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...
INTRODUCTION

Patients with schizophrenia have a two to three times higher mortality rate\cite{1,2} and a 20\%–25\% shorter life expectancy\cite{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\cite{4,5}. Metabolic syndrome and obesity are major cardiovascular risk factors in patients with schizophrenia\cite{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\cite{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\cite{7,8}. Although such metabolic disturbances are partially attributed to unhealthy lifestyle behaviors such as smoking, poor diet, and physical inactivity\cite{9}, evidence also indicates a shared pathophysiology between schizophrenia and metabolic disturbances\cite{10}. Meta-analyses of first-episode and drug-naïve patients with schizophrenia have indicated impaired glucose homeostasis and subclinical dyslipidemia before antipsychotic treatment\cite{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\cite{12}. Researchers aim to determine the common susceptible genes that contribute to both schizophrenia and type 2 diabetes mellitus\cite{13-15}. Other pathobiological factors contributing to metabolic disturbances in patients with schizophrenia have also been proposed. Mück-Seler et al\cite{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\cite{17}. Researchers have also suggested that schizophrenia and metabolic syndrome are both related to inflammatory and immune mechanisms\cite{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\cite{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 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/m²] 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: | Three or more of the following: | Three or more of the following: | Central obesity as defined by ethnicity/race, specific WC, but can be assumed if BMI > 30 kg/m² and with two or more of the following: |
|                    | BP: ≥ 140/90 mmHg | FPG: ≥ 110 mg/dL or on treatment for DM | FPG: ≥ 110 mg/dL or on treatment for DM | FPG: ≥ 100 mg/dL or on treatment for DM |
|                    | Abdominal obesity: WHR > 0.9 and > 0.85 for men and women, respectively, and/or BMI: > 30 kg/m² | BP: ≥ 130/85 mmHg | BP: ≥ 130/85 mmHg | BP: ≥ 130/85 mmHg or on treatment |
|                    | Triglycerides: ≥ 150 mg/dL or on treatment | Triglycerides: ≥ 150 mg/dL or on treatment | Triglycerides: ≥ 150 mg/dL or on treatment | Triglycerides: ≥ 150 mg/dL or on treatment |
|                    | HDL-C: < 35 mg/dL for men and < 39 mg/dL for women | HDL-C: < 40 mg/dL for men and < 50 mg/dL for women | HDL-C: < 40 mg/dL for men and < 50 mg/dL for women | HDL-C: < 40 mg/dL for men and < 50 mg/dL for women or on treatment |
|                    | Urine albumin excretion rate: ≥ 2 0 μg/min or urine albumin to creatinine ratio: ≥ 3 0 mg/g | WC: ≥ 102 cm for men and ≥ 88 cm for women | WC: ≥ 90 cm for men and ≥ 80 cm for women |

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[38]. 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 H₁ receptor antagonism promotes feeding, and the affinity for H₁ receptors is closely correlated with AIWG[69], with clozapine and olanzapine having the highest affinity. Researchers have also proposed that drugs with H₁ 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 β-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 β-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 α1- and α2-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_2c, histamine H1, ADRA1A, and dopamine D_2 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, ADRA3, ADRA2A, 5-HTR_1a, and 5-HTR_2a), and psychopathology severity as predictor variables, with a 93% prediction rate for weight gains among patients with schizophrenia treated with antipsychotics.

**METABOLIC MONITORING**

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 α-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$_2$ and serotonin 5-HT$_1A$ receptors as well as an antagonist of 5-HT$_2A$ 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.

SUPPLEMENTAL PRODUCTS
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 H₂, 5-HT₂, 5-HT₁, D₂, M₄, 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.

