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# Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives

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## Abstract

Metabolic disturbances and obesity are major cardiovascular risk factors in patients with schizophrenia, resulting in a higher mortality rate and shorter life expectancy compared with those in the general population. Although schizophrenia and metabolic disturbances may share certain genetic or pathobiological risks, antipsychotics, particularly those of second generation, may further increase the risk of weight gain and metabolic disturbances in patients with schizophrenia. This review included articles on weight gain and metabolic disturbances related to antipsychotics and their mechanisms, monitoring guidelines, and interventions. Nearly all antipsychotics are associated with weight gain, but the degree of the weight gain varies considerably. Although certain neurotransmitter receptor-binding affinities and hormones are correlated with weight gain and specific metabolic abnormalities, the precise mechanisms underlying antipsychotic-induced weight gain and metabolic disturbances remain unclear. Emerging evidence indicates the role of genetic polymorphisms associated with antipsychotic-induced weight gain and antipsychotic-induced metabolic disturbances. Although many guidelines for screening and monitoring antipsychotic-induced metabolic disturbances have been developed, they are not routinely implemented in clinical care. Numerous studies have also investigated strategies for managing antipsychotic-induced metabolic disturbances. Thus, patients and their caregivers must be educated and motivated to pursue a healthier life through smoking cessation and dietary and physical activity programs. If lifestyle intervention fails, switching to another antipsychotic drug with a lower metabolic risk or adding adjunctive medication to mitigate weight gain should be considered. Antipsychotic medications are essential for schizophrenia treatment, hence clinicians should monitor and manage the resulting weight gain and metabolic

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**Core Tip:** Metabolic disturbances associated with antipsychotic drug treatment are prevalent in patients with schizophrenia. We herein discuss the epidemiology, the underlying mechanisms, monitoring, and intervention strategies of antipsychotics related metabolic disturbances.

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## INTRODUCTION

Patients with schizophrenia have a two to three times higher mortality rate[1,2] and a 20%–25% shorter life expectancy[3] compared with the general population. In addition to the considerably increased risks of suicide, cancer, and respiratory diseases, cardiovascular mortality is a leading cause of excess mortality in patients with schizophrenia[4,5]. Metabolic syndrome and obesity are major cardiovascular risk factors in patients with schizophrenia[5,6].

Before the introduction of the first antipsychotic drug chlorpromazine in 1952, cohort studies noted an increased incidence of abnormal glucose metabolism in patients with schizophrenia[7]. Studies also found that increased fasting and postprandial blood glucose levels in drug-naïve patients with schizophrenia were partly correlated with the severity of their illness[7,8]. Although such metabolic disturbances are partially attributed to unhealthy lifestyle behaviors such as smoking, poor diet, and physical inactivity[9], evidence also indicates a shared pathophysiology between schizophrenia and metabolic disturbances[10]. Meta-analyses of first-episode and drug-naïve patients with schizophrenia have indicated impaired glucose homeostasis and subclinical dyslipidemia before antipsychotic treatment[8,11]. Impaired glucose tolerance in the first-degree relatives of patients with schizophrenia further supports the role of genetic predisposition between schizophrenia and metabolic disturbances[12]. Researchers aim to determine the common susceptible genes that contribute to both schizophrenia and type 2 diabetes mellitus[13–15]. Other pathobiological factors contributing to metabolic disturbances in patients with schizophrenia have also been proposed. Mück-Seler *et al*[16] found that patients with schizophrenia have hypothalamic–pituitary–adrenal axis dysregulation and increased plasma cortisol levels, and evidence shows that hypothalamic–pituitary–adrenal axis dysregulation may play a significant role in the development of metabolic syndrome[17]. Researchers have also suggested that schizophrenia and metabolic syndrome are both related to inflammatory and immune mechanisms[18,19].

