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Abstract

Although clozapine, olanzapine, and other atypical antipsychotic drugs (APDs) have fewer extrapyramidal side effects, they have serious metabolic side effects such as substantial weight gain, intra-abdominal obesity, and type 2 diabetes mellitus. Given that most patients with mental disorders face chronic, even life-long, treatment with APDs, the risks of weight gain/obesity and other metabolic symptoms are major considerations for APD maintenance treatment. This review focuses on the effects of APDs on weight gain, appetite, insulin resistance, and glucose dysregulation, and the relevant underlying mechanisms that may be help to prevent and treat metabolic side effects caused by APD therapy.

Keywords

weight, insulin, effects, resistance, antipsychotic, medications, appetite

Disciplines

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Effects of Anti-psychotic Medications on Appetite, Weight, and Insulin resistance

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Conflict of Interest:

Nil

KEYWORDS

- Anti-psychotic
- Appetite
- Obesity
- Weight gain
- Insulin Resistance

- glucose dysregulation

KEY POINTS

- Although some atypical anti-psychotic drugs, particularly olanzapine and clozapine, have more severe weight gain side-effects, all anti-psychotics including typical anti-psychotics currently used clinically may cause some degree of weight gain.
- There are time-dependent changes of weight gain associated with anti-psychotic medication with a three stage time-course development; particularly rapid weight gain in the initial stage is a good indicator for a long-term outcome of weight gain and obesity.
- Accumulated data suggest that increasing appetite and food intake, as well as delayed satiety signalling, are key behavioural changes related to weight gain/obesity induced by anti-psychotics.
- Anti-psychotics may induce insulin resistance, glucose dysregulation, and even type II diabetes mellitus independent of weight gain and adiposity.
- There are also time-dependent changes for insulin and glucose dysregulation associated with anti-psychotic medication.
- Current evidence from clinical trials in first episode psychotic patients shows typical anti-psychotics such as haloperidol have relatively high risk for weight gain/obesity and glucometabolic side-effects.

- Monitoring weight gain is important but not enough. A periodic monitoring of blood sugar may also be required during anti-psychotic therapy, particularly for drugs with high diabetic liabilities such as olanzapine and clozapine.
- There are marked individual variations in weight gain and other metabolic side-effects associated with anti-psychotics. For example, irrespective of the anti-psychotic drug, some patients lose weight, some maintain weight and some gain weight.
- Mechanisms for anti-psychotic related weight gain, insulin resistance and glucose dysregulation have yet to be elucidated. Current results suggest that antagonistic effects of atypical anti-psychotics on serotonin 5-HT_{2C} and histamine H₁ receptors play an important role in weight gain/obesity side-effects, whereas muscarinic M₃ receptors have been identified as most closely linked with diabetic side-effects. However, blockade of dopamine D₂ receptors may be a common mechanism for these metabolic side-effects in both atypical and typical anti-psychotics.

INTRODUCTION

Mental disorders are the greatest overall cause of disability.¹ Anti-psychotic drugs (APDs) are the most widely prescribed medications and are used frequently to control various mental disorders such as schizophrenia, bipolar disorder, dementia, major depression, Tourette's syndrome, eating disorders and even substance abuse.^{2, 3} Unfortunately, APDs may cause some serious side-effects including extra-pyramidal and metabolic side-effects. Since typical APDs were introduced into clinics in the 1950s, their side-effects of increasing body weight have been reported, but have gained less attention because these drugs often have worse and problematic extra-pyramidal side-effects.⁴ In the 1980s-1990s, clozapine, olanzapine and other atypical APDs with reduced extra-pyramidal side-effects were widely introduced into psychiatric clinics and currently form the first line of APD treatment.^{5, 6} Unfortunately, atypical APDs, particularly clozapine and olanzapine, cause serious metabolic side-effects, such as substantial weight gain, intra-abdominal obesity, hyperlipidemia, insulin resistance, hyperglycemia, and type II diabetes mellitus (T2DM).⁷⁻¹⁰ These adverse effects are a major risk for cardiovascular disease, stroke and premature death (by 20-30 years).^{7, 11} In addition to medical consequences, weight gain and obesity can lead to non-compliance with medication - a primary problem for the treatment of schizophrenia, since cessation of APD treatment dramatically (up to 5-times) increases the relapse rate for these patients.^{12, 13} Given that the majority of patients with psychiatric disorders face chronic, even life-long, treatment with APDs, the risks of weight gain/obesity and other metabolic symptoms are major considerations for individual APD maintenance treatment. This review will focus on the effects of APDs on weight gain, appetite, insulin resistance and glucose dysregulation, as well as relevant underlying mechanisms that may be help to prevent

and treat weight gain, obesity, and other metabolic side-effects caused by APD therapy.

