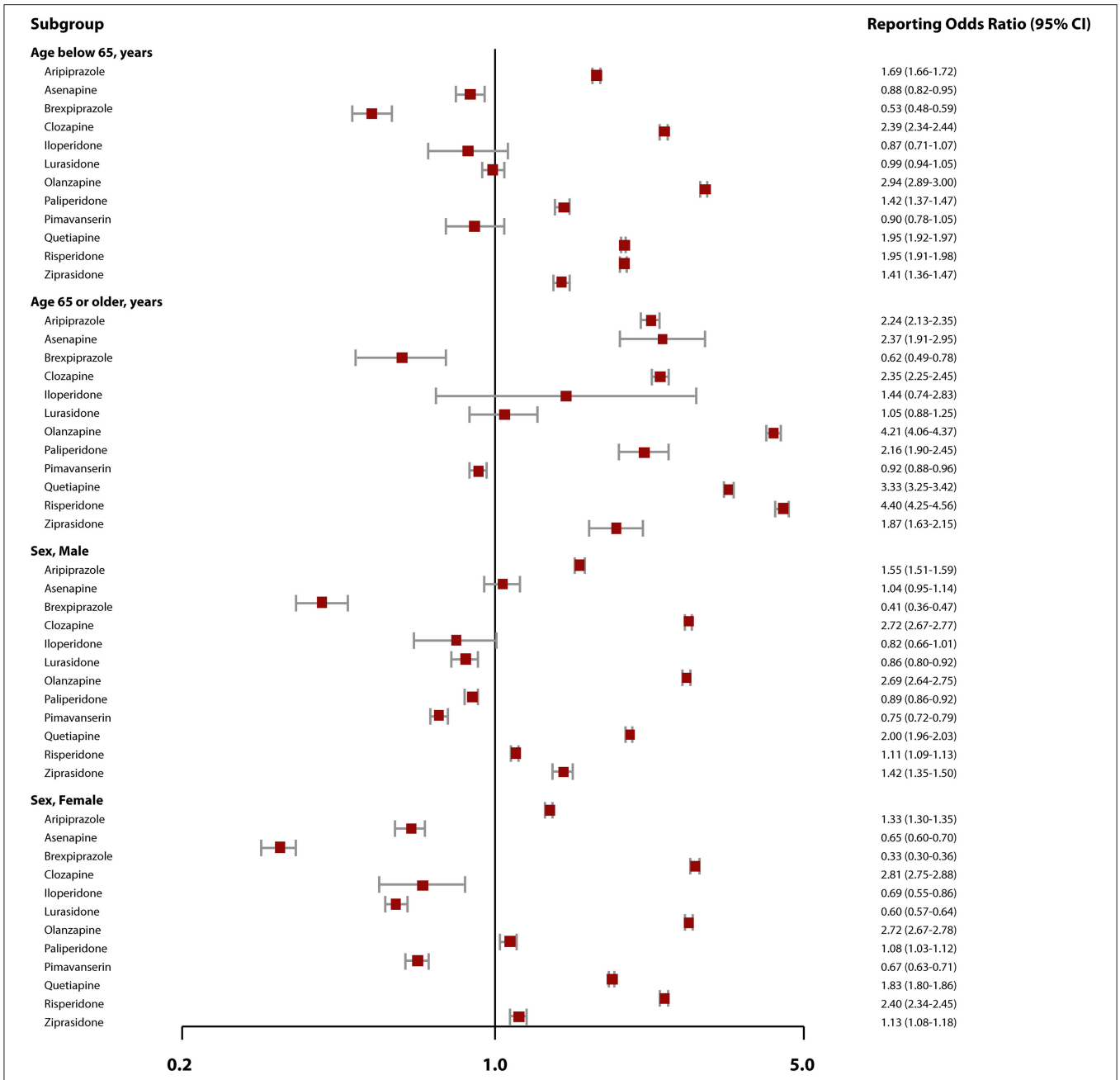

FIGURE 1 | Safety signals of hospitalization associated with atypical antipsychotics use by age and sex. CI, confidence interval. A safety signal is present when the 95% confidence interval of the reporting odds ratios is >1. The maroon-colored square boxes denotes the reporting odds ratio estimates; horizontal lines represents the 95% CI.

and aripiprazole (39), a cohort study comparing individual AAPs may be needed to characterize the risk of hospitalization related to different AAP use compared to each other. Such analysis should consider the clinical indication of an AAP in its design (9, 37, 38).

The fact that we did not observe safety signals among all users of AAPs approved after 2004 (paliperidone, pimavanserin, iloperidone, asenapine, lurasidone, and brexpiprazole) suggests the absence of the "*Weber effect*" (40). In this phenomenon, AE reporting peaks at the end of the second year after a regulatory authority approves a drug (41). The absence of significant safety signals might not be unrelated to the fact that, over the past decade, improvements in drug developments have contributed to having newer alternatives with limited AE profiles that result in hospitalizations (42). For example, pimavanserin has little or no D2-receptor affinity but, with a predominant 5-HT2A receptor

affinity, may be helpful in PD-associated psychotic symptoms, for whom most other APs tend to worsen motor function (1). For aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, the hospitalization-related safety signal estimates were precise, as evident by the relatively narrow 95% CI of the RORs. This observation might be related to the fact that they are more frequently used AAPs across wide-ranging clinical indications throughout the study period (2004–2021). Thus, they received more reports of AE-related hospitalizations. While clinicians are encouraged to avoid using new drugs when older, similarly efficacious alternatives are available (43), individualized consideration of the likelihood that using a drug results in AE-related hospitalization will help improve the health outcomes of patients with a clinical indication for AAPs.

Study Limitations

This study's findings should be interpreted while considering the following limitations. First, signal detection methods employed in the current study can only identify potential drug safety risks but not rule them out. This is because spontaneous reports to FAERs only contained information on persons exposed to a drug and had an AE but with no information about persons who took the drug and did not experience an event. Second, due to its passive surveillance nature and reporting fatigue among clinicians and patients, the FAERS database is subject to underreporting (44). Third, the study could not compare AAPs by formulations and indications. With the established evidence that the use of LAI AAPs was associated with a lower risk of hospitalizations than orals (45), the study would have estimated this possible difference in a subgroup analysis if we had this information at our disposal. Fourth, the study could not estimate the time from exposure to a drug and incidence of hospitalization because such information cannot be estimated reliably using the FAERs data. Fifth, since hospitalization is recorded as a result of an AE occurring at any drug dose in the FAERs database, we were unable to provide information regarding different doses of AAPs. Finally, the study wasn't able to provide information on the specific type of AEs that resulted in hospitalization. Despite these limitations, spontaneous reports represent a valuable tool to monitor potential new safety signals concerning AAPs.

CONCLUSIONS

In this cross-sectional assessment of data from the FAERs, users of clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone were significantly more likely to report being hospitalized than users of other AAPs. However, given that the FAERs database is limited by having information on spontaneous reports of persons exposed to a drug and experienced an AE, but without information on those who did not have the event, a cohort study comparing the risk of hospitalization among users of individual AAPs against each other is needed to further delineate these safety signals.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

ETHICS STATEMENT

The study was exempt from ethical review by the University of South Carolina Institutional Review Board because all analyzed datasets are de-identified and publicly available.

AUTHOR CONTRIBUTIONS

IY and CT: drafting and revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data. IK, EC, SA, and NM: drafting and revision of the manuscript for content, including medical writing for content, and study concept or design. All authors contributed to the article and approved the submitted version.

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Medication Gaps and Antipsychotic Polypharmacy in Previously Hospitalized Schizophrenia Patients: An Electronic Cohort Study in Three Canadian Provinces

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Background: Real world evidence about antipsychotics focuses on rehospitalization. Modeling the time course of pharmacotherapy would show patients' adherence to medications and physicians' adherence to medication guidelines. We aimed to calculate the cumulative time spent in second generation antipsychotics (SGAs), gaps, antipsychotic polypharmacy, and clozapine in discharged schizophrenia patients.

Methods: Hospitalization and pharmacy dispensing data from 2008–2018 in Manitoba, Saskatchewan, and British Columbia were linked and an electronic cohort ($N = 2{,}997$) was created (mean follow-up: 49 months, SD = 38). Cohort members were required to have a minimum of 6 weeks medicated with aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone.

Results: The multistate model predicted that schizophrenia patients accumulated 44 months in SGA monotherapy, 4 months in polypharmacy, 11 months in medication gaps and 17 days in clozapine over a 5-year period. The majority of transitions were between SGA and medication gap. Accumulated time in medication gaps was seven times as much as in clozapine. Each 10% delay in SGA initiation post-discharge was associated with a 2, 1, and 6% higher risk for polypharmacy (95% CI: 1.01–1.02), gap (95% CI: 1.01–1.01), and clozapine (95% CI: 1.04–1.08), respectively.

Interpretation: Schizophrenia patients accumulated more time unmedicated and in polypharmacy compared to clozapine. Either treatment guidelines for schizophrenia are not followed, or real-world challenges hamper their implementation.

Keywords: polypharmacy, real world evidence (RWE), treatment guideline implementation, antipsychotics, schizophenia, adherence - compliance - persistance

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INTRODUCTION

Pharmacotherapy remains the mainstay of treatment for schizophrenia (1). Yet with few specific treatment guidelines, prescribers necessarily rely upon clinical acumen in collaboration with patients. High-quality evidence for first-episode psychosis is even scarcer, as ethical considerations discourage placebo-controlled trials (1).

An exception is clozapine for treatment-resistant schizophrenia, which continues to be strongly supported (1, 2). There is also evidence to suggest clozapine for patients with prominent negative symptoms (3, 4), aggression (5), suicidality (6), and comorbid substance use (7). However, clozapine is prescribed less frequently than would be expected by its indications (2, 8, 9), suggesting either an implementation failure or treatment guidelines that overestimate real-world effectiveness. Real world studies on clozapine tend to focus on more severely ill patients, so it is hard to estimate at what point it is introduced in treatment (10).

According to the Maudsley Treatment Review and Assessment Team (TREAT), various practical considerations contribute to the under-prescribing (or delayed initiation) of clozapine (11). Among these are: identifying treatment refractory patients, ascertaining if previous treatment was adequate, establishing the patient's willingness to engage, and weighing the risks vs. benefits of clozapine for each patient (11). These steps require close coordination among different care providers. Patients on their part may refuse blood tests, and this can delay clozapine initiation (12). There are also barriers on the side of clinicians such as fear of serious side-effects, the burden of constant monitoring, and a self-reported lack of competence (12). Among patients who have agreed to clozapine treatment, several reasons are given for discontinuing: intolerable side effects, non-compliance with blood monitoring, and dysfunctional beliefs about clozapine treatment (13).

Advanced statistical techniques such as network meta-analysis have recently been used to rank large numbers of antipsychotics in terms of efficacy and tolerability/safety with data from clinical trials (3, 14). It remains less clear if these rankings inform clinical practice. The extensive selection criteria found in most trials is a constraint to the generalizability of the findings, thereby making it necessary to examine real-world data (15).

Here, we analyzed prescription and hospitalization data for patients with schizophrenia from three Canadian provinces, with the following objectives:

1. Estimate the dispensing frequency of several second-generation antipsychotics (SGA).
2. Estimate the prevalence of (i) initial SGA, (ii) polypharmacy, (iii) unmedicated treatment gaps, (iv) clozapine, (v) rehospitalization, as well as the cumulative time spent and total visits (or returns) to each state.
3. Calculate the probability of transitions between states and how these are affected by socio-demographic characteristics.

METHODS

Patient Involvement

One-on-one interviews with six persons with schizophrenia and a mental health nurse were held to elicit their lived experience and inform our research questions. After obtaining the results, one patient provided feedback. Recruiting patients, a vulnerable group, was approved by the university ethics board and all participants gave their informed consent and received a small honorarium. Our research was conducted in accordance with the Helsinki declaration of respect for patients.

Data Sources

This was a retrospective study of administrative data about hospitalizations and pharmacy dispensing data in British Columbia, Manitoba, and Saskatchewan from 2008–2018. Hospitalization data consisted of emergency room visits captured in the National Ambulatory Care Reporting System (NACRS) and inpatient stays in the Discharge Abstract Database (DAD). Psychotropic medications were obtained from the National Prescription Drug Utilization Information System Database (NPDUIS)—a Canada-wide register of publicly funded medications dispensed by pharmacies in the community. Despite this national scope, the provincial (territorial) programs only cover low income people and seniors, except for the provinces in this study. Hospitalization and medication files were provided separately by the Canadian Institute of Health Information (CIHI). We linked these files using a unique person identifier provided by CIHI. Our data captured all mental-health related visits and >85% of all psychotropic medications. The exceptions were medications used in hospital and those covered by federal programs. Also, patients emigrating from the three Canadian provinces may have had their records truncated.

Cohort Formation

Patients in an electronic register differ importantly from those enrolled in randomized clinical trials. Trial participants satisfy explicit inclusion and exclusion criteria, thereby ensuring that they are a homogenous group. In contrast, patients in our registries only had the common characteristic of visiting the hospital for a mental condition and obtaining medications from a pharmacy. As such, our first task was to identify a more-or-less homogenous cohort in diagnosis and severity of illness. Accordingly, we formed a cohort of patients using their first hospital visit as an index date and applied the following criteria:

1. Schizophrenia diagnosis (ICD-10 codes: F20.1–F20.9).
2. Adult onset (i.e., aged 19+ at index hospital visit, allowing for the possibility that the true illness onset may have been 18 or younger).
3. Medicated for at least 6 weeks with one of the following SGAs after the hospital visit: aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

We further applied the following criteria in order to capture patients with less serious presentations (i.e., excluding resistant or seriously ill patients):

4. First hospital visit did not contain an ICD code for intentional self-injury or poisoning (X60–X84).
5. Patient was not already on SGA polypharmacy (i.e., not medication resistant).
6. Patient was not already on clozapine or a less-commonly dispensed SGA.

Applying these criteria to the 7,897 patients with a schizophrenia diagnosis at the index visit yielded a cohort of 2,997 people (**Figure 1**). The socio-demographic characteristics

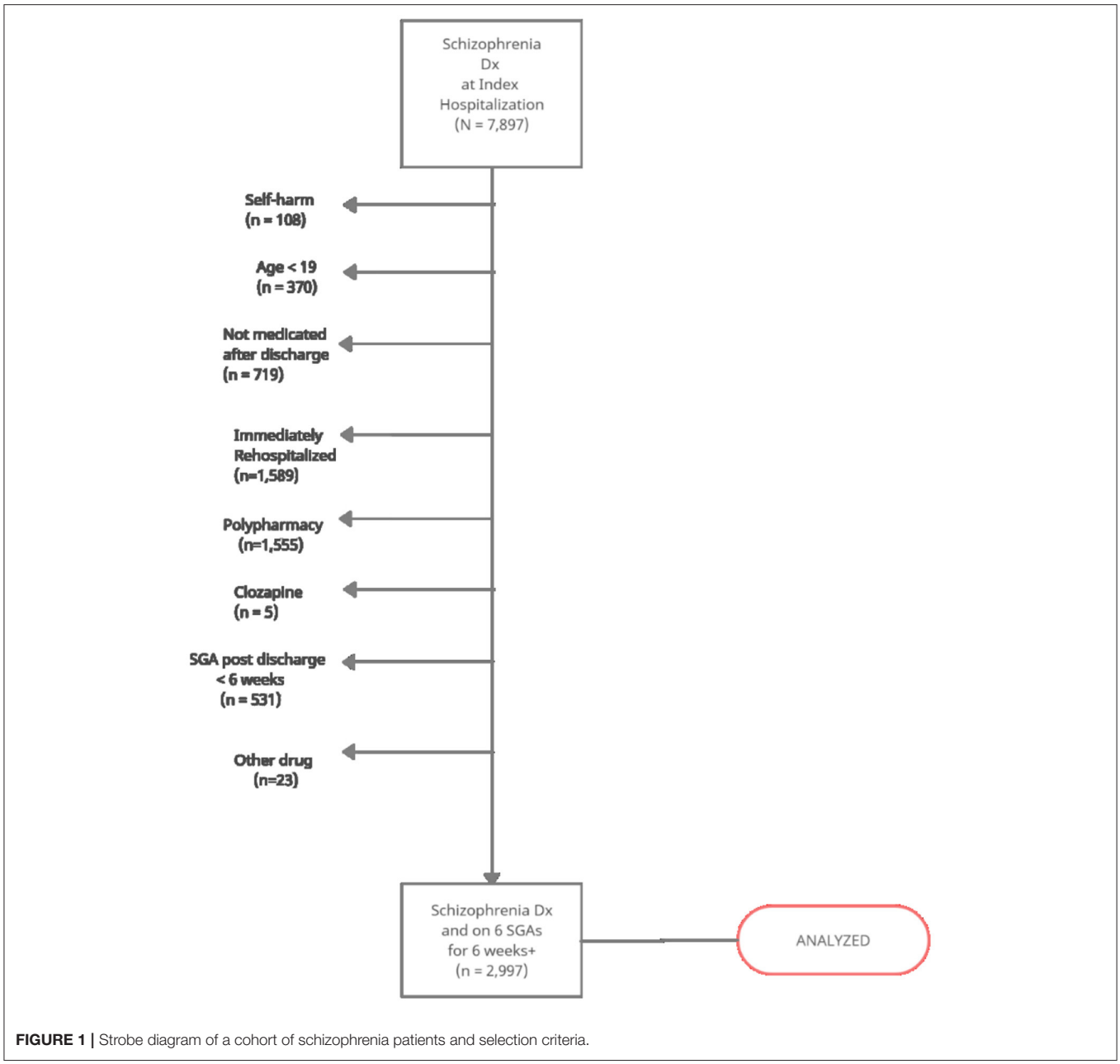

FIGURE 1 | Strobe diagram of a cohort of schizophrenia patients and selection criteria.

of these people at their index visit are summarized in **Table 1**. For each cohort member, SGA refills (and rehospitalization, if applicable) were followed until February 2019 or loss to follow-up, whichever came first. Cohort members had a mean follow-up time of 49 months (SD = 38) and this did not differ by province.

Classification of Treatment States

Each person in the cohort had a longitudinal record of hospitalizations and medication refills. We sorted these records from earliest to most recent. We were interested in four transient states: (1) initial antipsychotic, (2) polypharmacy, (3) unmedicated (treatment gaps), and (4) clozapine. Each person had to have spent at least 6 weeks on SGA monotherapy. This was based on the guideline that response to treatment (if it happens at all) can typically be observed within the first 6–8 weeks (16). The terminal state was rehospitalization. From SGA monotherapy, each person could progress to any of the transient States (2–4), with repeated visits. Follow-up ended when a person was rehospitalized, the person ran out of data, or the cut-off of CIHI data was reached. In the latter two cases, the person was considered lost to follow-up. The assignment of states, especially gaps and polypharmacy (discussed below), was greatly facilitated by the Stata newspell package (17).

Definition of Polypharmacy, Clozapine, and Rehospitalization States

A patient was assigned to the polypharmacy state if two or more psychotropic medications overlapped during follow-up. These psychotropic medications were not limited to the six SGAs in State 1 but included asenapine, chlorpromazine, flupentixol, fluphenazine, haloperidol, levomepromazine, lithium, loxapine, lurasidone, perphenazine, pimozide, pipotiazine, prochlorperazine, sulpiride, trifluoroperazine, and zuclopenthixol. If clozapine overlapped with another medication, this period was assigned to clozapine. Rehospitalization in this study was defined as a hospital visit associated with a mental health condition (ICD F code) or self-harm (ICD X60–X84).

TABLE 1 | Demographic profile of schizophrenia patients at index hospitalization in three Canadian provinces.

Variable	Manitoba	Saskatchewan	British Columbia
N	609 (20)	272 (9)	2,116 (71)
Mean age (SD)	48 (19)	51 (19)	44 (17)
Sex			
Male (%)	367 (60)	156 (57)	1,284 (61)
Female (%)	242 (40)	116 (43)	832 (39)
Initial SGA			
Aripiprazole (%)	22 (4)	11 (4)	167 (8)
Olanzapine (%)	230 (38)	59 (22)	558 (26)
Paliperidone (%)	15 (2)	11 (4)	218 (10)
Quetiapine (%)	115 (19)	73 (27)	336 (16)
Risperidone (%)	220 (36)	107 (39)	800 (38)
Ziprasidone (%)	7(1)	11 (4)	37 (2)
Residence			
Rural, remote, or unclassified area of residence	90 (15)	46 (17)	177 (8)
Urban	519 (85)	226 (83)	1,939 (92)
Mean days to first SGA dispense after discharge from index hospitalization (SD)	45 (144)	54 (209)	37 (131)
Mean months to first clozapine dispense (SD)*	30 (34)	13 (14)	41 (28)

**Calculated only for 57 people who were ever put on clozapine; Number (% of total patients): Manitoba: 9 (1.5), Saskatchewan: 3 (1.1), B.C: 45 (2.1).*

Treatment Gap Calculation

Since all hospitalizations and all psychotropic refills were captured, the follow-up period for each person could be classified into the five states above, subject to the limitation that we did not have quantity and dose at each refill. For this reason, we could not be sure that a person possessed adequate medication during the period between refills, or if there was a gap for which a person was unmedicated. People filled prescriptions at irregular intervals. According to a paper about estimating medication adherence, the grace period between consecutive refills, in various studies, ranges from 15 to 120 days (18). Based on typical prescribing practices, we fixed the grace period at 30 days. Treatment gap was therefore operationally defined as the period starting from day 31 to the date of the subsequent refill (**Supplementary Figure S1**).

Analysis

We fitted a multistate survival model (MSM) using the R package msm (19). This was based on several considerations: (1) The msm package is capable of handling continuous (vs. discrete) time transitions. (2) It handles intermittently observed events (i.e., refills). (3) The msm package allows for cyclic transitions. A MSM is comparable to a simple survival model except that the hazard is calculated for transitions between transient states (i.e., SGA, polypharmacy, gap, and clozapine) and from transient states to the absorbing state (rehospitalization). For a schematic of the states and transitions in our model, please refer to **Supplementary Figure S2**. We had four candidate predictor variables: age at index hospitalization, the interval between hospital discharge and the first pharmacy dispense date, rural/remote/unclassified area of residence vs. urban, and gender.

TABLE 2 | Number (%) of patients in a stage by follow-up time (months). The denominator is the total number of patients remaining in the cohort at a given month.

