



The Onset of Glucose Dysregulation Among Adults Treated with Antipsychotics: A Systematic Review of Cohort Studies

Riri Erwina Putri¹, Hedy Nadhrati Surura^{2*}

¹Department of Emergency, Datu Beru General Hospital, Aceh, Indonesia

²Department of Psychiatry, Universitas Syiah Kuala, Aceh, Indonesia

*Corresponding Author : hedyanadhrati3@gmail.com

Abstrak

Farmakoterapi antipsikotik, khususnya agen generasi kedua, diakui luas efektif dalam menangani gangguan psikotik, namun sangat terkait dengan konsekuensi metabolik yang merugikan, termasuk gangguan dalam homeostasis glukosa selain peningkatan berat badan dan dislipidemia. Meski demikian, waktu pasti terjadinya disfungsi regulasi glukosa dalam kondisi dunia nyata masih belum sepenuhnya terkarakterisasi. Tinjauan sistematis ini bertujuan untuk mensintesis bukti dari studi kohort mengenai insidensi dan waktu munculnya disfungsi regulasi glukosa pada orang dewasa yang menjalani pengobatan dengan antipsikotik. Mengikuti pedoman PRISMA, pencarian sistematis dilakukan di PubMed, Scopus, dan ScienceDirect untuk studi kohort yang dipublikasikan dalam lima tahun terakhir, dengan fokus pada pasien dewasa yang melakukan pemeriksaan glukosa plasma puasa, HbA1c, hasil uji toleransi glukosa oral, atau insidensi diabetes mellitus. Kualitas metodologis dinilai menggunakan alat Cochrane Risk of Bias 2. Sebanyak delapan studi kohort dengan lebih dari 60.000 partisipan dan durasi tindak lanjut antara satu hingga dua puluh tahun dimasukkan. Hasil menunjukkan bahwa disfungsi regulasi glukosa sering muncul dalam 6-12 bulan setelah memulai terapi dengan agen berisiko tinggi seperti klopazin dan olanzapin, dengan risiko kumulatif yang terus meningkat seiring paparan jangka panjang. Faktor dasar seperti BMI tinggi, dislipidemia, dan riwayat keluarga diabetes secara konsisten berhubungan dengan onset lebih awal. Sementara itu, lingkungan rawat inap terstruktur dengan intervensi diet dan olahraga tampak mampu mengurangi perburukan metabolik meski pada penggunaan jangka panjang clozapine. Secara keseluruhan, pengobatan antipsikotik pada orang dewasa secara konsisten terkait dengan peningkatan risiko disfungsi regulasi glukosa, yang umumnya muncul dalam bulan hingga tahun pertama terapi. Hal ini menekankan pentingnya pemantauan proaktif sejak inisiasi pengobatan serta implementasi strategi pencegahan untuk mengurangi beban kardiometabolik jangka panjang.

Kata Kunci : *Antipsikotik, Disregulasi glukosa, Diabetes melitus, Studi kohort*

Abstract

Antipsychotic pharmacotherapy, particularly second-generation agents, is widely recognized for its efficacy in psychotic disorders but is strongly associated with adverse metabolic consequences, including disturbances in glucose homeostasis in addition to weight gain and dyslipidemia, though the precise time-to-onset of glucose dysregulation under real-world conditions remains insufficiently characterized. This systematic review aimed to synthesize cohort evidence on the incidence and timing of glucose dysregulation in adults treated with antipsychotics. Following PRISMA guidelines, systematic searches were conducted in PubMed, Scopus, and ScienceDirect for cohort studies published in the past five years, focusing on adult patients with outcomes including fasting plasma glucose, HbA1c, oral glucose tolerance test results, or incidence of diabetes mellitus, with methodological quality appraised using the Cochrane Risk of Bias 2 tool. Eight cohort studies with more than 60,000 participants and follow-up durations ranging from one to twenty years were included, showing that glucose dysregulation often emerged within 6–12 months of initiating high-risk agents such as clozapine and olanzapine, with cumulative risk increasing over prolonged exposure. Baseline factors such as elevated BMI, dyslipidemia, and family history of diabetes were consistently associated with earlier onset, while structured inpatient environments with diet and exercise interventions appeared to mitigate metabolic



deterioration despite long-term clozapine use. Overall, antipsychotic treatment in adults is consistently linked to an increased risk of glucose dysregulation, typically arising within the first months to years of therapy, highlighting the importance of proactive monitoring from treatment initiation and the implementation of preventive strategies to reduce long-term cardiometabolic burden.

