Effects and Intervention Strategies of Second-Generation Antipsychotics on Metabolism of Patients with Bipolar Disorder

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Abstract. Bipolar Disorder (BD) is a chronic mental illness characterized by alternating manic-depressive episodes, with 0.53% as its global lifetime prevalence. Clinical treatment needs to follow the principle of long-term management based on medications. During the manic episodes of bipolar disorder patients, both first-generation antipsychotics (e.g., chlorpromazine and haloperidol) and second-generation antipsychotics (e.g., olanzapine, clozapine, quetiapine, and risperidone) can provide effective therapeutic outcomes. However, these medications may also negatively impact physiological indicators such as blood glucose, blood lipid, and blood pressure through mechanisms like drug-induced neuroregulation, insulin resistance, and mitochondrial damage. This metabolic disorder may increase the risk of developing chronic diseases such as coronary heart disease and type 2 diabetes. This review focuses on the metabolic disorders caused by the use of second-generation antipsychotics alone or in combination with mood stabilizers (lithium salts/valproate). It systematically evaluates the intervention efficacy of hypoglycemic/lipid-regulating drugs and integrates traditional Chinese medicine-assisted treatment regimens. The research results provide multi-dimensional management strategies for the clinical prevention and treatment of antipsychotic-related metabolic abnormalities.

Keywords: Bipolar Disorder; Second-generation; Metabolic; Adverse Effects; Obesity; Side Effects; Intervention; Strategies; Treatment.

1. Introduction

Bipolar Disorder (BD) is characterized by recurrent episodes of abnormal emotional state, including mania, hypomania, depression and mixed episodes. According to the DSM-5-TR diagnostic criteria, BD is mainly divided into type I (requiring at least one manic episode) and type II (requiring at least one hypomanic episode and one major depressive episode) (Oliva et al., 2025). Its suicide risk is 20-30 times higher than that of the general population (Plans et al., 2019) and the global prevalence rate reached 0.48% in 2019 (Collaborators, 2022). Besides the core emotional symptoms, BD can cause organic damage to multiple systems. For the circulatory system, the American Heart Association proposed that the process of atherosclerosis in adolescent BD patients is accelerated and the risk of early-onset cardiovascular disease is significantly increased (Goldstein et al., 2015). When it comes to the respiratory system, Zareifopoulos and colleagues found that the incidence of chronic obstructive pulmonary disease (COPD) in patients with schizophrenia and bipolar disorder is approximately 1.573 times and 1.551 times higher, respectively, compared to the general population (Zareifopoulos et al., 2018). Finally, regarding the nervous system, compared with non-BD people, bipolar disorder may increase the risk of stroke incidence (1.43 times) and mortality (1.54 times), with the susceptibility rate of men higher than that of women (Yuan et al., 2022). In view of BD with complex emotional disorders, high mortality and multi-system damage, it is of great clinical value to establish a systematic disease management plan.

Drug therapy is the basic intervention for bipolar patients, which needs to follow the principle of staged treatment. The goal of acute phase is symptom control, while the maintenance phase focuses on recurrence prevention. Commonly used clinical drugs include mood stabilizers, antipsychotics and antidepressants (Geddes & Miklowitz, 2013). Antipsychotics can be divided into two generations

according to the mechanism of action. The first-generation drugs (typical antipsychotics) take dopamine D2 receptor antagonism as the core mechanism, covering phenothiazines, butyryl benzene and other compounds. However, its clinical application is limited due to significant extrapyramidal reaction (EPS) (Chokhawala & Stevens, 2020). The second-generation drugs (atypical antipsychotics) such as olanzapine and risperidone show advantages in mitigating negative symptoms (apathy, hypovolition, etc.) by dually regulating 5-HT2A/D2 receptors, and the incidence of ESP is reduced (Orzelska-Górka et al., 2022).

Although second-generation drugs have better efficacy, their metabolic risks still need to be vigilant. Some research have shown that the metabolic disorder of different antipsychotics significantly varies. Clozapine and olanzapine lead to the highest risk of metabolic syndrome, followed by risperidone and quetiapine, while aripiprazole, ziprasidone and high-efficiency drugs have the lowest risk (Association, 2020). Such metabolic disorder can further increase the risk of coronary heart disease (Daumit et al., 2008) and type 2 diabetes (Sapunar et al., 2009). Given that BD patients should receive long-term treatment with second-generation antipsychotics (or combined mood stabilizers), medical staff need to establish a metabolic monitoring system (Oliva et al., 2025). This review article systematically reviews the effects of second-generation antipsychotics alone or in combination with mood stabilizers on metabolic parameters of patients with BD and their intervention strategies, so as to provide evidence-based evidence for clinical prevention and treatment of drug-related metabolic syndrome.