Follow-up time in months	SGA	Polypharmacy	Medication Gap	Clozapine	Rehospitalized
0	2,997 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6	2,067 (79.5)	96 (3.7)	430 (16.5)	4 (0.2)	4 (0.2)
12	1,757 (75.8)	95 (4.1)	446 (19.2)	7 (0.3)	12 (0.5)
18	1,543 (73.0)	116 (5.5)	423 (20.0)	16 (0.8)	17 (0.8)
24	1,394 (72.3)	108 (5.6)	388 (20.1)	18 (0.9)	21 (1.1)
30	1,240 (71.3)	108 (6.2)	347 (19.9)	19 (1.1)	26 (1.5)
36	1,113 (70.3)	120 (7.6)	303 (19.1)	16 (1.0)	32 (2.0)
42	995 (69.5)	100 (7.0)	283 (19.8)	19 (1.3)	35 (2.4)
48	874 (67.6)	105 (8.1)	256 (19.8)	19 (1.5)	39 (3.0)
54	817 (69.1)	83 (7.0)	218 (18.4)	21 (1.8)	44 (3.7)
60	740 (69.2)	73 (6.8)	184 (17.2)	23 (2.2)	49 (4.6)

RESULTS

State Prevalence Up to 60 Months

As **Table 2** shows, the proportion of schizophrenia patients who were on an SGA was close to 70% at up to 5 years. However, at any single time except at baseline, 16–20% of patients had a gap in treatment and 5–7% were on polypharmacy. The total proportion of patients who received clozapine (whether by itself or with another antipsychotic) never reached 3% over the entire follow-up ($n = 57$ people). Close to 5% of remaining cohort members were rehospitalized at 5 years.

Over a 5-year (60-month) period, the accumulated time spent in each of the states were: 44 months in initial SGA, 4 months in polypharmacy, 11 months in medication gaps, and 17 days in clozapine. On average, patients had 10 spells of SGA monotherapy, 1 spell of polypharmacy, 10 untreated spells and <1 clozapine spell. SGA monotherapy and gaps tend to cycle back-and-forth as shown in **Supplementary Figure S3**.

Transition Probabilities Between States

At 3 months, there was an 18% percent chance of a gap in treatment given that one was on an SGA. Given that a patient has a medication gap, returning to an SGA was most likely but there was a 22% chance of continuing to be unmedicated. People on clozapine had a 73% chance of remaining on clozapine. The probability of rehospitalization at 3 months was close to zero (**Table 3**).

The transition probabilities including loss to follow-up for the entire follow-up period is depicted in **Supplement Figure S3**. Over the entire follow-up period, only 57 patients (1.9%) ever received clozapine and 64 people (2.1%) were rehospitalized.

Effect of Socio-Demographic Covariates on Transitions From SGA

Here we focus on how socio-demographic characteristics modify the transitions from SGA, since this is the initial state. See **Supplementary Table S1** for the complete results. Each 10% increase after age 19 represented a 3, 2, and 7% risk reduction for polypharmacy, gap, and clozapine, respectively. Each 10% delay in first SGA dispense after discharge was associated with a 2, 1, and 6% higher risk for polypharmacy, gap, and clozapine, respectively. Living in a non-urban area was associated with a 33% lower risk of polypharmacy, a 22% higher risk of a medication gap, and 27% lower risk of being treated with clozapine. Female patients, compared to males had a 20% higher risk of transitioning to polypharmacy from an initial SGA. Female patients on polypharmacy were 88% more likely to have a medication gap. None of the variables predicted rehospitalization from any state.

TABLE 3 | Probability of transitioning to (remaining in) a state from a given state at 3 months.

From / To	SGA	Polypharmacy	Gap	Clozapine	Rehospitalized
SGA	78	4	18	0	0
Polypharmacy	41	46	12	0	0
Gap	72	5	22	0	0
Clozapine	16	1	10	73	0
Rehospitalized	0	0	0	0	1

Cell entries are percentages.

TABLE 4 | Hazard ratios (95% CI) on selected transitions for four covariates.

From:	To:	Index Age (each 10 pct increase from 19 years)	Initial Medication Delay (each 10 percent increase from discharge)	Rural/Remote/ Unclassified vs. Urban (reference)	Female vs. Male (reference)
SGA	Polypharmacy	0.97 (0.96–0.97)*	1.02 (1.01–1.02)*	0.67 (0.55–0.81)*	1.20 (1.08–1.32)*
SGA	Gap	0.98 (0.98–0.98)*	1.01 (1.01–1.01)*	1.22 (1.16–1.27)*	0.99 (0.96–1.02) n.s.
SGA	Clozapine	0.93 (0.91–0.95)*	1.06 (1.04–1.08)*	0.73 (0.26–2.06) n.s	0.72 (0.36–1.44) n.s.
Polypharmacy	Gap	0.98 (0.97–0.98)*	1.00 (1.00–1.00) n.s.	1.77 (1.42–2.20)*	1.88 (1.63–2.17)*
Polypharmacy	Clozapine	0.93 (0.89–0.97)*	1.03 (1.00–1.07)*	0.93 (0.14–6.11) n.s.	1.21 (0.40–3.63) n.s.
Gap	Clozapine	0.97 (0.96–0.98)*	1.04 (1.04–1.05)*	0.40 (0.19–0.85)*	Not entered

The two left columns represent the outcome, third to sixth columns are predictors that modify the baseline hazard. Predictor variables are entered simultaneously. Asterisk (*) indicates significance at p = 0.05.

DISCUSSION

We had two main findings: (i) schizophrenia patients accumulated substantial periods without medication (treatment gaps), and (ii) patients are on polypharmacy 7 times as long as they are on clozapine.

Although we did not have access to the reasons for treatment gaps, we offer two possibilities. First, patients may have recovered from their illness so as not to require medication, but relapsed sometime later. Up to 20% of schizophrenia patients only experience a single episode as noted in the Canadian Schizophrenia Guidelines (1). This is also consistent with unmedicated rates in naturalistic longitudinal studies in the US (20) and Finland (21). In these studies, ongoing medication was associated with disease severity, and most of the unmedicated patients were clinically stable (20, 21). Therefore, some treatment gaps may reflect periods of recovery and prudent prescribing on the part of physicians.

Alternatively, patients may have needed medications but stopped taking them because of tolerability, logistical, or financial reasons. This fits with the 22% higher risk of treatment gaps among non-urban dwellers from an initial SGA and a 77% higher risk of a gap from polypharmacy (**Table 4**). Adherence to medications is influenced by patient insight into their illness, perceived efficacy of the medication, family support, and the availability of case managers (22, 23). Patients in non-urban areas may have more limited contact with physicians, community health managers, and health services in general.

Regarding affordability, it is estimated that 10% of Canadians cannot afford out-of-pocket medication expenses (24). Up to 80% of people with schizophrenia are unemployed (25), so it is possible that some medication gaps are a result of poverty. Unlike universal healthcare coverage, prescription medications are left for provincial governments to decide (26). According to the schizophrenia patients we interviewed, affordability was not a problem because clozapine was paid for by the Saskatchewan provincial government. However, they were generally unable to join the job market—even if they wanted—because their income would count against what they receive from the government.

Although the prevalence of polypharmacy was lower than other studies (27, 28), patients in this cohort were still 7 times as likely to be on polypharmacy as on clozapine. This likely reflects the extent that clozapine is underutilized. Notably, a Canadian study noted that polypharmacy is more prevalent than any antipsychotic monotherapy (29). In the US, <5% of schizophrenia patients were treated with clozapine in 2008 (30)—still higher than the 2% of patients in this cohort. By comparison, up to 50% of schizophrenia patients are on polypharmacy (31) despite the lack of compelling evidence for its efficacy (32). A high polypharmacy rate therefore may therefore represent a gap between treatment guidelines and implementation.

The single biggest barrier to clozapine utilization is probably administrative burden associated with patient monitoring (33). A mental health nurse we interviewed stated that a brand name manufacturer of clozapine relieves some of the administrative burdens by monitoring the patients' blood test results for signs of neutropenia. Patient refusal to initiate (or continue) clozapine treatment may have also contributed to underutilization (12, 34). The three provinces varied significantly with regard to clozapine initiation, with British Columbia waiting more than 3 years on average. By comparison, a study of outpatient schizophrenia patients in Manitoba reported that clozapine was initiated at 8.9 years for males and 7.7 years for females, on average (35). Two-thirds of them had been on 3 or more antipsychotics before the switch to clozapine (35). Delayed initiation of clozapine treatment—perhaps by lingering in mono- or polypharmacy—tends to reduce its efficacy (36).

With evidence-based guidelines being recommendatory, they cannot compel physicians and patients to use clozapine. However, a softer approach that eases administrative burden, provides logistical support, and alleviates patient and clinician concerns has been recommended (37). There is a debate about the ethics of offering monetary rewards for adherence to medications, and a few randomized control studies have been undertaken (38, 39). But the possibility that such an incentive is tantamount to coercion has made it a contentious topic (40).

The finding that older people were at lower risk of polypharmacy, unmedicated periods, and clozapine could mean that they had later onset of the disease. Younger age of onset tends to be associated with a worse prognosis (41). The finding that delay to the first pharmacy claim from hospital discharge increases the risk for polypharmacy, unmedicated periods, and clozapine treatment has implications for the provision of health services. Transitioning from hospital to the community is known to be a vulnerable period in which medication compliance is paramount (42, 43). The use of depot antipsychotics and intensive community treatment programs may improve adherence and prognosis (44–46).

Female patients had higher risk of polypharmacy. Similar results have been reported elsewhere (28, 47, 48) but not invariably (49, 50). Schizophrenia has earlier onset in men than in women and earlier onset is associated with a more severe course of illness (5). Some have reported that women are more adherent to treatment than men (5–7), so we are unsure if this finding reflects a gender difference per se or confounding by other variables.

Our findings are subject to several limitations. We did not know the true age of schizophrenia onset and used age at index hospitalization as a proxy. Given the mean age at index hospitalization (>40 years), it is highly improbable that patients in the cohort were first-onset cases. Since they probably lived with schizophrenia for a decade or more, it is more surprising that clozapine was dispensed to so few and so late in the treatment. Unfortunately, the data cannot distinguish if this is a result of under-prescribing or patients refusing to accept clozapine medication—something that needs to be further studied. Our data sources did not contain clinical notes and symptoms, so we did not have indications for the antipsychotic prescriptions, and the reasons for polypharmacy. Likewise, we could not examine the effect of gaps and polypharmacy on symptoms. Some periods classified as polypharmacy may have been gradual transitions from one SGA to another. Earlier Canadian studies have estimated the prevalence of polypharmacy

upon hospital discharge at 19 to 40 percent (29, 51, 52). These are consistent with our finding that polypharmacy is more prevalent than treatment with clozapine. Finally, our data did not include mortality—this may have contributed to the low re-hospitalization rate.

DATA AVAILABILITY STATEMENT

The data used in this paper were acquired from the Canadian Institute of Health Information, with the agreement of the provinces of British Columbia, Saskatchewan, and Manitoba. The terms of the agreement prohibit the sharing of data without the prior consent of the provinces. Requests to access these datasets should be directed to Smriti Fernandez, smfernandez@cihi.ca, www.cihi.ca.

AUTHOR CONTRIBUTIONS

LB, GM, and RJL contributed to the design of the study. LB and AS performed the statistical analysis. EP wrote the introduction and discussion sections. EP and LB presented preliminary results at a meeting and gathered comments. LB wrote the methods and results sections. SH, EP, RL, KJ, and GM contributed to the interpretation of results. All authors contributed to the submitted version. LB, GM, KJ, and RJL acquired funding and the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.917361/full#supplementary-material

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Factors influencing prolactin levels in chronic long-term hospitalized schizophrenic patients with co-morbid type 2 diabetes mellitus

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Background: For long-term hospitalized patients suffering from schizophrenia, metabolic disease and hyperprolactinemia (HPRL) are common comorbidities. This article is aimed at analyzing the factors influencing comorbid type 2 diabetes mellitus (T2DM) on prolactin (PRL) levels in long-term hospitalized patients suffering from schizophrenia.

Methods: This study included 378 long-term hospitalized patients with schizophrenia. Common metabolic markers and PRL levels of included samples were collected, and the severity of psychopathology was assessed using the Positive and Negative Symptoms Scale (PANSS). Based on the patients with or without T2DM, the samples were divided into two groups. The differences in clinical parameters between the two groups were compared, and the effects of the parameters on the PRL levels were analyzed.

Results: Compared with non-DM patients, the patients in the DM subgroup had lower PRL levels ($P < 0.0001$) and rather severe psychiatric symptoms ($P = 0.016$). Female, treated by risperidone, and high levels of triglyceride (TG) were faced with risk for HPRL ($B = 26.31$, $t = 5.39$, $P < 0.0001$; $B = 19.52$, $t = 4.00$, $P < 0.0001$; $B = 2.71$, $t = 2.31$, $P = 0.022$, respectively). Meanwhile, co-morbid DM and aripiprazole treatment were protective factors ($B = 15.47$, $t = 3.05$, $P = 0.002$; $B = -23.77$, $t = -2.47$, $P = 0.014$; respectively). Ultimately, in the DM subgroup, the dose of metformin was found to be a protective factor for HPRL ($B = -0.01$, $t = -1.46$, $P = 0.047$), while female and aripiprazole were risk factors ($B = 16.06$, $t = 3.26$, $P = 0.001$; $B = 20.13$, $t = 2.57$, $P = 0.011$; respectively).

Conclusion: Aripiprazole is a protective factor for HPRL in long-term hospitalized patients, whereas the female is a risk factor. Metformin is beneficial in reducing PRL levels in patients with co-morbid DM. More aggressive and effective interventions are required for preventing adverse drug reactions in women and patients with co-DM.

KEYWORDS

long-term hospitalized, chronic, schizophrenia, diabetes mellitus, metabolic indicators, prolactin

Introduction

Globally, disability-adjusted life-years (DALYs) for mental disorders increased from the 13th leading cause in 1990 to the 7th leading cause in 2019 (1). During this time, the age-standardized incidence rate (ASIR) and age-standardized DALYs rate (ASDR) of schizophrenia in China increased by 0.3 and 3.7%, respectively (2). According to data from China's Guangdong Province, one of the reasons for the increased burden of schizophrenia in China is the large population base and aging population (3). Due to the unknown etiology and a lack of specific drugs, the cure rate for schizophrenia is low. According to a meta-analysis, approximately one-third of patients with first-episode schizophrenia were unresponsive or resistant to antipsychotic treatment (4). With the prolongation of the disease, the increase in the number of attacks, the randomization of prescription drugs, and other factors, the treatment response rate of schizophrenia becomes lower, and the response time becomes longer (5). Thus, many schizophrenic patients in China are indwelled in psychiatric hospitals for long-term in-patient treatment due to the aforementioned factors as well as due to reasons related to patients' families and the loss of their working capacity caused by mental disability.

Metabolic syndrome is one of the common comorbidities of schizophrenia. Significant metabolic disturbances have been reported in schizophrenia, prior to the use of antipsychotics (6, 7). These metabolic disturbances are observed in approximately one-third of the total sick population (8). Furthermore, the widespread use of second-generation antipsychotics in recent years has had a negative impact on the metabolic syndrome of schizophrenic patients. Among them, two antipsychotics, clozapine, and olanzapine have rather prominent effects on metabolism (9). Diabetes mellitus (DM) is a globally prevalent metabolic disease. According to the International Diabetes Federation, about 537 million adults are currently living with DM, and the number is expected to increase to 643 million by 2030 (10). The need to manage metabolic comorbidities during hospitalization, particularly diabetes, is common in patients with schizophrenia predisposed to metabolic diseases. According to some studies, the comorbidity rate of severe mental illness and diabetes varies from 3.7 to 4.2% (11, 12). Another study from New Zealand reported that 41% of schizophrenic patients taking clozapine had abnormal blood sugar levels, and 26.48% suffered from co-DM (13).

Hyperprolactinemia (HPRL) is another common adverse reaction to antipsychotic drugs. The incidence of HPRL affects approximately 67–70% of patients taking antipsychotic drugs, depending on gender (14), and prolactin (PRL) levels were found to be affected dose-dependently with the use of antipsychotics (15). Although it has been suggested that the high levels of serum PRL caused by antipsychotic drugs can improve blood flow to some brain regions of patients, thereby acting as a neuroprotective agent (16, 17), a long-term HPRL status has a wide range of adverse physical effects, such as osteoporosis, male sexual dysfunction, breast development, female amenorrhea, gynecological tumors, etc. (18). Therefore, HPRL is regarded as one of the primary reasons for the decline in patient medication adherence.

Despite extensive and numerous studies on metabolic disorders and HPRL in schizophrenia, only a few studies have focused on the metabolic levels of long-term hospitalized schizophrenia patients and their relationship with PRL levels. Based on the huge population base of long-term hospitalized schizophrenic patients in China, the present research analyzed the factors affecting the PRL levels of long-term hospitalized patients, especially the patients with T2DM, in comparison with common metabolic indexes and PRL levels of co-T2DM and non-comorbid T2DM of schizophrenic patients. This study will provide suggestions and methods for the effective intervention of HPRL in this patient population.

Materials and methods

Subjects

A total of 378 patients with schizophrenia hospitalized for a long duration at Wuhan Mental Health Center and Suzhou Guangji Hospital from June 2018 to May 2019, were selected for this study.

Inclusion criteria

1. Meet the diagnostic criteria for schizophrenia mentioned in the International Classification of Diseases 10th Revision (ICD-10).
2. Age 18–70 years old, male or female.
3. The course of a psychiatric disorder is at least 6 years.
4. At least one-time point during the study period had 2 years of continuous hospitalization.
5. The total score of the Positive and Negative Symptom Scales (PANSS) was greater than 60 points.
7. There has been no antipsychotic adjustment in the last 3 months.
8. Type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia were not excluded as common metabolic syndromes.

Exclusion criteria

Bipolar disorder, intellectual developmental disorder, dementia, severe depression, substance dependence, and other types of mental illnesses were excluded. Patients who use exogenous insulin (including those with T2DM requiring exogenous insulin for glycemic control and those with type 1 diabetes mellitus) and those with severe physical conditions other than the usual metabolic diseases that limit their capacity to carry out everyday tasks, such as severe heart disease, cerebral infarction sequelae, etc., were also excluded from the study. Additionally, patients with conditions including polycystic ovarian syndrome and PRL-secreting pituitary tumors that alter PRL levels were not included.

This study was reviewed and approved by the ethics committee of Wuhan Mental Health Center. The guardians of all participants knew about this study and signed informed consent.

Research design

This study was designed as a cross-sectional study under natural observation conditions. The samples were divided into comorbid T2DM and non-T2DM groups based on whether the enrolled patients had T2DM. The differences in metabolic parameters between the two groups were compared, and the influencing factors of PRL levels in chronic long-term hospitalized patients with schizophrenia were analyzed. The influencing factors of PRL levels in subgroups of T2DM were further analyzed.

The PANSS assessment was completed on the same day for patients who met the inclusion criteria to determine the severity of the patient's mental symptoms. The patient's age, course of the disease, age of onset, duration of hospital stays, education level, and other information were extracted from the electronic medical record system. General clinical data such as body mass index (BMI), body weight (BW), abdominal circumference (AC), and type and dose of antipsychotic drugs in the last week (including the dose and type of hypoglycemic drugs), were extracted for patients with comorbid diabetes. The levels of fasting blood glucose (FBG), renal function, blood lipids, etc., detected for patients within the past month were also collected. For women of childbearing age with a regular menstrual cycle or taking antipsychotic medications that cause oligomenorrhea, the detection time of PRL was unified as the ovulation period of the patient's menstrual cycle. The aforementioned parameters were entered into the self-created Excel spreadsheet program.

The PANSS evaluation was conducted in two sub-centers, each with two uniformly trained residents or attending physicians with more than 5 years of working experience.

Data analysis

The mean and standard deviation of the normally distributed continuous measurement data were calculated, including the counts of the categorical variables. The independent sample *t*-test was used to compare data from different groups. The Chi-square test was used for the comparison of rates. The multiple linear regression model was constructed to analyze the influencing factors of PRL. All statistical tests were given a significance level of $P < 0.05$ (two tails).

Results

General clinical treatment characteristics

Table 1 presents the demographic and general clinical data of 378 patients with chronic schizophrenia in long-term hospitalization.

Differences in clinical parameters between schizophrenia patients with and without diabetes mellitus

The patients were divided into two groups based on whether they had comorbid DM, namely the group with DM (marked as group A) and the group without DM (marked as group B). The two groups were compared in terms of general clinical treatment, common metabolic parameters, and PRL (Table 2). Compared with group B, the course of disease, fasting blood glucose (FBG), uric acid (UA), triglyceride (TG), and PANSS scores were significantly increased in group A ($P < 0.0001$, $P < 0.0001$, $P = 0.011$, $P < 0.0001$, $P = 0.016$, respectively). Meanwhile, the onset age, blood uric acid (BC), high-density

TABLE 1 The general clinical characteristics of the included patients.

Index	Included patients (n = 378)
Age—years	
Mean (SD)	48.12 (9.82)
Range	25–70
Gender—(n, %)	
Female	228, 60.32%
Male	150, 39.68%
Onset age—years	26.80 (8.97)
Course of disease—years	21.32 (9.34)
Length of hospital stay—years	4.56 (1.19)
Combined diabetes—(n, %)	
Yes	147, 38.89%
Metformin	72, 48.98%
Co-metformin	51, 34.69%
Others	24, 16.33%
No	231, 61.11%
Educational background—(n, %)	
High school and above	138, 36.51%
Middle school and below	240, 63.49%
Prescription drugs—(n, %)	
Clozapine	99, 26.19%
Combined with clozapine	96, 25.40%
Olanzapine	27, 7.14%
Risperidone	42, 11.11%
Quetiapine	27, 7.14%
Aripiprazole	15, 3.97%
Others	72, 19.05%

Metformin, metformin monotherapy for diabetes; Co-metformin, combined metformin for diabetes; Others, other drug regimens for diabetes.

lipoprotein (HDL), low-density lipoprotein (LDL), and PRL were significantly decreased (P = 0.041, P = 0.001, P = 0.041, P = 0.021, P < 0.0001, respectively). Furthermore, the prescribed antipsychotic medications were significantly different between the two groups (P = 0.007).