WEIGHT GAIN AND OBESITY INDUCED BY ANTI-PSYCHOTICS

Weight gain/obesity side-effects: Typical vs Atypical APDs. It had been reported since the 1950s that treatment with some typical APDs (such as chlorpromazine) is associated with weight gain, however many psychiatrists still believe that atypical APDs are associated with significant weight gain and obesity side-effects, but typical APDs are not.¹⁴ For example, the commonly used typical APD, haloperidol, was once believed to have a minimal weight gain side-effect.¹⁴ However, a recent report on the European First-Episode Schizophrenia Trial (EUFEST) has clearly shown that one year treatment with haloperidol caused clinically significant weight gain ($\geq 7\%$ from baseline) in 53% of patients, with an average weight gain of 7.3 kg.¹⁵ A dramatic weight gain (9.56 kg) was also observed in another study of first episode patients with 1 year treatment with haloperidol.¹⁶ Therefore, while certain atypical APDs (such as olanzapine and clozapine) might lead to greater weight gain, typical APDs could also lead to significant weight and other metabolic changes in patients.

Underestimation of weight gain and obesity side-effects has also been the case for atypical APDs. In 2005, the NIH funded CATIE (The Clinical Anti-psychotic Trials of Intervention Effectiveness) study reported the effects of atypical APDs olanzapine, quetiapine, risperidone and ziprasidone on body weight over an 18 months period in chronic schizophrenia patients who had an average of over 14 years' APD medication history.¹⁷ The CATIE study found that olanzapine treatment caused significant weight gain ($\geq 7\%$ from baseline) in a higher proportion of patients (30%) than quetiapine

(16%), risperidone (14%) and ziprasidone (7%). Patients treated with olanzapine also gained more weight (average add 0.9 kg (2 lb) per month) than patients treated with quetiapine (average add 0.23 kg (0.5 lb) per month) and risperidone (average add 0.18 kg (0.4 lb) per month), while ziprasidone treated patients lost body weight (average lose 0.14 kg (-0.3 lb) per month).¹⁷ However, the subsequent EUFEST and CAFE (Comparison of Atypical Anti-psychotics for First Episode) studies showed that these atypical APDs caused more severe weight gain in first episode schizophrenia patients.^{15, 18} The CAFE study reported that after a 12 week treatment, significant weight gain ($\geq 7\%$ body weight) occurred in a large number of first episode schizophrenia patients treated with olanzapine (59.8%), compared to risperidone (32.5%) and quetiapine (29.2%). Furthermore, after 52 weeks' treatment, 80% of olanzapine-treated patients gained $\geq 7\%$ body weight (with an average 1.76 kg (3.88 lb) per month), compared to 57.6% of risperidone- (with an average 1.28 kg (2.81 lb) per month) and 50% of quetiapine-treated (with an average 1.29 kg (2.85 lb) per month) patients.¹⁸ The EUFEST study confirmed that, after 12 months' treatment, olanzapine caused the most significant weight gain in first episode schizophrenia (in 86% of patients with an average 1.16kg (2.56 lb) per month) compared to quetiapine (in 65% of patients with an average 0.88kg (1.94 lb) per month), amisulpride (in 63% of patients with an average 0.81kg (1.78 lb) per month) and ziprasidone (in 37% of patients with an average 0.4 kg (0.88 lb) per month).¹⁵ In another study of first episode patients, dramatic weight gain was observed in all olanzapine (average 12.02 kg), risperidone (8.99kg) and haloperidol (9.56kg) treatment for 1 year.¹⁶ It is interesting that ziprasidone and amisulpride have been widely regarded as atypical APDs with low weight gain risk in previous studies;¹⁰ ziprasidone was even found to cause weight loss in the CATIE study.¹⁷ Therefore, it is worth exploring why a lesser

weight gain side-effect was observed in the CATIE study. The main difference between these studies was that subjects in the CATIE study had a chronic APD medication history (average over 14 years) compared to first episode patients in the EUFEST and CAFE without previous APD medication.^{15, 17, 18} These clinical trials indicate that previous studies on chronic schizophrenia patients may have underestimated the magnitude of weight gain/obesity side-effects associated with APDs. Furthermore, although mean weight gain and the incidence of clinically significant weight gain may vary between APDs, olanzapine and clozapine have the highest risk; accumulated evidence indicates that both typical and atypical APDs have greater weight gain and other metabolic side-effects than placebo-level effects.^{9, 10, 15}