2. Effects of Second-Generation Antipsychotics Monotherapy or Combined Therapy with Mood Stabilizers on Metabolism

The pathological mechanism of glucose and lipid metabolism disorder induced by second-generation antipsychotic drugs (SGAs) presents multiple targets. Take olanzapine, which has the highest metabolic risk, as an example. By antagonizing the histamine H1 receptor in the hypothalamus, it significantly up-regulates the expression of neuropeptide Y (NPY), thus enhancing the activity of the appetite regulation center and ultimately leading to weight gain. Notably, animal studies have demonstrated that selective H1 receptor agonists can effectively reverse such hyperphagia (Chen et al., 2020). Another drug with high metabolic risk, clozapine, acts by interfering with mitochondrial dynamics. Studies have shown that this drug can induce decreased mitochondrial membrane potential, abnormal morphology and decreased ATP synthesis. This energy metabolism disorder may affect blood glucose and the fatty acid oxidation process (Contreras-Shannon et al., 2013). In addition, the mechanism of insulin resistance induced by SGAs has been widely supported by research (Dipta et al., 2021; Li et al., 2018).

According to the available evidence, there are significant drug-to-drug differences in the metabolic risk of SGAs, which presents a consistent pattern in the population of patients with schizophrenia and bipolar disorder. In terms of patients with schizophrenia, based on a systematic analysis of 32 antipsychotics by Huhn M et al.(2019), the effects of SGAs on body weight were tertiary. Olanzapine and clozapine constituted the high-risk group with quetiapine as a moderate risk. Aripiprazole, ziprasidone, and lurasidone constituted the low-risk group. This grading system is highly consistent with the *Expert Consensus on the Management of Metabolic Syndrome in Schizophrenia in China* (Association, 2020). In the population with bipolar disorder, the study of Kadakia et al. (2021) and Li et al. (2024) revealed a similar metabolic risk profile. Olanzapine remains the most prominent in the impact on weight and blood lipids, while aripiprazole and lurasidone maintain the lowest risk, with quetiapine positioned intermediately. Although two studies exhibited heterogeneity in quantitative measures of olanzapine-induced blood glucose elevation, both confirmed statistically significant negative impacts on composite metabolic risk.

As a special therapeutic drug, clozapine needs to balance the efficacy and multiple risks. According to the study of Delgado et al. (2020), among 151 patients with bipolar disorder, the incidence of weight gain caused by clozapine was about 10.06%, which was lower than the incidence

of other non-metabolic side effects (sedation 49.6%, constipation 31.8%, salivation 29.8%). However, special attention should be paid to its risk of agranulocytosis, which triggers its use as a second-line treatment in clinical guidelines (Mijovic & MacCabe, 2020).

Mood stabilizers (including antiepileptic drugs such as lithium salts, sodium valproate and carbamazepine, and some atypical antipsychotics) are the core drugs in the treatment of bipolar disorder. Their metabolic safety has also attracted increasing attention. In terms of blood lipid effects, the 12-month monotherapy data of children with epilepsy proved that carbamazepine had a significantly stronger effect on the increase of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) than sodium valproate. However, there was no statistical difference between the two drugs in terms of triglyceride changes (Voudris et al., 2006). The metabolic characteristics of lithium salt are selective. Compared with sodium valproate, it has a lower risk of weight gain and blood glucose fluctuation, but it does not show advantages in the TG, TC and BMI (Vita et al., 2024). Moreover, the overall metabolic risk of mood stabilizers is lower than that of second-generation antipsychotics. Based on the pooled analyses, antipsychotic monotherapy elicited significantly higher weight gain than mood stabilizer monotherapy regimens in short-term treatment ≤ 12 weeks (Correll, 2007).

However, in clinical practice, the synergistic effect of the two types of drugs is not a simple risk superposition. Studies have confirmed that when second-generation antipsychotics (olanzapine, risperidone, etc.) are combined with mood stabilizers (valproate, lithium salt, etc.) for more than 6 months, the levels of TC, TG and LDL-C in the combination treatment group are significantly lower than those in the antipsychotic group (Zheng, 2020). This metabolic protective effect is particularly apparent in olanzapine treatment. SHEN (2023) and He (2022) confirmed that the combination of sodium valproate can improve the efficacy of olanzapine and reduce its metabolic side effects.

Further analysis indicated that the metabolic risk during combination therapy mainly depended on the antipsychotic type. According to Lu Wenwen who constructed a clear gradient relationship, in the combination regimen of lithium carbonate, the intensity of metabolic influence was olanzapine>quetiapine> risperidone (Lu, 2021). It suggests that clinical decision-making should comprehensively consider the synergistic effect and risk of drug combination, and optimize metabolic safety while ensuring efficacy.

In summary, the metabolic risks associated with second-generation antipsychotics and mood stabilizers are multifaceted and vary significantly across different drugs and patient populations. Clinicians must carefully balance therapeutic efficacy with metabolic safety, tailoring treatment strategies to individual patient needs and considering the synergistic and antagonistic effects of drug combinations.

