

# Antipsychotic Drug-Induced Insulin Resistance: A Narrative Literature Review

## *Insulinooporność Indukowana Lekami Przeciwpowpsychotycznymi: Przegląd Narracyjny Piśmiennictwa*

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### KEY WORDS:

- insulin resistance
- antipsychotics
- diabetes
- appetite
- obesity

### ABSTRACT

Insulin resistance is a metabolic disorder and a key factor in the pathogenesis of conditions such as type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD), and atherosclerosis. Risk factors for insulin resistance include genetic and environmental influences, such as overweight/obesity, low physical activity, and the use of certain medications, including glucocorticosteroids or antipsychotics.

Antipsychotics (neuroleptics) are widely used in the treatment of various mental disorders, primarily schizophrenia, and such therapy is often lifelong. Due to the mechanism of action via receptors, including serotonergic, muscarinic, and histaminergic, atypical (second-generation) antipsychotics cause metabolic disorders of varying severity. Clozapine and olanzapine have the worst metabolic profiles and aripiprazole and lurasidone are associated with the mildest profiles. Regardless of the potential for developing metabolic complications from specific antipsychotics, baseline predictors of susceptibility are sought in patients. To date, studies have identified risk factors such as higher body weight, male gender, and non-white ethnicity.

Despite clear evidence of an increased risk for insulin resistance and, consequently, metabolic syndrome and high cardiovascular risk, insufficient attention is paid to early diagnosis, prevention, and treatment of carbohydrate and lipid metabolism disorders in patients taking neuroleptics. Improved management in this area could benefit not only physical health but also adherence to medical recommendations and the overall effectiveness of psychiatric treatment. This narrative review aims to comprehensively examine the pathophysiological mechanisms, diagnostic approaches, and therapeutic strategies related to disturbances in carbohydrate metabolism observed in patients with schizophrenia undergoing treatment with various antipsychotic medications.

### SŁOWA KLUCZOWE:

- insulinooporność
- leki przeciwpowpsychotyczne
- cukrzyca
- apetyt
- otyłość

### STRESZCZENIE

Insulinooporność jest zaburzeniem metabolicznym i kluczowym elementem patogenezy chorób, takich jak cukrzyca typu 2, stłuszczeniowa choroba wątroby związana z zaburzeniami metabolicznymi (MASLD), czy miażdżyca. Czynniki ryzyka rozwoju obniżonej wrażliwości tkanek obwodowych na insulinę są czynniki genetyczne i środowiskowe, np. nadwaga/otyłość, niewielka aktywność fizyczna, ale także przyjmowanie niektórych leków, takich jak glikokortykosteroidy, czy leki przeciwpowpsychotyczne.

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Leki przeciwpsychotyczne (neuroleptyki) są szeroko stosowane w leczeniu różnych zaburzeń psychicznych, przede wszystkim schizofrenii i zazwyczaj taka terapia trwa całe życie. Ze względu na mechanizm działania poprzez hamowanie receptorów, m.in. serotoninowych, muskarynowych, czy histaminowych, leki przeciwpsychotyczne atypowe (drugiej generacji) powodują zaburzenia metaboliczne o różnym stopniu nasilenia, z kłozapiną i olanzapiną wykazującymi najgorsze profile metaboliczne i aripiprazolem i lurasydonom o najłagodniejszych profilach. Niezależnie od potencjału rozwoju powikłań metabolicznych po zastosowaniu konkretnego leku przeciwpsychotycznego, poszukuje się u pacjentów wyjściowych predyktorów podatności na ich występowanie. Do tej pory w badaniach opisane zostały takie czynniki ryzyka jak wyższa masa ciała, płeć męska i rasa inna niż biała.

Pomimo ewidentnych dowodów na zwiększone ryzyko rozwoju insulinooporności, a w konsekwencji zespołu metabolicznego i wysokiego ryzyka sercowo-naczyniowego, niewiele uwagi przywiązuje się do wczesnego rozpoznawania, profilaktyki i leczenia zaburzeń gospodarki węglowodanowej i lipidowej u pacjentów stosujących neuroleptyki. Poprawa postępowania w tym zakresie może wpływać nie tylko na ich zdrowie fizyczne, ale także przestrzeganie zaleceń lekarskich i efekty leczenia zaburzeń psychicznych. Niniejszy przegląd narracyjny ma na celu kompleksowe omówienie mechanizmów patofizjologicznych, metod diagnostycznych oraz strategii terapeutycznych związanych z zaburzeniami gospodarki węglowodanowej obserwowanych u pacjentów ze schizofrenią leczonych różnymi lekami przeciwpsychotycznymi.

## Background

Antipsychotics, commonly known as neuroleptics, are divided into two main categories: the first-generation (typical) and the second-generation (atypical). First-generation drugs inhibit dopamine receptors, whereas those from the second generation additionally influence other receptors (for monoamines and acetylcholine), leading to improved outcomes for negative and cognitive symptoms and variations in side effects. Although atypical neuroleptics do not cause as severe neurological symptoms as typical ones, their main adverse effects are metabolic complications, including antipsychotic induced weight gain (AIWG), metabolic syndrome (with abnormalities, such as visceral obesity, insulin resistance, hypertension, dyslipidemia), impaired glucose tolerance, diabetes, and therefore increased cardiovascular risk. Furthermore, these factors adversely influence individuals' quality of life, adherence to medication regimens, and perpetuate stigma and foster social isolation (1-3). Individuals with schizophrenia exhibit a significantly reduced life expectancy compared to the general population, with a difference of approximately 20 years, and experience obesity, type 2 diabetes and hypercholesterolemia 3 to 5 times more frequently (4-6). Moreover, a meta-analysis revealed that patients with first-episode schizophrenia also had higher levels of plasma glucose (fasting and after 2 hours in oral glucose tolerance test - OGTT), fasting insulin, and greater insulin resistance compared with healthy controls (6). These data demonstrate the scale of the problem and the necessity for enhanced monitoring in this patient population, even prior to initiating antipsychotic treatment. Significant variations are observed among neuroleptics in their propensity to induce metabolic adverse effects. Pillinger et al. investigated changes in carbohydrate and lipid metabolism and body weight during acute treatment of schizophrenia. The greatest increases in body weight, total cholesterol, triglycerides, and glucose levels occurred in patients taking clozapine, and in BMI and LDL levels with olanzapine. The most substantial decrease in HDL level was associated with amisulpride use. Therefore, olanzapine and clozapine, although the most effective drugs, have the most unfavorable metabolic profiles. The least metabolic disturbances were caused by aripiprazole, brexpiprazole,

cariprazine, lurasidone, and ziprasidone (4). This is a crucial guide for clinicians in selecting or changing an antipsychotic treatment in patients who may be suspected of developing obesity, insulin resistance, etc.