Time-course of APD-induced weight-gain/obesity. Although various APDs cause weight gain at different magnitudes, both typical and atypical APDs exhibit a similar temporal course of weight gain that includes three stages: Stage 1, an early acceleration stage in which APDs induce a rapid increase in body weight gain within the first few months of treatment (e.g. about 3 months for clozapine, olanzapine, risperidone, and haloperidol); Stage 2, a middle stage in which body weight continues to increase at a much steadier rate for at least the period of a year or longer; and Stage 3, further treatment will lead to a plateau of weight gain, representing a possible ‘ceiling effect’ of APDs, in which patients will maintain the heavier weight with on-going APD treatment.^{19, 20} For example, first episode psychosis patients treated with olanzapine or haloperidol gained weight rapidly during the first 12 weeks (mean \pm SD: olanzapine, 9.2 \pm 5.31 kg; haloperidol, 3.7 \pm 4.9 kg), then continued to gain weight till a plateau was reached (olanzapine, 15.5 \pm 9.6 kg; haloperidol, 7.1 \pm 6.7 kg) at approximately 1 year and weight gain remained at this high level (olanzapine,

15.4±10.0 kg; haloperidol, 7.5±9.2 kg) at the end of 2 years.²⁰ The BMI changes during the 2 year study period followed a pattern similar to that for weight gain; in the olanzapine group the mean BMI increased from 23.6±4.8 (Mean ± SD) at the baseline to 26.4±4.6 at 12 weeks, 28.8±4.5 at 1 year, and 28.3±4.0 at 2 years, compared with haloperidol group with an increase from 23.9±4.5 at the baseline to 24.8±4.1 at 12 weeks, 26.2±4.3 at 1 year and 26.6±4.4 at 2 years.²⁰ Several long-term studies indicate that some APDs may take a much longer time to reach the plateau.^{19, 21, 22} This temporal course is well mimicked in an animal model of olanzapine-induced weight gain.^{23,24} Although the final weight plateau is often reached after several years, accumulated evidence indicates that rapid weight-gain in the first few weeks (Stage 1) of APD treatment is a strong indicator for the long-term outcome of weight gain and obesity.²⁵⁻²⁷ Therefore, although the time-course of weight gain has been observed to have a similar pattern in various APDs, the exact weight gain time-course induced by a specific APD still remains for further research.

Are weight-gain and obesity side-effects of APD dose dependant? To date, the possible relationship between APD dosages and associated weight gain has not been systematically investigated. Simon and colleagues reviewed publications between 1975 and 2008 and suggested that olanzapine and clozapine appear to have dose/serum concentration-dependant weight gain side-effects.²⁸ For example, Perry and colleagues reported associations of weight gain with both olanzapine dosages and plasma concentrations.²⁹ More recently, in an 8-week, randomized clinical trial of olanzapine 10, 20, and 40 mg (oral) doses in 634 patients with schizophrenia or schizoaffective disorder, a significant dose-related change in weight gain was found, which suggested higher than standard doses of olanzapine may be associated with

greater weight gain compared to standard doses.³⁰ This was supported by a study into long-acting olanzapine injection, in which clear dose-dependent changes of weight gain were observed; a high dose (300mg every 2 weeks) had a higher weight gain than medium (405 mg every 4 weeks) and low (150 mg every 2 weeks) doses in schizophrenia patients.³¹ Risperidone-induced weight gain could be dose related to some extent but data are contradictory, while no study assessed risperidone serum concentrations in association with weight gain.²⁸ Current evidence indicates that other APDs including aripiprazole, amisulpride, quetiapine, sertindole and ziprasidone have no dose-related metabolic effects, however no study assessed serum concentration of these APDs.²⁸ Therefore, prescribing the lowest possible effective doses, at least for clozapine, olanzapine and risperidone, will be helpful in minimising the weight gain side-effect.

THE EFFECTS OF ANTI-PSYCHOTIC MEDICATION ON APPETITE/FOOD INTAKE

Theoretically, body weight gain results from imbalance between energy intake and energy expenditure, in which both over eating and/or less energy expenditure (such as decreasing resting metabolism and activity) may contribute to overweight and obesity. Over the past 15 years, accumulated data from both clinical and animal studies suggest that increasing appetite and food intake, as well as delayed satiety signalling, are key behavioural changes related to APD-induced weight gain/obesity.³²⁻³⁴ On the other hand, there is less understanding of to what extent changes of resting metabolism rate and activity/sedation affect weight gain associated with APD medication, although current evidence suggests that they may play an important role in the development of APD-induced weight gain.^{19, 35, 36}