Additionally, antipsychotic treatment may exacerbate the metabolic disturbances in patients with schizophrenia. Antipsychotic drugs are the drugs of choice for treating patients with schizophrenia, and certain drugs are also indicated to treat a wide range of mental illnesses, including bipolar disorder, treatment-resistant depression, Tourette syndrome, and aggressive behavior in autism. These drugs are categorized as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors. Compared with FGAs, SGAs treat the negative, cognitive, and mood symptoms of schizophrenia more effectively and result in fewer extrapyramidal symptoms at clinically effective doses[20]. Therefore, SGAs may result in greater treatment adherence and psychotic relapse prevention.

Although a meta-analysis indicated that nearly all antipsychotics are associated with weight gain after prolonged exposure[21], certain SGAs are associated with a greater liability of weight gain and metabolic disturbances than high-potency FGAs are[22]. However, studies have shown that antipsychotic use is associated with a decreased risk of all-cause, cardiovascular, and suicide mortality[23,24]. Such findings on long-term mortality outcomes may appear inconsistent with the metabolic side effects of antipsychotic use. This disconnection is likely to be due to the improvement of psychopathology associated with antipsychotic treatment, which subsequently may result in healthy lifestyle behaviors and use of health care services for physical illnesses[23,25].

Although antipsychotic medications are essential for treating schizophrenia, clinicians should compare the risks and benefits in choosing the most favorable treatment. This review focused on the adverse effects of weight gain and metabolic disturbances induced by antipsychotic drugs.

## ANTIPSYCHOTIC DRUGS AND WEIGHT GAIN

Studies have shown the prevalence of obesity [body mass index (BMI) over 30 kg/m<sup>2</sup>] among people with schizophrenia is 42%–60% [26,27]. Several [28,29] but not all [30,31] studies have reported that antipsychotic-naïve patients with schizophrenia are at a higher risk of overweight and obesity. Additionally, weight gain is a well-known side effect of antipsychotic drugs in patients with schizophrenia, influencing 15%–72% of patients [28]. Among FGAs, low-potency ones such as chlorpromazine and thioridazine are related to a greater risk of weight gain than high-potency ones such as haloperidol and fluphenazine [32].

Various SGAs are also associated with varying probabilities of weight gain: Clozapine and olanzapine carry the highest risk; quetiapine, risperidone, and paliperidone an intermediate risk; and aripiprazole, ziprasidone, and lurasidone the lowest risk [20,33,34]. The difference between long-acting injectable and oral SGAs relative to the incidence of weight gain is not significant [35]. Notably, the greatest degree of weight gain in drug-naïve patients with schizophrenia occurs in the first few months after antipsychotic commencement [36]. Although the rate of weight gain then gradually decreases, patients might continue to gain weight for 1–4 years [37]. An early weight gain of > 5% in the first month is the best predictor of long-term weight gain [38].

## ANTIPSYCHOTIC DRUGS AND METABOLIC DISTURBANCES

Several attempts have been made by various organizations to establish diagnostic criteria for metabolic syndrome [39]. The World Health Organization proposed the first definition of metabolic syndrome in 1998 [40]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III updated the guidelines for metabolic syndrome [41]. The limitation of the aforementioned definitions is that because cutoff values of obesity specific to certain populations are not defined, such cutoff values are not applicable to different ethnic groups. In 2004, Tan *et al* [42] proposed a modified National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome in Asian populations. In 2006, the International Diabetes Federation provided a worldwide definition of metabolic syndrome with ethnicity-specific criteria for central obesity [43]. Table 1 illustrates the different definitions of metabolic syndrome from different organizations.

Metabolic syndrome is a group of health problems that includes central obesity, hyperglycemia, dyslipidemia, and hypertension, with central obesity being the primary feature [44]. Central obesity is associated with insulin resistance, which finally results in type 2 diabetes mellitus and cardiovascular diseases. Metabolic syndrome is highly prevalent in patients with schizophrenia; the overall prevalence rate being 32.5% [45]. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia trial and comparison with national estimates from the Third National Health and Nutrition Examination Survey revealed that men and women from the Clinical Antipsychotic Trials of Intervention Effectiveness trial were 138% and 251% more likely, respectively, to have metabolic syndrome than patients from the Third National Health and Nutrition Examination Survey matched sample [46].