3. Intervention Strategies for Metabolic Abnormalities Caused by Second-Generation Antipsychotics in Bipolar Patients

3.1 Application of Hypoglycemic and Lipid-Lowering Drugs

Among metabolic-modulating drugs in patients with psychiatric disorders, metformin shows clear intervention value. Animal studies showed that after 10-week combined treatment with olanzapine and metformin, the quality of white adipose tissue and brown adipose tissue was lower than that in the single-drug group. Although there was no difference in fasting blood glucose between groups, the insulin resistance index was decreased (Shamshoum et al., 2023). Clinical studies further validate its efficacy. A retrospective cohort analysis proved that clozapine combined with metformin for 6 months resulted in a reduction in weight gain and a widening differences at 12 months (Stogios et al., 2022). In addition to body weight, metformin can be used to improve patients' BMI, fasting blood glucose, HOMA-IR, blood lipids and other metabolic indicators (Wu et al., 2016).

Regarding the dosing regimen of metformin, international guidelines recommend a stepped incremental strategy. Fitzgerald I et al. recommended starting at 500 mg daily, increasing by 500 mg every 1-2 weeks, with a target dose of 2000 mg/day (Fitzgerald et al., 2022). Carolan A et al. proposed

initiating at 500 mg/day for one week, followed by 1 g/day in the second week, then weekly adjustments up to 2 g/day (Carolan et al., 2024). The Chinese consensus also advises starting at 500 mg/day and titrating to 1000-1500 mg/day within one week (Association, 2020). Besides, Notably, Peng et al.'s meta-analysis found no statistical difference in efficacy between <1000 mg/day and >1000 mg/day groups (Peng et al., 2024). Based on the available evidence, this review recommends an initial dose of 500 mg/d, increasing by 500mg weekly, and the maximum dose does not exceed 2000 mg/d. The final dose needs to be adjusted according to efficacy, tolerability and liver and kidney function.

For those with poor efficacy of metformin, Prasad et al. proposed that semaglutide, a GLP-1 receptor agonist, should be considered (Prasad et al., 2023).

3.2 Switch to Antipsychotic Drugs with Relatively Small Metabolic Effects

According to the *Chinese Expert Consensus on the Management of Metabolic Syndrome of Schizophrenia* (Association, 2020), second-generation antipsychotics such as amisulpride, aripiprazole and lurasidone have relatively little effect on metabolic indicators. In the selection of antiepileptic drug, based on existing research (Hu, 2023; Voudris et al., 2006), sodium valproate is more conducive to maintaining lipid homeostasis than carbamazepine and oxcarbazepine, as evidenced by its lesser adverse impact on total cholesterol, triglycerides, and low-density lipoprotein cholesterol.

This study also explored whether bipolar disorder could be managed with monotherapy using mood stabilizers that have minimal metabolic impact. However, based on two meta-analyses (Hesapcioglu et al., 2024; Kishi et al., 2021), mood stabilizers alone have unsatisfactory effects in acute mania control and long-term maintenance treatment. However, combination strategies (such as lithium salt combined with oxcarbazepine or valproate) can significantly reduce the risk of recurrence of mood disorders. Finally, when bipolar patients have persistent depressive symptoms, if the patients have a high metabolic risk, it is recommended to combine SSRIs (fluoxetine) or bupropion with a low risk of mania and metabolic risk. At the same time, it is necessary to avoid drugs such as paroxetine that carry substantial weight gain risks (Gill et al., 2020; Petimar et al., 2024). The metabolic effects of citalopram and escitalopram need more research to support them.

3.3 Traditional Chinese Medicine Therapy Assists in Improving Antipsychotic-Related Metabolic Abnormalities

Traditional Chinese medicine has unique advantages in the intervention of metabolic abnormalities. Modified Yueju Decoction can significantly improve TG, Fasting Blood Glucose and HDL levels (Wu, 2023). Liuyu Decoction (a traditional Chinese herbal formula) not only regulates blood lipids and blood glucose, but also improves insulin resistance (decreased Homa-IR, increased Homa-β) and relieves psychiatric symptoms (Yu, 2019). Wendan Decoction (a traditional Chinese formula to warm the gall) is not only effective in treating symptoms such as anxiety and insomnia, but also helpful in controlling metabolic syndrome caused by Olanzapine (Liu, 2018). Acupuncture therapy (including electroacupuncture) has shown application value in the management of metabolic complications such as drug-induced obesity and hyperprolactinemia by regulating lipid metabolism indicators and blood glucose levels (Du, 2011; Ren, 2020).