## Molecular Mechanisms of Antipsychotic Drug-Induced Insulin Resistance

Physiologically, insulin secreted from the pancreatic  $\beta$ -cells enables glucose uptake resulting in the formation of a highly efficient „renewable” energy source for periods of reduced nutrient availability. In skeletal muscle cells, insulin binding to insulin receptor tyrosine kinase (IRTK) activates a signalling pathway and promotes glucose uptake via glucose transporter type 4 (GLUT-4), which is translocated to the plasma membrane. Subsequently, it stimulates glycogen synthesis. In hepatocytes, insulin decreases gluconeogenesis and increases both glycogenesis and hepatic de novo lipogenesis. Finally, in adipocytes, insulin reduces lipolysis, which contributes to the suppression of hepatic glucose production (by reducing substrates for gluconeogenesis), but also enhances lipogenesis and adipogenesis (7-11).

Insulin resistance is defined as an impaired response to increased insulin stimulation of insulin-target tissues. The state of chronic hyperinsulinemia often precedes hyperglycemia, leading to  $\beta$ -cells insufficiency and predominantly type 2 diabetes. Moreover, insulin resistance is associated with a range of abnormalities involving metabolic syndrome, atherosclerosis, endothelial dysfunction, proinflammatory and prothrombotic state, MASLD, polycystic ovary syndrome, chronic kidney disease, Alzheimer's disease, and cancers, including breast, uterine, colorectal cancer, etc (12-14). The links between schizophrenia, diabetes, and insulin resistance have been studied for many years, mainly due to the adverse effects of antipsychotic drugs, such as AIWG or dysglycaemia. Increasing knowledge of these mechanisms allows for better prevention and treatment of metabolic disorders among patients treated with antipsychotics.

First of all, antipsychotics can induce insulin resistance independently of increased body weight and food intake. This is supported by studies in which participants did not

gain weight but developed glycemic disturbances (e.g. in OGTT) after taking antipsychotics (15), even in healthy volunteers (16), and after a single dose of an antipsychotic such as olanzapine (17), but also in certain cases after aripiprazole, considered „metabolically sparing” (18). In short, insulin binds to insulin receptors, leading to autophosphorylation and activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway (Fig. 1). Hence, abnormalities in this signalling pathway result in the development of insulin resistance (19). Research shows that antipsychotic medications may reduce the phosphorylation of insulin receptor substrate 1 (IRS1) and impede the function of Akt (20). Engl et al., using skeletal muscle cell lines, demonstrated that olanzapine interferes with glycogen synthesis in myotubes by reducing the activity of PI3K. The amount of glycogen decreased with both the dosage and the duration of exposure. However, this change was not observed after amisulpride (21). Clozapine, another antipsychotic with a poor metabolic profile, has been associated with a 40% decrease in insulin action on its receptor, a 60% reduction in IRS1 tyrosine phosphorylation, and a 40% reduction in Akt phosphorylation, resulting in reduced glucose uptake in neuronal and skeletal muscle cell lines (22). The effects of antipsychotics on other substrates in the insulin signaling pathway require further investigation. These findings underscore the need for early diagnosis of carbohydrate and lipid metabolism disorders, even in patients with normal BMI who are taking antipsychotics.

Secondly, antipsychotics contribute to insulin resistance through obesity. A meta-analysis indicated that almost one-third of patients taking antipsychotics develop metabolic syndrome. Another study showed that the initial six months of treatment are characterized by a pronounced increase in weight, a trend that often persists with continued treatment (23). The diabetogenic potential of antipsychotic medications in relation to weight gain is summarized in Table 1.

The arcuate nucleus (ARC) located in the hypothalamus plays a vital role in regulating appetite and energy homeostasis, and it is made up of two groups of neurons: ARC-POMC, expressing pro-opiomelanocortin (POMC), which is cleaved to an anorexigenic  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), binding to melanocortin 3 and 4 receptors (MC3/4). The second group are ARC-AgRP/NPY neurons, expressing orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY), which inhibit ARC-POMC neurons and MC3/4 receptors in the paraventricular nucleus (24, 25). The antagonism of the serotonin 5-HT<sub>2C</sub> receptors results in the suppression of ARC-POMC neurons, which in turn lowers  $\alpha$ -MSH levels and increases appetite. On the other hand, antagonizing muscarinic M3 receptors decreases GABA-ergic inhibition towards ARC-POMC neurons, leading to a reduction in appetite. Histamine H1 receptors antagonism stimulates 5' AMP-activated protein kinase (AMPK - a potent orexigenic driver), which enhances the secretion of NPY and AgRP, increasing appetite (24, 26). Chen et al. also point to a role for antagonizing dopamine D2 receptors in increasing appetite, as do Mukherjee et al., who emphasize the role of the mesolimbic reward pathway in this mechanism. However, the latter researchers indicate that antagonism of M3 receptors increases appetite via the acetylcholine pathway (20, 26). Scientists have posited that blocking M3 receptors may lead to weight gain, particularly because medications like olanzapine and clozapine strongly bind to these receptors (27). However, M3 receptor knock-out rodent models consistently show decreased food consumption, along with possible benefits in glucose regulation and energy use (28).

