REVIEW

A Review of Switching Strategies for Patients with Schizophrenia Comorbid with Metabolic Syndrome or Metabolic Abnormalities

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Abstract: Metabolic syndrome (MetS) in patients with schizophrenia occurs 2–3 times more frequently than in the general population. Antipsychotic medication is a primary risk factor for patients with MetS. In particular, the widely used second-generation antipsychotics can affect glucose and lipid metabolism and can induce insulin resistance and other metabolic abnormalities through various receptors. Notably, the metabolic risks of various antipsychotics may differ because of their different pharmacological affinity to MetS-related receptors. Several previous studies have shown that switching from high to low metabolic risk antipsychotics may improve patients' metabolic parameters. The current review aims to discuss the strategies for switching antipsychotic medications and the impact on metabolic abnormalities in patients with schizophrenia.

Keywords: antipsychotics, switch, metabolic syndrome

Epidemiology and Risk Factors of MetS in Patients with Schizophrenia
Definition and Diagnostic Criteria of MetS

Schizophrenia is a chronic mental disorder characterized by high personal and social burden and is among the top ten medical disorders to cause disability.[1] Patients with schizophrenia have significant morbidity and premature mortality, with an average life expectancy of about 80–85% that of general population. Metabolic syndrome (MetS) among patients with schizophrenia may explain part of this difference and has recently received considerable attention. The definition and diagnostic criteria of MetS vary among several different international academic organizations, causing inconsistencies in the understanding and diagnosis of MetS. Therefore, in 2005, based on the definitions of the World Health Organization (WHO) and the National Cholesterol Education Program Expert Panel Adult Treatment Panel III (NCEP-ATP-III), the International Diabetes Federation (IDF) issued a global consensus definition of MetS, namely with central obesity (defined by waist circumference) as a necessary condition plus any two of the following four factors: (1) raised triglycerides (TG); (2) reduced high-density lipoprotein (HDL-C) levels; (3) raised blood pressure; and (4) raised fasting plasma glucose.[2] In recent years, there has been a trend to eliminate the necessary condition of waist circumference, which would change the definition to match the NCEP ATP-III standard that MetS can be diagnosed by meeting any three of the five conditions (adding

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central obesity as a qualifying but not sufficient condition).[3] Chinese guidelines for the prevention and treatment of type 2 diabetes have led to a new definition of MetS based on characteristics of the Chinese population, which differs from international standards primarily in that they do not regard abdominal obesity (that is, central obesity) as a necessary condition for diagnosis.[4]

Prevalence of MetS in Patients with Schizophrenia

Previous studies have demonstrated that the risk of MetS in patients with schizophrenia is two to three times higher than that of the general population.[5–7] A systematic review and meta-analysis of 126 studies (including data on more than 20,000 patients) has shown that the average prevalence of MetS in patients with schizophrenia was 32.5%.[8] Similar results were demonstrated in another meta-analysis, with a prevalence rate of 33.4%.[9] Studies from some countries in Europe, America, and Asia have shown a prevalence rate of 22.8–40.9%.[6,10–14] Several surveys and studies in China between 2006 and 2017 have demonstrated a similar prevalence of MetS in Chinese outpatients and inpatients with schizophrenia, between 25.4 and 43.9%.[15–19]

Effects of MetS on Patients with Schizophrenia

MetS is a major challenge for patients with schizophrenia, not only because of its direct impact on the increased incidence and mortality of cardiovascular disease but also because of the influence on the outcome of mental illness. First, MetS can increase the risk of cardiovascular disease and, subsequently, death;[20] cardiovascular disease is, indeed, the leading cause of death in patients with schizophrenia.[21] The risk of death from cardiovascular disease in patients with schizophrenia who are aged 16–50 years is over three times that of the general population.[22] A multi-center cross-sectional study of 1452 outpatients with schizophrenia demonstrated that within ten years, those with MetS had a significantly higher risk of coronary heart disease and cardiovascular death and comprised a significantly higher proportion of extremely high to high risk of coronary heart disease and extremely high to high risk of cardiovascular death compared to patients without MetS ($p < 0.001$). Second, patients with MetS have demonstrated significantly higher total positive and negative syndrome scale (PANSS)

scores, positive symptom scores, and negative symptom scores than those without MetS, suggesting more serious psychotic symptoms.[23] Patients with MetS are more likely to have reduced medication compliance and are at an increased risk of mental illness recurrence.[24,25] The FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) cohort study demonstrated that MetS is a strong predictor of a one year recurrence rate of schizophrenia, but is unrelated to the severity of the disease, insight into the disease, or treatment (including drug compliance). The risk of recurrence within 12 months in patients with MetS is three times that in patients without MetS (OR = 3.0; 95% CI: 1.1, 8.4).[25] In addition, MetS may impair the cognitive function of patients with schizophrenia.[26]