Keywords : Antipsychotics, Glucose dysregulation, Diabetes mellitus, Cohort studies

Introduction

Antipsychotic pharmacotherapy remains a cornerstone in the management of psychotic disorders; however, it is consistently associated with adverse metabolic sequelae. In addition to weight gain and dyslipidemia, an expanding body of evidence demonstrates clinically significant disturbances in glucose homeostasis during antipsychotic exposure. Notably, the extent of metabolic liability is not uniform across agents. Comparative findings from a large-scale network meta-analysis highlight substantial inter-drug variability in metabolic outcomes, with clozapine and olanzapine generally exhibiting the most unfavorable profiles, whereas several partial agonists and newer agents appear to confer comparatively lower metabolic risk(1). Furthermore, both narrative and quantitative syntheses indicate that antipsychotic exposure may increase the risk of diabetes through indirect mechanisms mediated by adiposity as well as direct effects on insulin sensitivity and secretion, thereby highlighting the clinical imperative for proactive preventive strategies and systematic monitoring(2) Despite the growing body of evidence, much of the comparative metabolic data is derived from randomized controlled trials (RCTs) that are generally short in duration and frequently exclude individuals at highest cardiometabolic risk. This methodological limitation restricts the external validity of findings for long-term outcomes, such as the development of diabetes or persistent deterioration in HbA1c. Moreover, network meta-analyses of RCTs primarily capture short- to medium-term changes in body weight, lipid profiles, and glucose levels, rather than the real-world incidence of dysglycemia observed over prolonged treatment periods. Consequently, robust longitudinal observational studies are essential to elucidate both the incidence and temporal trajectory of glucose dysregulation in routine clinical practice, as well as to delineate drug-specific risks under naturalistic prescribing conditions(1).

Emerging cohort studies provide preliminary but critical insight into the timing of glucose dysregulation following initiation of antipsychotic therapy. For example, a population-based cohort in Taiwan observed that individuals newly diagnosed with schizophrenia exposed to antipsychotics had significantly elevated hazard ratios for developing type 2 diabetes compared to non-exposed controls, with divergence apparent

within the first few years of treatment(3). Other studies likewise note rapid metabolic shifts: impaired fasting glucose or glycemic changes have been documented as early as six months post-initiation with high-risk agents like clozapine, olanzapine and other second-generation antipsychotics. These findings underscore the necessity of quantifying the time-to-onset of glucose dysregulation, when metabolic thresholds are crossed in routine clinical populations, not merely under controlled trial conditions, to better guide monitoring intervals and preventive strategies(4).

Methods

The search was performed using databases from Scopus, Pumed and Science Direct by the latest PRISMA guidelines. Eligible studies were restricted to publications from the previous five years and Cohort studies were included. The keywords are ("Adults" OR "Patients") AND ("Antipsychotics" OR "First-generation antipsychotics" OR "Second-generation antipsychotics") AND ("Glucose dysregulation" OR "Diabetes mellitus" OR "Hyperglycemia" OR "Impaired fasting glucose" OR "Impaired glucose tolerance") AND ("Cohort study" OR "Prospective cohort" OR "Retrospective cohort"). Identified articles from all databases were screened for duplication. Screening of identified records was conducted based on titles and abstracts, and studies meeting exclusion criteria were removed. Ultimately, eligible articles were incorporated into the qualitative synthesis. Inclusion of studies in this systematic review was determined according to the Population, Intervention, Comparison, and Outcome (PICO) framework. The target population comprised adults exposed to antipsychotic treatment. The intervention of interest was the assessment of glucose regulation using established measures (HbA1c, fasting plasma glucose [FPG], fasting blood glucose [FBG], oral glucose tolerance test [OGTT], or postprandial glucose [PPG]). The comparator group consisted of individuals without antipsychotic exposure, those treated with alternative agents, or unexposed periods (if applicable). The primary outcomes were the progression of glucose dysregulation (including prediabetes or diabetes, or increases in HbA1c) and time-to-onset or progression of these events. The methodological quality of the included studies was appraised using the Cochrane Risk of Bias 2 tool.