There is also emerging evidence for the role of 5-HT<sub>1/2a</sub> receptors in neuroleptic-induced hyperphagia (26). It is worth noting that genetic polymorphisms in receptor genes - such as 5-HT<sub>2C</sub> and D2 - may be associated with a greater susceptibility to AIWG, depending on the specific alleles present (29, 30). An increased appetite contributes to weight gain and expansion of adipose tissue, which results in accumulation of macrophages and inflammation (increased pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6), increased release of free fatty acids (FFAs), and abnormal secretion of leptin, adiponectin, resistin, and retinol binding protein-4 (RBP4). These adipocyte- and macrophage-derived substances affect the insulin-GLUT-4 pathway (e.g. FFAs inhibit IRS phosphorylation) and lead to muscle and liver lipid accumulation and further inflammation, resulting in systemic insulin resistance. Moreover, changes in the secretion of adipokines may result in increased food consumption and decreased energy expenditure by influencing the hypothalamus (20, 26, 31, 32, 33). Two key molecular mechanisms of antipsychotic-induced insulin resistance are demonstrated in Figure 1.

Recently, an altered gut microbiome has been identified as a key factor in antipsychotic-related obesity in animal models. Gut dysbiosis contributes to overeating and weight gain via peripheral factors (leptin, ghrelin) and vagal signaling (26, 34). Studies on mice have shown a negative correlation between the presence of *Akkermansia muciniphila* and both insulin resistance and inflammation. Antipsychotics can significantly reduce the abundance of these bacteria (35). Research has shown that the composition of the microbiome is often less optimal in drug-naïve patients suffering from schizophrenia, bipolar disorder, and major depressive disorder with psychotic characteristics, so whether antipsychotics or the underlying disorder mainly causes this condition is questionable (26). Moreover, the sedative effects of neuroleptics, particularly of strong H1 antagonists, can contribute to decreased energy expenditure, playing a role in weight gain (20, 24).

It is worth mentioning that recent research has focused on how  $\beta$ -cells damage, which seems to be a necessary stage, contributes to antipsychotic-induced diabetes. Insulin release from islet  $\beta$ -cells is diminished, particularly by olanzapine and clozapine. Antipsychotics interact with multiple  $\beta$ -cell receptors, resulting in lower levels of insulin secretion through blockade of M3, adrenergic  $\alpha$ 1, 5-HT<sub>2A</sub> receptors, and adenosine triphosphate (ATP) (20). Studies have revealed that the affinity of atypical antipsychotics for M3 receptors may serve as a marker for diabetes susceptibility. Notably, olanzapine and clozapine, which exhibit the highest diabetes prevalence, are potent M3 antagonists (36). Moreover, the impairment of  $\beta$ -cells induced by antipsychotics may occur via the apoptotic route in mitochondria by decreased antiapoptotic Bcl-2, cytochrome c release, apoptosome formation, and caspase activation, also primarily demonstrated in studies involving olanzapine and clozapine (20, 37).

### Insulin Resistance in First-Episode Schizophrenia

Signs indicating metabolic syndrome were noted in patients suffering from schizophrenia, even prior to the advent of antipsychotic treatment. Nowadays, data from studies involving drug-naïve patients with the first episode of psychosis (FEP) confirm a pre-existing disturbance in glucose metabolism. In a meta-analysis, FEP was associated with insulin resistance, impaired glucose tolerance, but normal fasting

glucose levels, suggesting there might be overlapping inflammatory pathways between schizophrenia and type 2 diabetes (38). Another meta-analysis showed that fasting glucose, 2-hour glucose level in the OGTT and fasting insulin in drug-naïve patients were significantly increased, but there was no significant difference in glycosylated haemoglobin (HbA1c) level compared to healthy controls (39). Moreover, Petrikis et al. evaluated glucose and lipid metabolism under fasting conditions in 40 FEP patients. Insulin, C-peptide levels, and HOMA-IR were higher, while HDL levels were lower in the patient group compared to healthy controls (40). Furthermore, those suffering from schizophrenia have increased serum levels of IL-1 $\beta$ , C-reactive protein (CRP), and TNF- $\alpha$  (41). Additionally, a meta-analysis on the influence of antipsychotics on cytokine levels in FEP concluded that antipsychotic use was associated with reduced levels of both pro-inflammatory cytokines - such as IL-1 $\beta$ , IL-6, IFN- $\gamma$ , and TNF- $\alpha$  - and anti-inflammatory cytokines, including IL-4 and IL-10 (42). The inflammatory component has been indicated in other mental diseases, e.g. depression or bipolar affective disorder, and a growing body of evidence shows the link between inflammation and the microbiome in their pathogenesis (43). In addition, Schwarz et al. noticed that before treatment, higher levels of IL-18, were linked to greater increases in BMI following 6 weeks of atypical antipsychotic treatment. Conversely, higher baseline levels of IL-6 receptor and epidermal growth factor (EGF) were associated with smaller weight gain (44).

These findings highlight the need for early diagnosis, prevention, and treatment of carbohydrate disorders in this population and suggest that OGTT may be particularly useful.

### **Biomarkers of insulin sensitivity/resistance in schizophrenia**

Currently, there is ongoing research to identify diagnostic tools for assessing insulin resistance or insulin sensitivity that correlate well with the gold standard, the hyperinsulinaemic-euglycaemic clamp, which is a time-consuming, cost-prohibitive, and therefore rarely used in clinical practice. More practical alternatives should be relatively low-cost, well-validated, reliable, and easy to interpret. The most valuable indicators include single-time-point blood tests (e.g., fasting glucose, insulin, lipid panel), simple anthropometric measurements (such as BMI, waist circumference, and waist-to-height ratio), and specific biomarkers of inflammation and adipocyte-derived molecules (adipokines). There is also a whole area to explore new biomarkers of insulin resistance, including radiological assessment of body fat, miRNAs, and metabolomes (45). Assessing baseline risk for metabolic complications, as well as monitoring during antipsychotic treatment, aims to introduce primary prevention and prompt intervention if disorders such as AIWG, impaired glucose tolerance, or diabetes emerge. Table 2 summarizes the most commonly used indicators of insulin resistance and sensitivity in experimental and clinical studies involving populations with schizophrenia.