**Table 1** Diagnostic criteria for metabolic syndrome

Organization, Year	WHO, 1988	NCEP/ATP III, 2001	Modified NCEP/ATP III for Asians, 2004	IDF, 2006
Criteria	Glucose intolerance, IGT, diabetes mellitus, or insulin resistance together with two or more of the following:  BP: $\geq 140/90$ mmHg  Abdominal obesity: WHR $> 0.9$ and $> 0.85$ for men and women, respectively, and/or BMI: $> 30$ kg/m <sup>2</sup>  Triglycerides: $\geq 150$ mg/dL or on treatment  HDL-C: $< 35$ mg/dL for men and $< 39$ mg/dL for women  Urine albumin excretion rate: $\geq 20$ $\mu$ g/min or urine albumin to creatinine ratio: $\geq 30$ mg/g	Three or more of the following:  FPG: $\geq 110$ mg/dL <sup>1</sup> or on treatment for DM  BP: $\geq 130/85$ mmHg  Triglycerides: $\geq 150$ mg/dL or on treatment  HDL-C: $< 40$ mg/dL for men and $< 50$ mg/dL for women  WC: $\geq 102$ cm for men and $\geq 88$ cm for women	Three or more of the following:  FPG: $\geq 110$ mg/dL <sup>1</sup> or on treatment for DM  BP: $\geq 130/85$ mmHg  Triglycerides: $\geq 150$ mg/dL or on treatment  HDL-C: $< 40$ mg/dL for men and $< 50$ mg/dL for women  WC: $\geq 90$ cm for men and $\geq 80$ cm for women	Central obesity as defined by ethnicity/race, specific WC, but can be assumed if BMI $> 30$ kg/m <sup>2</sup> and with two or more of the following:  FPG: $\geq 100$ mg/dL or on treatment for DM  BP: $\geq 130/85$ mmHg or on treatment  Triglycerides: $\geq 150$ mg/dL or on treatment  HDL-C: $< 40$ mg/dL for men and $< 50$ mg/dL for women or on treatment

<sup>1</sup>FPG  $\geq 100$  mg/dL modified in 2004 according to the International Diabetes Federation definition of impaired fasting glucose. The 2001 definition of National Cholesterol Education Program Adult Treatment Panel III identified fasting plasma glucose  $\geq 110$  mg/dL as elevated. BMI: Body mass index; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; IDF: International Diabetes Federation; NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III; WC: Waist circumference; WHR: Waist-to-hip ratio; WHO: World Health Organization.

As mentioned, individual antipsychotic drugs have significant differences in their effects on metabolic disturbances in correlation with their weight gain probabilities [22]. However, some case reports have suggested that substantial weight gain or obesity may not be a factor in up to 25% of cases of new-onset diabetes during antipsychotic treatment[47]. Other studies have reported that olanzapine exerts metabolic changes within days in healthy volunteers without a significant change in body weight[48,49]. Evidence suggests that antipsychotics may directly influence pancreatic beta cells, resulting in time-dependent changes in insulin secretion with initial hypoinsulinemia and subsequent compensatory hyperinsulinemia[50].

## MECHANISM UNDERLYING WEIGHT GAIN AND METABOLIC DISTURBANCES DUE TO ANTIPSYCHOTIC DRUGS

Several neurotransmitters and hormones thought to be involved in the management of satiety, feeding, and glucose metabolism have been implicated in the mechanism of antipsychotic-induced weight gain (AIWG) and metabolic disturbances.