Results

A total of 79 records were initially identified through database searching (Scopus = 46, PubMed = 13, Science Direct = 20). After removal of duplicates (n = 2) and automated exclusions (n = 62), 15 records remained for title and abstract screening. Of these, 4 were excluded, leaving 11 reports assessed for retrieval. One full text could not be retrieved, and

10 reports were evaluated for eligibility. Finally, 7 cohort studies fulfilled the inclusion criteria and were included in this systematic review (Table 1). Across the eight included cohort studies, a total sample of >60,000 participants with schizophrenia spectrum disorders was analyzed, with follow-up durations ranging from 12 months to 20 years. Antipsychotics evaluated included both first-generation and second-generation agents, with clozapine, olanzapine, risperidone, and quetiapine being the most frequently studied. Regarding time to onset of glucose dysregulation, there was considerable variation between studies. The study's quality was assessed using the Cochrane Risk of Bias 2 tool

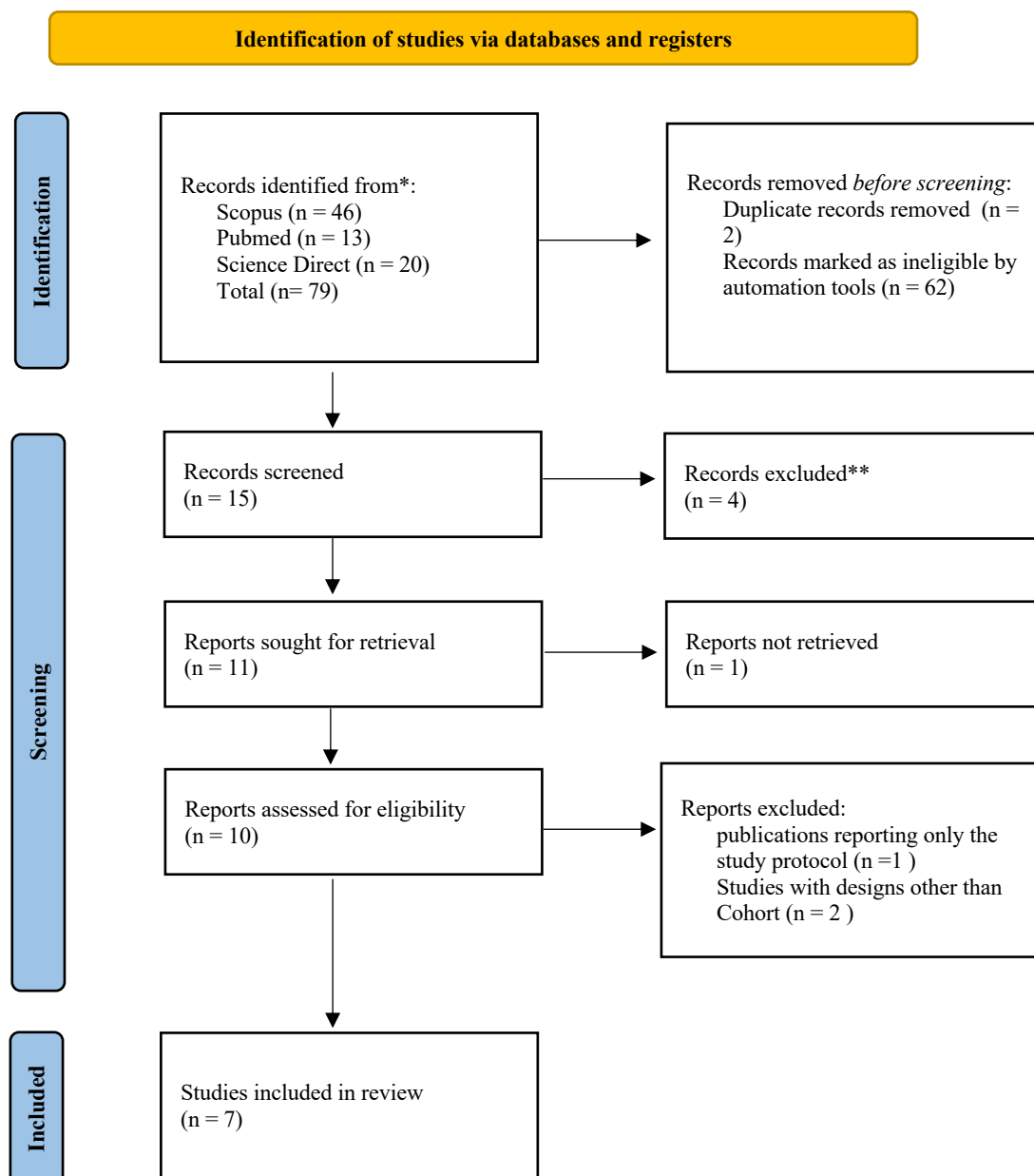


Figure 1. PRISMA flow diagram of study selection process

This data table consists of seven studies that have been selected and synthesized (5–11).

Table 1. Table of Data

Author	Design & Sample	Population & Antipsychotics	Follow-up	Glucose Outcome	Main Findings	Summary
Madsen NM et al. (2025)	Two cohort studies: (1) Nationwide register-based cohort (1999–2019, n=31,856) (2) Regional cohort (2016–2022, n=2,671)	First-episode schizophrenia; exposure = any antipsychotic prescription; multiple agents (FGAs & SGAs including clozapine, olanzapine, risperidone, quetiapine, aripiprazole, lurasidone, etc.)	Nationwide: up to 20 years; Regional: 2 years (HbA1c data, extended up to 5 years)	Diabetes diagnosis (ICD-10) or redeemed prescription of glucose-lowering drug (GLD); HbA1c \geq 48 mmol/mol	- Nationwide: Antipsychotics \uparrow diabetes risk (HRR = 2.04, 95% CI: 1.75–2.38). - Drug-specific: clozapine (HRR 1.74), quetiapine (HRR 1.47), aripiprazole (HRR 1.54), lurasidone (HRR 2.66). HbA1c remained stable at 37 mmol/mol during first 2–5 years (p>0.05).	<10% developed diabetes during follow-up; risk doubles with antipsychotics, particularly SGAs; onset of HbA1c dysregulation not evident within first 2–5 years, suggesting diabetes onset occurs later.