While lifestyle changes and weight loss are often recommended to mitigate insulin resistance and diabetes, their efficacy is limited, and practical implementation can be challenging. The choice of medication is the primary baseline risk factor in predicting AIWG. However, antipsychotic switching or dose reduction is not possible in some cases, e.g., in those taking clozapine for treatment-resistant schizophrenia.

New evidence-based guidelines recommend metformin to prevent AIWG when initiating antipsychotic treatment. It is a cost-effective medication that does not cause hypoglycemia, inhibits hepatic gluconeogenesis, and improves insulin sensitivity. In practice, metformin is frequently recommended for managing diabetes and helps to either prevent or reverse insulin resistance and prediabetes (56, 57). The adjunctive use of metformin with antipsychotics can result in a reduction of weight gain by approximately 4 kg (the doses ranged from 500 mg to 2 g daily). Moreover, Agarwal et al. showed that metformin was associated with a decrease in HOMA-IR and fasting glucose in overweight or obese patients with schizophrenia spectrum disorders and early comorbid prediabetes or type 2 diabetes receiving antipsychotic medications, independently of weight loss (58). The classification of AIWG risk groups and specific interventions are shown in Figure 3 (57).

When addressing overweight or obesity, also induced by antipsychotic medications, GLP-1 agonists have shown a more significant impact compared to metformin. However, due to issues with supply, expenses, and prescribing limitations, it can be challenging to access this therapy (57). It is worth emphasising that in a study evaluating the adjunctive aripiprazole in patients with metabolic abnormalities treated with olanzapine, participants experienced significant decreases in BMI and triglyceride levels, and a significant increase in adiponectin levels after 8 weeks (59). Similar results in research involving clozapine support the use of aripiprazole for metabolic improvement and cardiovascular risk reduction in this population (60). However, it should be noted that the addition of aripiprazole results in antipsychotic polypharmacy, which necessitates collaboration with a psychiatrist. Further studies are needed to determine the safety and durability of the therapeutic effects of this medication on metabolic disorders.

### **Conclusions**

The widespread use of antipsychotics underscores the need for effective monitoring of their adverse effects. Preventing complications is always a more prudent and cost-effective approach. Schizophrenia is associated with a reduced life expectancy and a high risk of mortality from cardiovascular causes. Metabolic disorders also occur before the inclusion of neuroleptics, so they are not solely treatment-related. There are no specific diagnostic tools tailored for detecting metabolic disorders in patients treated with antipsychotics. The most commonly used tests are fasting plasma glucose, OGTT, HbA1c, BMI, and waist circumference. The effective agent that prevents antipsychotic-induced weight gain in this group of patients is metformin. Currently, further research is needed to establish a standardized diagnostic pathway for drug-naïve patients with first-episode psychosis, particularly to determine the optimal timing for conducting metabolic assessments following diagnosis. The initial baseline evaluation aims to identify a medication with a more favorable profile (such as aripiprazole) for patients at elevated metabolic risk. A family history may also contribute to a patient's susceptibility to glycaemic disturbances. The physical health of people with mental illness leads to better adherence to treatment and better functioning, and therefore, it becomes the object of interest for psychiatrists and other healthcare professionals.

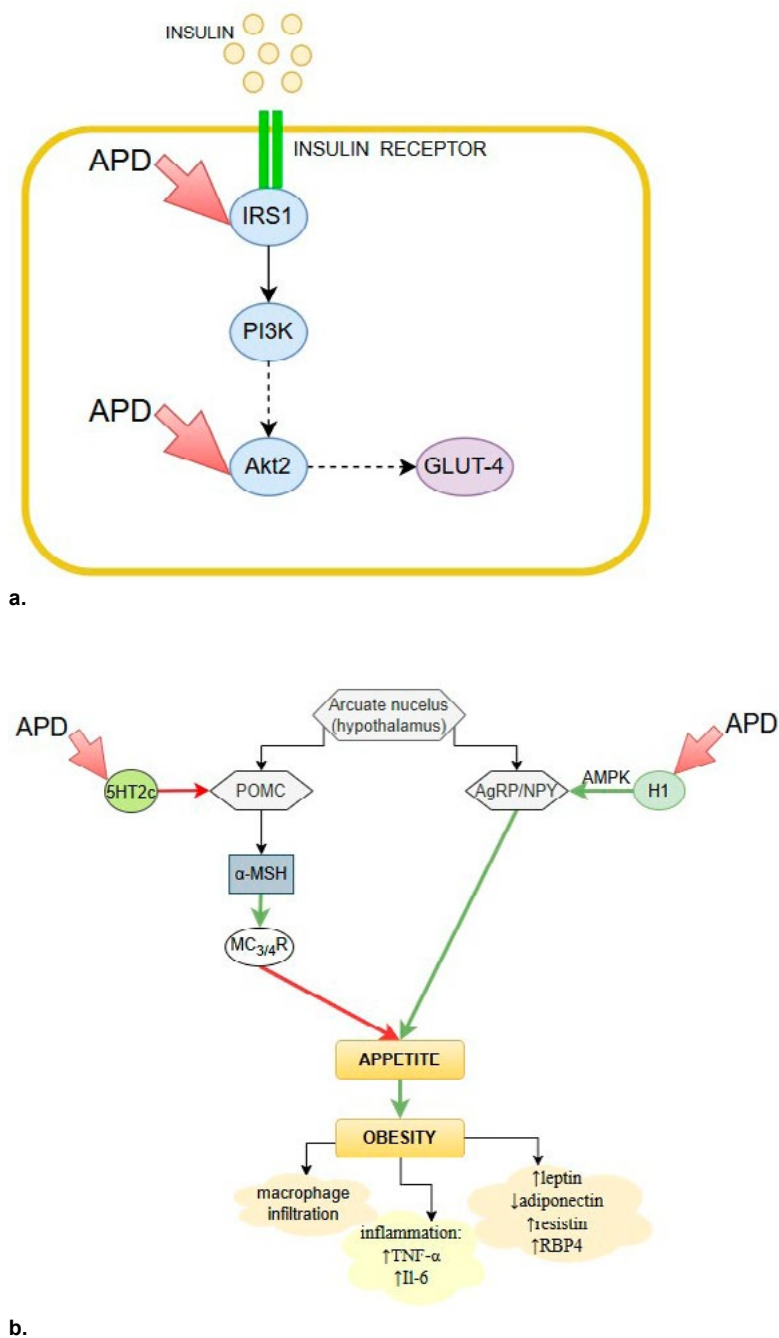
**Table 1. The diabetogenic potential of antipsychotic drugs in relation to weight gain.**