Etiological Risk Factors for MetS in Patients with Schizophrenia

Despite the controversy, increasing evidence suggests that schizophrenia itself is an independent risk factor for MetS.[27] In patients with first-episode schizophrenia, there is already an impairment of glucose tolerance and insulin resistance and their glucose, insulin, and cortisol levels are higher than in the general population.[28] Even in patients with psychotic symptoms who have not yet been diagnosed with schizophrenia, the prevalence of a diagnosis of MetS is higher than in the general population, including symptoms such as increased blood pressure, increased waist circumference, and rapid glucose increase, among others.[29] Studies have found that schizophrenia has genetic factors that are susceptible to MetS; there are overlaps between schizophrenia and MetS with some pathogenic genes. For example, the homozygosity of the methylenetetrahydrofolate reductase (MTHFR) gene C677Thr is associated with an increased risk of schizophrenia and coronary heart disease and the adrenergic α1A receptor (ADRA1A) gene Arg347 allele is associated with the severity of MetS in patients with schizophrenia.[30–32] The pathophysiological process of metabolic abnormalities in schizophrenia may be related to hypothalamic-pituitary-adrenal (HPA) axis disorders, insulin resistance, and increased levels of inflammatory factors.[27,32,33] In addition, demographic and behavioral susceptibility factors are present in patients with schizophrenia, such as age, gender, course of disease, family history, and ethnic factors, which may also be susceptibility factors for MetS.[8,15,33,34] In particular, multiple studies have confirmed the influence

of age and disease course and the prevalence of MetS increases with the course of disease and with age.[6,8,9] In addition, schizophrenic patients' sedentary lifestyle, lack of regular exercise, poor diet, substance abuse, smoking, and other deleterious health behaviors may increase the risk of MetS; these behaviors may also be related to the negative symptoms of schizophrenia and have a susceptibility to stress.[5]

Antipsychotics as a Risk Factor for MetS

In addition to disease factors, antipsychotics are also an important risk factor for MetS. A meta-analysis that included a total of 26 studies of patients with first-episode schizophrenia, 19 studies of patients with untreated schizophrenia, and 78 studies of patients with schizophrenia treated with antipsychotics demonstrated that the incidence of MetS increased significantly after patients received antipsychotics and the risk of increased waist circumference, hypertension, elevated triglycerides, decreased HDL-C, and diabetes also increased significantly.[8]

Antipsychotics affect glucose, lipid metabolism, and weight gain through multiple receptor pathways, thereby increasing the risk of MetS in patients with schizophrenia.[33,35,36] For example, antipsychotics can antagonize receptors such as 5-HT ($5-HT_{2C}$) and histamine (H1), which can lead to an increase in appetite and weight gain and can antagonize central and peripheral muscarinic receptors (M3) and directly act on pancreatic islet β cells to affect insulin secretion and glucose metabolism.[33,36] H1 receptors are localized in the hunger and satiety centers held in the hypothalamus and are responsible for hyperphagia.[36,37] The occurrence of diabetes may, then, be related to the antagonism of M3 receptors, which are located in the β cells of the pancreas and can regulate insulin release and change the blood glucose metabolism. M3 receptor antagonism can affect glucose metabolism, leading to diabetes, ketoacidosis, and hypertonic syndrome, among other disorders.[36,37] In addition, H1, M1, and adrenergic α1 receptor antagonism may have a sedative effect, leading to a sedentary lifestyle and obesity in patients with schizophrenia.[32,36] The correlation between H1, $5-HT_{2C}$, and M3 receptor antagonism (based on receptor occupancy) with weight gain and diabetes risk has also been demonstrated in some model analyses and pharmacoepidemiology-pharmacodynamic (PE-PD) research methods, particularly H1 and $5-HT_{2C}$ antagonism.[38–40]

Different antipsychotics share different pharmacological affinity to $5-HT_{2C}$, H1, and M3 receptors. Among the first-generation antipsychotics, Chlorpromazine has the highest antagonistic effect on MetS-related receptors, particularly $5-HT_{2C}$ and H1 receptors, while Sulpiride and Haloperidol have no or very poor antagonistic effects. In contrast, the pharmacological effects of second-generation antipsychotics (SGAs) are more complicated and may have effects on a variety of MetS-related receptors. Based on the receptor occupancy rate, Clozapine has a high antagonistic effect on $5-HT_{2C}$, H1, and M3 receptors, followed by Olanzapine, Quetiapine, and Asenapine. Lurasidone, Aripiprazole, and Ziprasidone have weak antagonism, while Amisulpride has no antagonism to these receptors.[38–40] Some newer SGAs, such as Brexpiprazole and Cariprazine, also seem to have weak or no antagonism on MetS-related receptors.[36]

The overall risk of MetS caused by various antipsychotics is consistent with their pharmacological properties. Among them, Clozapine and Olanzapine have the highest risks for blood glucose, blood lipids, weight gain, and MetS, followed by Quetiapine, Risperidone, and Paliperidone, while Lurasidone, Ziprasidone, Amisulpride, Aripiprazole, and newer antipsychotics like Brexpiprazole and Cariprazine have the lowest risks. Among the first-generation antipsychotics, Chlorpromazine, with a high affinity for H1 and $5-HT_{2C}$ receptors, is associated with a higher risk of weight gain, dyslipidemia, and abnormal blood glucose, while Haloperidol and Sulpiride have a relative lower risk.[40–44] Table 1 shows the relative MetS risks of antipsychotics based on an integrated analysis of the different international guidelines and meta-analyses.

Apart from antipsychotics, mood stabilizers, such as lithium and antiepileptics, may also contribute towards increase in metabolic risks.[45] As mood stabilizers are often used as add-on therapy for patients with schizophrenia in the clinical practice,[46] combining antipsychotics with mood stabilizers seem to lead to greater metabolic risks.