REFERENCES

1 Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry 2010; 196: 116-121 [PMID: 20118455 DOI: 10.1192/bjp.bp.109.087512]

2 Osby U, Correia N, Brandt L, Ekborn A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000; 45: 21-28 [PMID: 10978869 DOI: 10.1016/s0920-9964(99)00191-7]

3 Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. Schizophr Res 2011; 131: 101-104 [PMID: 21741216 DOI: 10.1016/j.schres.2011.06.008]

4 Bushe CJ, Taylor M, Haukka J. Mortality in schizophrenia: a measurable clinical endpoint. J Psychopharmacol 2010; 24: 17-25 [PMID: 20923917 DOI: 10.1177/1359786810382468]

5 Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, Lindenmayer JP, Manoukian SV, Banerji MA, Lebovitz HE, Hennekens CH. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. J Clin Psychiatry 2004; 65 Suppl 7: 4-18 [PMID: 15151456]

6 Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatry 2012; 25: 83-88 [PMID: 22249081 DOI: 10.1097/YCO.0b013e32835035ca]

7 Freyberg Z, Aslanoglou D, Shah R, Ballon JS. Intrinsic and Antipsychotic Drug-Induced Metabolic Dysfunction in Schizophrenia. Front Neurosci 2017; 11: 432 [PMID: 28084446 DOI: 10.3389/fnins.2017.00432]

8 Pillingter T, Beck K, Gojihila C, Donocik JG, Iauhar S, Howes OD. Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. JAMA Psychiatry 2017; 74: 261-269 [PMID: 28097367 DOI: 10.1001/jamapsychiatry.2016.3803]

9 Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. Front Psychiatry 2014; 5: 137 [PMID: 25309466 DOI: 10.3389/fpsyt.2014.00137]

10 Hoffman RP. The Complex Inter-Relationship Between Diabetes and Schizophrenia. Curr Diabetes
Chang SC et al. Metabolic disturbances with antipsychotic drugs

Rev 2017; 13: 528-532 [PMID: 28000544 DOI: 10.2174/15733998126666161201205322]

Misiak B, Staszykiewicz B, Łaczniański L, Frydecka D. Lipid profile disturbances in antipsychotic-naïve patients with first-episode non-affective psychosis: A systematic review and meta-analysis. Schizophr Res 2017; 190: 18-27 [PMID: 28325572 DOI: 10.1016/j.schres.2017.03.031]

Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH. Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia. Diabet Med 2007; 24: 481-485 [PMID: 17381506 DOI: 10.1111/j.1464-5410.2007.02092.x]

Hackinger S, Prins B, Mamakou V, Zengini E, Marouli E, Brichtl M, Serafetindis I, Lammissou K, Kontaxakis V, Dedoussis G, Gonidakis F, Thanopoulou A, Tentolouris N, Tsezou A, Zeggini E. Evidence for genetic contribution to the increased risk of type 2 diabetes in schizophrenia. Transl Psychiatry 2018; 8: 252 [PMID: 30470734 DOI: 10.1038/s41398-018-0304-6]

Cao H, Chen J, Meyer-Lindenberg A, Schwarz E. A polygenic score for schizophrenia predicts glycemic control. Transl Psychiatry 2017; 7: 1295 [PMID: 29249829 DOI: 10.1038/s41398-017-0044-z]

Malan-Müller S, Kilian S, van den Heuvel LL, Bardien S, Asmal L, Warrich L, Emsley RA, Hemmings SM, Seedat S. A systematic review of genetic variants associated with metabolic syndrome in patients with schizophrenia. Schizophr Res 2016; 170: 1-17 [PMID: 26621002 DOI: 10.1016/j.schres.2015.11.011]

Mück-Seler D, Pivac N, Jakovljević M, Brzović Z. Platelet serotonin, plasma cortisol, and dexamethasone suppression test in schizophrenic patients. Biol Psychiatry 1999; 45: 1433-1439 [PMID: 10356025 DOI: 10.1016/s0006-3223(99)00174-7]

Rosmond R, Björntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med 2000; 247: 188-197 [PMID: 10692081 DOI: 10.1046/j.1365-2796.2000.00603.x]

Steiner J, Bernstein HG, Schiltz K, Müller UJ, Westphal S, Drexhage HA, Bogerts B. Immune system and glucose metabolism interaction in schizophrenia: a chicken-egg dilemma. Prog Neuropsychopharmacol Biol Psychiatry 2014; 48: 287-294 [PMID: 23085507 DOI: 10.1016/j.pnpbp.2012.09.016]

Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? J Psychopharmacol 2012; 26: 33-41 [PMID: 22472311 DOI: 10.1177/0269881111431622]