Antipsychotic	Risk of diabetes	Weight gain
Clozapine	+++	+++
Olanzapine	+++	+++
Risperidone	++	++
Quetiapine	++	++
Amisulpride	++	++
Ziprasidone	++	+
Aripiprazole	+ / ++	+
Lurasidone	+ / ++	+
Haloperidol	+	++

Values: +++ high, ++ moderate, + / ++ low/moderate, + low. Source: Kosmalski et al. Diagnosis and management of hyperglycaemia in patients treated with antipsychotic drugs, Endokrynol Pol 2022 (5).

**Table 2. Strengths and limitations of insulin resistance and sensitivity indices in studies involving individuals diagnosed with schizophrenia and/or undergoing antipsychotic therapy.**

Biomarker of insulin resistance or sensitivity	Strengths	Limitations
<b>Homeostatic Model Assessment-Insulin Resistance (HOMA-IR)</b>  $= \text{fasting glucose (mmol/l)} \times \text{fasting insulin (mU/l)} / 22.5$	<ul style="list-style-type: none"> <li>Widely used in numerous studies across various populations for a long time, with a good correlation with hyperinsulinemic-euglycemic clamp (45) and BMI (46).</li> <li>Simple formula.</li> </ul>	<ul style="list-style-type: none"> <li>No consensus on the cut-off point (in the study involving patients with schizophrenia, it was set at 1.7) (47).</li> <li>Serum insulin measurement required.</li> </ul>
<b>Matsuda index</b>  $= 10,000 \div \sqrt{[(\text{fasting glucose (mg/dl)} \times \text{fasting insulin (}\mu\text{U/mL)}) \times (\text{mean OGTT glucose (mg/dL)} \times \text{mean OGTT insulin (}\mu\text{U/mL)})]}$	<ul style="list-style-type: none"> <li>Incorporating both hepatic and peripheral insulin sensitivity.</li> <li>It correlates with BMI and triglycerides in patients treated with olanzapine (48).</li> </ul>	<ul style="list-style-type: none"> <li>Serum insulin measurement and OGTT required.</li> <li>Multiple timed samples (high costs, time-consuming).</li> </ul>
<b>Triglycerides/glucose (TyG)</b>  $= \text{Ln}(\text{fasting triglycerides (mg/dl)} \times \text{fasting glucose (mg/dl)} / 2)$	<ul style="list-style-type: none"> <li>Routine and cost-effective blood tests.</li> <li>Potential predictor of insulin resistance for patients with schizophrenia (49).</li> </ul>	<ul style="list-style-type: none"> <li>No optimal cut-off (in a recent study involving patients with schizophrenia, the best cut-off value was 8.94) (49).</li> <li>More complex calculations.</li> </ul>
<b>Leptin/Adiponectin ratio (L/A)</b>  $= \text{leptin (ng/mL)} / \text{adiponectin (}\mu\text{g/mL)}$	<ul style="list-style-type: none"> <li>Associated with metabolic syndrome in patients with schizophrenia (the best cut-off was 0.61) (50).</li> <li>One-time sampling.</li> </ul>	<ul style="list-style-type: none"> <li>Limited availability.</li> <li>Very expensive.</li> </ul>
<b>Inflammation biomarkers</b>	<ul style="list-style-type: none"> <li>A significant correlation was found between HOMA-IR, IL-6, and metabolic syndrome in patients with schizophrenia (51).</li> <li>C-reactive protein (hs-CRP) in psychiatric studies has been suggested as a potential marker of metabolic syndrome risk in schizophrenia (52).</li> </ul>	<ul style="list-style-type: none"> <li>No established cut-off values.</li> <li>Affected by the significant impact of comorbidities.</li> </ul>



**Fig. 1.** Main molecular mechanisms of antipsychotic-induced insulin resistance - direct effects of antipsychotics (a) and via increased appetite and obesity (b). Red arrows indicate inhibitions and green arrows indicate stimulation. Dashed arrows indicate bypassing of some steps of the insulin signaling pathway. Binding insulin to the receptor and its autophosphorylation activates IRS1, and then PI3K, which in subsequent steps (not shown) leads to phosphorylation of Akt2. Finally, translocation of GLUT-4 to the membrane for glucose uptake in glucose-consuming cells occurs. Antipsychotic treatment can lead to a decrease in insulin-stimulated IRS1 phosphorylation and inhibit Akt, causing insulin resistance. Antipsychotics also inhibit 5-HT2c and H1 receptors, which causes a reduction in anorexigenic POMC and an elevation in orexigenic AgRP and NPY, leading to an increase in appetite, weight gain, and finally obesity, associated with insulin resistance via inflammation and dysregulated adipokine secretion (in the main text). APD - antipsychotic drugs, IRS1 - insulin receptor substrate 1, PI3K - phosphoinositide 3-kinase, Akt - protein kinase, GLUT-4 - glucose transporter type 4, POMC - proopiomelanocortin, AgRP - agouti-related peptide, NPY - neuropeptide Y, α-MSH - α-melanocyte stimulating hormone, MC3/4R - melanocortin 3 and 4 receptors, 5-HT2c - serotonin 5-HT2c receptor, H1 - histamine H1 receptors, TNF-α - tumor necrosis factor α, IL-6 - Interleukin 6 (20, 26, 31).