Analysis of influencing factors of prolactin levels in included patients

Using PRL as a dependent variable, the following variables were used as independent variables: gender, onset age, course of the disease, DM (0 = co-comorbidity, 1 = non-comorbidity), quetiapine, olanzapine, aripiprazole, risperidone, clozapine, FBG, BC, UA, TG, LDL, and PANSS scores (all the antipsychotics involved were marked as default 0 = non-prescribed, 1 = prescribed). A multiple linear regression model was constructed, shown in Table 3. We found that female, risperidone, and high levels of TG were risk factors for HPRL (B = 26.31, t = 5.39, P < 0.0001; B = 19.52, t = 4.00, P < 0.0001; B = 2.71, t = 2.31, P = 0.022, respectively). Meanwhile, co-DM, aripiprazole, and high levels of UA were protective factors for HPRL (B = 15.47, t = 3.05, P = 0.002; B = −23.77, t = −2.47, P = 0.014; B = −0.05, t = −2.49, P = 0.013; respectively).

Analysis of influencing factors of prolactin levels in schizophrenia patients with diabetes mellitus

Based on the above findings, we investigated the factors influencing PRL levels in schizophrenia patients suffering from DM (Table 4). Multiple linear regression models were constructed, using PRL levels as the dependent variable, whereas metformin dose, gender, aripiprazole, risperidone, UA, and TG were considered as independent variables (The antipsychotics involved were marked by 0 = non-prescribed, 1 = prescribed). Finally, we found that metformin was a protective factor for HPRL (B = −0.01, t = −1.46, P = 0.047), whereas female and aripiprazole were risk factors for HPRL (B = 16.06, t = 3.26, P = 0.001; B = 20.13, t = 2.57, P = 0.011, respectively).

Discussion

The present study reported that the schizophrenia group with DM had an earlier onset of mental illness, a longer overall psychiatric course, and more severe residual psychiatric symptoms under natural observation conditions. Other metabolic indicators (such as TG, UA, and HDL) were also poorly controlled, apart from poor control of blood sugar levels. Additionally, PRL levels in DM clinical subgroup were lower than in those without DM subgroup. When the factors affecting PRL in the included population were particularly focused, it was found that co-DM, prescription aripiprazole, and UA levels were the protective factors of PRL, whereas female, prescription risperidone, and high levels of TG were found to be functioning as risk factors. We further analyzed the influencing factors of PRL in the subgroup of comorbid DM and found that metformin dose and male were the protective factors of HPRL. However, the prescription aripiprazole lost its protective effect on HPRL and became a risk factor.

Antipsychotics induce HPRL by blocking dopamine D_2 receptors on anterior pituitary PRL-releasing cells. Thus the release of PRL from these cells is no longer inhibited by dopamine and more PRL is secreted (19). Despite the reported studies, no specific intervention is required when antipsychotic-induced PRL levels are below 50 ng/mL (20). A guideline suggests that interventions are only needed for symptomatic antipsychotic-induced HPRL (18). However, some guidelines recommend more aggressive treatment and intervention for antipsychotic-induced HPRL, even without symptoms (21). Regardless, the negative effects of HPRL are well-defined and pervasive, necessitating aggressive intervention and meticulous

TABLE 2 Differences in general clinical treatment and metabolic parameters between patients with diabetes and without diabetes.

Variable	Group A	Group B	t/χ^2	*P*
Age—years	46.96 ± 10.20	48.86 ± 9.52	−1.84	0.067
Gender—(n, %)			2.50	0.114
Female	96, 65.31%	132, 57.14%		
Male	51, 34.69%	99, 42.86%		
Onset age—years	26.04 ± 9.35	27.98 ± 8.24	−2.05	0.041*
Course of disease—years	22.81 ± 8.50	18.98 ± 10.12	3.83	<0.0001*
Length of hospital stay—years	4.59 ± 1.24	4.55 ± 1.17	0.37	0.713
Educational background—(n, %)			0.01	0.967
High school and above	54, 36.73%	84, 36.80%		
Middle school and below	93, 63.27%	146, 63.20%		
Prescription drugs—(n, %)			17.61	0.007*
Clozapine	33, 22.45%	66, 28.57%		
Combined with clozapine	38, 25.85%	57, 24.68%		
Olanzapine	11, 7.48%	15, 6.49%		
Risperidone	12, 8.16%	30, 12.99%		
Quetiapine	15, 10.20%	12, 5.19%		
Aripiprazole	12, 8.16%	3, 1.30%		
Others	26, 17.69%	48, 20.78%		
BW—kg	60.60 ± 11.04	59.96 ± 10.49	0.57	0.569
AC—cm	80.24 ± 8.76	79.72 ± 8.73	0.56	0.579
BMI—kg/m^2	22.75 ± 8.85	21.79 ± 3.44	1.48	0.139
FBG—mmol/L	7.33 ± 2.89	5.25 ± 1.00	10.02	<0.0001*
BUN—mmol/L	3.84 ± 3.06	3.79 ± 1.47	0.19	0.851
BC—mmol/L	63.89 ± 20.77	71.56 ± 21.06	−3.47	0.001*
UA—mmol/L	415.63 ± 121.80	385.31 ± 104.96	2.57	0.011*
TC—mmol/L	4.59 ± 1.11	4.69 ± 1.06	−0.89	0.375
TG—mmol/L	3.03 ± 2.38	2.08 ± 1.32	4.97	<0.0001*
HDL—mmol/L	0.99 ± 0.25	1.05 ± 0.28	−2.05	0.041*
LDL—mmol/L	2.24 ± 0.82	2.43 ± 0.80	−2.31	0.021*
PRL—ng/mL	31.27 ± 26.55	53.29 ± 49.53	−4.96	<0.0001*
PANSS	89.06 ± 11.11	86.17 ± 11.42	2.43	0.016*

Group A, schizophrenia comorbid diabetes; Group B, schizophrenia without diabetes.
BW, body weight; AC, abdominal circumference; BMI, body mass index; FBG, fasting blood glucose; BUN, blood urea nitrogen; BC, blood creatinine; UA, blood uric acid; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRL, Prolactin; PANSS, Positive and Negative Symptom Scales.
*$P < 0.05$.

management. Reducing drug dosages, switching antipsychotic drug types, co-prescribing dopamine agonists, and adding low-dose aripiprazole are typical therapies in psychiatric therapeutic care for HPRL, with the last having a greater level of evidence and recommendation (22). A further established safe and efficient strategy is the co-prescription of dimethicone (23).

We discovered in this study that patients with co-DM had more severe psychopathology, younger onset, and longer disease duration. This should indicate that patients are more likely to receive antipsychotic prescriptions earlier, for a longer duration, and in higher doses. It also indicates that patients are more likely to be metabolized by earlier prescriptions of clozapine, which has a more pronounced side effect (9). This might also contribute to the development of diabetes comorbidities like elevated UA levels and unfavorable lipid profiles. Some studies suggest that the dose of antipsychotics influences some adverse medication reactions (such as hyperglycemia, HPRL, weight gain, and so on) in schizophrenic patients (23). This research is based on chronic psychotic patients with a long course of the disease; thus, it is difficult to trace the types of antipsychotic drugs, they have been taking in their medical history. The types of antipsychotic drugs prescribed are also differing and complex; thus, association analysis of metabolic markers with the dose and exposure time of antipsychotics could not be performed. Only a portion of the qualitative analysis was carried out.

Aripiprazole, as a relatively unique antipsychotic drug, has the pharmacological effect of partially activating the D_2 receptor, which has been demonstrated in numerous studies and is recognized by the industry to improve HPRL caused by antipsychotics. Simultaneously, aripiprazole has also been

TABLE 3 Influencing factors of prolactin levels: Multiple linear regression model.

	B(SE)	95%CI	*t*	*P*
Constant	16.40 (26.18)	−35.08 to 67.88	0.63	0.531
Gender (male vs. female)	26.31 (4.88)	16.71–35.90	5.39	<0.0001*
Onset age—years	−0.24 (0.26)	−0.75 to 0.26	−0.96	0.339
Course of disease—years	−0.10 (0.26)	−0.61 to 0.41	−0.37	0.710
Diabetes mellitus	15.47 (5.07)	5.50–25.45	3.05	0.002*
Quetiapine	−10.99 (7.18)	−25.10 to 3.13	−1.53	0.127
Olanzapine	−0.73 (7.33)	−15.15 to 13.68	−0.10	0.920
Aripiprazole	−23.77 (9.64)	−42.72 to −4.82	−2.47	0.014*
Risperidone	19.52 (4.89)	9.92–29.13	4.00	<0.0001*
Clozapine	2.35 (5.39)	−8.25 to 12.95	0.44	0.663
FBG—mmol/L	−2.01 (1.06)	−4.09 to 0.07	−1.90	0.058
BC—mmol/L	0.07 (0.11)	−0.15 to 0.29	0.62	0.536
UA—mmol/L	−0.05 (0.02)	−0.09 to −0.01	−2.49	0.013*
TG—mmol/L	2.71 (1.18)	0.40–5.02	2.31	0.022*
LDL—mmol/L	1.13 (2.52)	−3.83–6.09	0.45	0.655
PANSS	−0.20 (0.18)	−0.55 to 0.16	−1.09	0.277

FBG, fasting blood glucose; BC, blood creatinine; UA, blood uric acid; TG, triglyceride; LDL, low-density lipoprotein; PANSS, Positive and Negative Symptom Scales.
*$P < 0.05$.

TABLE 4 Influencing factors of prolactin levels in patients with diabetes mellitus: multiple linear regression model.

	B(SE)	95%CI	*t*	*P*
Constant	11.46 (14.05)	−16.32 to 39.24	0.82	0.416
Metformin dose—mg	−0.01 (0.00)	−0.01 to 0.00	−1.46	0.047*
Gender (male vs. female)	16.06 (4.93)	6.33–25.80	3.26	0.001*
Aripiprazole	20.13 (7.84)	4.63–35.63	2.57	0.011*
Risperidone	−7.28 (5.09)	−17.35 to 2.78	−1.43	0.155
UA—mmol/L	−0.501 (0.02)	−0.05 to 0.03	−0.61	0.541
TG—mmol/L	1.16 (1.00)	−0.82 to 3.14	1.16	0.249

UA, blood uric acid; TG, triglyceride.
*$P < 0.05$.

recommended in the guidelines for treating prolactinoma and HPRL in endocrinology (24). The present study also reported a positive protective effect of prescription aripiprazole upon PRL levels in chronic long-term hospitalized patients with schizophrenia. However, this protective effect was not reflected in the subgroup including patients with comorbid DM. We have yet to come across any report on the interaction between aripiprazole, PRL, and DM. This does not exclude the possibility of anomalous results as a result of insufficient statistical strength, due to a lack of cases in the subgroup prescribing aripiprazole (12, 8.16%). In the future, we will investigate whether the abnormal metabolic indicators, insulin resistance, and PRL levels of co-DM patients have a deeper unexplored influence mechanism on the protective effect of aripiprazole on hyperprolactin.

The fact that the subgroups with co-DM had lower PRL levels was another significant finding in this study. Here, it must be emphasized that metformin is not only the basic drug and first-choice drug for diabetes treatment (25), but also an effective drug against HPRL caused by antipsychotic drugs (23). Therefore, prescription metformin to people with schizophrenia and diabetes is a choice that can help patients in many different ways. The fact that metformin protects against HPRL and has a dose-dependent impact is also a crucial finding. An expert consensus also agrees that high-dose metformin is more effective in improving antipsychotic-induced HPRL (26). Researchers also believe that this pharmacological property of metformin is related to its ability to improve endogenous dopaminomimetic activity (23, 27). Furthermore, there are few studies where researchers demonstrated the connection between PRL and diabetes. One study found that PRL was inversely related to glucose levels in young, healthy subjects (28). Another study reported an inverse relationship between serum PRL levels and insulin in men who were overweight or obese (29). However, the mechanism underlying this has not been clearly articulated. Our findings indicate that patients with co-morbid DM had more severe psychiatric symptoms and lower PRL levels; whereas high levels of PRL had a protective effect on the brain and reduced the psychiatric symptoms of the patients (17, 30). This may be another reasonable explanation for the lower PRL level in the clinical subgroup of diabetes.

Differences due to gender were also evident in PRL levels in schizophrenia patients, and female was at greater risk of HPRL. This risk persists in the subgroup of co-diabetes. A study of new-onset drug-naive schizophrenia reported that women had higher mean PRL levels than men (31). Another study on patients with first-episode non-affective psychosis reported smaller changes in mean PRL level in men than in women (32). However, higher PRL levels imply a wider range of PRL-related adverse effects (33), severe abnormalities in glucose and lipid metabolism (34), and significant impulsive behavior (35). In the present study, the psychiatric symptoms were found to be more severe in the group with DM. To summarize, female may be at a disadvantage in maintaining low levels of PRL throughout the disease. We, therefore, suggest that this phenomenon be specifically taken into account as a risk factor for HPRL when prescribing treatment medications for female patients. There are also some shortcomings in this study. Since the enrolled sample comprised chronic patients who were hospitalized for a long time, they were prescribed more complicated medications, including antipsychotics and hypoglycemic drugs. Hence, only qualitative analysis was performed when carrying out statistical analysis, and the effect of medication dose on statistical results is thus not known. When performing subgroup analysis,

the sample size of the diabetes subgroup prescribed with aripiprazole was small, which may affect the statistical efficacy. In the future, more stringent inclusion criteria will be employed, and the sample size will be further expanded to compensate for these deficiencies.

Conclusion

In short, co-morbid DM is associated with extreme residual psychiatric symptoms and more severe adverse effects (including metabolic abnormalities and HPRL) in patients with long-term hospitalization due to chronic schizophrenia. Aripiprazole is a protective factor for HPRL in long-term hospitalized patients and female is a risk factor, while metformin is beneficial in reducing PRL levels in patients with co-morbid DM. More aggressive and effective interventions are needed for fighting adverse drug reactions in women and patients with co-morbid DM.

Data availability statement

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

Ethics statement

This study was reviewed and approved by the Ethics Committee of Wuhan Mental Health Center. All subject guardians knew about this study and signed informed consent.

Author contributions

JM and YL made substantial contributions to the conception and design of the study. JZ drafted the manuscript. HW and SH polished and re-edited the language and logic of the manuscript. YZ and XL were responsible for setting up and complementing and modifying the contents of the manuscript. JM gave final approval for 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.

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Case report: Treatment of psychiatric symptoms for an acromegalic patient with pituitary adenoma

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Acromegalic patients always demonstrate a wide range of clinic manifestations, including typical physical changes such as acral and facial features, as well as untypical neuropsychiatric and psychological disturbances. However, there is still a lack of clinical guidance on the treatment for acromegalic patients with psychiatric comorbidities. We therefore share this case to provide a reference for clinicians to manage the acromegalic patients with psychiatric symptoms. This case report describes a 41-year-old male with an 8-year history of acromegaly due to growth hormone-secreting pituitary adenoma, the maximum cross-sectional area of which was 42 mm × 37 mm demonstrated by pituitary magnetic resonance imaging (MRI). The patient received conservative medicine treatment by regularly injecting with Sandostatin LAR 10 mg per month. Two days before admission, he suddenly presented with an acute psychotic episode. In addition to the typical acromegaly-associated changes, his main clinical presentations were olfactory/auditory hallucinations, reference/persecutory delusions, instable emotion and impulsive behavior. Considering the schizophrenic-like psychoses and course features, he was diagnosed with Brief Psychotic Disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) after a multidisciplinary consultation and evaluation. He was prescribed Aripiprazole, which had less extrapyramidal symptoms and minimal influence on prolactin elevation, with the dose of 5 mg per day to control the psychiatric symptoms and he responded quite well. At the time of discharge and the follow-up 2 month later, the patient was stable without recurrence of any psychotic symptoms. The levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) 1 week after discharge were 2.22 ng/mL [normal range (0–2.47 ng/mL)] and 381 μg/L [normal range (94–284 μg/L)], respectively, which were similar to those before the psychotic episode. Results from this report further supported that small dose of Aripiprazole had little influence on hormonal levels and the development of pituitary macroadenoma. This particular case emphasizes the importance

for the clinician to master and carefully identify the possible symptoms of mental disorders associated with acromegaly, and also highlights the need for further investigation in more efficient treatment strategies for acromegalic cases with psychiatric comorbidities.

KEYWORDS

acromegaly, pituitary tumor, mental disorders, Aripiprazole, case report

Introduction

Acromegaly is a rare and chronic illness, typically characterized by changes in appearance, skeletal deformities, and metabolic disorders, caused by abnormally high levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The clinical symptoms of acromegalic patient are mostly (95%) attributed to chronic hypersecretion of GH and pituitary adenoma (1). Diagnosis of acromegaly includes measurements of IGF-1, followed by oral glucose tolerance testing (OGTT) for GH suppression and magnetic resonance imaging (MRI). Specifically, IGF-1, secreted by liver due to the binding of growth hormones and their receptors, is recommended for patients with typical clinical symptoms of acromegaly (2). The estimated annual incidence rates range between 2 and 11 cases per million, which is a statistically abnormal phenomenon (3). It has been reported that the life expectancy of acromegalic patients is reduced by 30%, and they have 2.4- to 4.8-fold increased mortality rate as compared to the general population, mostly attributed to the complications of cardiovascular, cerebrovascular, and pulmonary dysfunction (4).

Acromegalic patients demonstrate a wide range of clinical manifestations, in addition to the typical changes (acral and facial features), some of which can be neuropsychiatric and psychological disturbances. Limited studies have been carried out to describe emotional and behavioral alterations with acromegaly, suggesting that acromegalic patients suffer from an increased prevalence of mental disorders and a higher risk of maladaptive personality traits (5, 6). In contrast, other studies demonstrated that psychiatric symptoms were likely to be presented before the acromegaly diagnosis in most acromegalic cases, and the average time span between the onset of mental disorders and the acromegaly diagnosis ranged from 9.4 to 22.4 years (6). It is unknown whether the diagnosis of mental disorders was an indicator or a preclinical stage of the disease status for acromegaly. Nevertheless, the coexistence of both psychopathological and acromegalic features might indicate the presence of a causal relationship between mental disorders and acromegaly, which remains to be determined. Therefore, it is of great clinical significance to advocate early diagnosis and effective treatment of acromegaly with mental disorders as soon as possible in order to prevent further damage and improve long-term prognosis.

So far, there is still a lack of clinical guidance on how to optimize the treatment for acromegalic patients with neuropsychiatric comorbidities. In this report, we present a case of acromegaly accompanied with schizophrenic-like psychoses, and the purpose is to propose suggestions and precautions for the psychopharmacological treatment.

Case history

Case presentation

The patient, a 41-year-old male, married, Han nationality of Chinese, had a history of acromegaly for 8 years. At the beginning, he came to see a doctor with the complaints of eyesight loss in his right eye. Then, he was recommended to Department of Neurosurgery in a famous general hospital in Shanghai, China. After conducted completed examinations, he finally got a definite diagnosis of acromegaly attributed to GH-secreting pituitary macroadenoma. At the time of diagnosis, the invasive pituitary adenoma had compressed the optical chiasm and invaded the surrounding tissues demonstrated by the patient's pituitary MRI. After required brain surgery consultation, a surgical approach was not considered necessary mainly because of high risk and cost, and then medical intervention with Sandostatin LAR (Octreotide acetate microspheres for injection) was started. The patient received the injection of Sandostatin LAR 10 mg per month with regularly monitoring of GH/IGF-1 levels (**Figure 1**) and pituitary MRI (**Figure 2**) at Department of Endocrinology of the same hospital. In general, his physical condition remained stable except for the lost eyesight, which was irreversible due to the delayed diagnosis and intervention.

On August 3, 2022, he suddenly developed acute psychotic symptoms of hallucination, paranoid ideation, seriously impulsive and aggressive behaviors. His family initially took him to Department of Emergency in the original general hospital. According to his preliminary laboratory and imageological examinations, there was no sufficient evidence

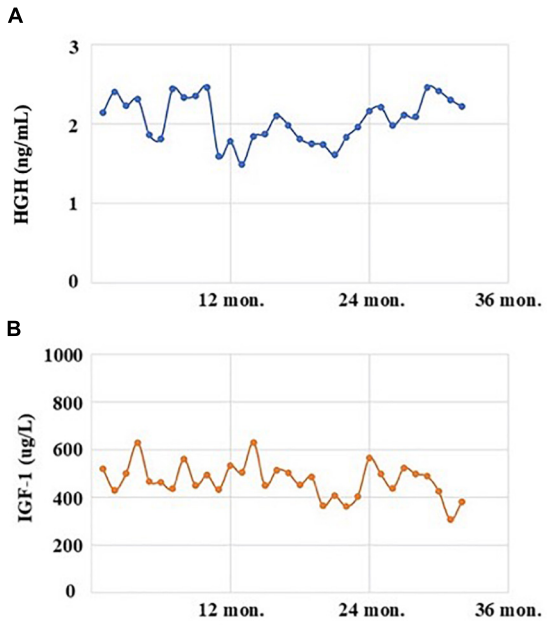

FIGURE 1
The levels of human growth hormone (HGH, normal range: 0–2.47 ng/mL; **A**) and insulin-like growth factor 1 (IGF-1, normal range: 94–284 μg/L; **B**) of the acromegalic patient with the treatment of Sandostatin LAR in recent 3 years.

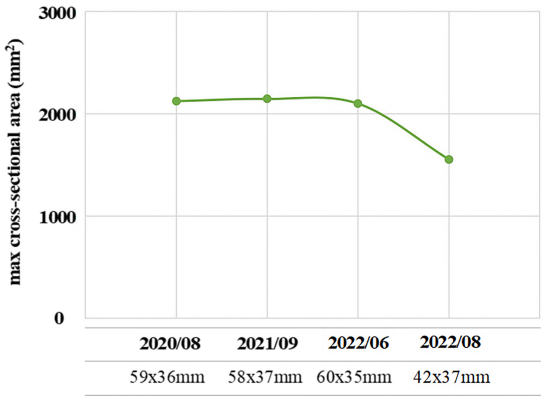

FIGURE 2
The maximum cross-sectional area (mm^2) of the pituitary macroadenoma measured by pituitary magnetic resonance imaging (MRI) of the acromegalic patient with the treatment of Sandostatin LAR in recent 3 years.

indicating the possibility of patient's psychotic symptoms due to severe sepsis, intracerebral hemorrhage or other acute organic diseases. Since the patient's GH/IGF-1 levels have been stable in recent 3 years, and brain imaging didn't suggest exacerbation of original pituitary macroadenoma, whether there was a causal relationship between the psychosis episode and the pituitary remained to be further investigated in a longer time. Therefore, after a multidisciplinary consultation and evaluation, the patient was later referred to our hospital, a specialized psychiatric hospital in Shanghai, China, on August 5, 2022.