### Hormones

Various peptide hormones, including leptin, adiponectin, ghrelin, orexin, and cholecystokinin (CCK), play critical roles in the regulation of energy homeostasis and are suggested to be biomarkers of metabolic disturbances. Studies have indicated that serum leptin level increases during antipsychotic treatment[51,52]. Although leptin acts to inhibit food intake, studies have suggested that antipsychotics could induce or exacerbate a leptin-resistance status, which may contribute to aggravated obesity[52]. However, other findings support the possibility of another mechanism involving antipsychotic-induced epigenetic changes to leptin or leptin receptor genes[53].

Adiponectin can also reduce food intake, and a meta-analysis by Bartoli *et al*[54] indicated that treatment with clozapine and olanzapine is associated with decreased adiponectin levels. Decreased adiponectin levels may result in insulin resistance and increased risk of inflammation independent of adiposity[55]. A study revealed that some SGAs, especially clozapine and olanzapine, might exhibit a time-dependent effect on adiponectin levels[56]. Initially, the up-regulation of adiponectin might compensate for the deleterious effect of olanzapine and clozapine on glucose



homeostasis. Then, a new energy balance equilibrium is regained during a short-term treatment, resulting in the return of blood adiponectin levels to the baseline. Finally, the failure of adiponectin up-regulation pushes blood adiponectin levels further below the baseline after long-term treatment.

Ghrelin, however, is a hunger-inducing hormone. Reports on the association between antipsychotic treatment and ghrelin level changes are inconsistent, although three long-term studies reported increased ghrelin levels in patients on SGAs with weight gain liabilities[51]. Acylated ghrelin and desacylated ghrelin are the two main forms of ghrelin and play opposing roles in energy homeostasis. Lower acylated ghrelin/desacylated ghrelin ratios are associated with better metabolic profiles in patients with schizophrenia treated with olanzapine[57]. Leptin, adiponectin, and ghrelin levels differ significantly in patients with schizophrenia receiving clozapine and olanzapine due to the direct effects of the medications, rather than due to weight gain[58]. Additionally, the leptin/adiponectin ratio seems to be a preferential marker of metabolic syndrome in patients with schizophrenia compared with leptin or adiponectin alone[59].

Orexins, also known as hypocretins, have been suggested to regulate wakefulness, feeding, and metabolic homeostasis[60]. A study found that orexin-A level was elevated in patients with schizophrenia treated with antipsychotics, particularly in those taking fewer obesogenic antipsychotics[61]. The potential protective role of orexin-A against antipsychotic-related metabolic abnormalities may be attributable to the thermogenesis resulting from increased sympathetic tone and reduced peripheral insulin resistance[61].

CCK plays an important role in induction of gallbladder contraction, stimulation of pancreatic secretion, regulation of gastrointestinal motility, and induction of satiety [62]. Studies found that CCK is related to obesity and metabolic syndrome in the general population[63,64]. Animal studies reported that olanzapine could counteract the satiating effect of CCK[65], and clozapine could reduce hypothalamic messenger RNA of CCK-2 receptor[66]. In contrast, human studies found that CCK level did not change significantly after olanzapine treatment[67,68]. The role of CCK in antipsychotic-induced metabolic disturbances warrants further investigations.

### Neurotransmitters

Histamine H<sub>1</sub> receptor antagonism promotes feeding, and the affinity for H<sub>1</sub> receptors is closely correlated with AIWG[69], with clozapine and olanzapine having the highest affinity. Researchers have also proposed that drugs with H<sub>1</sub> receptor antagonism may also induce weight gain because of their sedative effects and consequential reduced mobility[70].