Leucht S, Cipriani A, Pinelli L, Mavridis D, Orey D, Richter F, Samara M, Barbu C, Engel RR, Geddes JR, Kissling W, Stief MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; 382: 951-962 [PMID: 23810019 DOI: 10.1016/s0140-6736(13)60773-3]

Bak M, Fransen A, Janssen J, van Os J, Dukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One 2014; 9: e94112 [PMID: 24763306 DOI: 10.1371/journal.pone.0094112]

Pilling S, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, Beck K, Natesan S, Elizabeth F, Cipriani A, Howes OD. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020; 7: 64-77 [PMID: 31860457 DOI: 10.1016/S2215-0366(19)30416-X]

Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiilsonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry 2020; 19: 61-68 [PMID: 31922669 DOI: 10.1002/wps.20699]

Vermeulen J, van Rooijen G, Doedens P, Numminen E, van Tricht M, de Haan L. Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis. Psychol Med 2017; 47: 2217-2228 [PMID: 28397632 DOI: 10.1017/S0033291717000873]

Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? World Psychiatry 2018; 17: 149-160 [PMID: 29855433 DOI: 10.1002/wps.20516]

Coen D. Body mass index in persons with schizophrenia. Can J Psychiatry 2001; 46: 549-555 [PMID: 11526812 DOI: 10.1177/070674370104600610]

Strassnig M, Brar JS, Ganguli R. Body mass index and quality of life in community-dwelling patients with schizophrenia. Schizophr Res 2003; 62: 73-76 [PMID: 12765746 DOI: 10.1016/s0920-9964(02)00441-3]

De Hert M, Correll CU, Bobes J, Cetkovick-Bakmas M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndetei DM, Newcomer JW, Uwakwe R, Leucht S. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011; 10: 52-77 [PMID: 21379357 DOI: 10.1002/wps.20516]

Thakore JH, Mann JN, Vlahos I, Martin A, Reznik R. Increased visceral fat distribution in drug-naïve and drug-free patients with schizophrenia. Int J Obes Relat Metab Disord 2002; 26: 137-141 [PMID: 11791159 DOI: 10.1038/sj.iob.0801840]

Foley DL, Morley KL. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch Gen Psychiatry 2011; 68: 609-616 [PMID: 21306937 DOI: 10.1001/archgenpsychiatry.2011.2]
Chang SC et al. Metabolic disturbances with antipsychotic drugs

31 Dasgupta A, Singh OP, Rout JK, Saha T, Mandal S. Insulin resistance and metabolic profile in antipsychotic naïve schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 1202-1207 [PMID: 20606470 DOI: 10.1016/j.pnpbp.2010.06.011]

32 American Diabetes Association. American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004; 65: 267-272 [PMID: 15003083 DOI: 10.4088/jcp.v65n0219]

33 Allison DB, Mentore JL, Heo M, Chandler LP, Cappellari JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1668-1696 [PMID: 10553730 DOI: 10.1176/appi.156.11.1686]

34 Rummel-Klug C, Komossa K, Schwarz H, Hunger H, Schmid F, Lobos CA, Kissling W, Davis JM, Leucht S. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010; 123: 225-233 [PMID: 20692814 DOI: 10.1016/j.schres.2010.07.012]

35 Park SC, Choi MY, Choi J, Park E, Tchoe HJ, Suk JK, Kim YH, Won SH, Chung YC, Bae KY, Lee SK, Park CM, Lee SH. Comparative Efficacy and Safety of Long-acting Injectable and Oral Second-generation Antipsychotics for the Treatment of Schizophrenia: A Systematic Review and Meta-analysis. Clin Psychopharmacol Neurosci 2018; 16: 361-375 [PMID: 30466208 DOI: 10.9785/cpn.2018.16.4.361]

36 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011; 8: 114-126 [PMID: 22009159 DOI: 10.1038/nrendo.2011.156]

37 Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat 2017; 13: 2221-2241 [PMID: 28883733 DOI: 10.2147/NDT.S136099]