Upon admission, the patient additionally reported a history of hypertension for 3 years, which had been controlled stable by taking Nifedipine controlled-release tablet 30 mg per day. He reported no history of heart or respiratory disease, diabetes, epilepsy, or drug allergy. There was no other personal or familial history of physical illness or psychosis.

Investigation

Physical examination showed typical characteristic changes in the patient's appearance, such as enlarged hands and feet, prognathism (excessive protrusion of the mandible or maxilla), enlargement of the supraorbital ridges, the tongue, the nose, and thickening of the lips. Moreover, visual field perimetry demonstrated a hemianopsia in his right eye because of optic chiasm compression by the enlarged pituitary adenoma. The patient's contrast-enhanced MRI of the pituitary gland revealed a pituitary macroadenoma and the maximum cross-sectional area was 42 mm × 37 mm, which had compressed the optical chiasm, invaded the skull base bone, and surrounded blood vessels in sellar area. Furthermore, his frontal bone, parietal bone and occipital bone were detected diffusely thickening and ballooning (Figure 3). The level of GH was 2.30 ng/mL [normal range (0–2.47 ng/mL)], and the level of IGF-1 was 307 μg/L [normal range (94–284 μg/L)], which were examined on July 20, 2022, before the psychosis episode. In addition, the levels of serum myocardial enzymes were elevated: lactate dehydrogenase (LDH) 2,52I U/L [normal range (120–250 IU/L)], creatine kinase (CK) 1,788 U/L [normal range (50–310 U/L)], creatine phosphokinase MB (CK-MB) 46 U/L [normal range (0–25 U/L)]. The electrocardiogram (ECG) indicated sinus tachycardia with a heart rate of 122 beats per minute. Since the patient didn't have history of heart disease, didn't complain of any serious symptoms, such as chest pain or pressure, severe shortness of breath or dizziness, or faintness, and there was no indication of acute myocardial infarction of his ECG, cardiovascular diseases could be eliminated. The most probable reason for the elevation of enzymes was attributed to skeleton muscle injury because the patient was extremely agitated and overactive before admission. Results of other laboratory tests including blood/urine/stool routine, liver and renal function, electrolytes, thyroid function, prolactin level and auxiliary examinations were without obvious abnormalities. Further psychiatric examination found that the patient was conscious with normal orientation. Olfactory and auditory hallucinations were observed. It was noted that he had apparent reference/persecutory delusions, sense of being tracked and monitored. Moreover, his emotion was irritable, and behavior was disturbed, so that he assaulted his parents since he thought they would harm and deceive himself.

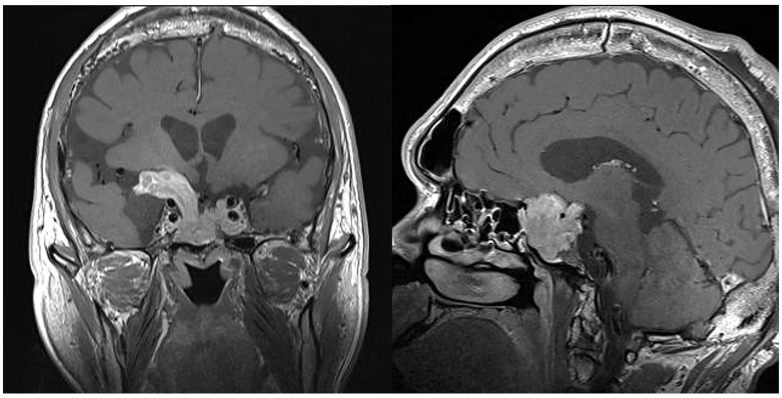

FIGURE 3
The magnetic resonance imaging (MRI) of coronal **(left)** and sagittal **(right)** sections showing a pituitary macroadenoma. Specifically, the maximum cross-sectional area was 42 mm × 37 mm, which had compressed the optical chiasm, invaded the skull base bone, and surrounded blood vessels in sellar area.

Diagnosis

First of all, for an adult male presented with first-episode acute psychiatric symptoms, it is prior to include organic diseases in differential diagnosis of functional mental disorders. But there was no disturbance of consciousness in this patient. Moreover, he had completed necessary examinations and received multidisciplinary consultation and evaluation in a general hospital before being admitted to our hospital, evidence for the psychotic symptoms due to the progression of pituitary macroadenoma or other organic diseases was insufficient at the moment. Secondly, the patient had no previous history of smoking, alcohol drinking, drug or caffeine abuse, and the results of his urine drug screening in hospital were negative. In addition, he had regularly injected with Octreotide (somatostatin receptor ligands, SRLs; the first-line drug for medical intervention in persistent acromegalic patients) for several years, but no side effects were reported. Hence, his psychiatric symptoms due to psychoactive substances or non-addictive substances could also be excluded. Collectively, considering the patient's schizophrenic-like psychoses and course features, he was diagnosed with Brief Psychotic Disorder according to the criteria of DSM-5. However, it is necessary to follow the patient's clinical manifestations, GH/IGF-1 levels and prognosis for a longer time in the future to confirm the diagnosis and whether there is a causal relationship between the psychiatric symptoms and the probably progressing pituitary adenoma in this acromegalic patient.

Therapeutic intervention

Aripiprazole was prescribed to the patient with an initial dose of 5 mg per day. About 3 days later, the patient's hallucinations and delusions partially decreased, and his agitated behaviors also significantly improved. Reexamination of ECG and serum myocardial enzymes demonstrated normal results. After 1 week, the patient's psychiatric symptoms totally disappeared, and he was discharged from our hospital and would continue with his regular treatment for acromegaly.

Outcome and follow-up

Two months later, this patient accepted our follow-up by a phone call. He was sticking with the medication treatment of Aripiprazole 5 mg per day, regularly injected with Octreotide as before, and he remained in stable condition without recurrence of any psychotic symptoms. The levels of GH and IGF-1 after discharge on August 19, 2022, were 2.22 ng/mL [normal range (0–2.47 ng/mL)] and 381 μg/L [normal range (94–284 μg/L)], respectively, which indicated that treatment with small dose of Aripiprazole had not significant influence on the hormonal levels.

Discussion

Acromegaly is a relatively rare disease associated with excessive production of GH by the adenoma. The disease was initially described by Pierre Marie in 19th century, which has been the subject of interest for centuries (7). The clinical presentations of acromegalic patients are always insidiously, causing significant diagnostic delay by five additional years since the symptom onset (3). A retrospective study with 324 acromegalic patients revealed that 96.3% of the patients were not diagnosed until serious acromegaly-associated comorbidities such as facial and acral changes had developed, resulting in poor prognosis and higher healthcare burden (8). Consistently, for the acromegalic case in this report, the pituitary adenoma

had developed to be macroadenomas at the time of detection, which caused the patient's irreversible eyesight loss, increased great risk for adverse surgical outcomes, and even let the patient miss the opportunity for brain surgery. It has also been reported that some acromegalic patients would demonstrate with neuropsychiatric disturbances at the early stage of disease, and therapy with dopamine antagonists might precede the diagnosis of acromegaly. However, very little was found in previous studies on the treatment options for mental disorders in acromegalic patients with pituitary adenoma.

In clinical practice, it is necessary to master and carefully identify the possible symptoms of mental disorders associated with acromegaly, in order to improve the efficiency of diagnosis and reduce the rate of misdiagnosis. The current case report described the effective treatment for an acromegaly patient diagnosed with Brief Psychotic Disorder, which can provide a reference for clinicians to manage the acromegalic patients with psychiatric comorbidities.

Acromegaly and mental disorders

A wide range of neuropsychiatric symptoms have been reported in acromegalic patients, including neurocognitive complications, psychiatric and psychological symptoms, alteration in personality and relevant somatic comorbidities (9). As mentioned in the literature review, the prevalence of neurocognitive dysfunctions was 2–33% in acromegaly, mostly affecting memory and attention (10). The prevalence of psychiatric disorders in acromegaly reached 63%, mostly involving depression, followed by psychosis and anxiety (11). Specifically, psychiatric morbidity according to General Health Questionnaire-28 (GHQ-28), mainly anxiety and insomnia, occurs in 50% of acromegalic patients (12). Sievers et al. conducted a cross-sectional study to investigate the prevalence of mental disorders among 81 patients with acromegaly (6). Results consistently showed that the lifetime prevalence of mental disorders in acromegalic group was 45.7%, and the 12-month prevalence was nearly three times higher than normal control subjects (6). Another observational study with larger sample size ($N = 115$) demonstrated that mental disorders were diagnosed in 79.1% of acromegalic patients and schizophrenia spectrum disorders were found in 4.3% which significantly exceed that in the general population (13).

However, evaluation of psychiatric or psychological symptoms has revealed inconsistent findings. In addition to the differences in the prevalence of psychiatric morbidities among acromegalic patients, some earlier studies were unable to demonstrate a relationship between the severity of psychopathological symptoms and alterations in GH levels (14). The contradictory findings might attribute to the methodological problems, lack of standardized evaluation techniques, heterogeneous study populations or insufficient sample sizes. It is worth highlighting that standardized evaluation and dynamic monitoring of acromegaly with an interdisciplinary approach, such as psychological and psychiatric consultation is needed.

There are many possible causes of psychological or psychiatric disorders combined with acromegaly, which might be related to the impaired body image, brain structure changes particularly the extension of adenoma to the fronto-temporal region, pituitary adenomas associated hormonal disturbance (hyperpituitarism and hypopituitarism), as well as the treatment with dopamine agonists. Specifically, it has been evidenced that patients with active untreated acromegaly suffer mental disorders, which are associated with irreversible effects of high GH/IGF-1 levels on central nervous system, and their severity increases according to hormone hypersecretion. Sievers et al. firstly demonstrated a disturbed macroscopic brain architecture, e.g., increased total gray and white matter volumes, in acromegaly by *in vivo* high-resolution MRI studies (15). Additionally, associations have also been reported between time delay of diagnostic process and psychosocial impairment (16). The acromegalic case in this report mainly presented with apparent hallucinations and delusions, as well as secondary behavioral disturbances. It remains unclear whether long-term GH and IGF-1 excessively secreting alters the psychopathological risk by influencing brain morphology or function in such acromegalic case.

Acromegaly and antipsychotic treatment

Treatment aims for acromegaly mainly include normalization of GH and IGF-1 levels, destruction or excision of tumor size, and reduction of acromegaly-associated comorbidities (17). Current therapeutic interventions include transsphenoidal surgery (gold standard), radiotherapy and medical intervention (18). However, acromegalic patients with neuropsychiatric symptoms are still confronting with a stubborn therapeutic challenge at the present time.

Prior studies have shown that some acromegalic cases initially present with mental disorders long before being diagnosed and treat with antipsychotics, some of which might promote the disease progression. Koroglu et al. reported a case of paranoid schizophrenia who was prescribed risperidone for 14 years and was finally diagnosed of acromegaly with pituitary macroadenoma (19). Iglesias et al. also reported three cases of schizophrenic patients treated with antipsychotics (paliperidone, amisulpride, clozapine, and haloperidol) for several years who finally developed acromegaly due to a GH-secreting pituitary macroadenoma (20). They considered that schizophrenia and/or its antipsychotic therapy with dopamine antagonists in the long term might be in relation with the development of acromegaly, and the potential

pathophysiological mechanisms were related to the alterations in dopaminergic neurotransmission due to psychiatric disease itself or its pharmacological treatment.

Dopamine is a neurotransmitter produced in several areas of the brain and plays multiple functions. Specifically, dopamine is a precursor of norepinephrine, which can increase and inhibit GH secretion via α- and β-adrenergic pathways, respectively. There were some earlier studies reporting that Chlorpromazine was effective in markedly decreasing the concentration of serum GH and improving clinical manifestations in acromegalic patients (21). The potential explanations of chlorpromazine acting in acromegaly were considered to be associated with its effects of adjusting the adrenergic activity in central nervous system and consequently reducing the level of GH, but further cohort studies were needed to clarify the mechanisms.

Currently, the relationships between antipsychotics and pituitary tumors have drawn public attention (22). In clinical practice, atypical antipsychotic drugs have become common choices particularly in the treatment of psychotic disorders for less extrapyramidal side effects and well tolerance. However, the endocrinological side effects, especially the associated hyperprolactinemia and pituitary tumors, have been frequently observed. An analysis of the European pharmacovigilance database (EudraVigilance) was carried out to assess the association between antipsychotics and pituitary, the highest proportional reporting ratio values were found for Amisulpride, then Risperidone and Paliperidone. Sulpiride and Haloperidol showed a higher risk among typical antipsychotics (23). Similarly, Szarfman et al. conducted a retrospective pharmacovigilance study to analyze the disproportionality of seven widely used antipsychotic medications (Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone, and Haloperidol) with pituitary tumors by screening the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) Database (24). Results demonstrated that Risperidone had the strongest association with pituitary tumors, followed by Haloperidol, Ziprasidone, and Olanzapine, while the association for Clozapine and Quetiapine was relative weak. Specifically, the most important clinically relevant finding was that the use of Aripiprazole would not increase the risk of pituitary tumors. It has been explained that the affinities for occupying and blocking the D_2 receptors correspond to the strength of the association between antipsychotics and pituitary tumors (25). It is important to note that Aripiprazole has a unique pharmacological profile for its weak partial agonist activity at the D_2 receptors, with less extrapyramidal symptoms and minimal prolactin elevation. As for the current case of acromegaly, we thus chose Aripiprazole for the treatment of psychiatric symptoms in order to avoid aggregating the procession or reoccurrence of pituitary macroadenoma itself. Results from this case further supported that small dose of Aripiprazole had little influence on the fluctuation of GH and IGF-1 levels, which might be one of the appropriate choices for the treatment of acromegaly with mental disorders. These findings raise the need for clinical awareness and strengthen the importance for larger cohort studies with a longer follow-up to validate the optimized psychopharmacological treatments and to ensure the generalization of research findings.

Limitations

On one hand, the follow-up time was relatively short to see the long-term influence for the current antipsychotic treatment on hormonal levels of the acromegalic patient. On the other hand, the findings from a single case may not apply to general patients, which limit the significance in clinical practice. Further randomized controlled trials (RCT) are pending to verify the effects or safety for the psychopharmacological treatments in acromegaly with neuropsychiatric comorbidities.

Conclusion

Since only few reports on acromegalic patients accompanied with prominent mental disorders are available, experiences summed up from herein case are as follows: (1) Clinicians should pay attention to the diagnosis and treatment of mental disorders in acromegalic patients, GH/IGF-1 levels and pituitary MRI should be regularly evaluated when antipsychotics are prescribed. (2) Moreover, it is important for psychiatrist to keep an eye on the presence of morphological modifications in order to make early diagnosis for acromegalic patients. (3) Treatments for acromegaly always require a teamwork of neurosurgeons, endocrinologists, radiation oncologists and psychiatrists, it is valuable of a multidisciplinary evaluation and management. Conclusively, this enlightening case might inspire clinicians to further study the causal relationship between mental disorders and acromegaly, and to investigate more efficient treatment strategies for similar cases.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZS prepared the study design and drafted the manuscript. EC, YWu, and XM critically revised and edited the manuscript. YWang and DP contributed to the study design and revision for important intellectual content. All authors contributed to the article and approved the final 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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Dual orexin receptor antagonists for treatment of insomnia: A systematic review and meta-analysis on randomized, double-blind, placebo-controlled trials of suvorexant and lemborexant

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Study objectives: Recent treatment guidelines for chronic insomnia recommend pharmacological and non-pharmacological therapies. One of the contemporary drug options for insomnia includes dual orexin receptor antagonist (DORA), such as suvorexant and lemborexant. We conducted a systematic review and meta-analysis for the treatment of insomnia with suvorexant and lemborexant based on randomized, double-blind, placebo-controlled Trials.

Methods: We conducted a comprehensive search on three databases (PubMed/Medline, Web of Science, and Cochrane Library) till August 14, 2021, without any restrictions to retrieve the relevant articles. The effect sizes were computed presenting the pooled mean difference or risk ratio along with 95% confidence interval of each outcome.

Results: Our search showed eight articles (five for suvorexant and three for lemborexant). Results of diary measures, rating scales, polysomnography results, treatment discontinuation, and adverse events were measured. All efficacy outcome measures favorably and significantly differed in the suvorexant compared to placebo. Safety profile did not differ significantly except for somnolence, excessive daytime sleepiness/sedation, fatigue, back pain, dry mouth, and abnormal dreams. Important adverse events including hallucinations, suicidal ideation/behavior and motor vehicle accidents did not differ between suvorexant and placebo. All the efficacy outcomes significantly

differed between lemborexant 5 and lemborexant 10 compared to placebo. Somnolence rate for lemborexant 5 and lemborexant 10 and nightmare for lemborexant 10 were significantly higher than placebo.

Conclusion: The present meta-analysis reported that suvorexant and lemborexant are efficacious and safe agents for the patients with insomnia. Further data in patients with insomnia and various comorbid conditions are needed.

KEYWORDS

insomnia, orexin receptor antagonist, suvorexant, lemborexant, randomized trial, meta-analysis

Introduction

Insomnia is a condition in which a person has difficulty falling asleep or staying asleep (1) with associated consequences like daytime fatigue and sleepiness (2–4). Insomnia is a major health challenge in the general population (5). Various studies around the world have reported that the insomnia was a high prevalent disease, affecting around 10–30% of the general population (1, 6, 7). Around 30–40% of adults in the US report insomnia symptoms at some point in a given year (8) and in China the prevalence of any type of insomnia symptoms was 22.1% (9). It is more common in the elderly, women, and people with medical and mental illness (6, 7, 10). There are three necessary diagnostic criteria for insomnia in clinical practice: complaint of trouble falling or staying asleep, adequate opportunity for sleep, and daytime dysfunction (11–14).

Recent treatment guidelines for chronic insomnia recommend pharmacological and non-pharmacological therapies (15). Current armamentarium of contemporary drug options for insomnia include gamma-aminobutyric acid type-A receptor agonists, non-benzodiazepine Z-drugs, sedative-hypnotic benzodiazepines, sedative antidepressants, melatonin receptor agonists, sedative antihistamines, and dual orexin receptor antagonists, such as suvorexant and lemborexant (15). The orexin/hypocretin system has been developed as a target for the treatment of insomnia (16). Orexins are neuropeptides that have a role in regulating the sleep-wake cycle by maintaining wakefulness (17).

Suvorexant is a dual orexin receptor antagonist that promotes sleep through selective antagonism of the endogenous oroxin-stimulating neuropeptides in the orexin receptors OX1R and OX2R (18, 19). Lemborexant is another dual orexin receptor antagonist and acts as a competitive antagonist in both orexin receptors, which can possibly stop the awakening by blocking binding of orexin (20).

Several meta-analyses reported the findings of clinical trials for the effectiveness of both suvorexant and lemborexant (21), suvorexant alone (22–26), and lemborexant alone (27, 28) in insomnia patients with different study population and results. We performed a meta-analysis among largest number of randomized, double-blind, placebo-controlled trials of suvorexant and lemborexant in insomnia patients to explore the efficacy and safety profile in more detail as it may relate to use of these agents in mental health clinics.

Abbreviations: DORA, dual orexin receptor antagonists; PRISMA, preferred reporting items for systematic reviews and meta-analyses; FRESH, subjective refreshed feeling on waking (0–4 scale); sNAW, subjective number of awakenings; sQUAL, subjective quality of sleep (1–4 scale); sTSO, subjective time to sleep onset (minutes); sTST, subjective total sleep time (minutes); sWASO, subjective wake after sleep onset (minutes); sSOL, subjective sleep onset latency (minutes); sSE, subjective sleep efficiency (percentage); WMD, weighted mean difference; CGI-I, clinical global impression-improvement scale (1–7 scale); CGI-S, clinical global impression-severity scale (1–7 scale); ISI, insomnia severity index (0–28 scale); TST, total sleep time (minutes); LPS, latency to onset of persistent sleep (minutes); PGI-I, patient global impression-improvement scale (1–7 scale); PGI-S, patient global impression-severity scale (0–5 scale); WASO, wakefulness after persistent sleep onset (minutes); TEAE, treatment-emergent adverse event.

Materials and methods

Study design

The reporting of the present meta-analysis is in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocols (29). The PICO (population, intervention, control, and outcomes) question was: Do suvorexant and lemborexant improve various relevant clinical efficacy and safety outcomes at various time points in patients with insomnia compared to placebo group? The outcomes of interest include diary measures, rating scales and adverse events.

Identification of articles

A comprehensive search was performed by in three databases of PubMed/Medline, Web of Science, and Cochrane Library until August 14, 2021, without any restrictions to retrieve the relevant articles. The search strategy was ("suvorexant" or "lemborexant") and ("insomnia") and ("random*" or "trial*"). Moreover, the citations of the retrieved articles linked to the subject were examined to ensure that no study was missed and then the titles and

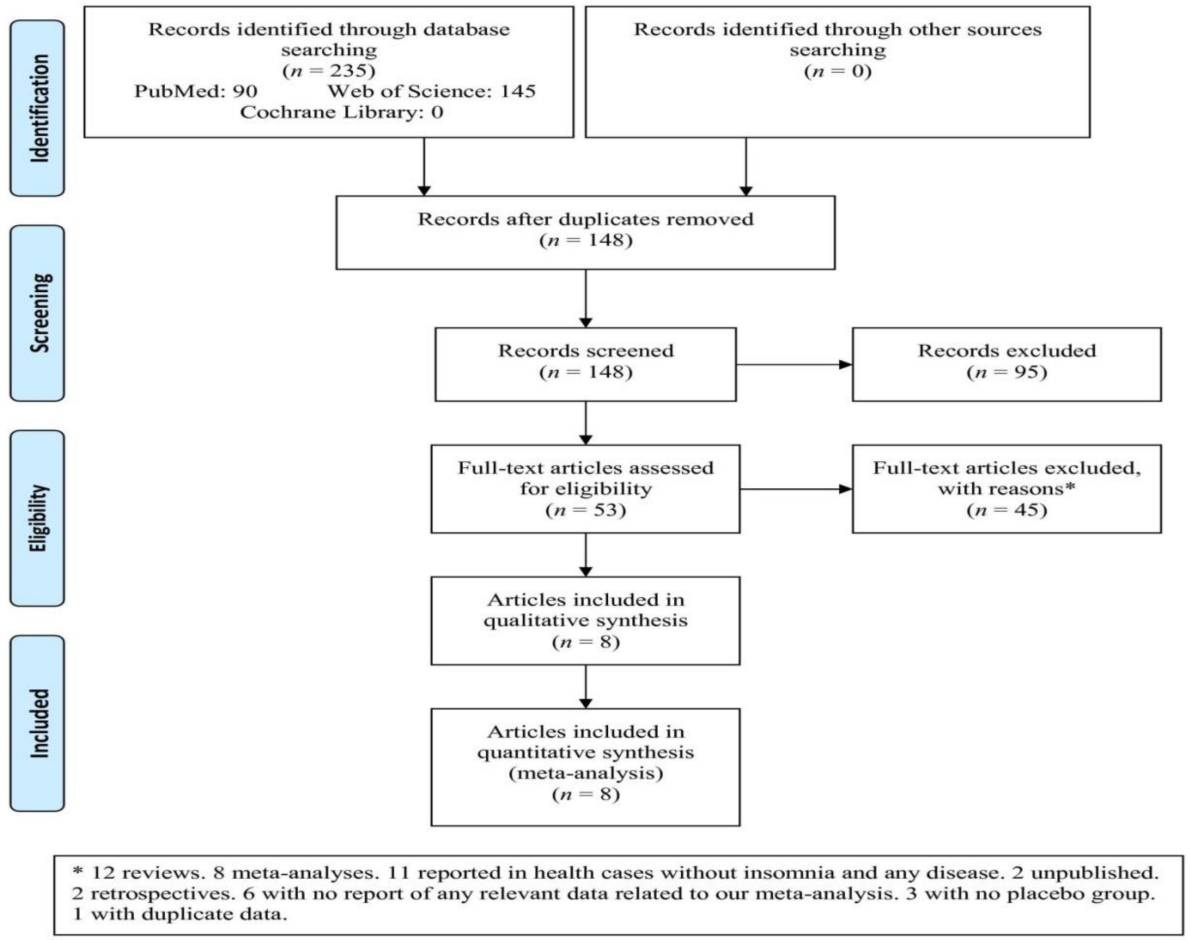

FIGURE 1
Flowchart of the study selection. *Twelve reviews. Eight meta-analyses. Eleven reported in health cases without insomnia and any disease. Two unpublished. Two retrospectives. Six with no report of any relevant data related to our meta-analysis. Three with no placebo group. One with duplicate data.