Ishibashi M et al. (2020)	Nationwide all-case surveillance using Clozaril Patient Monitoring Service (CPMS); n=3,746 patients with schizophrenia (2009–2016)	Treatment-resistant schizophrenia; all patients on clozapine (mean dose ~318 mg/day)	Mean treatment duration 91.7 weeks (~1.8 tahun); data up to \geq 24 months	GI defined as FPG \geq 126 mg/dL, casual glucose \geq 200 mg/dL, or HbA1c \geq 6.5%	- 11.7% (428/3654) developed new-onset GI. - Mean time to onset: 56.7 \pm 61.1 weeks (~13 months) after clozapine initiation. - Risk factors: older age (OR 1.03, p<0.001), higher baseline HbA1c (OR 6.9, p<0.001), longer treatment duration (OR 1.01, p<0.001). - HbA1c in new-onset GI group rose	Onset of glucose dysregulation typically occurs within 1 year of clozapine treatment (mean ~13 months). HbA1c gradually increases during treatment, indicating subacute to chronic development rather than immediate onset.

					significantly at 1–6 months and continued to rise up to 24 months.	
Garrido-Torres N et al. (2023)	Prospective longitudinal cohort (PAFIP); n=244 FEP patients (antipsychotic-naïve) vs n=166 controls	First-episode psychosis, drug-naïve at baseline; treated with risperidone, aripiprazole, ziprasidone, quetiapine	3 years	Metabolic syndrome (ATP III); FPG ≥100 mg/dL; triglycerides ≥150 mg/dL; HDL low; BP ≥130/85; waist circumference criteria	<p>- Baseline MetS prevalence similar (6.6% FEP vs 5.4% controls).</p> <p>- At 3 years: MetS ↑ to 18.3% in FEP vs 8.1% controls (p=0.028).</p> <p>- Hyperglycemia prevalence ↑ from 6.1% to 21.2% in FEP (p=0.001); controls 4.8%→8.1%.</p> <p>- Predictors: baseline altered waist circumference (OR=1.07, p=0.011), triglycerides (OR=1.02, p=0.043), and low HDL (OR=0.91, p=0.008).</p> <p>- Risperidone increased risk of high BP at 3 years (OR=2.53, p=0.031).</p>	Dysglycemia begins to emerge within 3 years of initiating antipsychotics in FEP patients: prevalence of hyperglycemia tripled (6.1%→21.2%). Onset relatively early (≤3 years) , particularly in those with abnormal baseline metabolic markers.
de Filippis R et al. (2021)	Prospective observational, 5-year inpatient follow-up; n=21 TRS patients (mean age	Chronic schizophrenia, all on clozapine (mean 266 mg/day, continuous ≥5 years); some on co-medications (valproate, aripiprazole, haloperidol)	5 years	Fasting glucose, cholesterol, triglycerides, liver/kidney function, BMI, blood counts	<p>- No significant change in glycemia, cholesterol, HDL, LDL, triglycerides during 5 years (all p>0.05).</p> <p>- Mean weight decreased by -8.98 kg, BMI -3.0 kg/m²</p>	With structured diet + physical activity in a long-term inpatient facility, no evidence of glucose dysregulation over 5 years of clozapine.