Altered eating behaviours have been reported in a number of clinical studies with treatment involving various APDs. Gothelf and colleagues first reported that increased food intake, but not resting energy expenditure and physical activity, was associated with olanzapine-induced weight gain in schizophrenia patients.³⁷ A randomized double-blind study has found that both clozapine and olanzapine are associated with food craving and binge eating over the 6-week treatment period.³⁸ Compared to those with clozapine, patients receiving olanzapine tended to have higher rates of food craving (olanzapine 48.9% vs clozapine 23.3%) and binge eating (olanzapine 16.7% vs clozapine 8.9%), which also occurred earlier (1 week vs 3 weeks for binge eating).³⁸ Eating behaviour in patients treated with atypical APDs (clozapine, olanzapine, risperidone, quetiapine or ziprasidone) were also compared with health controls by recording appetite sensation before and after a standardized breakfast using visual analogy scales, and found that: (1) atypical APD-treated patients showed greater adiposity and a higher degree of hunger following the standardized breakfast; and (2) patients had significantly higher cognitive dietary restraint, disinhibition, and susceptibility to hunger than controls.³³ The patients treated with atypical APDs were also more reactive to external eating cues.³⁴ Furthermore, a recent study reported that, consistent with the significant increase of body weight, food consumption and disinhibited eating, one week treatment with olanzapine enhanced both the anticipatory and consummatory reward response to food rewards in the brain reward circuitry, including the inferior frontal cortex, striatum and anterior cingulate cortex, but decreased activation in the brain region (the lateral orbital frontal cortex) thought to inhibit feeding behaviour.³⁹

These clinical findings are confirmed in animal studies that APD-induced hyperphagia is repeatedly found in animal models of APD-induced weight gain.^{23, 40-43} Furthermore, recently olanzapine has been found to selectively increase rat's responding to sucrose pellets in an operant conditioning without affecting free-feeding intake of sucrose; in contrast sibutramine (a noradrenaline/serotonin reuptake inhibitor and a weight reducing agent) prevented the increase of rat's responding to sucrose pellets induced by olanzapine.⁴⁴ It has been well established that the hypothalamic arcuate nucleus (Arc) plays a crucial role in appetite and energy homeostasis through activation of two distinct populations of anorexigenic and orexigenic neurons: neurons that express appetite inhibiting cocaine- and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC), and neurons that express appetite stimulating agouti-related peptide (AgRP) and neuropeptide Y (NPY).⁴⁵ Using the animal model for olanzapine-induced weight gain, it has been revealed that olanzapine elevated expression of appetite stimulating AgRP and NPY and decreased appetite inhibiting POMC.^{46, 47} These results suggest that patients treated with APDs may develop abnormal eating behaviours in response to altered appetite sensations and increased susceptibility to hunger which may lead to a positive energy balance and contribute to body weight gain.

INSULIN RESISTANCE, GLUCOSE DYSREGULATION, AND DIABETES ASSOCIATED WITH ANTI-PSYCHOTIC MEDICATION

Effects of atypical APDs. Validated evidence over the past 20 years has indicated that APD medication significantly increases the risk of insulin resistance, glucose dysregulation and the development of T2DM.^{5, 48, 49} Although patients with psychiatric disorders such as schizophrenia have been observed to have an increased

risk of developing diabetes regardless of antipsychotics, suggesting that the disease itself may be a predisposed risk factor,⁵⁰⁻⁵² APD medication has been widely recognized as a main contributor for these metabolic disorders.^{48, 49} An analysis of the US FDA Adverse Event database also showed that adjusted report ratios for T2DM were the following: olanzapine 9.6 (95% confidence interval (CI) 9.2-10.0), risperidone 3.8 (3.5-4.1), quetiapine 3.5 (3.2-3.9), clozapine 3.1 (2.9-3.3), ziprasidone 2.4 (2.0-2.9), aripiprazole 2.4 (1.9-2.9), and haloperidol 2.0 (1.7-2.3), which suggests differential risks of diabetes across various APDs.⁵³

Owing to relatively short trial periods, many clinical trials have not been able to capture most new cases of diabetes, however numerous studies have shown strong relationships between APDs and indicators of insulin resistance and glucose dysregulation.^{48, 54} In the CATIE study in chronic schizophrenia patients, fasting blood glucose (FBG) was most elevated compared to baseline with olanzapine (15.0±2.8 mg/dl; mean ± standard error), followed by quetiapine (6.8±2.5 mg/dl), risperidone (6.7±2.0 mg/dl), perphenazine (5.2±2.0 mg/dl), and least elevated with ziprasidone (2.3±3.9 mg/dl).¹⁷ The EUFEST study has reported a similar incident rate of hyperglycemia among various APDs after one year treatment with haloperidol (18%), amisulpride (21%), olanzapine (30%), quetiapine (22%) and ziprasidone (22%), with a significant increase of fasting insulin level (haloperidol 2.0±1.4 mU/L, amisulpride 8.6±3.1 mU/L, olanzapine 2.5±3.9 mU/L, quetiapine 2.1±1.2 mU/L and ziprasidone 0.1±2.0 mU/L).¹⁵ Chronically elevated insulin levels and concurrent hyperglycemia are consistent with insulin resistance, and may indicate T2DM.⁵⁵ In fact, numerous clinical studies have reported that chronic APD treatment increases insulin-resistance. Using the homeostasis model assessment (HOMA) index for