TABLE 1 Characteristics of articles included in the meta-analysis.

References	Clinical trials.gov identifier	Phase	Duration	Age range, years	Reported treatment
Herring et al. (34)	NCT00792298	2	1 month	18–64	Suvorexant
Michelson et al. (36)	NCT01021813	3	1 year	≥18	Suvorexant
Herring et al. (23)*	NCT01097616 and NCT01097629	3	3 months	<65 and ≥65	Suvorexant
Fan et al. (32)	–	3	6 months	18–64	Suvorexant
Murphy et al. (37)	NCT01995838	2	6 months	19–80	Lemborexant
Rosenberg et al. (38)	NCT02783729	3	1 month	55–88	Lemborexant
Herring et al. (33)	NCT02750306	3	1 month	50–90	Suvorexant
Kärppä et al. (35)	NCT02952820	3	6 months	≥18	Lemborexant

*This article included four independent studies.

abstracts of the relevant articles were evaluated; subsequently, the full texts of the articles following the eligibility criteria were downloaded.

Inclusion and exclusion criteria

The inclusion criteria were: (1) published randomized, double-blind, placebo-controlled trials; (2) studies reporting outcomes of suvorexant or lemborexant compared to placebo in insomnia patients; (3) participants had age $\geq$ 18 years at the time of enrollment. We rejected the following study types: Meta-analyses, studies with incomplete data, studies without a placebo group, conference papers, reviews, case-reports, studies reporting the outcomes in healthy individuals, unpublished studies, book chapters, studies with duplicate data and comment.

Data abstraction

One author (MS) extracted the data of the articles included in the meta-analysis. The extracted data were: first author, publication year, phase of the trial, duration of treatment, participants age range, type of treatment, sample size based on each outcome, and mean difference (MD) or risk ratio (RR) of each outcome. Another author (HK) re-checked them. Disagreements between the two authors were resolved by third author (AS).

Statistical analysis

The effect sizes were computed using the Review Manager 5.3 (RevMan 5.3) presenting the MD or RR along with 95% confidence interval (CI) for each outcome. To estimate the pooled MD or RR significance, the Z-test was applied with a *p*-value (two-sided) less than 0.05 considered as significant. An I^2 statistic ($P_{heterogeneity} < 0.1$ or $I^2 > 50\%$) showed a significant heterogeneity and random-effects model was performed (30), and if the heterogeneity was insignificant, a fixed-effect model was applied (31).

Results

Study selection

Among three databases, 235 articles were retrieved that after removing duplicates and irrelevant articles based on titles/abstracts, 53 full-text articles were assessed (**Figure 1**). Subsequently, 45 articles were excluded based on the reasons (12 reviews, eight meta-analyses, 11 reported in health cases without insomnia and any disease, two unpublished, two

TABLE 2 The mean changes of efficacy outcome (diary measures) results from baseline in suvorexant vs. placebo.

Diary measures	*N*	No. of cases (suvorexant/placebo)	WMD	95% CI	*P*-value	I^2, %
sTST at week 1	5	1,739/1,732	21.05	16.00, 26.10	<0.00001	64
sTST at month 1	6	1,719/1,724	21.39	18.17, 24.61	<0.00001	0
sTST at month 3	4	1,113/1,328	19.10	14.63, 23.56	<0.00001	46
sTSO at week 1	5	1,739/1,732	−8.72	−11.04, −6.39	<0.00001	40
sTSO at month 1	6	1,719/1,724	−8.72	−11.03, −6.41	<0.00001	0
sTSO at month 3	4	1,113/1,328	−8.23	−10.92, −5.55	<0.00001	25
sWASO at week 1	4	1,231/1,480	−7.91	−10.21, −5.60	<0.00001	18
sWASO at month 1	5	1,683/1,675	−8.33	−10.70, −5.96	<0.00001	0
sWASO at month 3	4	1,113/1,328	−6.45	−9.20, −3.70	<0.00001	0
sQUAL at week 1	4	1,231/1,480	0.11	0.05, 0.17	0.0004	38
sQUAL at month 1	6	1,738/1,731	0.17	0.12, 0.22	<0.00001	0
sQUAL at month 3	4	1,113/1,328	0.02	−0.12, 0.17	0.74	81
sNAW at week 1	4	1,231/1,480	0.02	−0.40, 0.09	0.52	0
sNAW at month 1	5	1,683/1,675	−0.01	−0.07, 0.05	0.72	18
sNAW at month 3	4	1,113/1,328	0.00	−0.06, 0.06	1.00	0
sFRESH at week 1	4	1,231/1,480	0.10	0.06, 0.14	<0.00001	0
sFRESH at month 1	5	1,638/1,675	0.23	0.17, 0.29	<0.00001	34
sFRESH at month 3	4	1,113/1,328	0.14	0.08, 0.21	<0.0001	0

95% CI, 95% confidence interval; *N*, number of comparisons/studies; sFRESH, subjective refreshed feeling on waking (0–4 scale); sNAW, subjective number of awakenings; sQUAL, subjective quality of sleep (1–4 scale); sTSO, subjective time to sleep onset (minutes); sTST, subjective total sleep time (minutes); sWASO, subjective wake after sleep onset (minutes); WMD, weighted mean difference.

retrospectives, six with no report of any relevant data related to our meta-analysis, three with no placebo group, and one with duplicate data). Finally, eight articles were included in the meta-analysis that one article involved four independent studies (23, 32–38).

Characteristics of the studies

The meta-analysis included 11 studies based on eight articles (**Table 1**). All articles were registered in Clinical trials.gov, except for one (32). Six articles were phase 3 (32, 33, 35, 36, 38, 39), and two were phase 2 trials (34, 37). All participants in the studies were age 18 years or older. Five articles including eight studies reported suvorexant therapy (32–34, 36, 39). Three publications with three studies reported lemborexant therapy in insomnia patients (35, 37, 38).

Efficacy measures for suvorexant vs. placebo

Results of diary measures for suvorexant therapy

Six efficacy outcomes [subjective total sleep time (sTST), subjective time to sleep onset (sTSO), subjective wake after

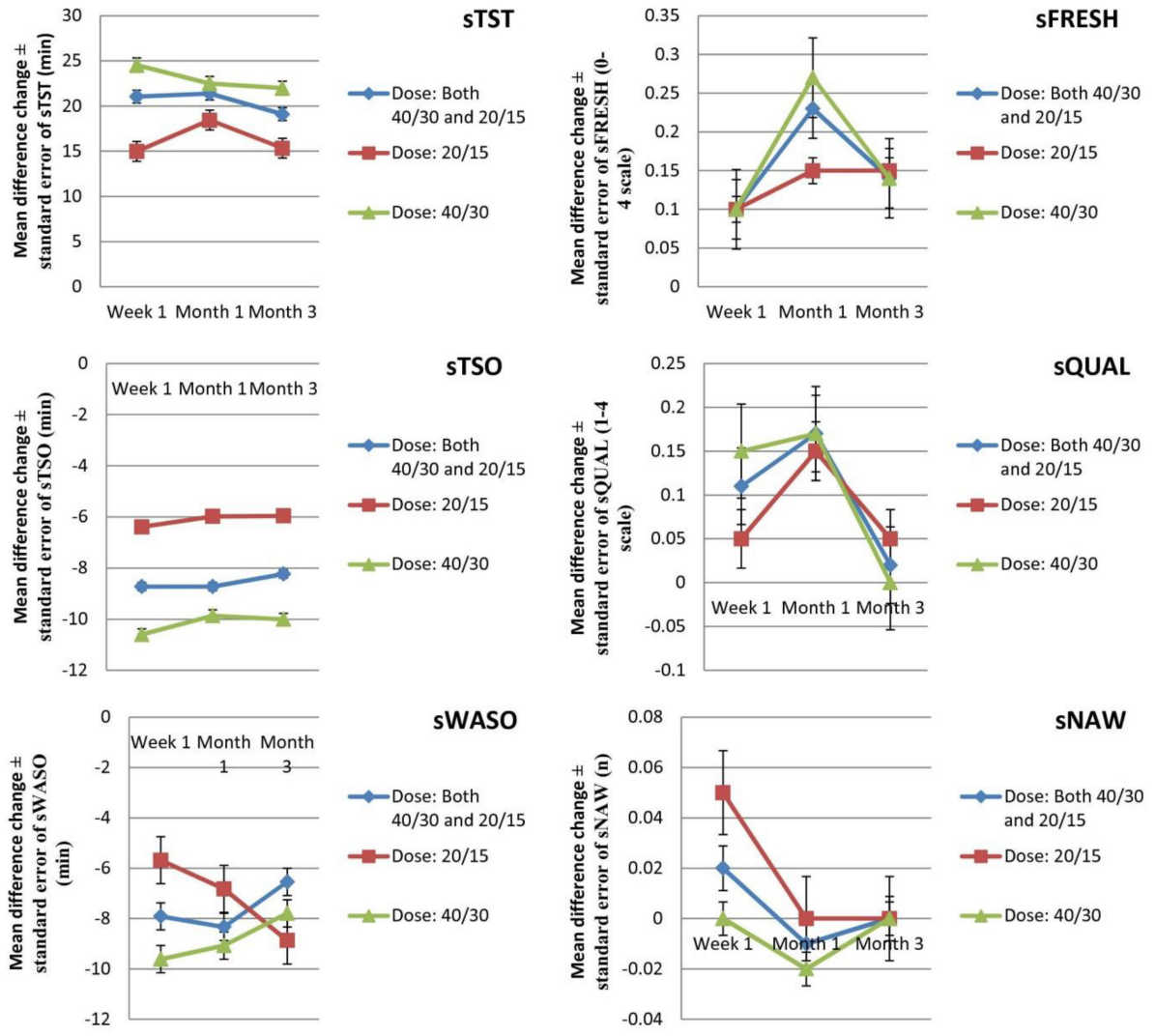

FIGURE 2
The mean changes efficacy outcome (diary measures) results from baseline in suvorexant vs. placebo for three times. sFRESH, subjective refreshed feeling on waking (0–4 scale); sNAW, subjective number of awakenings; sQUAL, subjective quality of sleep (1–4 scale); sTSO, subjective time to sleep onset (minutes); sTST, subjective total sleep time (minutes); sWASO, subjective wake after sleep onset (minutes); WMD, weighted mean difference.

TABLE 3 Analysis of the mean changes of efficacy outcomes from rating scales and polysomnography from baseline in suvorexant vs. placebo.

	N	No. of cases (suvorexant/placebo)	WMD	95% CI	*P*-value	I^2, %
Rating scale						
ISI at month 1	6	1,726/1,715	−1.50	−1.78, −1.22	<0.00001	26
ISI at month 3	4	1,106/1,318	−1.50	−1.88, −1.11	<0.00001	46
CGI-S at week 2	4	1,173/1,408	−0.38	−0.45, −0.30	<0.00001	0
CGI-S at month 1	6	1,812/1,802	−0.38	−0.44, −0.31	<0.00001	13
CGI-S at month 3	4	1,106/1,318	−0.38	−0.53, −0.22	<0.00001	76
PGI-S at week 2	4	1,173/1,408	−0.42	−0.49, −0.35	<0.00001	44
PGI-S at month 1	5	1,670/1,659	−0.40	−0.50, −0.30	<0.00001	65
PGI-S at month 3	4	1,106/1,318	−0.37	−0.46, −0.29	<0.00001	14
CGI-I at week 2	4	1,173/1,408	−0.40	−0.48, −0.32	<0.00001	22
CGI-I at month 1	5	1,670/1,659	−0.40	−0.47, −0.33	<0.00001	0
CGI-I at month 3	4	1,106/1,318	−0.45	−0.53, −0.37	<0.00001	0
PGI-I at week 2	4	1,173/1,408	−0.47	−0.58, −0.35	<0.00001	54
PGI-I at month 1	5	1,670/1,659	−0.48	−0.56, −0.41	<0.00001	0
PGI-I at month 3	4	1,106/1,318	−0.42	−0.54, −0.29	<0.00001	55
Polysomnography						
TST at month 1	2	199/193	29.47	14.13, 44.81	0.0002	0
LPS at day 1	5	950/1,275	−13.40	−18.20, −8.59	<0.00001	57
LPS at month 1	6	1,046/1,345	−11.07	−13.88, −8.26	<0.00001	0
LPS at month 3	4	815/1,012	−6.37	−9.44, −3.31	<0.0001	35
WASO at day 1	4	916/1,140	−37.63	−41.04, −34.22	<0.00001	23
WASO at month 1	5	1,014/1,227	−25.80	−29.48, −22.12	<0.00001	0
WASO at month 3	4	815/1,006	−24.97	−31.26, −18.68	<0.00001	60
Response rate						
ISI responders at month 3	4	1,067/1,276	1.31	1.20, 1.42	<0.00001	0

95% CI, 95% confidence interval; CGI-I, clinical global impression-improvement scale (1–7 scale); CGI-S, clinical global impression-severity scale (1–7 scale); ISI, insomnia severity index (0–28 scale); TST, total sleep time (minutes); LPS, latency to onset of persistent sleep (minutes); PGI-I, patient global impression-improvement scale (1–7 scale); PGI-S, patient global impression-severity scale (0–5 scale); *N*, number of comparisons/studies; RR, risk ratio; WASO, wakefulness after persistent sleep onset (minutes); WMD, weighted mean difference. The percentage of patients who had a clinically meaningful improvement (responders), prospectively defined as ≥6-point improvement from baseline in ISI score (40).

sleep onset (sWASO), subjective quality of sleep (sQUAL), subjective number of awakenings (sNAW), and subjective refreshed feeling on waking (sFRESH)] were measured in the individuals (Tables 2, 3) during week 1 and months 1 and 3. All outcomes significantly differed in the suvorexant compared with placebo, with the exception of sQUAL at month 3, sNAW at week 1, sNAW at month 1, and sNAW at month 3. Figure 2 shows efficacy outcome results for suvorexant vs. placebo for three times.

Rating scales and polysomnography results for suvorexant therapy

The studies compared six rating scales [insomnia severity index (ISI), clinical global impression-severity scale (CGI-S), patient global impression-severity scale (PGI-S), clinical global impression-improvement scale (CGI-I), and patient global impression-improvement scale (PGI-I)], three outcomes from polysomnography [TST, latency to onset of persistent sleep (LPS), and WASO], and ISI responders. For the rating scales, ISI, CGI-S, PGI-S, CGI-I, and PGI-I for several time points were calculated. For polysomnography, TST at month 1 and LPS and WASO at day 1 and months 1 and 3 were calculated. ISI responders [the percentage of patients who had a clinically meaningful improvement (responders), prospectively defined as ≥ 6-point improvement from baseline in ISI score] were measured in month 3 (40). All outcomes from rating scales and polysomnography differed significantly between the two study groups.

Treatment discontinuation and adverse events for suvorexant therapy vs. placebo

The results of outcomes of treatment discontinuation and adverse events are shown in Table 4. The mean changes from baseline in weight and proportions of patients with ≥ 7% increase or decrease in weight (weight: ≥ 7%) has been calculated in two times intervals. Although discontinuation rates did not differ between the two study

TABLE 4 Treatment discontinuation and individual adverse events for suvorexant vs. placebo.

Adverse events	*N*	No. of cases (suvorexant/placebo)	RR	95% CI	*P*-value	I^2, %
Discontinuation due to all cause*	7	1,978/1,218	0.95	0.82, 1.10	0.48	0
Discontinuation due to intolerability*	7	1,978/1,218	1.00	0.74, 1.35	1.00	29
Discontinuation due to inefficacy*	7	1,978/1,218	0.75	0.52, 1.09	0.13	0
≥1 adverse event	7	1,986/1,228	1.07	0.99, 1.15	0.07	0
≥1 drug-related adverse event**	7	1,986/1,228	1.62	1.40, 1.89	<0.00001	10
≥1 serious adverse event	7	1,986/1,228	0.70	0.27, 1.84	0.47	52
Discontinued owing to adverse event	3	723/461	1.37	0.88, 2.13	0.16	0
Somnolence	7	1,986/1,228	3.26	2.29, 4.63	<0.00001	0
Excessive daytime sleepiness/sedation***	5	1,784/1,025	3.48	1.13, 10.67	0.03	0
Fatigue	6	1,844/1,085	2.09	1.28, 3.43	0.003	3
Cataplexy	6	1,926/1,168	Not estimable	–	–	–
Sleep paralysis	6	1,926/1,168	2.84	0.49, 16.35	0.24	0
Complex sleep–related behaviors	6	1,926/1,168	1.66	0.17, 15.84	0.66	0
Hypnagogic/hypnopompic hallucination	6	1,926/1,168	3.12	0.67, 14.47	0.15	0
Abnormal dreams	4	1,263/767	2.91	1.12, 7.60	0.03	0
Suicidal ideation/behavior	6	1,926/1,168	1.91	0.46, 7.92	0.38	20
Events indicative of abuse potential****	6	1,926/1,168	1.08	0.69, 1.68	0.74	0
Fall#	6	1,926/1,168	1.03	0.56, 1.89	0.92	19
Headache	7	1,986/1,228	1.13	0.86, 1.47	0.39	0
Dizziness	6	1,844/1,685	1.62	0.57, 4.57	0.36	85
Back pain	5	1,784/1,025	0.51	0.27, 0.97	0.04	0
Dry mouth	7	1,986/1,228	2.15	1.23, 3.76	0.008	0
Nasopharyngitis	5	1,784/1,025	0.95	0.71, 1.28	0.75	0
Motor vehicle accidents/violations##	5	1,660/963	1.21	0.72, 2.05	0.47	11
Sleep-onset paralysis	2	663/401	1.49	0.06, 36.41	0.81	–
Weight: ≥7% increase at month 3	4	1,250/1,514	1.38	0.78, 2.45	0.26	0
Weight: ≥7% decrease at month 3	4	1,250/1,514	1.85	0.84, 4.11	0.13	0

95% CI, 95% confidence interval; *N*, number of comparisons/studies; RR, risk ratio; weight: ≥7%, the mean changes from baseline in weight and proportions of patients with ≥ 7% increase or decrease in weight.

*The counts for discontinuations due to adverse events are based on the period in which the adverse event started.

**Drug-related adverse event a determined by the investigator to be related to the drug (determination made while blinded).

***Excessive daytime sleepiness was defined as a more persistent daytime sleepiness than typical next-day residual somnolence.

****Terms included depersonalization, derealization, dissociation, euphoric mood, mania, hallucination, and potential study medication misuse.

#Falls were adjudicated to determine whether they were suggestive of cataplexy.

##Includes spontaneously reported events when the patient was the driver and events elicited *via* a motor vehicle accidents and violations questionnaire.

groups, several safety outcomes were significantly higher in suvorexant compared to placebo for at least one drug-related adverse event, somnolence, excessive daytime sleepiness/sedation, fatigue, abnormal dreams, back pain, and dry mouth.

Efficacy measures for lemborexant vs. placebo

Diary measures results for lemborexant 5 therapy

Three outcomes [subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), and sWASO] were measured in the individuals with insomnia (Table 5) during first seven nights and month 1. All the outcomes significantly differed between the lemborexant 5 compared to placebo.

Results of diary measures for lemborexant 10 therapy

The outcomes of sSOL, sSE, and sWASO were measured in the insomnia patients (Table 6) during first seven nights and month 1. All the outcomes showed significant difference between the lemborexant 10 compared to placebo.

Supplementary Table 1 shows the outcomes of sTST, sSE, and sWASO in the insomnia patients during first seven nights and month 1 comparing 5 and 10 mg doses of lemborexant. None of the outcomes differed significantly between the comparison groups, with the exceptions of sSE at First seven nights and sSE at month 1.

TABLE 5 The mean changes of efficacy outcome (diary measures) results from baseline in lemborexant 5 vs. placebo.

Diary measures	*N*	No. of cases (lemborexant 5/placebo)	WMD	95% CI	*P*-value	I^2, %
sSOL at first seven nights	2	569/516	−12.05	−18.45, −5.55	0.0003	79
sSOL at month 1	2	550/496	−11.80	−21.70, −1.90	0.02	88
sSE at first seven nights	2	624/511	4.10	2.88, 5.32	<0.00001	0
sSE at month 1	2	543/490	3.16	0.84, 5.49	0.008	52
sWASO at first seven nights	2	571/516	−13.19	−19.33, −7.26	<0.0001	0
sWASO at month 1	2	551/596	−6.74	−13.12, −0.37	0.04	0

95% CI, 95% confidence interval; *N*, number of comparisons/studies; sSOL, subjective sleep onset latency (minutes); sSE, subjective sleep efficiency (percentage); sWASO, subjective wake after sleep onset (minutes); WMD, weighted mean difference.