38 Vandenberghe F, Gholam-Rezaee M, Saigí-Morgui N, Delacrétaz A, Choong E, Solida-Tozzi A, Kolly S, Thonney J, Gallo SF, Hedjai A, Ambresin AE, von Gunten A, Conus P, Eap CB. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. J Clin Psychiatry 2015; 76: e1417-e1423 [PMID: 26646038 DOI: 10.4088/JCP.14m09358]

39 Zafar U, Khalig S, AhmadHU, Manzoor S, Lone KP. Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links. Hormones (Athens) 2018; 17: 299-313 [PMID: 30171523 DOI: 10.1007/s42000-018-0051-3]

40 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15: 539-553 [PMID: 9686693 DOI: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S]

41 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults. JAMA 2001; 285: 2486-2497 [PMID: 11368702 DOI: 10.1001/jama.285.19.2486]

42 Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care 2004; 27: 1182-1186 [PMID: 15111542 DOI: 10.2337/diacare.27.5.1182]

43 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23: 469-480 [PMID: 16681555 DOI: 10.1111/j.1464-5491.2006.01858.x]

44 Canale MP, Manca di Villahermosa S, Martino G, Rovella V, Noce A, De Lorenzo A, Di Daniele N. Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity. Int J Endocrinol 2013; 2013: 865965 [PMID: 24288531 DOI: 10.1155/2013/865965]

45 Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophr Bull 2013; 39: 306-318 [PMID: 22207632 DOI: 10.1093/schbul/sbt145]

46 McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stoup T, Lieberman JA. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005; 80: 19-32 [PMID: 16137860 DOI: 10.1016/j.schres.2005.07.014]

47 Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005; 19 Suppl 1: 1-93 [PMID: 15998156 DOI: 10.2165/00023210-200519010-00001]

48 Vidalondo S, de Leeuw van Weenen JE, Frölich M, Roelfsema F, Romijn JA, Pijl H. Effects of olanzapine and haloperidol on the metabolic status of healthy men. J Clin Endocrinol Metab 2010; 95: 118-125 [PMID: 19906788 DOI: 10.1210/jc.2008-1815]

49 Albaugh VL, Singareddy R, Mauger D, Lynch CJ. A double blind, placebo-controlled, randomized crossover study of the acute metabolic effects of olanzapine in healthy volunteers. PLoS One 2011; 6: e22662 [PMID: 21857944 DOI: 10.1371/journal.pone.0022662]
Meltzer HY, Roth BL. H1-histamine receptor affinity predicts short-term weight gain for typical and episode psychosis. Association between symptom improvement and change of body mass index, lipid profile, and Basoglu C. Plasma orexin A, ghrelin, cholecystokinin, visfatin, leptin and agouti-related protein levels during 6-week olanzapine treatment in first-episode male patients with psychosis. O. Evans Tokushima Fatty (OLETF) rats.

Hegedűs C. The metabolic effects of chronic clozapine treatment on CCK-1 receptor deficient Otsuka Long H. Fleur SE, Adan RA. The acute effects of olanzapine on ghrelin secretion, CCK sensitivity, meal size, ingredients in obese individuals. Acta Endocrinol (Buchar) 2020; 16: 37-42 [PMID: 32685036 DOI: 10.4183/aeh.2020.37]

van der Zwaal EM, Chiu CC, Chen CH, Chen BY, Yu SH, Lu ML. The time-dependent change of insulin secretion in schizophrenic patients treated with olanzapine. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 866-870 [PMID: 20394794 DOI: 10.1016/j.pnpbp.2010.04.003]

Jin H, Meyer JM, Mudalair S, Jeste DV. Impact of atypical antipsychotic therapy on leptin, ghrelin, and adiponectin. Schizophr Res 2008; 100: 70-85 [PMID: 18260351 DOI: 10.1016/j.schres.2007.11.026]

Stubbs B, Wang AK, Vancampfort D, Miller BJ. Are leptin levels increased among people with schizophrenia vs controls? Psychoneuroendocrinology 2016; 63: 144-154 [PMID: 26444588 DOI: 10.1016/j.psyneuen.2015.09.026]

Endomba FT, Tankeu AT, Nkeck JR, Tochie JN. Leptin and psychiatric illnesses: does leptin play a role in antipsychotic-induced weight gain? Lipids Health Dis 2020; 19: 22 [PMID: 32033608 DOI: 10.1186/s12944-020-01203-x]