insulin resistance (HOMA-IR), chronic (8 weeks to 5 months) treatment with olanzapine, clozapine and risperidone has been repeatedly reported to significantly increase HOMA-IR,⁵⁶⁻⁶¹ although risperidone was normally observed to have a lesser effect on HOMA-IR.^{58, 60, 61} Furthermore, patients with chronic olanzapine treatment also showed a greater decrease in insulin sensitivity during an oral glucose tolerance test (OGTT) than those treated with risperidone.⁶¹ Using a frequently sampled intravenous glucose tolerance test and minimal model analysis, significant insulin resistance and impairment of glucose effectiveness were reported in non-obese patients chronically treated with clozapine and olanzapine, but with a lesser effect in patients treated with risperidone and quetiapine.^{62, 63} Recently, a two-step euglycaemic, hyperinsulinaemic clamp procedure has been used to assess changes in insulin sensitivity in non-diabetic patients with schizophrenia or schizoaffective disorder treated with olanzapine or risperidone; it was found that both olanzapine and risperidone treatment caused a decrement in insulin sensitivity.⁵⁹ These results were confirmed in numerous animal studies using the HOMA-IR index or euglycaemic/hyperinsulinaemic clamp procedures: chronic treatment with olanzapine and clozapine caused insulin resistance, reduced insulin sensitivity and glucose dysregulation.⁶⁴⁻⁶⁸

The effects of APDs using haloperidol as an example. Although over the past 15 years the metabolic side-effects of atypical APDs have attracted most of the attention, there is evidence that treatment with some typical APDs also increases the risk of insulin resistance, glucose dysregulation and T2DM.^{11, 49, 69, 70} Since they were introduced to the clinics in the 1950s, chlorpromazine and thioridazine have been repeatedly reported to cause abnormal glucose tolerance, insulin resistance and even

T2DM.⁷⁰⁻⁷⁶ On the other hand, it was generally believed that haloperidol did not increase the risk of insulin resistance and T2DM,⁴⁹ however recent evidence from clinical trials in first episode patients showed that haloperidol may have a higher risk than originally thought. As discussed above, the EUFEST study has reported that one year treatment of haloperidol has a similar incident rate of hyperglycemia and increased fasting insulin levels to atypical APDs olanzapine and quetiapine.¹⁵ Another randomized, double-blind trial in first episode schizophrenia patients also found that both FBG and 2 hour post-prandial blood glucose (PPBG) were significantly increased by a 6-week treatment with haloperidol (FBG, 6.8±14.1/dl, mean ± standard deviation; PPBS, 6.7±12.6 mg/dl), olanzapine, (FBG, 6.6±12.7mg/dl; PPBS, 21.5±32.2 mg/dl) and risperidone (FBG, 4.3±12.5 mg/dl; PPBS, 21.0±23.4 mg/dl), with a similar incidence rate of diabetes induced by APD treatment (haloperidol 9.7%, olanzapine 11.4%, risperidone 9.1%) by WHO criteria.⁶⁹ A one year treatment of haloperidol in drug-naïve first episode patients showed a similarly increased insulin level and insulin resistance index (HOMA-IR) as olanzapine and risperidone.⁷⁷ Analyzing data from the Italian Health Search Database also showed that, in initially non-diabetic and APD-free patients, the diabetic risk ratios were 12.4% (95% CI 6.3-24.5) for haloperidol, 18.7% (8.2-42.8) for risperidone, 20.4% (6.9-60.3) for olanzapine, 33.7% (9.2-123.6) for quetiapine, and no significant difference between various drug groups.⁷⁸ These findings were confirmed by a large population-based study conducted in Denmark, which included 345,937 patients treated with an APD and 1,426,488 unexposed control subjects: a significantly higher relative risk compared with the general population was observed in drug-naïve patients treated with olanzapine (1.35, 95% CI 1.18-1.54), risperidone (1.24, 95% CI 1.09-1.40), sertindole (9.53, 95% CI 1.34-67.63), perphenazine (1.60, 95% CI 1.45-1.77),

ziprasidone (3.09, 95% CI 1.54-6.17), and haloperidol (1.32, 95% CI 1.17-1.49), but not in patients treated with aripiprazole, amisulpride or quetiapine.⁷⁹ These results suggest that treatment with haloperidol, like chlorpromazine and thioridazine, is associated an increased risk of glucose and insulin deregulation.