TABLE 6 The mean changes of efficacy outcome (diary measures) results from baseline in lemborexant 10 vs. placebo.

Diary measures	*N*	No. of cases (lemborexant 10/placebo)	WMD	95% CI	*P*-value	I^2, %
sSOL at first seven nights	2	576/516	−12.45	−16.94, −7.96	<0.00001	60
sSOL at month 1	2	555/496	−13.11	−19.37, −6.85	<0.0001	71
sSE at first seven nights	2	564/511	6.32	4.99, 7.64	<0.00001	3
sSE at month 1	2	541/490	5.54	1.52, 9.56	0.007	81
sWASO at first seven nights	2	572/516	−21.38	−31.51, −11.25	<0.0001	62
sWASO at month 1	2	550/496	−13.77	−28.65, 1.11	0.07	75

95% CI, 95% confidence interval; *N*, number of comparisons/studies; sSOL, subjective sleep onset latency (minutes); sSE, subjective sleep efficiency (percentage); sWASO, subjective wake after sleep onset (minutes); WMD, weighted mean difference.

TABLE 7 Treatment discontinuation and individual adverse events for lemborexant 5 vs. placebo.

Adverse events	*N*	No. of cases (lemborexant 5/placebo)	RR	95% CI	*P*-value	I^2, %
Discontinuation due to all cause	2	589/534	1.02	0.76, 1.37	0.91	20
Discontinuation due to intolerability	2	589/534	1.06	0.45, 2.46	0.90	0
Any TEAE	3	618/584	1.01	0.90, 1.13	0.86	0
Any treatment-related TEAE	3	618/584	1.69	1.29, 2.22	0.0001	0
Any severe TEAE	2	580/528	1.05	0.50, 2.20	0.89	43
Any serious TEAE	3	618/584	1.46	0.55, 3.90	0.45	0
Any TEAE leading to discontinuation of study drug	3	618/584	1.05	0.51, 2.15	0.89	0
Any TEAE leading to interruption of study drug	2	580/528	1.73	0.74, 4.07	0.21	0
Death	2	580/528	Not estimable	–	—	–
Somnolence	3	618/584	4.05	2.14, 8.06	<0.0001	0
Headache	3	618/584	1.24	0.82, 1.87	0.31	0
Upper respiratory tract infection	2	580/528	1.28	0.65, 2.52	0.48	0
Back pain	2	352/375	0.68	0.28, 1.63	0.39	–
Urinary tract infection	2	580/528	0.73	0.27, 1.96	0.53	0
Nightmare	2	352/375	4.16	0.69, 25.20	0.12	0
Abnormal dreams	2	352/375	1.39	0.51, 3.78	0.52	0
Dizziness	2	304/365	0.59	0.13, 2.60	0.49	–

95% CI, 95% confidence interval; *N*, number of comparisons/studies; RR, risk ratio; TEAE, treatment-emergent adverse event. A TEAE was defined as an adverse event with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. Participants with two or more TEAEs with the same preferred term are counted only once for that preferred term.

Treatment discontinuation and adverse events for leborexant therapy

Table 7 shows treatment discontinuation and individual adverse events for lemborexant 5 compared with placebo. There were only significant differences between two groups (lemborexant 5 and placebo) for any treatment-related treatment-emergent adverse event (TEAE) and somnolence.

Table 8 shows treatment discontinuation and individual adverse events for lemborexant 10 compared with placebo.

TABLE 8 Treatment discontinuation and individual adverse events for lemborexant 10 vs. placebo.

Adverse events	*N*	No. of cases (lemborexant 10/placebo)	RR	95% CI	*P*-value	I^2, %
Discontinuation due to all cause	2	591/534	1.30	0.98, 1.71	0.07	54
Discontinuation due to intolerability	2	591/534	1.83	0.86, 3.87	0.12	0
Any TEAE	3	614/584	1.15	0.87, 1.53	0.33	0.69
Any treatment-related TEAE	3	614/584	2.08	1.61, 2.70	<0.00001	0
Any severe TEAE	2	582/528	0.74	0.33, 1.66	0.46	0
Any serious TEAE	3	618/584	1.46	0.55, 3.90	0.45	0
Any TEAE leading to discontinuation of study drug	3	614/584	1.60	0.58, 4.39	0.36	0
Any TEAE leading to interruption of study drug	2	582/528	0.99	0.39, 2.50	0.97	0
Death	2	582/528	Not estimable	–	–	–
Somnolence	3	614/584	6.48	3.35, 12.56	<0.00001	0
Headache	3	614/584	0.97	0.62, 1.50	0.88	0
Upper respiratory tract infection	2	582/528	0.65	0.11, 3.98	0.64	60
Back pain	2	346/375	1.32	0.55, 3.19	0.53	0
Urinary tract infection	2	582/528	1.84	0.82, 4.13	0.14	14
Nightmare	2	346/375	8.46	1.56, 45.78	0.01	0
Abnormal dreams	2	346/375	2.12	0.12, 35.91	0.60	70
Dizziness	2	241/324	0.64	0.12, 3.47	0.61	–

95% CI, 95% confidence interval; *N*, number of comparisons/studies; RR, risk ratio; TEAE, treatment-emergent adverse event. A TEAE was defined as an adverse event with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. Participants with two or more TEAEs with the same preferred term are counted only once for that preferred term.

There were only significant differences between two groups (lemborexant 10 and placebo) for any treatment-related TEAE, somnolence, and nightmare.

Treatment discontinuation and adverse events for lemborexant 5 and 10 therapies

Supplementary Table 2 shows treatment discontinuation and individual adverse events for lemborexant 5 compared to lemborexant 10. There were only significant differences in somnolence and urinary tract infection between two groups (lemborexant 5 and lemborexant 10) for any TEAE leading to discontinuation of study drug.

Discussion

The present study reports on meta-analysis of suvorexant or lemborexant compared with placebo for the treatment of insomnia patients. Overall, both medications were significantly more efficacious compared to placebo. Suvorexant was superior to placebo with regard to the primary efficacy outcomes (sTST, sTSO, sWASO, sQUAL, and sFRESH). Suvorexant was also superior to placebo regarding outcomes from rating scales and polysomnography, with the exceptions of weight at month 3. This study showed that there were significant differences between suvorexant and placebo in the most adverse events, with the exception of somnolence, excessive daytime sleepiness/sedation, fatigue, back pain, dry mouth, and abnormal dreams that their prevalence in suvorexant group was higher than placebo group. In addition, lemborexant 5 and 10 was superior to placebo with regard to the primary efficacy outcomes (sTST, sSE, and sWASO), with the exception of sWASO at month 1 for lemborexant 10, and also there was no significant difference between lemborexant 5 and 10 and placebo in the most adverse events, with the exception of somnolence for lemborexant 5 and 10 and nightmare for lemborexant 10 was higher than placebo group. Lemborexant 10 was superior to lemborexant 5 with regard to sSE that being less of somnolence and urinary tract infection in Lemborexant 10 confirms superiority of Lemborexant 10 compared to lemborexant 5.

In the evaluation of suvorexant, attention was paid to the side effects that could be based on the mechanism. Narcolepsy is associated with a decrease in orexin neurons and possibly an orexinergic tone (41–43), raising the theoretical likelihood that blocking the orexin receptors may mimic the signs or symptoms of narcolepsy, especially cataplexy (23). No events adjudicated as cataplexy were observed in the present meta-analysis. Surveillance has been associated with a small number of reports of sleep-related hallucinations and sleep paralysis, both of which can happen spontaneously in the general population (44, 45). In the present meta-analysis, there was no

significant difference between suvorexant and placebo regarding hypnagogic/hypnopompic hallucination, sleep paralysis, and sleep-onset paralysis. Although orexin has been hypothesized to regulate weight (46), no difference with placebo in weight change was observed in the present meta-analysis.

The US Food and Drug Administration (FDA) has stated that their overall approach to insomnia medications is to use the lowest effective dose of suvorexant (47). Although one trial and the present meta-analysis based on the results of diary measures showed the 30 or 40 mg dose of suvorexant to be generally suitable and well-tolerated in insomnia patients, but the FDA concluded that the safety and tolerability data across the development programs, including results from driving studies in healthy participants, did not support the use of the 30 or 40 mg dose for the treatment of insomnia (36). Therefore, the FDA suggested that the totality of the clinical data supported the use of lower suvorexant doses of 10–20 mg (47). However, in the next trials, it is necessary to focus on the role of drug dosage in insomnia patients more carefully and better.

Studies have shown that treatment with lemborexant may alleviate some of the changes in sleep architecture seen in older people with insomnia (28, 35). In particular, the increase in TST and stage R sleep with lemborexant therapy illustrated in polysomnography recordings was consistent with the self-reported improvement in sleep retention associated with lemborexant in comparison with placebo. The present meta-analysis confirmed these results. Increased rates of somnolence showed evidence of dose-response in the lemborexant groups compared with placebo and increased rates of somnolence and urinary tract infection in lemborexant 10 compared with lemborexant 5 showed evidence of dose-response in the treatment of insomnia patients. However, sSE levels in lemborexant 10 was higher than lemborexant 5. Therefore, the researchers should consider the dose-response of lemborexant in the future trials more cautious.

Our analysis has a number of strengths: data from randomized, double-blind, placebo-controlled trials, and the number of patients evaluated were relatively large. In contrast, several limitations should be acknowledged. First, studies in this analysis included different drug dosing regimens. Second, some studies included few cases and may not have included statistical comparisons between the groups. Third, the number of studies included is limited, outcome measures and time points for heterogeneous analysis, and for some outcome measures, only a few studies have been reported.

Conclusion

The study showed that suvorexant and lemborexant are two efficacious and safe treatments for insomnia. As many patients with insomnia have significant comorbid conditions, further data in patients with insomnia and comorbid conditions are needed.

A brief summary

Current knowledge

Insomnia is a prevalent sleep disorder with various consequences. Pharmacotherapy and cognitive behavioral therapy for insomnia are main management strategies available. Dual orexin receptor antagonists are a new line of pharmacotherapeutic agents for management of insomnia. As DORA is a new line of therapy, practitioners may not be familiar with efficacy and side effects of these medications.

Study impact

Our meta-analysis indicated that DORAs are efficacious and safe. Better awareness of the efficacy and safety of this new mechanistic line of insomnia treatment may help practitioners to better manage their patients. As majority of clinical trials exclude patients with significant comorbid conditions, further studies needed to evaluate safety and efficacy in patients with insomnia and various comorbid conditions.

Data availability statement

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

Author contributions

HK: supervision of all steps, study design, and manuscript writing. MS: databases search, data analysis, and manuscript writing. SK: manuscript writing and editing and data analysis. MH: supervision of all steps, editing the manuscript, and scientific writing. AS: first idea, supervision, and manuscript writing 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1070522/full#supplementary-material

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Neutropenia after the coadministration of clozapine and nirmatrelvir-ritonavir in a patient with SARS-CoV-2 infection: A case report with a literature review

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Background: Schizophrenia is considered one of the major risk factors for mortality from SARS-CoV-2 infection. Early antiviral treatment is important to decrease the risk of mortality. Currently, Paxlovid (nirmatrelvir-ritonavir) has been widely used in SARS-CoV-2 patients with risk factors. However, drug–drug interactions with anti-psychotics are prominent and complicated.

Case presentation: We report a clozapine-treated patient with SARS-CoV-2 infection who developed neutropenia after coadministration with Paxlovid. In this case, clozapine was used for over 15 years, without neutropenia development. However, severe neutropenia (absolute neutrophil count = 523/μl) developed 3 days after the coadministration of Paxlovid 2 doses per day, valproic acid 1,000 mg per day and clozapine 100 mg per day. The development of neutropenia may be attributed to the complicated interaction among Paxlovid, SARS-CoV-2 infection, valproic acid, fluvoxamine and clozapine.

Conclusions: Neutropenia is a rare but life-threatening event if a concomitant infection occurs. The risk may increase during SARS-CoV-2 infection and the coadministration of clozapine and Paxlovid. Although the exact causes of neutropenia in this patient are not fully clear, the white blood cell count and absolute neutrophil count should be closely monitored during the administration of Paxlovid in clozapine-treated patients with SARS-CoV-2 infection.

KEYWORDS

neutropenia, clozapine, SARS-CoV-2, drug-related side effects and adverse reactions, drug interactions

Background

Antiviral treatment has been important since the outbreak of the SARS-CoV-2 pandemic. Nirmatrelvir-ritonavir (Paxlovid) is considered the most effective antiviral regimen. Compared to remdesivir and molnupiravir, Paxlovid can prevent more SARS-CoV-2 patients with risk factors from requiring hospitalization and was the first-line antiviral medication for SARS-CoV-2 until June 2022 (1). Because of the cytochrome P450 (CYP) 3A4, 1A2, and possibly 2D6 inhibition effect of ritonavir, drug–drug interactions should be considered when prescribing Paxlovid (2).

Schizophrenia is the second highest risk factor for dying from SARS-CoV-2 infection (3). Early administration of antiviral agents is essential for patients with schizophrenia who are infected by SARS-CoV-2. Currently, clozapine is broadly used in treatment-refractory patients with schizophrenia. *In vitro* and *in vivo* studies show that CYP3A4 and CYP1A2 are the major metabolic pathways, but CYP2D6 plays a minor role of clozapine metabolism (4, 5). Additionally, the CYP metabolic pathway may be affected by medications that inhibit or induce CYP. Thus far, the coadministration of clozapine with Paxlovid is contraindicated due to potential CYP1A2 inhibition. To date, there is no clinical report about the adverse effects of the coadministration of clozapine and Paxlovid in patients with active SARS-CoV-2 infection. Here, we present a patient who developed isolated neutropenia after the coadministration of clozapine and Paxlovid during active SARS-CoV-2 infection.

Case presentation

Ms. L was a 41-year-old Taiwanese Han female patient with schizophrenia. She had no known underlying physical disease, with normal blood sugar, blood pressure, serum low-density lipoprotein, total cholesterol and triacylglycerol levels. Her first psychotic symptoms occurred at the age of 20 years, with the manifestation of delusions of grandeur and religion, disorganized behaviors, and negative symptoms, including avolition and flat affect. She had several manic episodes with the presentation of expansive mood, hypertalkativeness, multiple goal-oriented behaviors, and flight of ideas. She was repeatedly admitted to the psychiatric ward due to psychotic or manic-like symptoms (15 times from 2007 to 2022) and had used clozapine since 2007. Although we did not measure blood level of clozapine, she even received fluvoxamine to increase clozapine blood levels and optimize the serum clozapine to norclozapine ratio in 2010. The clozapine dose ranged from 200 to 500 mg per day, and valproic acid and other antipsychotics (haloperidol and paliperidone) were sometimes used for augmentation due to poor response to clozapine. During the use of clozapine, the white blood cell (WBC) count ranged from 3,100 to 13,800/μl, and the absolute neutrophil count (ANC) ranged from 1,499 to 11,422/μl before April 10, 2022. The timing of blood sample, which depended on her appointments, was not fixed. On April 11, 2022, because she did not take medications regularly, the patient was admitted to the acute psychiatric ward due to psychotic exacerbation.

The patient's symptoms at the time of hospitalization included delusions of grandiosity and persecution, hypertalkativeness, elevated mood, irritability, decreased sleep needs, and increased verbal aggression toward her family. Medications at the time of hospitalization included paliperidone palmitate 525 mg every 3 months and valproic acid 1,000 mg and clozapine 200 mg daily. The blood profiles on April 11 showed a WBC count of 5,080 cells/μL and an ANC of 3,434 cells/μL. Since the patient missed taking clozapine and valproic acid for weeks, we restarted clozapine from 25 to 275 mg daily in the following 8 weeks. To elevate the blood level of clozapine, fluvoxamine maleate 50 mg daily was added on May 10, 2022. The WBC count and ANC were 6,170 and 2,795 cells/μL, respectively, on May 16 (the 6th day after adding fluvoxamine). On June 1, she developed a dry cough, and her body temperature rose to 39.0 degrees Celsius. The patient's hemogram revealed that her blood c-reactive protein level was 0.9 mg/dL, her WBC count was 4,450 cells/μL, and her ANC was 2,474 cells/μL. The results of her SARS-CoV-2 reverse transcription-polymerase chain reaction (RT–PCR) test on June 1 were positive, with a cycle threshold (ct) value of 12.5. She received one dose of Paxlovid (ritonavir 100 mg and nirmatrelvir 150 mg) every 12 h from June 2 to June 7 for acute SARS-CoV-2 infection. In total, 10 doses of Paxlovid were given. From the first day and the last day, she was given one dose to maintain an adequate prescription interval. To reduce the drug–drug interaction, her clozapine was tapered off to 175 mg on June 2 and then to 100 mg on June 3. Fluvoxamine was discontinued, and valproic acid was tapered off to 1,000 mg on June 2. On the routine blood test on June 5 (the third day after the coadministration of Paxlovid and clozapine), the WBC count and ANC were reduced to 3,490 and 523 cells/μL, respectively. We discontinued clozapine immediately, and valproic acid was tapered off to 500 mg on June 6. She did not have any upper respiratory tract symptoms, fever, or other signs of infection. Her blood clozapine level was not obtained. The patient's repeated SARS-CoV-2 RT–PCR tests showed Ct values of 25.0 on June 5 and 28.1 on June 8. The follow-up WBC count and ANC were 4,170 and 1,547 cells/μL, respectively, on June 8. Because the patient's agitation and delusions of grandiosity worsened, 100 mg per day of clozapine was reintroduced on June 9. On June 12, she had negative SARS-CoV-2 RT–PCR findings. The WBC count and ANC were 5,120 and 2,468 cells/μL, respectively, on June 13. We

Abbreviations: WBC, white blood cell; ANC, absolute neutrophil count; ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CYP, cytochrome P; COVID-19, coronavirus disease 2019.

TABLE 1 Summary of medications and laboratory data before and after SARS-CoV-2 infection.

	5/30	6/1	6/2	6/3	6/4	6/5	6/6	6/7	6/8	6/13	6/20	6/26
SARS-CoV-2 CT value	–	12.5	–	–	–	25.0	–	–	28.1	Negative	–	–
WBC count per uL	8,630	4,450	–	–	–	3,490	–	–	4,170	5,120	4,210	6,720
ANC per uL	6,300	2,474	–	–	–	523	–	–	1,547	2,468	1,372	3,884
Serum valproic acid level, ug/mL	–	–	–	–	–	62.0	–	–	–	–	65.3	82.2
Paxlovid dosage	0	0	1	2	2	2	2	1	0	0	0	0
Clozapine dosage, mg per day	250	275	175	100	100	0	0	0	0	125	150	150
Fluvoxamine dosage, mg per day	50	50	0	0	0	0	0	0	0	0	25	25
Valproic acid dosage, mg per day	1,500	1,500	1,000	1,000	1,000	1,000	500	500	500	1,000	1,200	1,200

–, not tested; ANC, absolute neutrophil count; CT, cycle threshold; WBC, white blood cell.

gradually titrated clozapine to 150 mg per day and added 25 mg fluvoxamine per day to stabilize the exacerbated psychotic symptoms and agitative status. Table 1 summarizes the patient's medications and laboratory data from May 30 to June 23.

Discussion and conclusions

Severe neutropenia with concomitant infections is a fatal complication that may be induced by immune-compromised status, immunosuppressive agents and even the prolonged use of antiviral therapy (6). Regarding the polypharmacy status and the comorbidity of SARS-CoV-2 infection, this unique case permits further discussion of the potential etiologies of neutropenia.

First, the initiation and titration of clozapine was reported to be associated with new-onset neutropenia. The pathogenetic mechanism of clozapine-related agranulocytosis was hypothesized, with clozapine potentially inducing antibodies against neutrophils, but the category and the type of antibody remained unclear (7). A current meta-analysis pointed out that neutropenia associated with clozapine occurs early with a substantial decline in risk after 1 year of exposure (8). Because our patient had used clozapine for nearly 15 years and we gradually titrated the clozapine dose, no neutropenia was noted before the current SARS-CoV-2 infection. Therefore, neutropenia due to clozapine alone is less likely.

Second, not only clozapine but also SARS-CoV-2 infection causes significant changes in the WBC count (9). Although neutropenia has been reported in post-COVID-19 cases, it is rare in cases of SARS-CoV-2 active infection without superimposed bacterial infection or malignancies (10–12). However, severe granulocytopenia has been reported in SARS-CoV-2-infected patients with the long-term use of clozapine (13, 14). A retrospective study also concluded that in patients treated with clozapine, the ANC, WBC count and lymphocyte count significantly decreased between baseline and the first 7 days of SARS-CoV-2 infection (15). Previous studies indicated that the decreased ANC is temporary (16). It rebounded to baseline in the second week even without the reduction of the clozapine dosage. Although the ANC is decreased, recent case series have illustrated the safe use of clozapine during SARS-CoV-2 infection (17). Smits et al. recommended the continuation of clozapine in SARS-CoV-2-infected patients even when they developed neutropenia (18). Therefore, we suggest that the neutropenia that occurred in our patient may be due to SARS-CoV-2 infection.

Third, neutropenia has been reported in human immunodeficiency virus (HIV)-infected patients with viral loads <20 copies/mL who were treated with clozapine and ritonavir previously (19), suggesting that the potential casual effect of neutropenia and the combination of ritonavir and clozapine. Ritonavir (a component of Paxlovid) is another inhibitor of both CYP1A2 and CYP3A4, which may increase blood level of clozapine. As we mentioned previously, Paxlovid is not recommended in clozapine-treated patients due to possible drug–drug interactions. Acute viral infection may increase blood level of clozapine in this patient (20, 21). One possible explanation could be that elevated α-1-acid glycoprotein concentrations during inflammation increase plasma clozapine-α-1-acid glycoprotein binding, results in elevated total clozapine plasma concentrations (22). In addition, concurrent use of valproate (23) and fluvoxamine (24, 25), has also been reported to elevate blood level of clozapine. However, no consensus exists to explain whether elevated clozapine levels increase the risk of neutropenia currently. We suggest that the coadministration of psychotropics and Paxlovid is one of the possible causes of neutropenia.

Fourth, valproate causes bone marrow suppression, which can be associated with idiosyncratic neutropenia (26). Although our patient had used valproate in the past, she did not develop neutropenia, and neutropenia due to valproate use alone is less likely.

Fifth, current evidence could not fully elucidate the causal relationship among Paxlovid, fluvoxamine and neutropenia. However, no report exists to describe whether fluvoxamine and Paxlovid may cause neutropenia. As a newly introduced medication, the adverse events caused by Paxlovid may need more investigation.