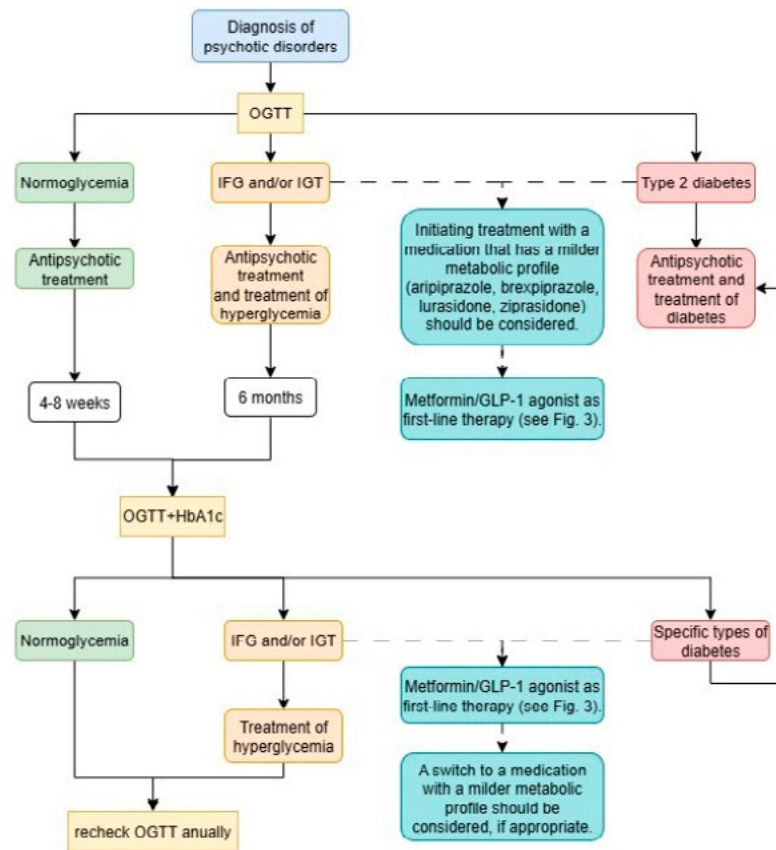


Fig. 2. Diagnostic approach for diabetes and prediabetes in patients taking antipsychotics (5). The dashed lines represent suggested management strategies in the event of disturbances in carbohydrate metabolism. GLP-1 - glucagon-like peptide-1, IFG - impaired fasting glucose, IGT - impaired glucose tolerance, HbA1c - glycated haemoglobin, OGTT - oral glucose tolerance test.

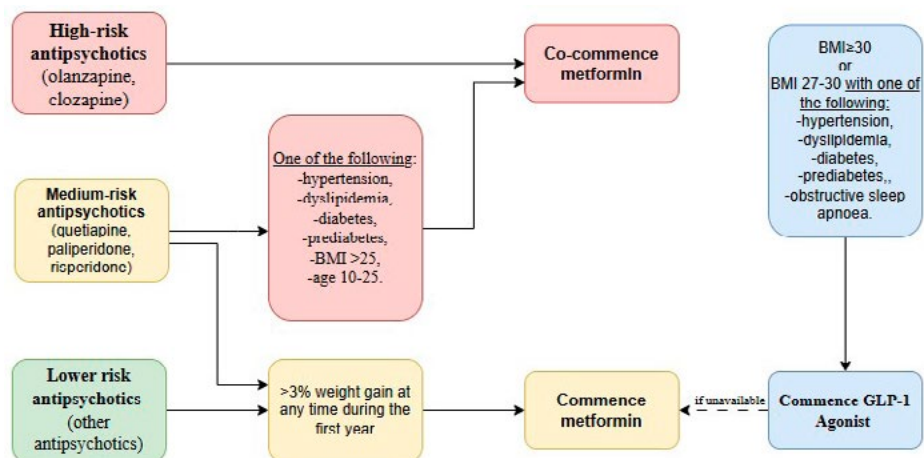


Fig. 3. Guidelines for the prevention of antipsychotic-induced weight gain (57).