General Management of MetS in Patients with Schizophrenia

Schizophrenia and MetS are chronic and, therefore, long-term management should be considered. First, paying attention to the baseline evaluation (prior to treatment), weighing the advantages and disadvantages, and carefully choosing antipsychotics with better efficacy and lower MetS risks according to the patient's condition, symptom

Table 1 Relative MetS Risk of Commonly Used Antipsychotics

Drug		Receptor Antagonism (Based on Receptor Occupancy)			MetS Risk – Lipids	MetS Risk – Glucose	MetS Risk – Body Weight
		5-HT$_{2C}$	H1	M3			
FGAs	Haloperidol	–	–	–	Low	Medium	Low
	Sulpiride	–	–	Low	Low	Low	Low
	Chlorpromazine	High	High	Low	High	High	High
SGAs	Clozapine	High	High	High	High	High	High
	Olanzapine	High	High	Low	High	High	High
	Risperidone	Medium	Medium	–	Medium	Medium	Medium
	Paliperidone	Medium	Low	–	Medium	Medium	Medium
	Quetiapine	Low	High	Low	Medium	Medium	Medium
	Ziprasidone	Medium	Low	–	Low	Low	Low
	Aripiprazole	Low	Low	–	Low	Low	Low
	Amisulpride	–	–	–	Low	Low	Low
	Asenapine	High	High	–	Medium	Medium	Medium
	Lurasidone	Medium	Low	–	Low	Low	Low
	Serindole	High	–	–	Low	Low	Medium
	Cariprazine	Low	Low	–	Low	Medium	Low
	Brexpiprazole	Low	Low	–	Low	Low	Low

Notes: Receptor antagonism: Results are excerpted from Aringhieri et al,[38] Montastruc et al,[40] Stahl et al[36]. Relative receptor antagonism ranking is based on receptor occupancy; "–" refers to no receptor occupancy. MetS risk of lipids/glucose/body weight: Relative MetS risk ranking is based on multiple international guidelines and meta-analyses, including Galletly et al,[42] Hasan et al,[43] Zhao et al. [44]
Abbreviations: FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; MetS, metabolic syndrome.

characteristics, duration, number of episodes, previous treatment, and adverse drug reactions, among other symptoms is important. Immediately after treatment initiation, metabolic parameters should be continuously monitored and the trend of changes in the metabolic parameters should be observed frequently to detect and intervene on metabolic abnormalities as soon as possible, particularly body mass index (BMI), waist circumference, blood pressure, fasting blood glucose, glycosylated hemoglobin, fasting triglycerides, HDL-C, and low-density lipoprotein cholesterol (LDL-C), and any other relevant metabolic parameters.[42,43] Various treatment guidelines have different requirements for the monitoring frequency of metabolic parameters, but they all require that body weight (i.e. BMI) is monitored the most frequently.

Abnormal changes in metabolic parameters within a short period of time may indicate long-term metabolic problems. Early intervention is required if changes are found during the monitoring of metabolic parameters. For example, after treatment with antipsychotics for one month, an increase in total cholesterol, LDL-C, TG, and non-HDL-C by 5% and a decrease in HDL-C by 5% can predict abnormal changes in blood lipids after three months.[47] Another study of adolescents also demonstrated that if weight gain exceeds the

baseline by 4% after treatment with atypical antipsychotics for one month, there is a higher risk of 15% weight gain after three months of treatment.[48] Therefore, guidelines often recommend that when weight gain exceeds 7%, sufficient attention should be given and non-pharmacological intervention should be started and when weight gain exceeds 10%, the existing treatment plan should be evaluated. To prevent further weight gain, it is essential to encourage weight loss and to switch medications if necessary.[43,44]

Common management methods of MetS include lifestyle intervention, switching to antipsychotics with a lower metabolic risk, and combining treatment with other drugs. Common lifestyle interventions include educational, dietary, and exercise programs. However, the effect of lifestyle intervention is still controversial, particularly in long-term treatment. A meta-analysis of 41 randomized controlled trials (RCT) showed that, compared with controls, the lifestyle intervention group significantly reduced their BMI by 0.63 kg/m^2 ($p = 0.002$), but after an average follow-up of 32 weeks, it was found that although the effect size of the remaining 17 RCTs was still adequate, it was no longer statistically significant. Another randomized, parallel controlled, superiority multi-center clinical trial showed that, in patients with psychiatric disorder

spectrum and abdominal obesity, life guidance or reasonable care was not superior to conventional treatment to reduce cardiovascular risk.[49,50] It is generally believed that lifestyle interventions from the beginning of antipsychotic treatment as a preventive strategy may reduce metabolic risks such as obesity in patients with schizophrenia and provide more benefits.[51,52]

Multiple studies have suggested that combination treatments can help control weight and improve metabolic parameters, including Metformin, Aripiprazole, Amantadine, Topiramate, Orlistat, Melatonin, Reboxetine, Zonisamide, Naltrexone, Bupropion, and Betahistine, among others.[53–62] A combination of Aripiprazole or other antipsychotics with a low metabolic risk may be a successful strategy. A meta-analysis and systematic review showed that, among patients with schizophrenia or schizoaffective disorder treated with Olanzapine or Clozapine, combining their current treatment with Aripiprazole at 5–15 mg per day for 8–16 weeks could decrease a patient's weight by 2.13 kg (95% CI: −2.87, −1.39 kg).[54] Another common combination strategy is the addition of hypoglycemic drugs. In recent years, several studies have suggested that a combined Metformin at 500–2000 mg per day can significantly improve metabolic parameters such as weight gain caused by antipsychotics.[63–66] An analysis of ten randomized controlled studies showed that combining Metformin with current treatment improved the metabolic abnormalities caused by antipsychotics and weight loss was significantly different compared with placebo (−3.17 kg; 95% CI: −4.44, −1.90 kg).[54] Although combined drugs may be effective for MetS, they also involve drug interactions and adverse effects caused by multi-drug therapy. For example, common adverse reactions of Metformin include nausea, abdominal distension, and diarrhea.[67]