	57.6y; 76% male)				(p=0.008). - Only significant lab change: ↓ red blood cell count (p=0.024).	Instead, metabolic profile remained stable or improved. Suggests environmental/lifestyle control may delay or prevent onset of dysglycemia.
Garcia-Rizo C et al. (2022)	Prospective cohort; n=236 FEP patients (age 7–35); assessed at baseline, 2, 6, 12, 24 months	First-episode psychosis, minimally treated or naïve; grouped by antipsychotic metabolic risk (high: clozapine/olanzapine, medium: risperidone/paliperidone/quetiapine, low: aripiprazole/amisulpride/ziprasidone/haloperidol)	24 months	Fasting plasma glucose	- Birth weight (BW) negatively correlated with glucose at 24 months (r = -0.167, p = 0.037). - LMMA: BW trend toward significance with glucose over time (F=3.22, p=0.073). - Age (F=8.31, p=0.004) and BMI (F=25.66, p<0.001) also associated with glucose rise. - Effect independent of antipsychotic type or dose.	In FEP patients, glucose abnormalities emerge within 2 years , influenced not only by antipsychotics but also early life factors (low birth weight) . Suggests onset of dysglycemia may occur as early as 24 months after treatment initiation, especially in vulnerable patients.
Miyakoshi T et al. (2023)	Multicenter prospective cohort across 43 sites; n = 706 analyzed (time-dependent Cox model; stratified by facility)	Adults with schizophrenia, schizoaffective disorder, or bipolar disorder initiating/switching antipsychotics; patients with prediabetes/possible diabetes at baseline were excluded. Agents examined as time-varying	12 months , with assessments at baseline, 3, 6, and 12 months . Time-to-event defined from study entry to hyperglycemic progression or end of observation.	Progression to hyperglycemia (from normal → prediabetes or probable diabetes) per Japanese monitoring guidance: fasting glucose, post-prandial glucose, or HbA1c	- Antipsychotic-specific hazards (time-dependent Cox): olanzapine HR 2.06 (95% CI 1.05–4.05); clozapine HR 4.25 (1.56–11.60); chlorpromazine HR 4.48 (1.21–16.57) . - Baseline risk factors: BMI ≥ 25 kg/m² HR	Hyperglycemic progression occurs within the first year of treatment (detected between scheduled checks at 3–12 months). Risk is elevated early during exposure to olanzapine, clozapine,

	type).	covariates included olanzapine, clozapine, chlorpromazine (CPZ), risperidone, quetiapine, aripiprazole, paliperidone, haloperidol, and others.		thresholds.	1.57 (1.02–2.41); triglycerides ≥ 150 mg/dL HR 1.72 (1.02–2.88). - Number of antipsychotics and daily CPZ-equivalent dose were not associated with risk.	and CPZ, and in patients with baseline overweight/obesity or hypertriglyceridemia-warranting close metabolic monitoring from initiation.
Zhuo C et al. (2021)	Retrospective cohort, multi-center medical records review; n = 3,162 inpatients with schizophrenia, antipsychotic-naïve at admission	First-episode schizophrenia patients initiating second-generation antipsychotics (SGAs): risperidone (n=1,734), olanzapine (n=978), clozapine (n=450)	12 months	Incidence of diabetes mellitus defined by ICD-10 coding and/or fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%	- After 1 year, incidence of diabetes was 4.17% overall. - Drug-specific incidence: clozapine 6.22%, olanzapine 5.62%, risperidone 2.54% ($p < 0.05$ for clozapine/olanzapine vs risperidone). - Risk factors: higher baseline BMI, family history of diabetes, and exposure to high-risk SGAs.	The onset of glucose dysregulation (progression to diabetes) occurred within the first year of antipsychotic treatment, particularly in patients on clozapine and olanzapine , with incidence >6%. Risperidone showed relatively lower risk.