Indirect effects of APD-induced weight gain and obesity vs direct effects of APDs

on insulin resistance and glucose dysregulation. Given the well-established association between obesity and insulin resistance and hyperglycemia, APD-induced dysregulation of glucose homeostasis has been frequently linked to the high weight gain and obesity propensity of these drugs. For example, many studies have found the increased HOMA-IR induced by chronic treatment of olanzapine, clozapine or risperidone was correlated with weight gain/adiposity.^{58, 77, 80} Weight gain and adiposity were also found to be significantly correlated with changes in insulin sensitivity in patients following a 12 week treatment with olanzapine and risperidone.⁵⁹ Recently, Kim et al. reported that body mass index contributed a quarter to a third of the variance in insulin resistance in olanzapine-treated patients.⁸¹ However, growing evidence demonstrated that treatment with APDs, particularly short-term treatment, can directly affect insulin resistance and glucose homeostasis independent of weight gain.⁸² In fact, clinical studies have shown impaired glucose regulation in some schizophrenia patients treated with APDs without weight gain.⁸³ Insulin resistance has also been reported to be induced by olanzapine treatment within days without weight gain.^{84, 85} Diabetic ketoacidosis has been reported in patients in early treatment with various APDs and without weight gain.⁸⁶ In APD-naïve schizophrenia patients, two weeks' treatment of olanzapine decreased insulin secretory response to a hyperglycemic challenge, which suggests that olanzapine

might directly impair pancreatic β -cell function.⁸⁷ Data from animal studies also showed that acute treatment, even a single acute dose, of olanzapine, risperidone or clozapine can cause hyperglycemia and hyperinsulinemia, impair insulin-sensitivity, and induce insulin-resistance.^{66, 88-91} An *in vitro* study also showed that olanzapine and clozapine can directly decrease glucose-stimulated insulin secretion from pancreatic β cells.⁹² Furthermore, olanzapine and clozapine can significantly decrease the insulin-stimulated glucose transport rate by about 40% in 3T3-L1 adipocytes, whereas clozapine and risperidone reduced the insulin-stimulated glucose transport rate by about 40% in primary cultured rat adipocytes.⁹³ Therefore, these typical APDs may directly induce insulin resistance by directly impairing insulin-responsive glucose resistance in adipocytes.⁹³

Time course of APD-induced insulin dysregulation. Although a growing body of evidence has shown that short-term/acute APD treatment decreases fasting plasma insulin levels and attenuates glucose-stimulated insulin response,^{87, 88, 91, 94} as discussed above, chronic treatment is associated with hyperinsulinemia, insulin-resistance and T2DM.^{49, 59, 95} The apparent conflict in reports between chronic and short-term APD treatment may be reconciled by a hypothesis of time-dependent changes of APD-induced insulin dysregulation. This hypothesis is supported by a recent report that found time-dependent changes of glucose-stimulated insulin response in individuals with schizophrenia: decreased insulin levels during the first 2 weeks' olanzapine treatment compared to their baseline levels, followed by a return to baseline levels after 4 weeks' treatment, and increased insulin response following 8 weeks' olanzapine treatment.⁹⁶ In another study in schizophrenia patients who started or switched to a different APD for 3 months, a time-dependent worsening of plasma

glucose levels was observed in subjects taking clozapine, olanzapine and quetiapine.⁹⁷ A recent animal study also demonstrated that acute treatment of rats with olanzapine showed both glucose dysregulation and insulin resistance, however rats treated intermittently with olanzapine (once per week) showed a marked worsening in both glucose dysregulation and insulin resistance over the time course of a 10 week treatment.⁶⁷ The mechanisms underlying this time-dependent change of APD-induced insulin and glucose dysregulation have not been investigated however.

NEUROPHARMACOLOGICAL MECHANISMS FOR APD-INDUCED WEIGHT GAIN AND GLUCOMETABOLIC SIDE-EFFECTS

In contrast to typical APDs (such as haloperidol) that are largely potent and selective D2 antagonists, atypical APDs have binding affinities for various neurotransmitter receptors, such as dopamine D₂, serotonin 5HT_{2A} and 5HT_{2C}, adrenergic α_{1-2} , muscarinic M₁ and M₃ and histamine H₁ receptors⁹⁸ Among these receptors, dopamine D2 and 5-HT₂ receptors play critical roles in the therapeutic effects of atypical APDs.^{99, 100} Accumulated evidence has revealed that the antagonistic properties of 5HT_{2C} and H₁ receptors are involved in APD-induced weight gain.^{32, 101, 102} In fact, among APDs, clozapine and olanzapine have the highest affinities for 5HT_{2C} and H₁ receptors, and have the highest risk of weight gain and obesity side-effects.^{36, 98, 103} Therefore, the neuropharmacological mechanisms reviewed here are mainly from studies in olanzapine and clozapine. It is worth noting that, due to the variations in receptor binding profiles between different APDs, the mechanisms underlying the weight gain and glucometabolic side-effects might not be exactly the same between various APDs.