The readers are warned not to overinterpret the findings described for this patient because this study has several limitations: (1) As a case report, the findings cannot be generalized. More investigation should be performed to illustrate the complicated interaction among clozapine, Paxlovid and SARS-CoV-2 infection. (2) Serum clozapine levels were not analyzed in this patient. We do not know the changes in blood clozapine levels after Paxlovid use. The further relationship between the clozapine level and neutropenia cannot be proven.

In conclusion, neutropenia is a rare but potentially life-threatening event. The risk of neutropenia may increase during SARS-CoV-2 infection. The coadministration of Paxlovid may also contribute to the risk of neutropenia in this patient. Although the exact causes of neutropenia in this patient are not fully clear, the WBC count and ANC should be closely monitored during the administration of Paxlovid in clozapine-treated patients with SARS-CoV-2 infection.

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

The studies involving human participants were reviewed and approved by Taipei Medical University-Joint Institutional Review No. N202207057. The patients/participants provided their written informed consent to participate in this study.

Author contributions

C-IL reviewed the case and wrote the manuscript. KG contributed to the case. C-HC revised the manuscript. All authors have read and approved the manuscript.

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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Citalopram-induced sleep bruxism in a breastfed infant: A case report

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Bruxism associated with antidepressant use is an under-recognized phenomenon. The use of citalopram has gained wide acceptance in the treatment of depression and anxiety disorders; however, the consumption of this medication during lactation and pregnancy has not been carefully characterized. There are limited studies about its side effects in the breastfeeding period. Here, we report a rare case of citalopram-induced sleep bruxism in a 9-month-old female breastfed infant whose mother used SSRI agent citaloporm for her anxiety disorder. Within 2 weeks of initiating her citalopram treatment, with a starting dose of 10 mg/day, the patient reported sleep bruxism in her infant. Thorough examinations of the infant were performed and no abnormal finding was reported. After ruling out other possible causes, the new-onset bruxism symptoms were attributed to the mother's recent use of citalopram, which was discontinued thereafter. The infant's symptoms of bruxism disappeared following the discontinuation of the medication by her mother. These findings and similar reports could draw more attention to bruxism or other possible symptoms in breastfed infants of mothers consuming psychotropic medications.

KEYWORDS

bruxism, citalopram, selective serotonin reuptake inhibitors (SSRIs), breastfeeding, side effect, antidepressant, case report

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most prevalent drugs utilized for the treatment of major depressive disorder. SSRIs work by targeting the serotonin transporter (SERT),[1] which leads to higher extracellular levels of serotonin; this is considered the basis of their mechanism of action, although other mechanisms have been proposed (1). SSRIs are generally safe and well tolerated. However, certain side effects have been reported to be associated with the use of SSRIs, including: sexual dysfunction, dry mouth, bleeding, weight gain, and gastrointestinal symptoms (2). They also have some side effects on the central nervous system, including akathisia, tremor, dystonia, and bruxism (3, 4).Antidepressant-associated bruxism may occur in pediatric and adult patients, most commonly among female patients (5). Both short-term and long-term use of antidepressants have been associated with bruxism. The most commonly reported offending agents are fluoxetine, sertraline, and venlafaxine. Symptoms may begin within 3–4 weeks of medication initiation and may resolve within 3–4 weeks of drug

1 Serotonin transporter (SERT or 5-HTT).

discontinuation, with the addition of buspirone, or by substitution with another pharmacologic agent. The incidence of this phenomenon is unknown (5).

"Bruxism" is an umbrella term under which fall various motor activities of the jaw muscles, such as grinding and clenching of the teeth as well as thrusting of the mandible (6). According to Lobbezoo et al., sleep bruxism and awake bruxism have been defined as "a masticatory muscle activity during sleep, characterised as rhythmic or non-rhythmic in otherwise healthy individuals" and "a masticatory muscle activity during wakefulness characterised by repetitive or sustained tooth contact and/or bracing or thrusting of the mandible in otherwise healthy individuals" respectively. It should also be noted that in both definitions, bruxism is not considered a movement disorder or sleep disorder (7).

Bruxism, characterized by teeth clenching or grinding, is considered an involuntary nonfunctional activity of the masticatory system. It might happen during sleep or while awake, consciously or unconsciously, and is not classified as a disorder, but as a behavior. This habit is common during childhood. Its prevalence in children ranges from 13 to 49% (8) and may have negative consequences on the stomatognathic system (9). SSRI's, including citalopram, have been shown to potentially induce sleep and/or awake bruxism (10).

Intergenerational effects, whether through medication or other means, have increasingly become of interest, especially in the field of psychiatry (11). We here, would like to report a case of citalopram-associated sleep bruxism in a female breastfed infant, which resolved by discontinuation of her mother's medication.

Case presentation

A 33-year-old Persian female patient referred to Ibn-Sina outpatient psychiatry clinic in Mashhad, Iran, in June 2019, with a mixed anxiety depressive disorder during her breastfeeding period. She had a history of anxiety prior to her pregnancy, and was under treatment with sertraline. She had previously shown symptoms of agitation and become irritable with her sertraline treatment, and had no tendency to continue using this medication. The patient was unemployed; described her family's economic status as "stable" and mentioned she had "strong emotional support" from her spouse. Her past surgical history included only a recent Cesarean section. She was breastfeeding her then, 9-month-old infant. Pregnancy seemed to have been a significant psychosocial stressor for her. The patient presented to our general adult psychiatry outpatient clinic with a 3-month history of mood symptoms; including low mood, anhedonia, insomnia, anxiety, loss of energy, and decreased appetite. Symptoms had significantly worsened over the 1-month period before she referred to us.

She had no suicidal or homicidal thoughts, intent, or plans as well as no history of suicide attempts or self-harm. The patient also had no history of psychotic symptoms or manic episodes. She had never smoked, nor used alcohol, cannabis, or any illicit substances. There were no significant findings in her physical examination. Her electrocardiography (EKG), including her corrected QT interval (QTc) was normal. Considering the patient's past history of sertraline-associated agitation, a 10-mg daily starting dose of citalopram was prescribed for her. Her symptoms began to decline 10 days after her consumption of citalopram was initiated. However, 2 weeks after the initiation of her treatment, she reported symptoms of bruxism in her infant. The infant was a term 9-month-old female, delivered through Cesarean section after an uneventful pregnancy, with no history of physical disorders, illnesses, or hospital admissions and no use of medications except supplements. The infant's diet consisted of her mother's breast milk five to six times per day, as well as standard supplementary nutrients given for 9-month-old infants consisting of such as fruits, vegetables, meat, and biscuits. She was not being fed with milk powder or any other formula and was not consuming any medications. The patient reported that her infant had sporadic, pulsatile, and momentary movements in her jaws, which usually began with movements of the head, especially during sleep. Furthermore, the mother mentioned her child had a habit of biting and clenching her teeth while awake.

Clinical findings

A thorough physical examination, including extra-oral and intra-oral assessment of the child by a pediatrician showed no abnormalities. Another intraoral examination was performed by a pediatric dentist who reported appropriate teeth growth and development in the child. The dentist reported no pathologic findings. The infant had no salivary drooling and was able to swallow efficiently with no evident cranial nerve dysfunction. However, bruxism was observed by the dentist during the examination.

Diagnostic assessment

After somatic and organic problems were ruled out, the infant's symptoms of bruxism were attributed to the excretion of citalopram in the mother's milk.

Therapeutic intervention

Citalopram, which was hypothesized as the main cause of the child's symptoms of bruxism, was discontinued, with bruxism symptoms resolving 72 h thereafter.

Follow-up and outcomes

The mother and her child were followed for 2 years. The infant's symptoms of bruxism stopped after her mother's use of citalopram was discontinued. She no longer had teeth clenching or grinding while awake or during sleep. The mother resumed to breastfeeding right away after the infant's symptoms disappeared with no further consequences and was referred to a psychotherapist for cognitive behavioral therapy (CBT) with improvements in both her depressive and anxiety symptoms.

Discussion

In this paper, we report sleep bruxism in a breastfed 9-month-old infant whose mother was under treatment with citalopram. The point of this case was to bring attention to the excretion of medications like SSRIs into breastmilk. Considering the onset of bruxism in the

infant shortly after the initiation of her mother's citalopram treatment and the cessation of this symptom following the discontinuation of the medicine, the infant's symptoms of bruxism were attributed to her mother's use of citalopram after ruling out other physical or organical causes. This is unique, as there are no similar studies in the current literature.

There is transfer of SSRI's including citalopram and escitalopram to human breast milk. A study by Pogliani et al. reported that all lactating women treated with fluoxetine or citalopram had relative infant doses (RID's) exceeding 10% (12). Previous studies have reported weight loss and drowsiness in breastfed infants of mothers who used citalopram (13). It should also be noted that the individual genetical characteristics of the mother and/or infant may also play a role in how their body metabolizes and responds to a medication. It has been reported that the polymorphism of CYP2C19 plays a crucial role in the N-demethylation of citalopram. As a result, poor metabolizers and extensive metabolizers of CYP2C19 show a significant difference in the disposition of citalopram *in vivo* (14). In this patient, the symptoms regressed merely by cessation of the medication. This was possibly due to the low level of the drug in the infant's serum.

A review paper by Wallem et al. had also concluded that there is an "apparent" relationship between treatment with SSRI's and the development of bruxism (15). Another systematic review by Melo et al. had found an association between the development of sleep bruxism in children and the use of psychotropic medications such as duloxetine, paroxetine, venlafaxine, and methylphenidate. However, they found no significant correlation between symptoms of bruxism and the utilization of medications such as citalopram, escitalopram, fluoxetine, and mirtazapine (16).

It is also noteworthy to take into consideration the possible effects of intra-uterine exposure to SSRI's on fetus brain development (17), although our patient was not using any antidepressant medication during her pregnancy. It is also of importance to note the fact that many factors in the early home environment can impact brain development in infants and children (18). According to Orsolini et al., paroxetine and sertraline have better neonatal safety profiles during breastfeeding compared to other SSRI medications (19).

Several therapeutic modalities have been suggested, but there is no consensus about which is the most efficient. Some studies have reported hydroxyzine to be an efficient treatment for sleep bruxism in children (20). Occlusal splints, orthodontic, physical, and psychological interventions have also shown to be effective in reducing bruxism (21).

Generally, symptoms tend to appear within 3–4 weeks of the initiation of antidepressant treatment or of undergoing dose titration. Symptom resolution may be achieved the addition of serotonin 1A (5HT1A) partial agonists (buspirone, tandospirone), by dose reduction, by medicine cessation, or by the addition of other pharmacologic agents including tricyclic antidepressants (amitriptyline), antipsychotics (aripiprazole, chlorpromazine), opipramol, norepinephrine-dopamine reuptake inhibitors (bupropion), or serotonin 2A/2C antagonist and reuptake inhibitors (trazodone) (22). Studies have also shown that clonidine can effectively reduce symptoms of sleep bruxism (23). Symptoms may also resolve over time without pharmacological intervention. The use of low-dose quetiapine has also been reported to be effective in the treatment of mandibular dystonia and SSRI-induced bruxism (24). The addition of buspirone has been reported to be successful in alleviating symptoms of bruxism in several cases. Buspirone, a weak 5-HT2C receptor antagonist, can potentially compete with serotonin to bind with 5-HT2C receptor, which can lead to improvement of bruxism (25).

This observation along with considering medications used for bruxism treatment can be instructive in both understanding the underlying pathophysiological mechanisms of antidepressant-associated bruxism, as well as in providing a foundation for treatment recommendations.

Limitations and suggestions for future studies

One of the limitations of this study is that since it is a case report, direct causal relationships cannot be determined. We should also take into account that as previously cited, given how common bruxism is in children, the infant's symptoms of bruxism may have been caused by other factors. In this patient, 2 weeks after the consumption of the drug (and thus, its excretion into the mother's breastmilk), the infant began to show symptoms. Another limiting factor is that this study reports the phenomenon observed in only one patient; larger sample sizers are needed to investigate this possible association.

In future studies, instrumental measures such a assessing sleep bruxism using polysomnography as well as genetical testings can be helpful as well. In addition, measuring citalopram concentration levels in the infant's serum or her mother's breastmilk would help make this attribution more concise. It is suggested that further studies be conducted on possible side effects and symptoms in breastfed children of mothers being treated with psychotropic medications. More studies containing larger populations are required to investigate the possible association of SSRI medications, including citalopram, with sleep bruxism. Similar results, if proven, could lead to pediatricians and other clinicians considering the possibility of medication-induced bruxism in children so that this phenomenon would not be overlooked, missed, or undiagnosed.

Conclusion

The use of SSRI medications has been associated with symptoms of bruxism in some individuals. The case presented in this study, was a breastfed infant whose mother was using citalopram. The infant began manifesting symptoms of sleep bruxism shortly after, which resolved following the discontinuation of the medication. Similar results, if proven, could suggest that breastfed infants of mothers being treated with SSRI's including citalopram, may present symptoms of bruxism. This could lead to a better understanding of the pathophysiological mechanisms underlying bruxism and the functions of SSRI's as well as provide pediatricians, psychiatrists, as well as other clinicians with more holistic and effective diagnostic and treatment plans.

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 Mashhad University of Medical Sciences Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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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The effect of adding curcumin to sodium valproate in treatment of patients with bipolar disorder in the acute phase of mania: A randomized double-blind clinical trial

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Background: Inflammatory processes play a role in the etiopathogenesis of bipolar disorder type 1. Full therapeutic responses are seldom seen and the ongoing inflammatory processes in the brain could lead to neuronal loss. Curcumin, a relatively safe herbal compound, has been shown to have anti-inflammatory effects. The present randomized double-blind clinical trial study aimed to investigate the effect of adding curcumin to the treatment regimen of BID.

Materials and methods: This randomized double-blind clinical trial was conducted on 78 patients diagnosed with BID according to the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) criteria. The sample were divided into two groups. Patients in both groups received sodium valproate starting at a dose of 600 milligrams per day and administered up to 20 milligrams per kilogram per day or the highest dosage of the patient's tolerance. Patients in the intervention group also received curcumin as nanomicelle in soft gelatin capsules 40 milligrams per day. The control group received placebo tablets with the same characteristics as the curcumin tablets. They were assessed by a psychiatrist using the Young Mania Rating Scale (YMRS), Mini-Mental State Examination (MMSE), Clinical Global Impression (CGI), and a medication side effect questionnaire at the beginning of the study, as well as in the first, second, and fourth weeks of the study.

Results: Among the 78 patients chosen to participate in the project, 54 people completed the trial. No specific side effect was observed in the two groups. Both groups showed an increase in their MMSE scores compared to the beginning of the study (value of $p < 0.001$). Although this increase was not statistically different between the two groups (value of $p = 0.68$). The YMRS score of both groups decreased significantly by the end of the study (value of $p < 0.001$); however, this decrease was not significantly different between the two groups (value of $p = 0.64$). In addition, the two groups experienced a significant increase in their CGI scores throughout the study (value of $p < 0.001$), this increase however was not statistically different between the two groups (value of $p = 0.88$).

Conclusion: The present study suggested that curcumin may not be a useful adjuvant agent in the management of patients with BID receiving sodium valproate as treatment.

Clinical trial registration: Iranian Registry of Clinical Trials (IRCT), identifier IRCT2016102530504N1.

KEYWORDS

curcumin, clinical trial, sodium valporate, bipolar disoder, bipolar disorder type 1

Introduction

Bipolar I disorder (BID) is a life-long episodic disease characterized by changes in a person's mood varying between mania and depression. During mania episodes, effective and timely diagnostic and therapeutic interventions are required to minimize the disorder's harmful effects on the individual as well as the interpersonal side effects which could easily interrupt the affected person's life (1). Therefore, investigating an effective medical treatment preserving various dimensions of the personal and social life of patients is the main focus of research. Psychopharmacological treatments are the first-line treatment. So far, mood stabilizers including carbamazepine, sodium valproate, and some antipsychotics have been used to treat the acute phase of mania (1). The necessity of performing more precise investigations to find new therapeutic approaches becomes more apparent by considering bipolar disorder's prevalence (1.5%), suicidal rate (10–20%), considerable recurrence, and the half effectiveness of single-drug therapy, as well as inefficient therapeutic interventions including drug augmentation for managing cases who show therapeutic resistance (1). The direct and indirect costs imposed on patients' families as well as society during the acute phase of the disease is much greater than the cost required for the proper and timely treatment of the disease (1). Although the underlying molecular mechanisms for BID are not fully understood, most available drugs regulate the abnormal level of specific biochemical factors. Curcumin, a relatively safe herbal compound, has been long used for the treatment of various diseases and has been suggested as a potential therapeutic option for psychiatric illnesses. Among various underlying mechanisms for the development of BID, some studies demonstrated that abnormal serum levels of brain-derived neurotrophic factor (BDNF) are seen in BID patients (2). Therefore, some of the main therapeutic drug regimens increase the BDNF levels while reducing BID symptoms. Similar to well-known treatments (including lithium and atypical antipsychotics), curcumin can increase BDNF levels in BID patients (3–5). Alongside the abnormal level of BDNF in BID patients, there is a growing line of evidence suggesting that oxidative stress mechanisms are involved in BID (6, 7). In this way, increased reactive oxygen species (ROS) production results in apoptosis of brain cells (6–11). Moreover, inflammatory processes affect neurotransmitter function and neuronal plasticity (12, 13), which play a part in the pathophysiology of neurodegenerative diseases (14). An increase in inflammatory markers including C-reactive protein (CRP), inflammatory cytokines, and tumor necrosis factor (TNF) alpha is seen in BID (15). Studies have shown that curcumin has antioxidant functions that can reduce ROS, regulate inflammatory responses and decrease apoptosis (16–19).

Since the use of curcumin has been long considered as a potent herbal drug in ancient Persian medical texts, many studies have been carried out on this subject but limited studies are evaluating its effects on psychiatric disorders including BID. The present study aimed to determine the effect of adding curcumin to the therapeutic regimen of patients with BID during the acute phase of mania (Figures 1–3).

Materials and methods

The present double-blind randomized clinical trial study approved by Mashhad University of Medical Sciences was conducted at Ibn-Sina Psychiatric Hospital in Mashhad, Iran from 2016 to 2017. A total number of 78 patients diagnosed with BID based on the Diagnostic and Statistical Manual of Mental Disorders 5, participated in the study.

Inclusion criteria

The inclusion criteria were as follows:

- Diagnosis of bipolar-1 disorder with recent mania episode based on DSM-5 diagnostic criteria by semi-structured interview by a psychiatrist and diagnostic confirmation with a score of at least 20 on the Young Mania Rating Scale (YMRS) (20).
- The absence of the diagnosis of schizophrenia, delirium, bulimia nervosa, anorexia nervosa, intellectual disability, autism, and attention deficit hyperactivity disorder (ADHD).
- Age between 18 and 50.
- No substance abuse in the last 3 months.
- No history of admission to psychiatric wards during the past 3 months.
- No history of seizure or epilepsy.
- The absence of suicidal or homicidal risk during the psychiatric interview.
- Not being pregnant.
- Lack of a history of susceptibility to sodium valproate or any herbal medicines.
- Patients who had received other medications during the last 2 weeks before or during the study (including mood stabilizer treatments) underwent a washout period based on the medication's half-life for patients receiving drugs with a long half-life.

A full interview was conducted for each patient by a psychiatric resident and informed consent was obtained from eligible patients or their legal guardians. All participants were assured that their information

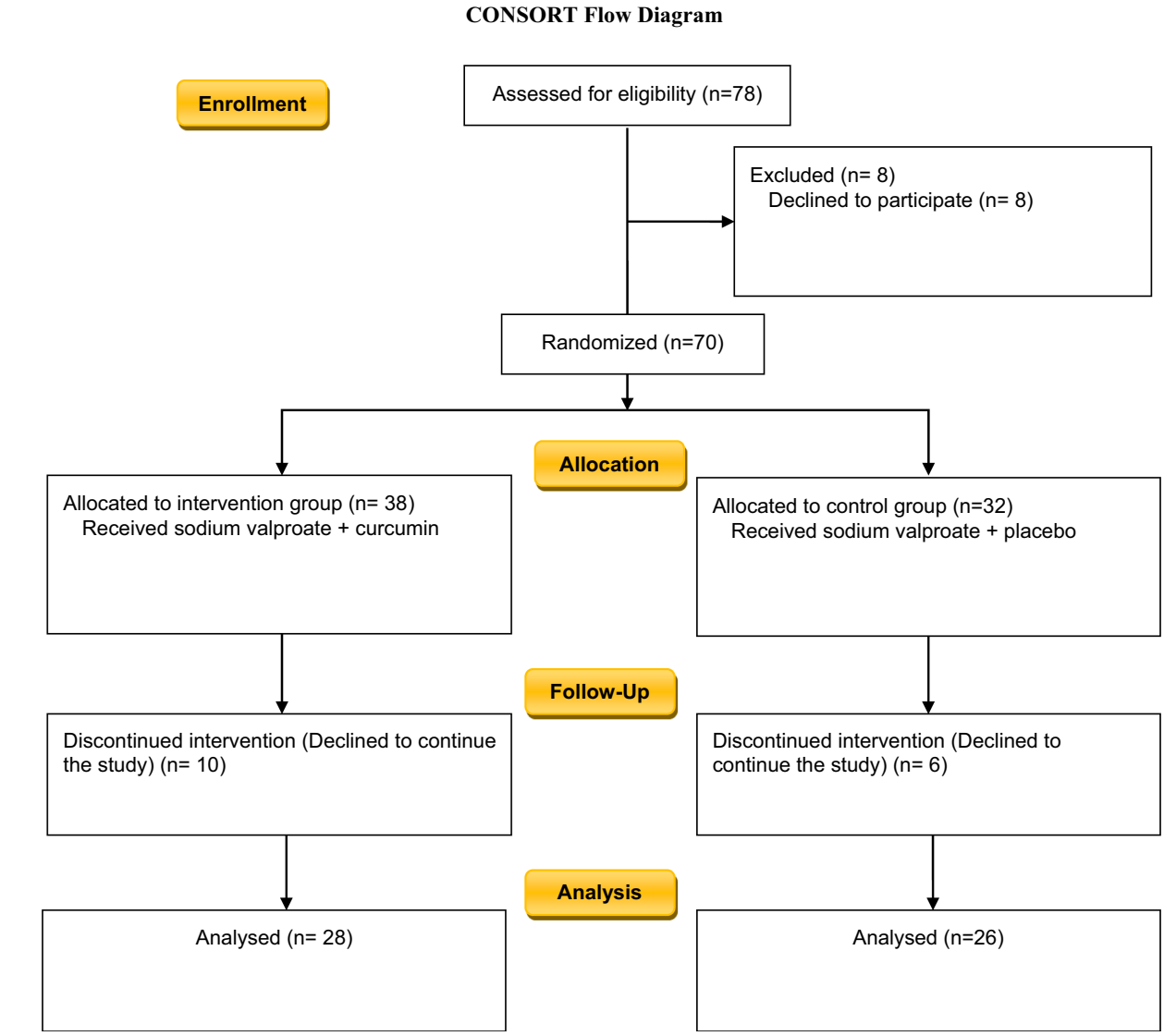

FIGURE 1
Study flow chart.

will be kept confidential, and that they would be able to leave the study at any time. Furthermore, patients who needed urgent intervention or were suspected of intensifying symptoms by the treatment were excluded from the study.