Discussion

Consistent cohort evidence suggests that antipsychotic use in adults is associated with an increased incidence of dysglycemia (ranging from elevated fasting glucose/HbA1c to new diabetes) with a pattern of risk that may arise relatively early after initiation of therapy. Several registry-based population studies have reported an increased incidence of diabetes in antipsychotic users compared to the general population, and the risk tends to increase with the duration of exposure and use of drug combinations, suggesting a causal relationship related to exposure (dose-or time-response)(9,12) Second-generation antipsychotics (SGAs) show a higher metabolic risk than first-generation, although the magnitude of the differences may vary between studies and may potentially be influenced by selection bias and clinical confounding factors. In a systematic review/meta-analysis, SGA was associated with an

increased risk of diabetes by about one-third compared to FGA, although the authors emphasized that this estimate may be overestimated; These findings remain relevant for risk assessment in clinical practice(13,14).

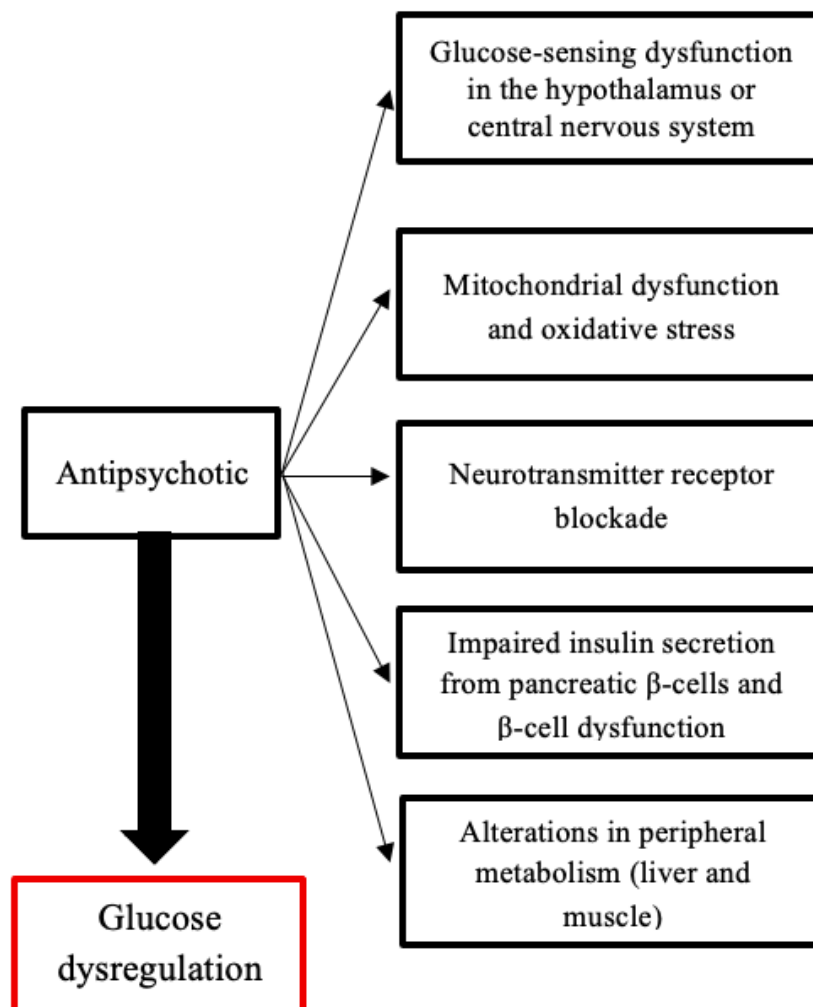


Figure 1. Causes of glucose dysregulation due to the use of antipsychotics

Dopamine (D2/D3) and serotonin (5-HTR2A, 5-HTR3A) receptors are expressed differently in each individual. Because antipsychotics work by blocking or modulating these receptors, the effects on insulin secretion may be more severe in people with certain receptor expression. Polymorphisms of genes that affect transporters (e.g. OCT1 for serotonin or glucose) as well as ER stress proteins will determine how susceptible β cells are to drug toxicity. That is why some patients quickly develop glucose intolerance, while others are relatively resistant despite receiving the same medication, So it can be concluded that Glucose dysregulation in antipsychotic users occurs as a result of complex interactions between pharmacological effects of drugs (receptor blockade, β cell disorders, metabolic changes), molecular mechanisms (mitochondrial dysfunction, oxidative stress, glucose-

sensing disorders in the CNS), as well as individual factors (genetics, metabolic status, lifestyle, duration of therapy). The differences in the onset of this disorder between patients can vary greatly. The onset of glucose metabolism disorders in antipsychotic users is thought to be related to the antagonistic effects of dopamine, serotonin (5-HT_{2C}), and histamine (H₁) receptors that can trigger increased appetite as well as weight gain in a relatively short period of time, while effects on insulin sensitivity and