Summary of Studies on Antipsychotics Switching Strategy for MetS in Patients with Schizophrenia

Another common management mode for MetS is to switch to an antipsychotic with lower metabolic risks, such as Aripiprazole, Amisulpride, or Ziprasidone, to improve metabolic parameters. Drug switching may improve MetS in patients with schizophrenia, but it also involves the risk of worsening and/or recurrence of psychotic symptoms. Therefore, issues such as poor control of psychotic symptoms, adverse reactions, and the possibility of weight

gain after switching to other drugs should be considered before switching to weigh the risks and benefits. Meanwhile, patients and caregivers must be informed of the possible consequences of switching drugs and corresponding treatment plans must be prepared.[68]

Currently, most studies focus on Aripiprazole, Amisulpride, or Ziprasidone when examining the strategy of switching to antipsychotics with lower metabolic risks, with a few focusing on Quetiapine or Lurasidone (Table 2). Most of the studies are multi-center, randomized controlled, open studies, but there are some are prospective, double-blind, and extended studies. The study population includes patients with psychosis spectrum disorder, primarily including schizophrenia, schizoaffective disorder, and, more infrequently, bipolar disorder, whose condition is stable and is treated with a stable dose of antipsychotics. In most cases, the switch occurs from SGAs with a high metabolic risk, such as Olanzapine, Clozapine, or Risperidone, and less frequently from first-generation antipsychotics such as Haloperidol, to drugs with a lower metabolic risk, such as Aripiprazole, Amisulpride, Ziprasidone, Quetiapine, or Lurasidone. Cross-tapering is the method most frequently adopted. The switch usually occurs due to the patient's significant weight gain, elevated blood lipids, and other metabolic abnormalities, or a clear diagnosis of MetS, resulting in poor treatment compliance. The observation period of the studies ranges from 6 to 52 weeks, of which a duration of 8, 12, or 24 weeks is the most common. The outcome of switching is usually subject to a comprehensive evaluation of metabolic parameters (including weight, BMI, waist circumference, blood pressure, blood lipid levels, rapid blood glucose, and insulin), efficacy parameters (commonly used include PANSS, clinical global impressions-severity (CGI-S), brief psychiatric rating scale (BPRS), and quality of life), and treatment interruption rates and adverse drug reactions.

Amisulpride (Two Primary Studies)

The existing studies show that a switch to Amisulpride to address treatment failure, intolerance, or excessive BMI due to the use of SGAs, including Olanzapine and Risperidone, among others, can significantly improve metabolic parameters such as body weight and BMI within 4–6 weeks and has demonstrated effects on other parameters such as blood glucose, blood lipids (TG, total cholesterol, HDL-C), blood pressure, and waist circumference at 12 months.[69,70] Lin et al further demonstrated that,

Table 2 Summary of Evidence for Switching to Antipsychotics with Lower MetS Risks

Post-Switching of Drug	Study	Study Population	Switching Schedule	Follow-Up Period	Outcome		Discontinuation/ Completion Rate
					Metabolic Parameters	**Psychotic Symptoms**	
Amisulpride	Lin CC. et al[69] Prospective and open label	92 inpatients with schizophrenia or schizoaffective disorder who were treated with SGAs; BMI > 27 kg/m^2	Initial group (n = 46): continue initial drug Switching group (n = 46): cross-tapering to Amisulpride within 4 weeks, maximum 1000 mg/d	12 months	Switching vs initial group: reduced body weight and BMI; improved TG and total cholesterol; increase HDL-C; reduced blood glucose; reduced blood pressure and heart rate; Switching group M12 vs baseline: reduced prevalence of MetS (30.4% vs 65.2%)	Switching group M12 vs baseline: no significant difference in BPRS and CGI-S scores	Switching group discontinuation rate: 28.3%
	Kim Y. et al[70] Multi-center, prospective and open label	37 outpatients with schizophrenia unresponsive or intolerant to antipsychotics (mostly with weight gain).	Cross-titration: switching to Amisulpride within 7 days, dose 400–800 mg/d	6 weeks	Switching Week 6 vs baseline: reduced body weight	Switching at Week 6 vs baseline: improved CGI-CB, CGI-S and SSS scores	Switching completion rate: 75.7%
Aripiprazole	Stroup TS. et al[73] Multi-center, parallel, randomized controlled study	215 patients with schizophrenia or schizoaffective disorder who were clinically stable after treatment with antipsychotics; increased risk of cardiovascular disease: BMI ≥ 27 kg/m^2; and non-HDL-C ≥130 mg/dl	Initial group (n = 106): continue initial drug. Switching group (n = 109): cross-tapering to Aripiprazole within 4 weeks, dose 5–30 mg/d	24 weeks	Switching vs initial group: reduced non-HDL-C, body weight, BMI, and TG levels	Switching vs initial group: no significant difference in efficacy failure rate, total PANSS, CGI-S, and SF-12 (MHS) scores; improved SF-12 (PHS) and IWQOL-lite scores	Switching vs initial group discontinuation rate: 43.9% vs 24.5%