Medications and questionnaires

Patients who agreed to participate in our trial were randomly assigned into two groups using a randomized number table. Patients in the intervention group received sodium valproate (starting at a dose of 600 mg/day and administrated up to 20 mg/kg/day or the highest dosage of the patient's tolerance) and curcumin as nanomicelle in soft gelatin capsules (Sinacurcumin®), 40 mg once daily. The oral bioavailability of curcumin is very low due to the hydrophobic nature of this compound. Kunnumakkara et al. (21) to improve the oral bioavailability of curcumin, we used SinaCurcumin oral capsules (Exir Nano, Tehran, Iran) in this study. SinaCurcumin is a registered product from curcuminoids in Iran (IRC: 1228225765). Curcuminoids are dietary polyphenols extracted from the dried rhizomes of Curcuma longa L (turmeric) and comprise curcumin, desmethoxycurcumin, and bisdemethoxycurcumin, which are together known as the C3 complex. Each soft gelatin capsule of SinaCurcumin contains 40 mg curcuminoids as nanomicelles, absorbed as equivalent to 500 mg curcumin tablets. The encapsulation efficiency of curcuminoids in nanomicelles is almost 100%. The mean diameter of nanomicelles is around 10 nm. The oral absorption of SinaCurcumin is at least 50 times more than the conventional powder of curcumin in mice (22). The control group received a placebo in addition to sodium valproate. Placebo soft gels were prepared by the same company, in the exact same appearance as the curcumin tablets, containing all ingredients of the other soft gel except curcumin, with the same dosing.

The Young Mania Rating Scale (YMRS) is a rating scale that is traditionally used to scale symptoms of mania; it is used by clinicians and psychiatrists and typically takes 15–30 min to complete. It consists of 11 items that require the patient to subjectively report their symptoms in the past 48 h. Its validity and reliability has been proven for the Iranian population (23). Clinical Global Impression (CGI) rating scales

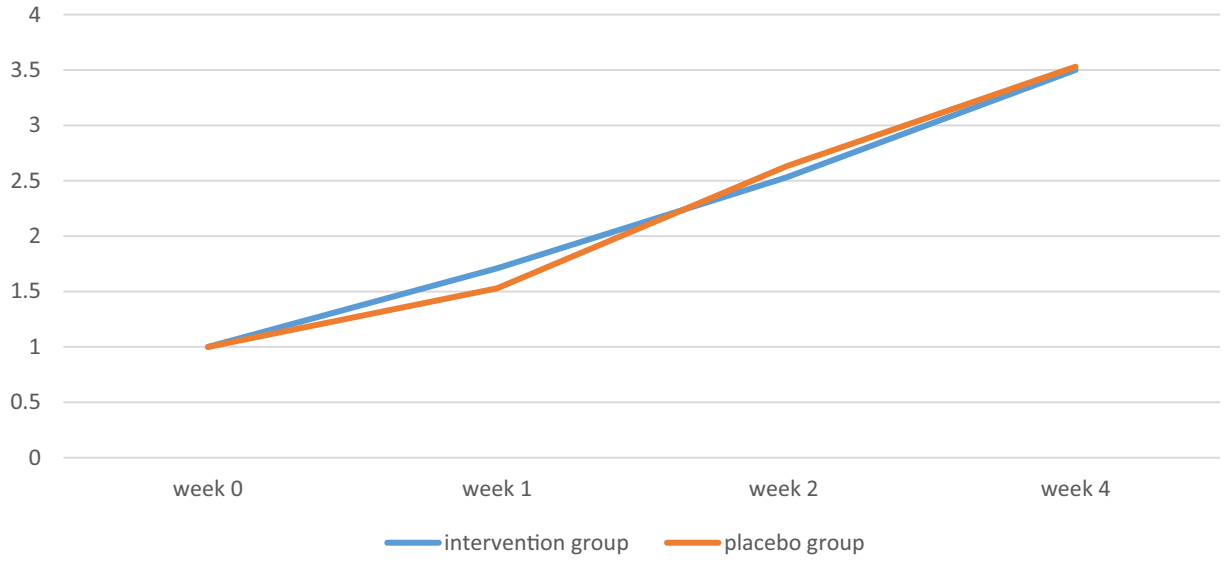

FIGURE 2
CGI scores of the two groups throughout the study.

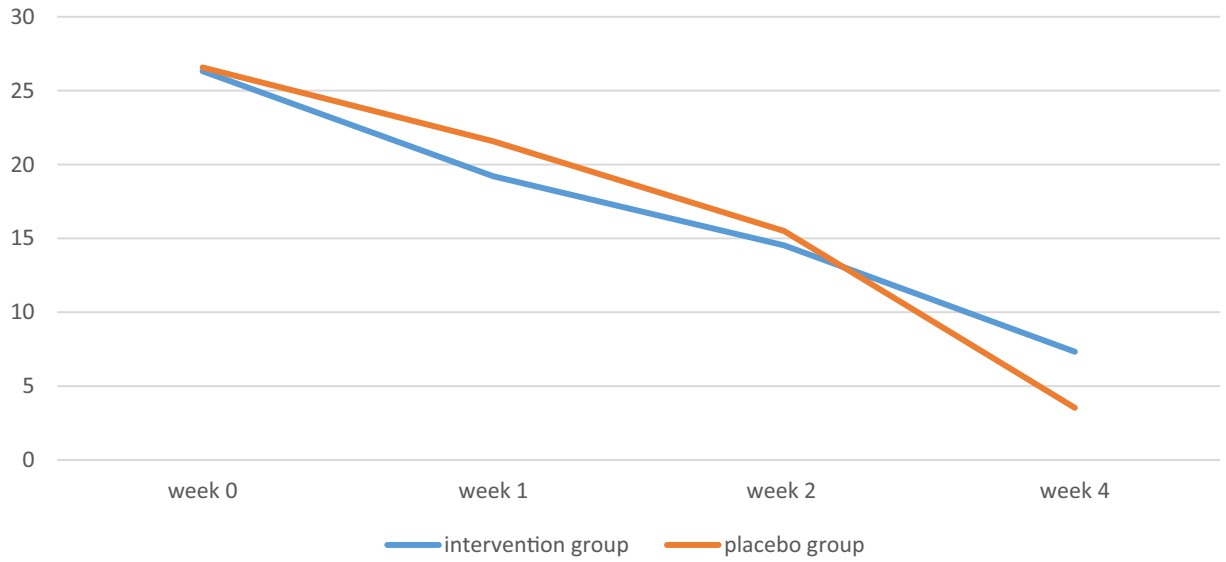

FIGURE 3
YMRS scores of the two groups throughout the study.

are used to measure the severity of mental disorders as well as their response to treatment. The CGI is used by clinicians and consists of three measures: severity of illness, global improvement, and efficacy index. The validity and reliability of CGI has been proven. It is rated on a 7-point scale, 1 representing normality and 7 representing "among the most severely ill patients" (24). The Mini-Mental State Examination (MMSE) is a 30-item questionnaire used to assess different aspects of cognition including orientation, memory, attention, recall, and registration. It is widely used to screen for dementia. A person can earn a maximum score of 30 from this questionnaire. The score 24 is considered as the standard cut-off for distinguishing normal from impaired cognition. The validity and reliability of this questionnaire has been approved for the Persian population (25).

Evaluations

Participants in both groups were evaluated at baseline, week one, week two, and week four of the study after receiving the assigned drug regimens using the clinical global impression (CGI) and YMRS (20, 26, 27). In addition, a self-report medication side effect questionnaire was used to investigate the possible side effects of the used medicine in the studied groups. Mini-mental state examination (MMSE) was performed at the end of the first and fourth weeks of treatment.

It should be noted that due to the lipophilic nature of curcumin, the oral absorption of curcumin in common oral forms (powder, capsule, and pill) may not be sufficient. In the present study, soft gelatin capsules containing curcumin nanomicelles (SinaCurcumin,

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TABLE 1 Demographical information of the studied population.

	Placebo group	Curcumin group	Value of *p*
Gender			
Male	6 (40.0%)	23 (65.7%)	
Female	9 (60.0%)	12 (34.3%)	
Age	32.42 ± 9.6	36.28 ± 10.73	0.17*
Age of onset of disease	25.57 ± 7.48	25.92 ± 7.01	0.85*
Job			
Homemaker	7 (26.9%)	12 (42.9%)	0.69**
Unemployed	16 (61.5%)	11 (39.3%)	
Retired	1 (3.8%)	1 (3.6%)	
Self-employed	1 (3.8%)	2 (7.1%)	
Full-time student	1 (3.8%)	2 (7.1%)	
Education			
Primary school	11 (42.3%)	16 (57.1%)	0.56**
High school diploma	12 (46.2%)	10 (35.7%)	
Higher than high school diploma	3 (11.5%)	2 (7.1%)	
Number of previous hospitalizations			
1 or less	10 (38.5%)	5 (17.9%)	0.17***
2–3 times	13 (50.0%)	16 (57.1%)	
More than 3 times	3 (11.5%)	7 (25.0%)	
History of inflammatory disease			
Yes	2 (7.7%)	3 (10.7%)	>0.99**
No	24 (92.3%)	25 (89.3%)	
Family history of depression			
Yes	15 (57.7%)	10 (35.7%)	0.1***
No	11 (42.3%)	18 (64.3%)	
History of depression			
Yes	10 (38.5%)	6 (21.4%)	0.17***
No	16 (61.5%)	22 (78.6%)	
History of physical illness			
Yes	8 (30.8%)	10 (35.7%)	0.77**
No	18 (69.2%)	18 (64.3%)	
Medicine			0.06**
Risperidone	9 (34.6%)	10 (35.7%)	
Alprazoplam	2 (7.7%)	8 (28.6%)	
Olanzapin	8 (30.8%)	4 (14.3%)	
Lithium	2 (7.7%)	5 (17.9%)	
Tranqopine	5 (19.2%)	1 (3–6%)	

*Independent *t*-test. **Fisher's exact test. ***Chi-squared test.

Tehran, Iran) were used. The curcumin in the soft gel is blocked in the hydrophobic section of curcumin nannies. These spherical nanomicelle particles have a size of about 10 nm and increase the water solubility of curcumin. After oral administration, soft gel capsules containing curcumin nannies disintegrate in the acidic environment of the stomach in less than 15 min. These nanomicelles remain there for at least 6 h before they get to the small intestine intact.

Upon reaching the small intestine, nanomicelles facilitate the transfer of curcumin from the inert surficial water layer of the intestinal epithelial cells, which inhibits the absorption of lipid-soluble compounds and increases the oral absorption of curcumin (Calculation of absorbed curcumin).

The possible side effects of the medications were evaluated by psychiatric residents in each visit using a checklist, and if necessary, the essential laboratory tests were ordered under the supervision of a psychiatrist.

Since there were no similar studies, the sample size could not be calculated using statistical formulas. Therefore, this study was done as a preliminary study with a sample size of at least 25 people in each group.

Descriptive statistics, including frequency tables, diagrams, and statistical indicators were used, and data analysis was done using SPSS software version 11.5. Kolmogorov–Smirnov test, Mann Whitney test, independent *t*-test, Fisher's exact test, and chi-square were applied and a value of p of less than 0.05 was taken as mean statistical significance. To control and determine the effect of confounding variables in case of heterogeneity between the two groups, appropriate statistical tests including covariance or logistic regression were used.

Results

Among the 78 individuals who agreed to take part in this study, 8 individuals discontinued sodium valproate, two patients changed their therapeutic regime as their diagnosis was changed, 8 persons refused to participate in the study and 4 cases were excluded because of their lack of cooperation. A total number of 54 individuals continued the study until the end.

The mean age of participants in the intervention group and control group was 36.28 ± 10.73 and 32.42 ± 9.60, respectively ($p = 0.172$). Most of the patients in the intervention group were male (23 versus 12 individuals) while most of the patients in the control group were female (9 versus 6 patients; $p = 0.091$). The patients' demographic data is summarized in Table 1.

No side effect was seen in any of the two groups. There was no significant difference between the two groups in terms of the MMSE score obtained on week 0 (value of $p = 0.16$), and week 4 (value of $p = 0.17$) of the study. However, in both groups, significantly higher MMSE scores were achieved by the end of the study compared to week 0.

The YMRS score significantly decreased in both the intervention group and the control group from week 0 to week 4 (value of $p < 0.001$). There was no statistically significant difference among the YMRS score of the two groups in week 0 (value of $p = 0.87$), week 1 (value of $p = 0.18$), week 2 (value of $p = 0.61$), and week 4 (value of $p = 0.71$) of the study.

By the end of the study, CGI scores of both groups had increased significantly (value of $p < 0.001$). However, there was no significant difference between the CGI scores of the control and the intervention group in week 1 (value of $p = 0.36$), week 2 (value of $p = 0.5$), and week 4 (value of $p = 0.88$) of the project.

The MMSE score was significantly different in each group by week 4 of the study ($p < 0.001$; Table 1). To compare these changes between the two groups, Mann–Whitney test was used and no significant difference was observed ($p = 0.68$). Although the decrease in YMRS scores in each group was significant overtime ($p < 0.001$; Table 1).

TABLE 2 Changes in MMSE scores of the two groups in 4weeks.

MMSE	Curcumin group	Placebo group	Value of *p*
Week 0	22.42 ± 4.8	20.92 ± 4.15	0.16*
Week 4	24.6 ± 4.55	23.53 ± 3.78	0.17*
Changes from week 0 to week 4	2.17 ± 2.4	2.61 ± 2.88	0.68*
Value of *p*	<0.001**	<0.001**	

*Mann–Whitney. **Wilcoxon test.

TABLE 3 Changes in YMRS scores among the two groups in the study.

YMRS score	Curcumin group	Placebo group	Value of *p*
Week 0	26.32 ± 6.13	26.57 ± 5.19	0.87*
Week 1	19.21 ± 6.78	21.57 ± 6.11	0.18*
Week 2	14.53 ± 7.08	15.5 ± 6.88	0.61*
Week 4	7.32 ± 6.27	7.96 ± 6.58	0.71*
Value of *p*	<0.001**	<0.001**	

Dependent *t*-test. **Repeated measure.

TABLE 4 Changes in the CGI score of the two groups in the study.

CGI score	Curcumin group	Placebo group	Value of *p*
Week 0	1 ± 0	1 ± 0	–
Week 1	1.71 ± 0.65	1.53 ± 0.5	0.36*
Week 2	2.53 ± 0.63	2.63 ± 0.65	0.5*
Week 4	3.5 ± 0.83	3.53 ± 0.7	0.88*
Value of *p*	<0.001**	<0.001**	

*Mann–Whitney. **Friedman test.

However, there was no significant difference among the study groups after 4 weeks ($p = 0.64$). Despite the significant increase in CGI scores in each group ($p < 0.001$; Table 1), there was no significant difference between the study groups after 4 weeks ($p = 0.93$).

While the percentage of response to treatment in the intervention group was higher than the control group, Fisher's exact test did not confirm any significant difference between the two groups ($p = 0.49$; Table 2). In both groups, more than half of the patients reported subsidence of symptoms which was greater in the intervention group but was not statistically significant among study groups ($p = 0.75$; Table 2).

Discussion

The present clinical trial study demonstrated that after 4 weeks of addition of curcumin to sodium valproate in BID-1 patients, there was not a significant improvement in MMSE, YMRS or CGI in contrast to patients receiving valproate alone (Tables 3, 4).

BID is a life-long episodic disease characterized by changes in a person's mood between mania and depression. During mania episodes, effective and timely diagnostic and therapeutic interventions are required to minimize side effects, which can easily interrupt an individual's normal life. Many BID patients often experience recurrent episodes throughout their lives if they do not receive proper treatment and follow up. The acute phase of manic episodes can have unpleasant effects on the patients' mental status and their family (1). Therefore, pharmaceutical treatment of patients' symptoms is an area of interest for researchers. Psychopharmacological treatments are the first line for treating BID. So far, mood stabilizers, including carbamazepine, sodium valproate, as well as antipsychotics, have been used to treat the acute phase of mania (1). Incomplete response to existing drugs among considerable number of patients made investigation for novel and effective medicines a global concern.

Although the exact mechanism of development of BID is not clear; inflammation, cellular apoptosis and increased BDNF level are considered among the probable mechanisms for BID. Curcumin is an old herbal medication which is thought to be effective in lowering inflammatory status, controlling apoptosis and regulating BDNF level (28). Nowadays, the complimentary usage of herbal and ancient medicine in modern practice has become an area of interest for many researchers. Thus many researchers are looking into using ancient herbal medicine in combination with new pharmacological drugs to find an effective treatment for BID.

Part of the anti-inflammatory effects of turmeric may be due to the inhibitory effects of curcumin on the activity of the hyaluronidase enzyme. Moreover, curcumin inhibits the expression of COX2 and the production of cytokines such as interferon-gamma and interleukin-6 which results in inhibiting the inflammatory responses (29). Previous studies have claimed curcumin has anti-inflammatory effects in deactivating free radicals. Moreover, they have reported anticancer effects for curcumin. These effects of curcumin are often dose-dependent vary based on the environment (29–31). Brietzke et al. (32) evaluated curcumin's anti-inflammatory and antioxidant properties and reported that this agent was notably affecting

depressive symptoms and cognitive impairment. However, they suggested further clinical trials to support their findings. A study by Arora et al. (33) demonstrated that curcumin could reduce behavioral deficits and depression in animal models in a dose-dependent manner. They also suggested that curcumin can increase dopamine and serotonin levels while decreasing inflammatory markers (33). Choudhary et al. (34) demonstrated similar effect for curcumin on mice and reported that curcumin can improve memory impairment, depression and behavioral problems. A recent review on clinical trials evaluating the role of curcumin in depressive patients demonstrated that among clinical trials, 2 studies found that curcumin has antidepressant activity in contrast to placebo groups after 8 and 12 weeks duration (35). Moreover, a paper by Yu et al. (36) demonstrated that the addition of 1,000 mg of curcumin to the selective serotonin reuptake inhibitor (SSRI) could improve the antidepressant effects of the SSRIs.

The only available animal study about the efficacy of curcumin in bipolar disorder is on animal mania models receiving ketamine (37). The rats had ketamine-induced hyperlocomotion and oxidative damage in prefrontal cortex and hippocampus. The authors demonstrated that pretreatment with curcumin could prevent hyperlocomotion and reverse the oxidative stress parameters (37). Our study was the first clinical trial on human subjects using curcumin as a treatment for BID and could not confirm a therapeutic effect for curcumin as an adjuvant for valproate. The curcumin therapeutic effects appear to be because of their neuroprotective and antioxidant effects, which increase the level of neurotrophic factors. Given the low bioavailability of the drug, it seems necessary to increase the dose. Concerning other studies on non-BID patients, a dose of 500 mg per day, which was used in ours, also seems to be a low dose of curcumin (38–41). Kulkarni et al. (42) recommended to start treatment with a dose of 20 mg based on the patient's weight and increase the dose to 80 mg per kg, which is about 1,500 mg per day to achieve the antidepressant effects of curcumin. Moreover, a four-week follow-up period may be limited and insufficient; and further studies with longer follow-ups may provide different results. It is suggested that future studies use higher doses of curcumin, as well as larger sample sizes and longer follow-up intervals to further investigate the possible effects of curcumin on the treatment of bipolar disorder. There are also other possible challenges that need to be considered regarding the addition of curcumin to the treatment regimen of different disorders, as further research is required to better investigate their possible efficacy as well as possible side effects on different body systems and probable interactions with other medications used by patients. It should also be noted that due to cultural reasons, it may cause a change in the patient's adherence to medication.

Limitations

The limited small sample size and the fixed dosage of the curcumin were our study's constraints. For future studies, we suggest the use of higher doses of curcumin, which is recommended to be administrated according to the curcumin serum levels of participants.

Conclusion

The present clinical trial study demonstrated that after 4 weeks of addition of curcumin to sodium valproate in BID patients, there was no significant improvement in MMSE, YMRS, or CGI in contrast to patients receiving valproate alone. Further clinical studies with higher doses, greater sample sizes and longer follow-up durations are needed.

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 Mashhad University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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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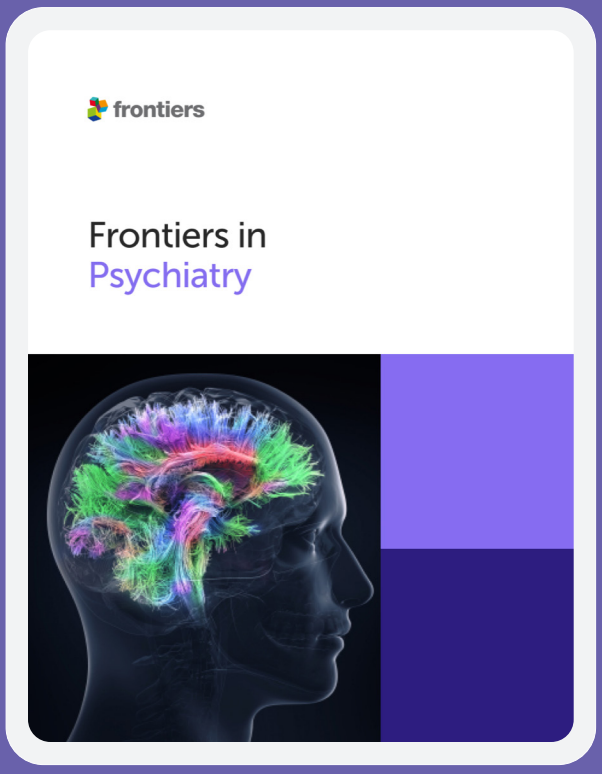

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