Bartoli F, Lax A, Crocanno C, Clerici M, Carra G. Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: a meta-analysis. Psychoneuroendocrinology 2015; 56: 179-189 [PMID: 25827962 DOI: 10.1016/j.psyneuen.2015.03.012]

Sapra M, Lawson D, Irannasheh A, Varma A. Adipsity-independent hypoapdointinemina as a potential marker of insulin resistance and inflammation in schizophrenia patients treated with second generation antipsychotics. Schizophr Res 2016; 174: 132-136 [PMID: 27211515 DOI: 10.1016/j.schres.2016.04.051]

Chen CY, Goh KK, Chen CH, Lu ML. The Role of Adiponectin in the Pathogenesis of Metabolic Disturbances in Patients With Schizophrenia. Front Psychiatry 2020; 11: 605124 [PMID: 33551872 DOI: 10.3389/fpsyg.2020.605124]

Wu TH, Chiu CC, Goh KK, Chen PY, Huang MC, Chen CH, Lu ML. Relationship between metabolic syndrome and acylated/desacylated ghrelin ratio in patients with schizophrenia under olanzapine medication. J Psychopharmacol 2020; 34: 86-92 [PMID: 31692408 DOI: 10.1177/0269881119885260]

Lu ML, Wang TN, Lin TY, Shao WC, Chang SH, Chou JY, Ho YF, Liao YT, Chen VC. Differential effects of olanzapine and clozapine on plasma levels of adipocytokines and total ghrelin. Prog Neuropsychopharmacol Biol Psychiatry 2015; 58: 47-50 [PMID: 25496829 DOI: 10.1016/j.pnpbp.2014.12.001]

Chen VC, Chen CH, Chiu YH, Lin TY, Li FC, Lu ML. Leptin/Adiponectin ratio as a potential biomarker for metabolic syndrome in patients with schizophrenia. Psychoneuroendocrinology 2018; 92: 34-40 [PMID: 29625373 DOI: 10.1016/j.psyneuen.2018.03.021]

Rani M, Kumar R, Krishan P. Role of orexins in the central and peripheral regulation of glucose homeostasis: Evidences & mechanisms. Neuropeptides 2018; 68: 1-6 [PMID: 29472002 DOI: 10.1016/j.npep.2018.02.002]

Chen PY, Chen CH, Chang CK, Kao CF, Lu ML, Lin SK, Huang MC, Hwang LL, Mondelli V. Orexin-A Levels in Relation to the Risk of Metabolic Syndrome in Patients with Schizophrenia Taking Antipsychotics. Int J Neuropsychopharmacol 2019; 22: 28-36 [PMID: 30204875 DOI: 10.1093/ijn/pyy075]
atypical antipsychotic drugs. *Neuropsychopharmacology* 2003; 28: 519-526 [PMID: 12629531 DOI: 10.1038/sj.ijz.55130027].

70. Panariello F, De Luca V, de Bartolomeis A. Weight gain, schizophrenia and antipsychotics: new findings from animal model and pharmacogenomic studies. *Schizophr Res Treatment* 2011; 2011: 459284 [PMID: 22985055 DOI: 10.1155/2011/459284].

71. MacNeil RR, Müller DJ. Genetics of Common Antipsychotic-Induced Adverse Effects. *Mol Neuropharmacology* 2016; 2: 61-78 [PMID: 2760321 DOI: 10.1159/000445802].

72. Reynolds GP, McGowan OO. Mechanisms underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol* 2017; 31: 1430-1436 [PMID: 28892404 DOI: 10.1177/0269881117722987].

73. Baptista T, Parada M, Hernandez L. Long term administration of some antipsychotic drugs increases body weight and feeding in rats. Are D2 dopamine receptors involved? *Pharmacol Biochem Behav* 1987; 27: 399-405 [PMID: 2889218 DOI: 10.1016/0091-3057(87)90340-6].

74. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment—pharmacological mechanisms. *Pharmacol Ther* 2010; 125: 169-179 [PMID: 19931306 DOI: 10.1016/j.pharmthera.2009.10.010].