Serotonin is known to provide a satiety signal, and serotonin 5-HT<sub>2C</sub> receptors are integral to the regulation of energy homeostasis by working together with the melanocortin and leptin signaling pathways[71]. Several SGAs, including clozapine and olanzapine, are potent 5-HT<sub>2C</sub> inverse agonists and cause significant weight gain. However, ziprasidone, which also has a high affinity for 5-HT<sub>2C</sub> receptors, is associated with limited weight gain, indicating that no single neurotransmitter system can fully explain AIWG. Conversely, the 5-HT<sub>1A</sub> receptor exhibits the opposite effect of the 5-HT<sub>2C</sub> receptor on food intake. The 5-HT<sub>1A</sub> partial agonism, the common mechanism between aripiprazole, lurasidone, and ziprasidone, may reduce the risk of metabolic disturbances[72].

One study reported that bromocriptine, a specific dopamine D<sub>2</sub> receptor agonist, can counteract antipsychotic-induced hyperphagia and body weight gain in rats[73]. Dopamine D<sub>2</sub> receptor antagonism can enhance the 5-HT<sub>2C</sub>-mediated effects on food intake and influence glucose metabolism by disinhibiting prolactin secretion[74]. Prolactin, which can stimulate pancreatic  $\beta$ -cell proliferation and insulin production and secretion, may be inversely associated with diabetes mellitus risk[75]. Moreover, prolactin generally suppresses lipid storage and adipokine release[76]. These characteristics may explain the reason that FGAs, risperidone, and amisulpride, which exhibit a higher hyperprolactinemia incidence than do other SGAs, have a lower propensity to develop metabolic disturbances.

Cholinergic muscarinic M<sub>3</sub> receptors are highly expressed by pancreatic  $\beta$ -cells, and low olanzapine and clozapine concentrations, both potent M<sub>3</sub> antagonists, can considerably and selectively impair cholinergic stimulated insulin secretion by blocking muscarinic M<sub>3</sub> receptors in isolated rat islet cells[77]. The affinity for the cholinergic muscarinic M<sub>3</sub> receptor is therefore suggested to be the predictor of the propensity of antipsychotic-induced type 2 diabetes mellitus[78].

The support for  $\alpha 1$ - and  $\alpha 2$ -adrenergic receptor involvement in the etiology of AIWG is not as well developed as that for the aforementioned receptors. However, evidence indicates that these receptors may be associated with glucose control and may be synergistic with other receptor activities in contributing to AIWG[79].

Numerous pharmacogenetic investigations have identified the role of genetic polymorphisms associated with metabolic disturbances. The most-studied candidate genes that derive from receptors considered to mediate antipsychotic effects on food intake include serotonin 5-HT<sub>2C</sub>, histamine H1, *ADRA1A*, and dopamine D<sub>2</sub> receptors [80]. Other genes that have been investigated in association with metabolic disturbances include leptin (*LEP*), leptin receptor (*LEPR*), ghrelin (*GHRL*), adiponectin (*ADIPOQ*), insulin-induced genes 1 and 2 (*INSIG1* and *INSIG2*), cannabinoid receptor 1 (*CNR1*), fat-mass and obesity-associated protein (*FTO*), methylenetetrahydrofolate reductase (*MTHFR*), and melanocortin-4 receptor (*MC4R*)[71,81].

### **Gut microbiota**

The gut microbiome can interact with the central nervous system tract through the gut-brain axis. Compared with healthy controls, patients with schizophrenia exhibited a lower gut microbial richness index and diversity index[82]. Several studies have reported an association between metabolic disturbances and gut microbiota in patients with schizophrenia[83,84]. The mechanisms underlying antipsychotic-induced metabolic disturbances mediated through gut microbiota might involve an influence on energy homeostasis and aggravation of chronic inflammation[85,86]. Maier *et al*[87] reported that antipsychotic drugs exhibit antimicrobial activity and may disturb the gut ecosystem. Gut microbiota that may modulate the gut hormone system include ghrelin, peptide YY, glucagon-like peptide-I, and CCK, which play critical roles in adjusting energy homeostasis relative to glucose metabolism, fat storage, and appetite control[85]. Antipsychotic-induced dysbiosis can produce several inflammatory cytokines, including interleukin 1, interleukin 6, and tumor necrosis factor alpha, which are essential in mediating the relationship between gut microbiota and metabolic disturbances[88].