Study / Design	Participants	Intervention	Duration	Efficacy / metabolic outcomes	Clinical outcomes	Discontinuation rate
Newcomer JW. et al[74] Multi-center, randomized, double-blind controlled study	173 patients with schizophrenia and schizoaffective disorder who were treated with olanzapine, with BMI ≥27 kg/m² and CGI-S score ≤4	Initial group (n = 85): Olanzapine continued. Switching group (n = 88): cross-tapering to Aripiprazole within 2 weeks, dose 10–30 mg/d	16 weeks	Switching vs initial group: improved changes of body weight, fasting total TG, fasting total cholesterol and HDL-C; numerically better in the changes of LDL-C; no difference in the changes of glycemic parameters	Switching vs initial group: worse CGI-I endpoint scores ($p < 0.001$)	Switching vs initial group discontinuation rate: 36% vs 26%
Wani RA. et al[75] Randomized, double-blind, open label	62 patients with schizophrenia who were stable on Olanzapine, comorbid with MetS	Initial group (n = 31): Olanzapine 10–20 mg/d continued. Switching group (n=31): cross-tapering to Aripiprazole within 4 weeks, dose 10–30 mg/d.	24 weeks	All parameters of MetS (waist circumference, blood pressure, TG, rapid blood glucose and HDL-C): deteriorated in the initial group; improved in the switching group; Switching vs initial group: reduced prevalence of MetS: 42.8% vs 100% at week 24	Switching vs initial group: no significant difference in PANSS total and CGI-I scores at week 24	Switching vs initial group discontinuation rate: 32.2% vs 16.1%
Casey DE. et al[76] Multi-center, randomized controlled, open label	311 outpatients with schizophrenia or schizoaffective disorder who were stably treated with SGAs and FGAs	Group 1 (n = 104): Aripiprazole started at 30 mg/d and the initial drug discontinued; Group 2 (n = 104): Aripiprazole started at 30 mg/d and the initial drug gradually decreased within 2 weeks; Group 3 (n = 103): Aripiprazole titrated to 30 mg/d within 3 weeks (10 mg/d in the first week, 20 mg/d in the second week, 30 mg/d in the third week), and the initial drug gradually decreased within 2 weeks.	8 weeks	Week 8 vs baseline: Moderately reduced body weight in three groups, with no significant difference among groups. No significant difference among groups in blood pressure, heart rate and other laboratory parameters.	Continuous improvement in PANSS total, positive and negative, CGI-S and CGI-I scores in three groups.	Group 1 vs Group 2 vs Group 3 discontinuation rate: 31% vs 34% vs 19%

(*Continued*)

Table 2 (Continued).

Post-Switching of Drug	Study	Study Population	Switching Schedule	Follow-Up Period	Outcome		Discontinuation/ Completion Rate
					Metabolic Parameters	Psychotic Symptoms	
	Kim SW. et al[77] Prospective and open label	61 patients with schizophrenia who were stably treated with SGAs	Cross-titration to Aripiprazole within 5–6 weeks, average final dose 18.8 mg/d.	26 weeks	Switching Week 26 vs baseline: improved the total cholesterol level; increased HDL-C level; reduced body weight; no difference in total TG, LDL, and blood glucose levels	Switching Week 26 vs baseline: improved cognitive functions; decreased PANSS total and factor scores.	Switching completion rate: 57.4%
	Chen YJ. et al[78] Prospective, randomized, open label	52 outpatients with schizophrenia or with schizoaffective or bipolar disorder who were treated with typical or atypical antipsychotics; TG/ HDL ≥ 3.5.	Switching to Aripiprazole group (N = 24): dose 5–30 mg/d; Switching to Ziprasidone group (N = 28): dose 40–160 mg/d; Cross-titration within 2 weeks.	52 weeks	Switching to Aripiprazole vs switching to Ziprasidone: both groups improved body weight, BMI, TG, HDL and TG/ HDL	No statistically significant group × time interaction in PANSS, CGI-S, and YMRS scores.	Completion rate: 71.2%, no difference between groups
Ziprasidone	Weiden PJ. et al[81] Long-term, randomized controlled, open label	185 outpatients with schizophrenia or schizoaffective disorder treated with Risperidone, Olanzapine, or typical antipsychotics; clinically stable but needed switching due to psychotic symptoms or adverse events.	Risperidone-Ziprasidone group (n = 43); Olanzapine-Ziprasidone group (n=71); typical antipsychotics-Ziprasidone group (n = 71) Cross-tapering to Ziprasidone within one week, median dose 120 mg/d.	52 weeks (maximum 58 weeks)	Risperidone-Ziprasidone group and Olanzapine-Ziprasidone group vs baseline: improved body weight, BMI, total cholesterol and TG; typical antipsychotics-ziprasidone vs baseline: no significant changes in weight and lipid parameters	Risperidone-Ziprasidone group and Olanzapine-Ziprasidone group vs baseline: improved PANSS negative scores; no significant changes in PANSS total and positive scores; typical antipsychotics-Ziprasidone vs baseline: improved PANSS total and negative scores; no significant changes in PANSS positive scores	Risperidone-Ziprasidone group vs Olanzapine-Ziprasidone group vs typical antipsychotics-Ziprasidone group discontinuation rate: 58% vs 64% vs 58%