## REFERENCES

- (1) Gałęcki P, Szulc A. *Psychiatria*. Wyd. 1 Edra Urban & Partner. Wrocław 2018.
- (2) Wichniak A, Dudek D, Heitzman J, i wsp. Redukcja ryzyka metabolicznego u chorych na schizofrenię przyjmujących leki przeciwpsychotyczne – zalecenia Polskiego Towarzystwa Psychiatrycznego. *Psychiatr Pol* 2019;53(6):1191-1218. doi:10.12740/PP/113222.
- (3) Dayabandara M., Hanwella R., Ratnatunga, S. et al. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatr Dis Treat* 2017;13:2231-2241 doi.org/10.2147/NDT.S113099.
- (4) Pillinger T, McCutcheon RA, Vano L, et al. 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(1):64-77. doi:10.1016/S2215-0366(19)30416-X.
- (5) Kosmowski M, Różycka-Kosmowska M, Basiak M, i wsp. Diagnosis and management of hyperglycaemia in patients treated with antipsychotic drugs. *Endokrynol Pol* 2022;73(5):872-884. doi:10.5603/EP.a2022.0071.
- (6) Pillinger T, Beck K, Gobjila C, et al. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;74(3):261-269. doi:10.1001/jamapsychiatry.2016.3803.
- (7) Vargas E, Joy NV, Carrillo Sepulveda MA. *Biochemistry, Insulin Metabolic Effects*. StatPearls Publishing; 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK525983/>.
- (8) Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. *Diabetes Metab J* 2022;46(1):15-37. doi:10.4093/dmj.2021.0280.
- (9) Rahman MS, Hossain KS, Das S, et al. Role of insulin in health and disease: an update. *Int J Mol Sci* 2021;22(12):6403. doi:10.3390/ijms22126403.
- (10) Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev* 2018;98(4):2133-2223. doi:10.1152/physrev.00063.2017.
- (11) White MF, Kahn CR. Insulin action at a molecular level - 100 years of progress. *Mol Metab* 2021;52:101304. doi:10.1016/j.molmet.2021.101304.
- (12) Dobrowolski P, Prejbisz A, Kuryłowicz A, i wsp. Zespół metaboliczny – nowa definicja i postępowanie w praktyce. Stanowisko PTNT, PTLO, PTL, PTH, PTMR, PTMSZ, Sekcji Prewencji i Epidemiologii PTK, „Klubu 30” PTK oraz Sekcji Chirurgii Metabolicznej i Bariatrycznej TChP. *Nadciśnienie Tętnicze Prakt* 2022;8(2):47-72.
- (13) Li M, Chi X, Wang Y, et al. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal Transduct Target Ther* 2022;7:216. doi:10.1038/s41392-022-01073-0.
- (14) Freeman AM, Acevedo LA, Pennings N. *Insulin Resistance*. StatPearls Publishing 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507839/>.
- (15) van Winkel R, De Hert M, Wampers M, et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2008;69(3):472-479. doi:10.4088/jcp.v69n0320.
- (16) Ballon JS, Pajvani UB, Mayer LE, et al. Pathophysiology of drug induced weight and metabolic effects: findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo. *J Psychopharmacol* 2018;32(5):533-540. doi:10.1177/0269881118754708.
- (17) Hahn MK, Wolever TM, Arenovich T, et al. Acute effects of single-dose olanzapine on metabolic, endocrine, and inflammatory markers in healthy controls. *J Clin Psychopharmacol* 2013;33(6):740-746. doi:10.1097/JCP.0b013e31829e8333.
- (18) Teff, K. L., Rickels, M. R., Grudziak, J., et al. Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. *Diabetes* 2013; 62(9), 3232–3240. doi:10.2337/db13-0430
- (19) Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb Perspect Biol* 2014;6(1):a009191. doi:10.1101/cshperspect.a009191.
- (20) Chen J, Huang XF, Shao R, et al. Molecular mechanisms of antipsychotic drug-induced diabetes. *Front Neurosci* 2017;11:643. doi:10.3389/fnins.2017.00643.
- (21) Engl J, Laimer M, Niederwanger A, et al. Olanzapine impairs glycogen synthesis and insulin signaling in L6 skeletal muscle cells. *Mol Psychiatry* 2005;10(12):1089-1096. doi:10.1038/sj.mp.4001729.
- (22) Panariello F, Perruolo G, Cassese A, et al. Clozapine impairs insulin action by up-regulating Akt phosphorylation and Ped/Pea-15 protein abundance. *J Cell Physiol* 2012;227(4):1485-1492. doi:10.1002/jcp.22864.
- (23) Bushe CJ, Slooff CJ, Haddad PM, et al. Weight change from 3-year observational data: findings from the worldwide schizophrenia outpatient health outcomes database. *J Clin Psychiatry* 2012;73(6):e749. doi:10.4088/JCP.11m07246.
- (24) Sudar FP Zekerallah SS, Paulzen M, et al. Unraveling antipsychotic induced weight gain in schizophrenia – A proof-of-concept study exploring the impact of the cumulative historical occupancy of different receptors by antipsychotics. *Psychiatry Res* 2025, 348, 116452. doi.org/10.1016/j.psychres.2025.116452.
- (25) Na J., Park B. S., Jang D., et al. Distinct Firing Activities of the Hypothalamic Arcuate Nucleus Neurons to Appetite Hormones. *Int J Mol Sci* 2022, 23(5), 2609. doi.org/10.3390/ijms23052609.
- (26) Mukherjee S, Skrede S, Milbank E, et al. Understanding the Effects of Antipsychotics on Appetite Control. *Front Nutr* 2022;8:815456. doi:10.3389/fnut.2021.815456.
- (27) Carnovale C, Lucenteforte E, Battini V, et al. Association between the glyco-metabolic adverse effects of antipsychotic drugs and their chemical and pharmacological profile: a network meta-analysis and regression. *Psychol Med* 2022;52(10):3768-3780. doi:10.1017/S0033291721000180.
- (28) Gautam D, Gavrilova O, Jeon J et al. Beneficial metabolic effects of M3 muscarinic acetylcholine receptor deficiency. *Cell Metab* 2006 Nov;4(5):363-75. doi: 10.1016/j.cmet.2006.09.008..
- (29) Wallace TJ, Zai CC, Brandl EJ, Müller DJ. Role of 5-HT(2C) receptor gene variants in antipsychotic-induced weight gain. *Pharmacogenomics Pers Med*. 2011;4:83-93. doi: 10.2147/PGPM.S11866.
- (30) Müller DJ, Zai CC, Sicard M, Remington E, et al. Systematic analysis of dopamine receptor genes (DRD1-DRD5) in antipsychotic-induced weight gain. *Pharmacogenomics J*. 2012 Apr;12(2):156-64. doi: 10.1038/tpj.2010.65.
- (31) Galic, S., Oakhill, J. S., Steinberg, G. R. et al. Adipose tissue as an endocrine organ. *Mol. Cell. Endocrinol* 2010, 316(2), 129–139. doi:10.1016/j.mce.2009.08.018.
- (32) Fryk E, Olausson J, Mossberg K, et al. Hyperinsulinemia and insulin resistance in the obese may develop as part of a homeostatic response to elevated free fatty acids: a mechanistic case-control and a population-based cohort study. *EBio-Medicine* 2021;65:103264. doi:10.1016/j.ebiom.2021.103264.