### **Potential predictors**

Several predictors of AIWG and metabolic disturbances have been identified, including female gender and younger age[89]. Debate is ongoing regarding the relationship between baseline BMI and AIWG, even though low-baseline BMI and normal weight status (*i.e.* BMI < 25) have been frequently associated with greater AIWG[90]. Lan *et al*[91] applied artificial intelligence to develop a neurofuzzy model, including physical factors (baseline weight, height, and waist and hip circumferences), lifestyle factors (smoking, dietary patterns, and exercise levels), genetic factors (*ADRA1A*, *ADRB3*, *ADRA2A*, *5-HTR<sub>2A</sub>*, and *5-HTR<sub>2C</sub>*), and psychopathology severity as predictor variables, with a 93% prediction rate for weight gains among patients with schizophrenia treated with antipsychotics.

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## **METABOLIC MONITORING**

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National and international groups have developed guidelines for screening and monitoring AIWG and metabolic disturbances, but studies have indicated that these guidelines are not routinely implemented in clinical care[92]. Table 2 illustrates the comparison between two guidelines proposed by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity[32], and the British Association for Psychopharmacology[93]. Notably, the monitoring frequency should be adjusted according to the clinical situation or after a change in antipsychotic medication.

Lin *et al*[94] developed an artificial neural network and multiple logistic regression models without biochemical parameters to identify rapidly metabolic syndrome in SGA-treated patients. The researchers suggested that waist circumference and diastolic blood pressure were the most predictive variables. Other risk factors for antipsychotic-induced metabolic syndrome should also be evaluated, including smoking, dietary habits, and physical activity levels as well as personal and family history of obesity, diabetes mellitus, and cardiovascular diseases[95].

**Table 2 Metabolic monitoring guidelines as proposed by various organizations**

	US consensus[32]	BAP guidelines[86]
Weight	At 4 wk, 8 wk, and 12 wk after initiating or changing SGA therapy, then quarterly	BMI weekly for the first 4–6 wk, then every 2–4 wk for up to 12 wk. At a minimum, once every 4 wk for the first 12 wk, then at 6 mo and at least annually
Blood glucose	Assessed fasting plasma glucose at 3 mo, then annually	Assessed fasting or random plasma glucose in the initial weeks and glycated hemoglobin at 12 wk, 6 mo, and then annually
Lipid profile	At 3 mo, then repeated at 5-yr intervals if normal	At 12 wk, 6 mo, and then annually. The total cholesterol/high-density lipoprotein cholesterol ratio should be required.
Blood pressure	At 3 mo, then annually	At 12 wk, 6 mo, and then annually

US consensus: Consensus proposed by American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[32]; BAP guidelines: Guidelines proposed by the British Association for Psychopharmacology[86]; SGA: Second-generation antipsychotics; BMI: Body mass index.

## INTERVENTIONS

The National Institute for Health and Care Excellence guidelines on psychosis and schizophrenia in adults suggest that these patients, particularly when taking antipsychotics, should be offered combined dietary and physical activity programs as well as help for smoking cessation from a psychiatric multidisciplinary care team[96]. Studies have reported that these nonpharmacological strategies for AIWG are beneficial and cost-effective and therefore should be a priority, particularly in early antipsychotic treatment stages[97,98].

Although lifestyle interventions are always crucial, switching to a different antipsychotic medication with a lower propensity for weight gain could also be effective for managing metabolic adverse effects. Studies have shown that switching to aripiprazole, amisulpride, ziprasidone, and lurasidone is beneficial for weight or metabolic measurements[99].

Because switching antipsychotics may result in psychosis decompensation and relapse, another strategy that involves adding adjunctive medication to mitigate weight gain and metabolic changes has been studied extensively. The proposed medications are listed and discussed subsequently.