Wang HH. et al[82] Accessor-blind, randomized controlled, open label	148 patients with schizophrenia spectrum disorder	Olanzapine monotherapy group (n = 31); Ziprasidone monotherapy group (n = 49); Olanzapine-to-Ziprasidone group (n = 35): cross-titration to Ziprasidone within 2 weeks, maximum dose 160 mg/d Olanzapine combining Ziprasidone group (n=33): Olanzapine maximum dose 20 mg/d, Ziprasidone 160 mg/d	12 weeks	Switching vs combination: No difference of changes in weight gain, glucose and lipid measures, but were higher than Olanzapine monotherapy group	Efficacy of both switching and combination group was comparable Olanzapine monotherapy and better than Ziprasidone monotherapy in reducing overall psychotic and negative symptoms.	Olanzapine, Ziprasidone monotherapy vs switching vs combination group completion rates: 87.1% vs 61.2% vs 77.1% 81.8%
Alptekin K. et al[83] Open label, international multicenter study	319 patients with stable schizophrenia or schizoaffective disorder who were treated with Haloperidol, Olanzapine, or Risperidone, with persistent symptoms or troublesome side effects	Haloperidol-Ziprasidone (n = 99); Olanzapine-Ziprasidone (n = 82); Risperidone-Ziprasidone (n = 104)	12 weeks	Haloperidol-Ziprasidone vs baseline: increased body weight; Olanzapine-Ziprasidone vs baseline; reduced body weight Risperidone-Ziprasidone vs baseline: non-significantly reduced body weight All three groups showed neutral effect on metabolic parameters;	All three switching groups vs baseline: significant improvement in PANSS, CGI, BPRS, GAF; More improvement in Haloperidol-Ziprasidone and Risperidone-Ziprasidone vs Olanzapine-Ziprasidone	Haloperidol-Ziprasidone vs Olanzapine-Ziprasidone vs Risperidone-Riprasidone group discontinuation rate: 32% vs 40% vs 14%
LI CH. et al[84] Open label	213 schizophrenia outpatients with MetS, who have been treated with Clozapine for more than 2 years.	Switching group (n = 68), cross-tapering to Ziprasidone within 4 weeks, dose 120–160 mg/d; Combination group (n = 126)	24 weeks	Switching and combination group vs baseline: reduced BMI and TG levels; Switching vs combination: increased HDL-C levels	Switching vs combination and baseline: reduced PANSS total, negative, cognition and anxiety factor scores ($p < 0.05$)	Overall completion rate:194/213.

(*Continued*)

Table 2 (Continued).

Post-Switching of Drug	Study	Study Population	Switching Schedule	Follow-Up Period	Outcome		Discontinuation/Completion Rate
					Metabolic Parameters	Psychotic Symptoms	
Quetiapine	Deberdt W. et al[80] Multi-center, double-blind, randomized controlled study	133 patients with schizophrenia or schizoaffective disorder who were treated with Olanzapine were in stable condition but were overweight or obese with at least one cardiovascular risk factor	Initial group (n = 68): continued Olanzapine switching group (n = 65): cross-titration switching to Quetiapine within 1 week, dose 300–800 mg/d	26 weeks	Switching vs initial group: No significant difference in changes of body weight, BMI, fasting blood glucose, insulin, TG, HDL-C, LDL-C, or total cholesterol levels between study endpoint and baseline.	Switching vs initial group: No significant difference in time to relapse; both groups improved PANSS scores, but reduced faster PANSS scores in initial vs switching group	Switching vs initial group completion rate: 43.1% vs 70.6%
Lurasidone	Stahl SM. et al.[36] Open label extension study	254 patients with schizophrenia who received 6-week treatment with fixed-dose Olanzapine 15 mg/d, Lurasidone 40 or 120 mg/d or placebo	Olanzapine-Lurasidone (n = 71); Lurasidone-Lurasidone (n = 118); Placebo-Lurasidone (n = 65): Placebo Open label extension study (n = 254)	24 weeks	Olanzapine-Lurasidone vs other groups: reduced body weight, BMI; improved blood lipid levels; all three groups showed minor improvement in blood glucose, insulin and glycosylated hemoglobin.	All three groups showed continuous improvement in PANSS total scores	Olanzapine-Lurasidone vs Lurasidone-Lurasidone vs placebo-Lurasidone group discontinuation rate: 56.3% vs 53.4% vs 58.5%
	Mattingly GW. et al[79] Open, randomized controlled, extended study	223 patients with schizophrenia or schizoaffective disorder in stable stage who were treated with Lurasidone or Risperidone for at least 12 months.	Lurasidone-Lurasidone group (n = 136): continued Lurasidone 40–120 mg/d Risperidone-Lurasidone group (n = 87): switching from Risperidone to Lurasidone.	24 weeks	Lurasidone-Lurasidone group vs Risperidone-Lurasidone group: changes in body weight; total cholesterol; TG; glucose	The total PANSS scores of the two groups continued to improve and the CGI-S improved moderately.	Lurasidone-Lurasidone group vs Risperidone-Lurasidone group completion rate: 80.1% vs 74.7%

Abbreviations: BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; BPRS, brief psychiatric rating scale; CGI-S, clinical global impressions-severity; CGI-CB, clinical global impressions-clinical benefit; SSS, subjective satisfaction scores; PANSS, positive and negative syndrome scale; SF-12 (MHS), medical outcomes survey-short form 12 item mental health score; SF-12 (PHS), medical outcomes survey-short form 12 item physical health score; IWQOL-lite, impact of weight on quality of life-lite questionnaire; LDL-C, low-density lipoprotein cholesterol; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; YMRS, young manic rating scale; GAF, global assessment of functioning.

compared with ~done drugs (Risperidone and Ziprasidone), following a switch to Amisulpride from previously used ~pine drugs (Olanzapine, Quetiapine, and Zotepine), body weight, BMI, and other metabolic parameters decrease more significantly.[69] Additionally, studies show that switching to Amisulpride causes improvement, or at least no deterioration, in psychotic symptoms, with improvement in CGI-S (−0.6±0.9, p = 0.001, week 6 vs baseline) and clinical global impressions-clinical benefits (CGI-CB) scores (−1.7±1.0, p<0.0001, week 6 vs baseline)[65] or no significant difference in the BPRS score (−0.1±8.1, p=0.913, month 12 vs baseline).[64] The safety assessment also shows good tolerability, minor side effects, and a completion rate of greater than 70% after switching. The treatment discontinuation rate after switching was 24.3%-28.3%, with withdrawals due to deterioration accounting for about half of the discontinuation rate. Furthermore, some clinical observational studies have demonstrated that the primary reason for switching from Olanzapine to Amisulpride is weight gain (72.6%) or the expectation of less weight gain with Amisulpride (84.1%).[71] Switching from typical antipsychotics to Amisulpride may improve patient compliance, including in patients who fail to comply with their previous treatment.[72]