Over the past thirty years the 5-HT receptor has been revealed to regulate appetite and body weight, mainly through acting at the hypothalamic 5-HT_{2C} receptors.¹⁰⁴ In fact, 5-HTergic neurons project to the hypothalamic POMC neurons that co-express 5-HT_{2C} receptors, and 5-HT has been found to influence appetite by activating anorexigenic POMC neurons and melanocortin 4 receptors.¹⁰⁴ Considering the finding that olanzapine decreases expression of POMC in animal studies,^{46, 47} APDs may therefore increase appetite by inhibiting POMC neurons through the 5-HT_{2C} receptors. It is interesting that 5-HT_{2C} agonists reduce food intake by advancing satiety, and these effects are reversed by 5-HT_{2C} antagonists.^{105, 106} These results suggested that blockade of 5-HT_{2C} receptors could possibly be the mechanism for the clinical findings that the treatment with both clozapine and olanzapine could induce food craving and binge eating in patients.³⁸ Furthermore, the role of 5-HT_{2C} in APD-induced weight gain was confirmed by an animal study which showed that the initial (5 days) increase in weight gain and food intake associated with olanzapine treatment could be mimicked by combining a 5-HT_{2C} antagonist (SB243213) with haloperidol, but not by an H₁ antagonist alone or combined with haloperidol.¹⁰⁷ However, there is clear evidence that 1-week and 12 weeks treatment with olanzapine reduces the expression of hypothalamic H₁ receptors, and H₁ receptor changes have been correlated with increased food intake and weight gain in rats.²⁴ Olanzapine and clozapine have been reported to activate hypothalamic AMPK pathway via H₁ receptors to increase food intake and body weight gain.¹⁰⁸ Olanzapine has also been reported to regulate feeding behaviour in rats by modulating histaminergic neurotransmission.¹⁰⁹ The role of the H₁ receptor in APD-induced weight gain has also been supported by findings that co-treatment of betahistine (an H₁ agonist and an H₃ antagonist) can significantly reduce olanzapine-induced weight gain in both

schizophrenia patients and animals.¹¹⁰⁻¹¹² It has also been postulated that different neural mechanisms are responsible for the three stages of weight gain induced by APDs.¹⁹

APD affinity for the Muscarinic M₃ receptor has been identified as most closely linked to its diabetic side-effects.¹¹³⁻¹¹⁵ and can even be used to predict its diabetogenic liability.¹¹³ Consistently, olanzapine and clozapine, two of the APDs associated with a high risk of insulin resistance, glucose dysregulation and diabetic side-effects, possess the highest M₃ receptor binding affinity.¹¹⁶ M₃ receptors play a crucial role in the regulation of insulin secretion through both the peripheral and central cholinergic pathways¹¹⁷. An in vitro study has shown that olanzapine and clozapine can impair cholinergic-stimulated insulin secretion.⁹² A recent animal study found that a single subcutaneous injection of darifenacin (a selective M₃ muscarinic antagonist) significantly decreased insulin response to glucose challenge compared to control.¹¹⁸ M₃ receptors are widely expressed in the hypothalamic arcuate (Arc) and ventromedial (VMH) nuclei, and the dorsal vagal complex of the brainstem, brain regions well-documented for their role in insulin and glucagon secretion and glucose homeostasis.^{119, 120} Recently, we found that a 2-week treatment with olanzapine decreased fasting insulin levels and correlated with an increase in M₃ receptor binding density in the Arc, VMH, and DVC.¹²¹ In addition, acute central treatment with olanzapine via intracerebroventricular infusion induces hepatic insulin resistance and increased hypothalamic AMPK expression.¹²² Results from the two studies suggest that olanzapine may block M₃ receptor signalling pathways in the brain, thus impacting insulin production and insulin resistance. Therefore, APDs may act through

both peripheral and central M₃ antagonism to impair compensatory insulin response, resulting in diabetes.