3.4 Life Behavior Interventions

The development of metabolic risk in bipolar disorder patients involves multiple factors. Beyond the impact of medications like second-generation antipsychotics, their lifestyle habits also require clinical attention. Epidemiological studies reveal a smoking prevalence of 30%-70% in this population, (2-3 times that of the general population) (Heffner et al., 2011), and 40%-70% of patients have comorbid alcohol use disorder (Grunze et al., 2021). These two types of addictive behaviors can significantly increase the risk of metabolic abnormalities. Thus, it is necessary to establish a systematic screening mechanism and timely intervention in clinical diagnosis and treatment. As for

lifestyle management, Ntalkitsi S et al. confirmed that the Mediterranean diet could improve the nutritional structure of patients with mental illness, reduce carbohydrate, sodium and total calorie intake, and combat abnormal serum total cholesterol, low-density lipoprotein cholesterol and urea levels caused by antipsychotics (Ntalkitsi et al., 2022). For exercise management, although the precise exercise prescription proposed by Zhang Qizhen et al. (formulating a personalized plan according to individual characteristics) can improve drug-induced obesity, However, it is highly challenging to overcome the implementation bottleneck caused by poor patient adherence (Zhang, 2023)**.** Based on the *Expert Consensus on the Management of Metabolic Syndrome in Schizophrenia in China* (Association, 2020), the specific exercise program suggests moderate-intensity exercise (50%-70% maximum heart rate), 3-5 times a week and 30 minutes of exercise prescription per day. For hospitalized patients, implementing clustered care strategies (integrating multidimensional metabolic management measures based on evidence-based medicine) may be effective in reducing the incidence of metabolic syndrome (Zhu, 2024).

4. Summary

Given the adverse effects of second-generation antipsychotics (or combined mood stabilizers) on metabolism, and the fact that bipolar patients often need long-term medication, clinicians should strengthen vigilance against drug-related metabolic disorders. Whether it is drug intervention or non-drug intervention, closely detecting patients' metabolic indicators and detecting abnormalities in time is the first priority. If it is necessary to prevent metabolic syndrome, this paper suggests that antipsychotic drugs with less impact on metabolism should be selected according to the actual situation of patients (efficacy, tolerance, economic level, real-time metabolism-related indicators, etc.). Besides, individualized diet and exercise programs should be used to prevent adverse consequences. When metabolic syndrome occurs, this paper suggests that metformin with sufficient evidence-based medical evidence should be the first choice for treatment while switching antipsychotic drugs. Relevant guidelines for traditional Chinese medicine treatment can also be referred to (Sun, 2023).

5. Implications

1. During the date searching, it is found that when the second-generation antipsychotic drugs are combined with mood stabilizers, their effect on metabolism is not a simple superposition, and even the effect of 1+1<1 appears. Thus, the advantages and disadvantages of this phenomenon should be reconsidered. It is hoped to carry out more clinical research and mechanism discussions in the future.

2. According to the study of Kishi et al. (2021) the combination of multiple mood stabilizers can prevent the recurrence of various mood episodes. Since the metabolic risk of mood stabilizers is less than that of many second-generation antipsychotics, it is also hoped that the therapeutic effect and safety of the combination of multiple mood stabilizers in the maintenance stage of bipolar disorder can be explored more in the future.

3. In recent years, non-pharmacological approaches—such as dietary interventions and structured exercise—have gained significant attention for managing metabolic issues in psychiatric patients. However, adherence to these strategies remains a critical yet under-addressed challenge that warrants urgent clinical focus.

4. Although metformin is often used to control the metabolic risk of patients with mental illness, it is still necessary to explore other hypoglycemic and lipid-lowering drugs in the case of metformin intolerance or poor efficacy.

5. At present, China has formulated a consensus on the management of metabolic syndrome in patients with schizophrenia. As for whether it can be applied to patients with bipolar disorder, more evidence is needed in the future.

6. Limitations

Some of the literature cited in this review is from 5 years ago, and some previous research conclusions may be replaced or revised by new discoveries. Using relatively old literature may cause research conclusions to lag behind the latest research results. Meanwhile, the cited references are mainly in Chinese and English with a lack of database papers in other languages. Due to the limitation of time and resources, some valuable studies have not been included in the discussion.

The metabolic effects and intervention conclusions of this review are partially based on clinical data of patients with schizophrenia. Due to the differences in pathogenesis, living habits and treatment plans between bipolar disorder and schizophrenia, the biological basis of drug metabolic response between the two groups of populations may vary. The generalizability of these findings requires validation through a dedicated cohort study specifically designed for bipolar disorder populations.

This study only focuses on the metabolic effects of second-generation antipsychotics alone and in combination with mood stabilizers. However, in clinical practice, bipolar patients sometimes need to use antidepressants in combination, while this paper does not include the effects of antidepressants alone and in combination on the metabolism of bipolar patients. In the future, a multi-drug exposure model needs to be established to improve the evaluation system.

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