Aripiprazole (Six Studies)
Aripiprazole studies have a follow-up period of 8, 12, 24, 26, or 52 weeks and most involve a switch from Olanzapine or Risperidone to Aripiprazole.[73–78] The results of the studies demonstrate that, when maintaining the original drug regimen, metabolic parameters such as waist circumference, blood pressure, TG, rapid blood glucose, and HDL-C continue to deteriorate, but almost all metabolic parameters improve after switching to Aripiprazole, with improvement in weight and blood lipids seen in the 4th week and continuing through weeks 16, 24, and even 52. Efficacy remains stable or improves after switching and the quality of life related to weight also improves significantly. After switching, the side effects are not obvious, and the tolerance is often good. However, the drop-out rate of the switching group was high, with most studies demonstrating above 30% and the discontinuation rate could reach 77.8% when the initial dose was above 15 mg per day.[77]

Lurasidone (Two Studies)
Lurasidone has been on the market for a short time and, to date, only two studies exist on switching from Olanzapine

or Risperidone to Lurasidone, both of which have a follow-up of six months.[36,79] The results demonstrate that switching from Olanzapine to Lurasidone significantly reduces body weight and BMI and improves blood lipids after six months of treatment, while blood glucose, insulin, and glycosylated hemoglobin improve less so. The efficacy continues to improve, with a good safety profile. After switching from Risperidone to Lurasidone, body weight, BMI, waist circumference, TG, and blood glucose decrease slightly, but total cholesterol increases and glycosylated hemoglobin remains unchanged. The efficacy continues to improve, side effects are not significantly different, and safety is satisfactory.[36,79] However, the treatment discontinuation rate is relatively high, ranging from 25.3% to 58.5%.

Quetiapine (One Study)
There are limited studies on switching to Quetiapine. One multi-center, double-blind, randomized controlled study explored the efficacy and metabolism of the effect of switching from Olanzapine to Quetiapine with a 24-week follow-up period. The results show that, compared with baseline, there was no significant change in body weight, BMI, fasting blood glucose, insulin, TG, HDL-C, LDL-C, or total cholesterol between the Olanzapine group and the Quetiapine group at the end of week 26.[80] Although there was no difference in the duration of the stable phase or the time to recurrence between the two groups, the total PANSS score of the Olanzapine group improved faster and the PANSS score of the Quetiapine group was significantly higher than the Olanzapine group. The treatment discontinuation rate and the discontinuation rate due to poor efficacy or psychiatric adverse events in the Olanzapine group were also higher than those in the Quetiapine group.

Ziprasidone (Five Studies)
Studies on Ziprasidone had a follow-up period of 12, 24, or 52 weeks, which included a switch from Olanzapine, Clozapine, Risperidone, or the typical antipsychotic Haloperidol to Ziprasidone.[81–84] The results showed that switching from Olanzapine to Ziprasidone is related to a significant improvement in body weight and continued improvement in other metabolic parameters such as waist circumference, systolic blood pressure, BMI, TG, and blood glucose. The efficacy parameters showed no difference when compared with baseline. The existing studies also suggested that the type of drug that the subject started

on reflects a difference on the impact on metabolic parameters and psychotic symptoms when switching to Ziprasidone. For example, bodyweight improved when switching from Olanzapine, with no difference when switching from Risperidone and even resulted in weight gain when switching from Haloperidol. Furthermore, efficacy improvements were more significant when switching from Risperidone and Haloperidol.[83] Study results also showed that weight, BMI, and TG of patients consistently improved during the 52-week follow-up when switching from Olanzapine or Risperidone to Ziprasidone, but nothing improved significantly except total cholesterol and efficacy when switching from the first-generation antipsychotics.[81]

Chen et al also compared the effects of switching to different drugs such as Ziprasidone and Aripiprazole on metabolism and efficacy. The results showed that during the 52-week follow-up, switching to two drugs may improve metabolic parameters with no differences between the groups. Ziprasidone tends to have superior effects of improving body weight and BMI, lowering total cholesterol, and increasing HDL-C, while Aripiprazole tends to have superior effects of lowering TG/HDL and HBA1c.[78] Another single-blind (accessor-blind) randomized open-label study compared the efficacy and tolerability of switching from Olanzapine to Ziprasidone and their combination. The results demonstrated that, compared with Olanzapine alone, both switching to Ziprasidone and adding Ziprasidone to Olanzapine can significantly improve metabolic parameters such as body weight, blood glucose, and blood lipids, with no significant difference between the Ziprasidone alone and combination groups.[82] The treatment discontinuation rate after switching varies widely, from the 8.9% to 64%, which may be related to the initial drug. For example, the dropout rate of switching from Olanzapine to Ziprasidone was 40%, which was higher than switching from Haloperidol (32%) or Risperidone (14%). The primary reason for dropout was the side effects.[83]

Brexpiprazole and Cariprazine

Newer antipsychotics, such as Brexpiprazole and Cariprazine, are associated with relatively lower MetS risks in lipids, glucose, and body weight and may become candidates for a switching strategy for patients with MetS. However, there are only two published studies available that discuss switching to Brexpiprazole and none for Cariprazine. For patients with schizophrenia, switching to Brepiprazole leads to a relatively low discontinuation rate of 17% at week 8.[85] Different cross-titration periods, which ranged from one to four weeks, all showed comparable improvement in the PANSS total score compared to baseline.[86] Nevertheless, none of these studies examined the effect of switching on metabolic parameters.