Since the introduction of APDs in the 1950s, binding at dopamine D₂ receptors (antagonism or partial agonism) remains the only mechanism common to therapeutic efficacy of all APDs.¹⁰⁰ There is evidence that both atypical and typical APDs can cause weight gain and other metabolic side-effects, particularly recent clinical data from studies in first episode patients that demonstrated haloperidol (a potent and selective D₂ antagonist) is associated with weight gain, insulin resistance, glucose dysregulation side-effects as discussed above; it is therefore reasonable to propose D₂ receptors as a possible common mechanism underlying these side-effects. Although it has been the subject of fewer investigations, there is some evidence supporting the involvement of D₂ receptors in APD-induced weight gain, insulin resistance, glucose dysregulation side-effects. As discussed above, only combined treatment of a 5-HT_{2C} antagonist with haloperidol can mimic olanzapine-induced weight gain.¹⁰⁷ A relationship between a functional promoter region polymorphism in *DRD2* and weight gain induced by olanzapine and risperidone has reported in first episode schizophrenia.¹²³ Dopamine and D₂ receptors are key components of the reward system controlling desire for food and hence body weight regulation.¹²⁴ Our previous study found that D₂ receptor density was significantly lower in the rostral part of the caudate putamen in obese mice compared to lean mice.¹²⁵ It is well established that blockade of dopamine D₂ receptor activity in the mesolimbic and nigrostriatal pathways is the common mechanism of APD action,^{100, 126} these pathways are also key pathways for food reward.¹²⁷ In fact, a reduced striatal activation was detected by fMRI during reward anticipation due to appetite-provoking in chronic schizophrenia

with APD treatment.¹²⁸ Therefore, APDs may increase appetite and food intake by acting on dopamine D₂-mediated reward.¹²⁷ It is interesting that D₂-like receptors are also expressed in pancreatic β -cells which function to inhibit glucose-stimulated insulin secretion,¹²⁹ and permanent lack of D₂ receptor mediated inhibition (such as in D₂ knock out mice *Drd2*^{-/-}) eventually results in glucose intolerance.¹³⁰ It has been reported that a single subcutaneous injection of raclopride (a D₂/D₃ selective antagonist) can enhance insulin secretion and marginally decrease insulin sensitivity.¹¹⁸ Therefore, this may provide a mechanism to explain why chronic treatment of some typical APDs (such as haloperidol) leads to glucose dysregulation hyperinsulinemia, and eventually diabetes.

SUMMARY

Over the past 20 years, it has been established that treatment with atypical APDs is associated with serious weight gain, obesity, and other metabolic side effects such as insulin resistance, glucose dysregulation and T2DM, however the metabolic side-effects associated with some typical APDs are possibly underestimated. Emerging evidence over the past 5-6 years from the studies in first episode psychotic and drug naïve patients show that some commonly used typical APDs (such as haloperidol) may also course significant weight gain, insulin resistance, glucose dysregulation, and even T2DM, particularly under chronic treatment. In fact, although some atypical APDs, particularly clozapine and olanzapine, have a higher liability than others in inducing metabolic side-effects, current evidence has indicated that all APDs have a greater weight gain and various metabolic side-effects than placebo-level effects.

It is worth noting that variations in weight gain and other metabolic side-effects are observed not only among APDs, but the marked individual variations have also been observed in all reported clinical studies and that, irrespective of the APD, some subjects lose weight, some maintain weight and some gain weight.^{15, 17} It is also worth noting that not all weight gain is detrimental. For those patients who are underweight prior to APD treatment, possibly reflecting that their psychotic illness has caused them to neglect themselves, weight gain associated with APD is beneficial if the medication results in these individuals returning to a pre-morbid and healthy weight.¹³¹ This individual variation could be related to both genetic and nongenetic factors (such as gender, age and initial body weight/BMI etc.).^{132, 133} Although there is no reliable biomarker for prediction of weight gain, several studies have identified female gender, younger age and a low BMI prior to the first APD treatment as risk factors for APD-induced weight gain and obesity.¹³³⁻¹³⁶ A diagnosis of undifferentiated schizophrenia or schizophrenia spectrum disorder was also identified as a possible predictor for APD-induced weight gain.^{133, 136} Since APD-induced weight gain has a time-dependent development, and particularly rapid weight gain in the first few weeks of APD treatment is a good indicator for a long-term outcome of weight gain and obesity,^{19, 27} weight monitoring during the early phase of APD therapy is crucial for prevention of this serious side-effect. It is important to note that insulin resistance and glucose dysregulation may develop independently of weight gain, therefore monitoring only weight gain is not enough, and a periodic monitoring of blood sugar may also be required during APD therapy, particularly for drugs with high diabetic liabilities such as olanzapine and clozapine. Although current evidence suggests that multiple neurotransmitter receptors such as 5-HT_{2C}, histamine H₁, muscarinic M₃ (and possibly also dopamine D₂ receptors), are involved in weight

gain/obesity and insulin and glucose dysregulation associated with APDs, one important issue that needs to be investigated is how these neurotransmitter systems interact during the time-dependent development of these side-effects. An improved understanding of the mechanisms underlying the time-dependent development of these metabolic side-effects could help in designing better strategies to prevent and treat these devastating side-effects and their associated cardiovascular disease, stroke and premature death.

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