- (33) Verma S, Hussain ME. Obesity and diabetes: an update. *Diabetes Metab Syndr* 2017;11(Suppl 1):73-79. doi:10.1016/j.dsx.2016.06.017.
- (34) Davey K, Cotter P, O'Sullivan O, et al. Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. *Transl Psychiatry* 2013;3:e309. doi:10.1038/tp.2013.83.
- (35) Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 2018; 555:623–8. doi: 10.1038/nature25979.
- (36) Weston-Green K, Huang XF, Deng C. Second generation antipsychotic-induced type 2 diabetes: a role for the muscarinic M3 receptor. *CNS Drugs* 2013;27(12):1069-1080. doi:10.1007/s40263-013-0115-5.
- (37) Ozasa R, Okada T, Nadanaka S, et al. The antipsychotic olanzapine induces apoptosis in insulin-secreting pancreatic  $\beta$  cells by blocking PERK-mediated translational attenuation. *Cell Struct Funct* 2013;38(2):183-195. doi:10.1247/csf.13012.
- (38) Perry BI, McIntosh G, Weich S, et al. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. *Lancet Psychiatry* 2016;3(11):1049-1058. doi:10.1016/S2215-0366(16)30262-0.
- (39) Yang W, Zheng L, Zheng B, et al. A meta-analysis of abnormal glucose metabolism in first-episode drug-naïve schizophrenia. *Psychiatr Danub* 2020;32(1):46-54. doi:10.24869/psyd.2020.46.
- (40) Petrikis P, Tigas S, Tzallas AT, et al. Parameters of glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis: evidence for insulin resistance. *Psychiatry Res* 2015;229(3):901-904. doi:10.1016/j.psychres.2015.07.041.
- (41) Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Rev Neurother* 2010; 10: 59–76. doi: 10.1586/ern.09.144.
- (42) Marcinowicz P, Więdocha M, Zborowska N, i wsp. A meta-analysis of the influence of antipsychotics on cytokines levels in first episode psychosis. *J Clin Med* 2021;10(11):2488. doi:10.3390/jcm10112488.
- (43) Ouabbou S, He Y, Butler K, et al. Inflammation in mental disorders: is the microbiota the missing link? *Neurosci Bull* 2020;36(9):1071-1084. doi:10.1007/s12264-020-00535-1.
- (44) Schwarz E, Steiner J, Guest PC, et al. Investigation of molecular serum profiles associated with predisposition to antipsychotic-induced weight gain. *World J Biol Psychiatry* 2015;16(1):22-30. doi:10.3109/15622975.2014.911298.
- (45) Kosmas CE, Sourlas A, Oikonomakis K, et al. Biomarkers of insulin sensitivity/resistance. *J Int Med Res* 2024;52(10):1285550. doi:10.1177/03000605241285550.
- (46) Steiner J, Berger M, Guest PC, et al. Assessment of insulin resistance among drug-naïve patients with first-episode schizophrenia in the context of hormonal stress axis activation. *JAMA Psychiatry* 2017;74(9):968. doi:10.1001/jamapsychiatry.2017.1983.
- (47) Lin C, Chen K, Zhang R, et al. The prevalence, risk factors, and clinical characteristics of insulin resistance in Chinese patients with schizophrenia. *Compr Psychiatry* 2020;96:152145. doi:10.1016/j.comppsy.2019.152145.
- (48) Guina J, Roy S, Gupta A, et al. Oral glucose tolerance test performance in olanzapine-treated schizophrenia-spectrum patients is predicted by BMI and triglycerides but not olanzapine dose or duration. *Hum Psychopharmacol* 2017 Jul;32(4). doi: 10.1002/hup.2604. Epub 2017 Jun 1. PMID: 28573760.
- (49) Yang Y, Ning X, Wang X, et al. Triglyceride/glucose index is a reliable predictor of insulin resistance in schizophrenia. *Schizophr Res* 2020;223:366-367. doi:10.1016/j.schres.2020.07.005.
- (50) Chen VC, Chen CH, Chiu YH, et al. Leptin/adiponectin ratio as a potential biomarker for metabolic syndrome in patients with schizophrenia. *Psychoneuroendocrinology* 2018;92:34-40. doi:10.1016/j.psyneuen.2018.03.021.
- (51) Yuan X, Yang Q, Yao Y, et al. Role of HOMA-IR and IL-6 as screening markers for the metabolic syndrome in patients with chronic schizophrenia: a psychiatric hospital-based cross-sectional study. *Eur Arch Psychiatry Clin Neurosci* 2024;274(5):1063-1070. doi:10.1007/s00406-023-01618-6.
- (52) Fond G, Lançon C, Auquier P, et al. C-reactive protein as a peripheral biomarker in schizophrenia. An updated systematic review. *Front Psychiatry* 2018;9:392. doi:10.3389/fpsy.2018.00392.
- (53) Mangurian C, Schillinger D, Newcomer JW, et al. Diabetes screening among antipsychotic-treated adults with severe mental illness in an integrated delivery system: a retrospective cohort study. *J Gen Intern Med* 2018;33(1):79-86. doi:10.1007/s11606-017-4205-9.
- (54) Cederholm J, Zethelius B. SPISE and other fasting indexes of insulin resistance: risks of coronary heart disease or type 2 diabetes. Comparative cross-sectional and longitudinal aspects. *Ups J Med Sci* 2019;124(4):265-272. doi:10.1080/03009734.2019.1680583.
- (55) Sasaki, N., Ueno, Y. & Higashi, Y. Indicators of insulin resistance in clinical practice. *Hypertens Res* 47, 978–980 (2024). <https://doi.org/10.1038/s41440-023-01566-7>
- (56) Zhuo C, Zhang Q, Wang L, et al. Insulin resistance/diabetes and schizophrenia: potential shared genetic factors and implications for better management of patients with schizophrenia. *CNS Drugs* 2024;38(1):33-44. doi:10.1007/s40263-023-01057-w.
- (57) Carolan A, Hynes-Ryan C, Agarwal SM, et al. Metformin for the prevention of antipsychotic-induced weight gain: guideline development and consensus validation. *Schizophr Bull* 2024:sbae205. doi:10.1093/schbul/sbae205.
- (58) Agarwal SM, Panda R, Costa-Dookhan KA, et al. Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: a pilot double-blind randomized clinical trial. *Transl Psychiatry* 2021;11(1):219. doi:10.1038/s41398-021-01338-2.
- (59) Wang LJ, Ree SC, Huang YS, et al. Adjunctive effects of aripiprazole on metabolic profiles: comparison of patients treated with olanzapine to patients treated with other atypical antipsychotic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 2013;40:260-266. doi:10.1016/j.pnpbp.2012.10.010.
- (60) Gupta B, Chee KS, Neo LQ, et al. Effect of aripiprazole as an adjunct to atypical antipsychotics on weight and metabolic profile: a 12-week open-label trial. *Ther Adv Psychopharmacol* 2021;11:20451253211046765. doi:10.1177/20451253211046765.