According to the existing research, switching to Aripiprazole, Amisulpride, Ziprasidone, or Lurasidone may become a feasible strategy for patients with schizophrenia comorbid with MetS, which may improve their metabolic parameters and continue to help their mental symptoms. However, the treatment discontinuation rate after switching remains relatively high, which may be related to the type of initial drug, the initial dose of the new drug, and the method of switching. Therefore, it is necessary to comprehensively evaluate the patient's disease characteristics and previous medications prior to switching, to pay attention to individual differences, and to select drugs in a targeted manner. In addition, most of the current studies utilized an open-label design with small sample sizes, various dosages of medications, and different switching modes. The lack of systematic review and meta-analyses also limits the promotion and application of these results. Furthermore, newer antipsychotics, including Lurasidone, Brexpiprazole, and Cariprazine are still relatively understudied and further studies examining the effect of these newer antipsychotics on metabolic parameters are needed. Their relatively high treatment cost may also limit their use. To minimize the risk of withdrawal symptoms, relapse, or recurrence, it is important to choose a suitable switching method.[87,88] Abrupt discontinuation, specifically referring to the use of the second antipsychotic on the second day immediately following the discontinuation of the original antipsychotic, should be avoided as much as possible in clinical practice; cross-tapering may be a safer choice.[68] Although it is the simplest strategy, abrupt discontinuation involves high risks related to withdrawals and drug interaction.[68] Cross-tapering refers to the gradual decrease of the first antipsychotic while gradually increasing the second antipsychotic to the appropriate therapeutic dose. This is the most commonly used switching method in clinical practice. During the overlap period of cross-tapering, both the risk of resurgence and the risk of adverse drug reactions can be minimized.[68] In the above switching studies, the cross-tapering method is frequently adopted.

There are also studies comparing the safety and efficacy of various switching methods when switching to

aripiprazole.[76] The switching methods compared include abrupt discontinuation (discontinuation of the original drug and direct addition of Aripiprazole to 30 mg per day), gradual reduction (the direct addition of Aripiprazole at 30 mg per day and then a gradual discontinuation of the original drug within two weeks), and cross-tapering (Aripiprazole titrated to 30 mg within three weeks while the original drug was stopped within two weeks). The results of the eight-week follow-up demonstrate that the body weight, PANSS total scores, and positive and negative symptom scores of the three groups improve, but with no statistical difference among the groups. However, another study comparing different switching strategies suggested that, although the long-term safety and efficacy outcomes of different strategies were equivalent, the abrupt discontinuation group suffered from a higher risk of early symptoms worsening compared with the cross-tapering group.[89] In conclusion, when choosing switching methods, drug factors such as the half-life of the original drug and the drug to be switched, common adverse effects, and possible drug interactions should all be considered.[68] Currently, however, it is believed that cross-tapering is still the most reliable method based on published studies and clinical practice and should be considered best practice.

A recent study also compared the metabolic effects of switching to antipsychotics with lower metabolic risks and combining them with metformin.[90] The initial drug was either switched to Aripiprazole or added with metformin, with a follow-up of 24 weeks. The BMI of the two groups decreased significantly. In the combination group, the fasting blood glucose significantly improved, insulin decreased, and blood lipids remained unchanged, while in the Aripiprazole group the blood glucose moderately improved. Additionally, the BPRS scores of all groups improved, with no difference among the groups, suggesting equal improvement of psychotic symptoms. The safety profiles were good, but the gastrointestinal reaction of patients in the combination group was more obvious.

Conclusion

In summary, patients with schizophrenia often have metabolic abnormalities or MetS, which can seriously affect the disease prognosis and quality of life. Use of SGAs is an important risk factor of MetS, particularly in those who have a higher antagonism profile of 5-HT2C, H1, and M3 receptors. Among the widely used SGAs, Clozapine and Olanzapine are most likely to cause MetS, while the

metabolic risk of Ziprasidone, Aripiprazole, Amisulpride, and newer antipsychotics like Lurasidone, Brexpiprazole, and Cariprazine are relatively low.

According to the few current studies, switching to an antipsychotic with a low metabolic risk, such as Amisulpride, Aripiprazole, Lurasidone, or Ziprasidone may improve the metabolic parameters of patients with schizophrenia without the deterioration of psychotic symptoms and with negligible side effects and a satisfactory safety profile. Therefore, a switching strategy may be an optimal choice for patients with schizophrenia comorbid with MetS or metabolic abnormalities. However, the reliability of the current studies is affected by factors such as open-label designs, different therapeutic doses, and high interruption rates.[53] Future systematic reviews and meta-analyses are in need to provide additional evidence-based support to develop safer, more effective, and more optimized treatment and management strategies for patients with schizophrenia with MetS.

Besides, combination therapies of antipsychotics with mood stabilizers, or antidepressants, or electroconvulsive therapy (ECT) are widely used in clinical practice, especially among patients with schizophrenia who do not respond sufficiently.[46,91–93] To avoid MetS risk caused by combination, selection of lower MetS risk options like bupropion and ECT should be considered. Future research specifically on minimization of MetS risk of combination therapy among patients with schizophrenia is needed.

Disclosure

Hui Ye is an employee of Sanofi. The authors report no other potential conflicts of interest in this work.

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