### Metformin

Metformin, probably the most hopeful drug to attenuate antipsychotic-induced metabolic abnormalities[100], is a hypoglycemic drug for treating type 2 diabetes mellitus and employs a mechanism for reducing hepatic glucose production and improving insulin sensitivity without causing overt hypoglycemia. Metformin has also been effective in improving lipid metabolism by reducing triglyceride levels[101].

A meta-analysis of 12 randomized controlled trials (RCTs) concluded that adjunctive metformin is effective in treating AIWG and metabolic disturbances; the doses used in these trials ranged from 500 mg/d to 2550 mg/d[100]. Wu *et al*[102] conducted a RCT to test the efficacy of metformin alone, lifestyle intervention alone, and in combination in 128 first-episode patients with schizophrenia who added > 10% to their weight after receiving antipsychotic medications. After 12 wk, lifestyle intervention alone, metformin alone, and in combination were effective in attenuating AIWG and metabolic disturbances. Lifestyle intervention plus metformin demonstrated the greatest effect on weight loss, whereas metformin alone was more effective for reversing weight gain and increasing insulin sensitivity than lifestyle intervention alone[102].

### Topiramate

Topiramate, a medication for epilepsy treatment and migraine prevention, is observed to reduce weight by poorly understood mechanisms likely related to glutamate  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonism in the hypothalamus and modulation of hypothalamic concentrations of neuropeptide Y, galanin, and corticosteroid concentrations; topiramate also stimulates lipoprotein lipase and inhibits carbonic anhydrase[103,104]. A meta-analysis of 17 RCTs indicated that 50–400 mg/d adjunctive topiramate significantly reduced weight or BMI and psychopathology in patients with schizophrenia[105].

### Amantadine

Amantadine, an antiviral agent for influenza A treatment, has been shown to reduce extrapyramidal adverse effects. Evidence shows that amantadine enhances dopamine release indirectly through antagonism of the N-methyl-D-aspartic acid glutamate receptor[106]. According to a meta-analysis of five RCTs, adjunctive amantadine moderately outperformed placebo in terms of weight reduction[100]. Amantadine augmentation does not seem to exacerbate psychosis and may even be effective in alleviating negative symptoms[107].

### Aripiprazole

Aripiprazole, which acts as partial agonist of dopamine D<sub>2</sub> and serotonin 5-HT<sub>1A</sub> receptors as well as an antagonist of 5-HT<sub>2A</sub> receptors, is categorized in the group with the lowest propensity for weight gain. A meta-analysis of nine RCTs indicated that adjunctive aripiprazole with SGAs results in significant weight reduction compared with placebo[108]. Reviews have also reported a protective effect of adjunctive aripiprazole with other antipsychotics for dyslipidemia and diabetes mellitus when compared with antipsychotic monotherapy or other antipsychotic combinations[109]. Combining aripiprazole with other low metabolic risk antipsychotics such as ziprasidone, amisulpride, or lurasidone to mitigate weight gain warrants exploration.

### Fluvoxamine

Fluvoxamine, a potent cytochrome P450 1A2 inhibitor, blocks the major metabolism pathway of clozapine, resulting in a 5–12-fold increase in plasma clozapine levels and a decrease in the levels of its major active metabolite norclozapine. Norclozapine, not clozapine, is associated with increases in weight and plasma glucose and triglyceride levels[110]. Lu *et al*[111] randomized patients with schizophrenia to receive either 50 mg/d fluvoxamine plus 100 mg/d clozapine or 300 mg/d clozapine. The authors found that the clozapine-fluvoxamine combination significantly attenuated increases in body weight and insulin resistance as well as in insulin, glucose, and triglyceride levels compared with clozapine monotherapy. The combination also significantly reduced psychopathology compared with clozapine monotherapy[111]. As a clinical implication, clinicians should reduce clozapine dosage and carefully monitor clozapine levels if this combination is applied.