75. Wang T, Lu J, Xu Y, Li M, Sun J, Zhang J, Xu B, Xu M, Chen Y, Bi Y, Wang W, Ning G. Circulating prolactin associates with diabetes and impaired glucose regulation: a population-based study. *Diabetes Care* 2013; 36: 1974-1980 [PMID: 23340889 DOI: 10.2337/dc12-1893].

76. Ben-Jonathan N, Hugo ER, Brandeis TD, LaPensee CR. Focus on prolactin as a metabolic hormone. *Trends Endocrinol Metab* 2006; 17: 110-116 [PMID: 16517173 DOI: 10.1016/j.tem.2006.02.005].

77. Johnson DE, Yamaazaki H, Ward KM, Schmidt AW, Lebel WS, Treadway JL, Gibbs EM, Zawalich WS, Rollena H. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perfused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. *Diabetes* 2005; 54: 1552-1558 [PMID: 15855345 DOI: 10.2337/diabetes.54.5.1552].

78. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find Exp Clin Pharmacol* 2005; 27: 289-304 [PMID: 16082416 DOI: 10.1088/sf.mf.2005.27.5.908643].

79. Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain: insights into mechanisms of action. *CNS Drugs* 2011; 25: 1035-1059 [PMID: 22133326 DOI: 10.2165/11596300-000000000-00000].

80. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 2012; 17: 242-266 [PMID: 21894153 DOI: 10.1038/mp.2011.109].

81. Kuo PH, Kao CF, Chen CH, Tsai YS, Lu ML, Huang MC. Polymorphisms of INSIG2, MC4R, and LEP are associated with obesity- and metabolic-related traits in schizophrenic patients. *J Clin Psychopharmacol* 2011; 31: 705-711 [PMID: 22020349 DOI: 10.1097/CPJ.0b013e3182346e84].

82. Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, Liu Y, Cheng K, Zhou C, Wang H, Zhou X, Gui S, Perry SW, Wong ML, Licinio J, Wei H, Xie P. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. *Sci Adv* 2019; 5: eaau8317 [PMID: 30775438 DOI: 10.1126/sciadv.aau8317].

83. Kanji S, Gorbovskaya I, Fonseka T, Yoshida K, Marshe V, MacKenzie M, Bercik P, Verdu E, Hahn MK, Müller DJ. Genetics of Common Antipsychotic-Induced Adverse Effects. *Mol Psychiatry* 2018; 23: 1715-1725 [PMID: 29555994 DOI: 10.1038/mp.2018.110].

84. Zeng C, Yang P, Cao T, Gu Y, Li N, Zhang B, Xu P, Liu Y, Luo Z, Cai H. Gut microbiota: An intermediary between metabolic syndrome and cognitive deficits in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; 106: 110097 [PMID: 32916223 DOI: 10.1016/j.pnpbp.2020.110097].

85. Skonieczna-Zadecka K, Loniewski I, Misera A, Stachowska E, Maciejewska D, Marlicz W, Gailing B. Generation antipsychotics and metabolism alterations: a systematic review of the role of the gut microbiome. *Psychopharmacology (Berl)* 2019; 236: 1491-1512 [PMID: 30460516 DOI: 10.1007/s00213-018-5102-6].

86. Maier I, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, Fernandes KC, Ho, Mori H, Patil KR, Bork P, Tyapas A. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 2018; 555: 623-628 [PMID: 29555994 DOI: 10.1038/nature25979].

87. Fonseka TM, Müller DJ, Kennedy SH. Inflammatory Cytokines and Antipsychotic-Induced Weight Gain: Review and Clinical Implications. *Mol Psychiatry* 2016; 2: 1-14 [PMID: 27606316 DOI: 10.1105/000441521].

88. Gebhardt S, Haberhausen M, Heinzl-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, Hebebrand J, Theisen FM. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. *J Psychiatr Res* 2009; 43: 620-626 [PMID: 19110264 DOI: 10.1016/j.jpsychires.2008.11.001].

89. Correll CU, Lenz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med* 2011; 17: 97-107 [PMID: 21185230 DOI: 10.1016/j.molmed.2010.10.010].
91 Lan TH, Loh EW, Wu MS, Hu TM, Chou P, Lan TY, Chiu HJ. Performance of a neuro-fuzzy model in predicting weight changes of chronic schizophrenic patients exposed to antipsychotics. *Mol Psychiatry* 2008; 13: 1129-1137 [PMID: 18180752 DOI: 10.1038/sj.mp.4002128]

92 De Hert M, Dekker JM, Wood D, Kahl KG, Holt RJ, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009; 24: 412-424 [PMID: 19682863 DOI: 10.1016/j.eurpsy.2009.01.005]

93 Cooper SJ, Reynolds GP; With expert co-authors (in alphabetical order), Barnes T, England E, Haddad PM, Head A, Holt R, Lingford-Hughes A, Osborn D, McGowan O, Patel MX, Paton C, Reid P, Shiers D, Smith J. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol* 2016; 30: 717-748 [DOI: 10.1177/0269881116645254]

94 Lin CC, Bai YM, Chen JY, Hwang TJ, Chen TT, Chiu HW, Li YC. Easy and low-cost identification of metabolic syndrome in patients treated with second-generation antipsychotics: artificial neural network and logistic regression models. *J Clin Psychiatry* 2010; 71: 225-234 [PMID: 19814949 DOI: 10.4088/JCP.08m04628yel]

95 Riordan HJ, Antonini P, Murphy MF. Atypical antipsychotics and metabolic syndrome in patients with schizophrenia: risk factors, monitoring, and healthcare implications. *Am Health Drug Benefits* 2011; 4: 292-302 [PMID: 25126357]

96 National Collaborating Centre for Mental Health (UK). *Psychosis and Schizophrenia in Adults: Treatment and Management: Updated Edition 2014*. London: National Institute for Health and Care Excellence (UK), 2014 [PMID: 25340235]

97 Chen CK, Chen YC, Huang YS. Effects of a 10-week weight control program on obese patients with schizophrenia or schizoaffective disorder: a 12-month follow up. *Psychiatry Clin Neurosci* 2009; 63: 17-22 [PMID: 19067957 DOI: 10.1111/j.1440-1819.2008.01836.x]

98 Bonfioli E, Berti L, Goss C, Muraro F, Burti L. Health promotion lifestyle interventions for weight management in psychosis: a systematic review and meta-analysis of randomised controlled trials. *BMC Psychiatry* 2012; 12: 78 [PMID: 22789023 DOI: 10.1186/1471-244X-12-78]

99 Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database Syst Rev* 2010; CD006629 [DOI: 10.1002/14651858.CD006629.pub2]

100 de Silva VA, Suraweeva C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry* 2016; 16: 341 [DOI: 10.1186/s12888-016-1049-5]

101 Zhou J, Massey S, Story D, Li L. Metformin: An Old Drug with New Applications. *Int J Mol Sci* 2018; 19: 2863 [PMID: 30241400 DOI: 10.3390/ijms19102863]

102 Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, He YQ, Liu YJ, Chen JD, Li LH. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* 2008; 299: 185-193 [PMID: 18182600 DOI: 10.1001/jama.2007.56-b]

103 Hahn MK, Cohn T, Teo C, Remington G. Topiramate in schizophrenia: a review of effects on psychopathology and metabolic parameters. *Clin Schizophr Relat Psychoses* 2013; 6: 186-196 [PMID: 23302448 DOI: 10.3371/CSRP.HACO.01062013]

104 Johannesen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008; 22: 27-47 [PMID: 18072813 DOI: 10.2165/00022310-200822010-00003]

105 Goh KK, Chen CH, Lu ML. Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. *Int J Psychiatry Clin Pract* 2019; 23: 14-32 [PMID: 29557263 DOI: 10.1080/13651501.2018.1449864]

106 Blanpied TA, Clarke RJ, Johnson JW. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. *J Neurosci* 2005; 25: 3312-3322 [PMID: 15800186 DOI: 10.1523/JNEUROSCI.4262-04.2005]

107 Zheng W, Wang S, Ungvari GS, Ng CH, Yang XH, Gu YH, Li M, Xiang YQ, Xiang YT. Amantadine for Antipsychotic-Related Weight Gain: Meta-Analysis of Randomized Placebo-Controlled Trials. *J Clin Psychopharmacol* 2017; 37: 341-346 [PMID: 28383359 DOI: 10.1097/JCP.0000000000000591]