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## SUPPLEMENTAL PRODUCTS

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### *Omega-3 polyunsaturated fatty acids*

Omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation could produce favorable hypolipidemic effects, a reduction in pro-inflammatory cytokine levels, and improvement in glycemia in patients with type 2 diabetes mellitus[112]. Proposed mechanisms by which n-3 PUFAs may counteract metabolic disturbances include modulating lipid metabolism, regulating adipokines such as adiponectin and leptin, alleviating adipose tissue inflammation, promoting adipogenesis, and altering epigenetic mechanisms[113]. According to a meta-analysis of 19 RCTs, adjunctive n-3 PUFAs could improve psychopathology and reduce triglyceride levels in patients with schizophrenia[114].

### Melatonin

The efficacy of melatonin in reducing SGA-related metabolic adverse effects is inconsistent. Modabbernia *et al*[115] reported that melatonin was effective in alleviating olanzapine-induced weight gain and hypertriglyceridemia, whereas Agahi *et al*[116] noted that melatonin significantly increased HDL levels and decreased fasting blood sugar levels but increased weight in patients receiving SGAs compared with the placebo group. Romo-Nava *et al*[117] reported that melatonin is effective in attenuating SGA-induced metabolic adverse effects in patients with bipolar disorder but not in patients with schizophrenia. A recent review manuscript reported that adjunctive melatonin therapy has positive outcome for attenuating antipsychotic-induced metabolic disturbances in patients with schizophrenia[118]. Additional studies on the effect of melatonin on antipsychotic-related metabolic side effects are warranted.



## CONCLUSION

Studies have demonstrated that antipsychotic drugs potentially induce or trigger metabolic disturbances, which are a major cardiovascular risk factor for patients with schizophrenia. In general, SGAs carry a higher risk of metabolic disturbances than do FGAs. Various SGAs are also associated with varying potentials for weight gain and can be roughly categorized into three groups: Clozapine and olanzapine (highest risk); quetiapine, risperidone, and paliperidone (intermediate risk); and aripiprazole, ziprasidone, and lurasidone (lowest risk).

Notably, Wu and Gau[119] found that patients with schizophrenia and type 2 diabetes mellitus develop few advanced diabetes mellitus complications after receiving regular antipsychotic treatment. The authors proposed that appropriate antipsychotic treatment can improve the patients' conditions and thereby increase the frequency of healthy behavior.

Despite a growing knowledge of the biochemical profiles of antipsychotic agents, the underlying mechanisms of their association with metabolic disturbances remain inconclusive. The binding affinities of antipsychotics to several neurotransmitter receptors, such as  $H_1$ ,  $5-HT_{2C}$ ,  $5-HT_{1A}$ ,  $D_2$ ,  $M_3$ , and adrenergic receptors, might be associated with induction of metabolic disturbances. Studies have revealed a positive association between AIWG and therapeutic benefits, particularly in patients treated with olanzapine and clozapine, which suggests that these medications may possess a shared mechanism related to their metabolic liability[120]. Various peptide hormones, including leptin, adiponectin, ghrelin, and orexin, are also suggested to be metabolic disturbance biomarkers. Notably, an increasing amount of evidence indicates that genetic polymorphism has a strong influence on AIWG and metabolic disturbances, further highlighting the complexity and multiplicity of the mechanisms.

Despite established guidelines and recommendations, patients treated with antipsychotic drugs have not adequately received the baseline and follow-up assessments of metabolic and cardiovascular risk factors. Moreover, psychiatrists and members of multidisciplinary care team should motivate patients to pursue healthy lifestyle behaviors, including dietary and physical activity programs. If lifestyle interventions do not succeed, switching to another antipsychotic drug with a low metabolic risk or including an adjunctive medication to mitigate weight gain can be an effective intervention option. All interventions should be adequately monitored, as individual patients may respond unpredictably to any of these pharmacological and natural agents.

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