108 Vancampfort D, Firth J, Correll CU, Solmi M, Siskind D, De Hert M, Carney R, Koyanagi A, Carvalho AF, Gaughran F, Stubbs B. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* 2019; 18: 53-66 [PMID: 30600626 DOI: 10.1002/wps.20614]

109 Ijaz S, Bolea B, Davies S, Savović J, Richards A, Sullivan S, Moran P. Antipsychotic polypharmacy and metabolic syndrome in schizophrenia: a review of systematic reviews. *BMC Psychiatry* 2018; 18: 275 [PMID: 30176844 DOI: 10.1186/s12888-018-1848-y]

110 Mendoza MC, Lindemayer JP. N-desmethylclozapine: is there evidence for its antipsychotic potential? *Clin Neuropharmacol* 2009; 32: 154-157 [PMID: 19483482 DOI: 10.1097/01.wnf.0b013e31818d4675]

111 Lu ML, Chen TT, Kuo PH, Hsu CC, Chen CH. Effects of adjunctive fluvoxamine on metabolic disturbance...
parameters and psychopathology in clozapine-treated patients with schizophrenia: A 12-week, randomized, double-blind, placebo-controlled study. Schizophr Res 2018; 193: 126-133 [PMID: 28688742 DOI: 10.1016/j.schres.2017.06.030]

O’Mahoney LL, Matu J, Price OJ, Birch KM, Ajjan RA, Farrar D, Tapp R, West DJ, Deighton K, Campbell MD. Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: a meta-analysis and meta-regression of randomized controlled trials. Cardiovasc Diabetol 2018; 17: 96 [PMID: 29981570 DOI: 10.1186/s12933-018-0740-6]

Albracht-Schulte K, Kalupahana NS, Ramalingam L, Wang S, Rahman SM, Robert-McComb J, Moustaid-Moussa N. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. J Nutr Biochem 2018; 58: 1-16 [PMID: 29621669 DOI: 10.1016/j.jnutbio.2018.02.012]

Goh KK, Chen CY, Chen CH, Lu ML. Effects of omega-3 polyunsaturated fatty acids supplements on psychopathology and metabolic parameters in schizophrenia: A meta-analysis of randomized controlled trials. J Psychopharmacol 2021; 35: 221-235 [PMID: 33586517 DOI: 10.1177/0269881120981392]

Modabbernia A, Heidari P, Soleimani R, Sobhani A, RoshanZA, Taslimi S, Ashrafi M, Modabbernia MJ. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J Psychiatr Res 2014; 53: 133-140 [PMID: 24607293 DOI: 10.1016/j.jpsychires.2014.02.013]

Agahi M, Akasheh N, Ahmadvand A, Akbari H, Izadpanah F. Effect of melatonin in reducing second-generation antipsychotic metabolic effects: A double blind controlled clinical trial. Diabetes Metab Syndr 2018; 12: 9-15 [PMID: 28847468 DOI: 10.1016/j.dsx.2017.08.004]

Romo-Nava F, Alvarez-Icaza Gonzalez D, Fresán-Orellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord 2014; 16: 410-421 [PMID: 24636483 DOI: 10.1111/bdi.12196]

Duan C, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. World J Psychiatr 2021; 11: 463-476 [DOI: 10.5498/wjp.v11.i8.463]

Wu CS, Gau SS. Association Between Antipsychotic Treatment and Advanced Diabetes Complications Among Schizophrenia Patients With Type 2 Diabetes Mellitus. Schizophr Bull 2016; 42: 703-711 [PMID: 26721264 DOI: 10.1093/schbul/sbv187]

Raben AT, Marsh VS, Chintoh A, Gorbovskaya I, Müller DJ, Hahn MK. The Complex Relationship between Antipsychotic-Induced Weight Gain and Therapeutic Benefits: A Systematic Review and Implications for Treatment. Front Neurosci 2017; 11: 741 [PMID: 29403343 DOI: 10.3389/fnins.2017.00741]