peripheral glucose metabolism may appear even before significant weight changes occur. Other biological mechanisms underlying glucose metabolism disorders due to glucose-sensing dysfunction in the hypothalamus or central nervous system, mitochondrial dysfunction and oxidative stress, as well as peripheral metabolic changes (liver and muscles) that can disrupt the body's glucose and can appear relatively quickly after initiation of antipsychotic therapy, even within a few weeks or months and not always depend entirely on weight gain (15).

A. Glucose-sensing dysfunction in the hypothalamus or central nervous system

In physiology, the hypothalamus "reads" the increase in circulatory glucose and suppresses endogenous glucose production (EGP); in the euglycemic clamp model, intracerebroventricular glucose (ICV) infusion increases the need for glucose infusions and lowers EGP, but both effects are canceled out by haloperidol and olanzapine, signaling a failure of central glucose sensing under antipsychotic exposure(16). Central glucose is metabolized via an astrocyte, neuron lactate shuttle; neuronal pyruvate is converted to acetyl-CoA and then malonyl-CoA, which inhibits CPT-1, elevates cytosolic long-chain acyl-CoA, and activates neuronal K-ATP channels that mediate EGP suppression. Beyond this lipid-sensing arm, ICV glucose activates PI3K signaling (Akt/SGK), engages VEGF signaling, and increases the activity of kinases (ERK, PKA, PKG) that facilitate K-ATP opening, effects that are blunted by haloperidol and olanzapine. Convergent omics evidence points to a hypothalamic HIF-1, VEGF, PI3K axis that is stimulated by central glucose yet inhibited by antipsychotics; lactate itself can upregulate VEGF via HCAR1, providing a link between glucose metabolism and VEGF-dependent kinase activation. In parallel, both drugs can inhibit pyruvate dehydrogenase (PDH), limiting acetyl-CoA and malonyl-CoA generation and thereby reducing the LCFA-CoA/K-ATP signal necessary for hepatic EGP suppression. A further contributing mechanism may be reduced hypothalamic glucose entry (potentially via diminished GLUT1) which would weaken central glucose's ability to suppress EGP; notably, VEGF can increase GLUT1 expression, linking transporter availability to the same pathway targeted by antipsychotics. Taken together, these data support a model in which antipsychotics disrupt central "glucose effectiveness" by dampening HIF-1/VEGF/PI3K,

kinase signaling, constraining PDH-dependent lipid intermediates, and possibly limiting glucose uptake, thereby preventing K-ATP activation and the normal hypothalamic suppression of hepatic glucose output(16).

B. Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction and oxidative stress due to antipsychotics, especially the second generation, originate from upstream disturbances in substrate utilization: the drug cuts off cellular glucose uptake (e.g. in the liver) and distorts glucose-fatty acid metabolism so that glucose/lipids accumulate, increasing the formation of ROS which then targets mitochondrial proteins and decreases the respiration of the electron transport chain (ETC)(17). Some SGAs induce a rapid switch to fat oxidation (RER and decreased O₂ consumption), accompanied by glucose intolerance and elevated plasma glucose, a form of loss of metabolic flexibility that burdens the mitochondria. At the organelle level, ROS is mainly from the leakage of the I/III complex electrons and dopamine metabolic pathways, oxidizes key enzymes (e.g., malat dehydrogenase, pyruvate kinase, 3-oxoacid-CoA transferase), triggers morphological changes (swelling) and depolarization of mitochondrial membranes (loss of $\Delta\psi_m$ -symbol of mitochondrial electrical potential differences), as well as decreases ATP synthesis; These findings were consistent in neuron/liver cell cultures with fluorescent markers ROS and $\Delta\psi_m$. In ETC itself, in vitro evidence suggests many antipsychotics may inhibit complex I-related respiration (some also affect complex II–IV), although drug-specific results may vary; studies on patients' lymphoblast cells also found that complex I/II activity deteriorated after clozapine/olanzapine/quetiapine exposure, signaling decreased respiratory efficiency and possible congenital susceptibility in some people with schizophrenia. So from these cycles it can be concluded that increased ROS inhibits the components of the Krebs and OXPHOS cycles so that ATP production falls, while the accumulation of glucose and fatty acids promotes dyslipidemia, hyperglycemia, and insulin resistance which builds a bioenergetic vicious circle that links antipsychotics with metabolic syndrome (18).

C. Neurotransmitter receptor blockade

The mechanism of glucose dysregulation due to the use of second-generation antipsychotics occurs through complex interactions between histaminergic and muscarinic pathways, each of which makes an important contribution to metabolic syndrome. Histamine is an important neurotransmitter in the central nervous system that plays a role in energy regulation, appetite, and glucose and lipid metabolism through the activation of histamine receptors, especially H1 receptors which are widely expressed in the hypothalamus in the

area of the arcuate nucleus and paraventricular nucleus. Under normal conditions, the activation of H1 receptors suppresses the hunger center, increases satiety, stimulates sympathetic activity, and promotes thermogenesis in brown adipose tissue, so that energy balance and glucose-lipid homeostasis can be maintained. However, the use of atypical antipsychotics such as clozapine, olanzapine, and quetiapine that have a high affinity for these receptors leads to H1 blockade, which inhibits such physiological functions and leads to hyperphagia, decreased energy expenditure, and visceral fat accumulation. The consequence of this change is weight gain which then worsens insulin resistance, but more than that, H1 blockade has also been shown to affect glucose and lipid homeostasis directly without having to be mediated by obesity, for example by decreasing the insulin sensitivity of peripheral tissues so that glucose is more difficult to enter muscle cells and adipose, as well as disrupting lipid metabolism which leads to an increase in triglycerides and cholesterol. In addition, this mechanism interacts with other neurotransmitter systems such as serotonin and dopamine, where H1 blockade can amplify the effects of 5-HT_{2C} antagonism in increasing appetite, making metabolic dysregulation even more complex. This whole mechanism produces a pathophysiological cycle in the form of increased energy intake, decreased thermogenesis, insulin resistance, lipid metabolism disorders, to the appearance of hyperglycemia and dyslipidemia, which ultimately lead to glucose intolerance and type 2 diabetes mellitus in antipsychotic users(19).

Muscarinic receptors, specifically the M₃ subtype have an important role in the regulation of glucose metabolism because they are located in cells β the pancreas and peripheral tissues that are sensitive to insulin. in physiology, activation of M₃ receptors by acetylcholine will increase the activity of calcium channels and intracellular signaling pathways, which ultimately stimulates the exocytosis of insulin granules and facilitates insulin secretion in response to increased blood glucose levels. Second-generation antipsychotics such as clozapine and olanzapine are known to have potential antagonism to the muscarinic M₃ receptor, thereby inhibiting this physiological mechanism and degrading the ability of cells β the pancreas to release insulin. As a result, insulin's response to glucose becomes inadequate, so blood glucose levels tend to increase. In addition, M₃ blockade also has implications for peripheral tissues such as the liver and muscles, as muscarinic receptors play a role in regulating insulin sensitivity and glucose uptake; Antagonism at this level leads to impaired glucose utilization in tissues and worsens insulin resistance. The cumulative effects of insulin secretion inhibition in the pancreas and peripheral insulin sensitivity disorders create a progressive state of hyperglycemia. Furthermore, some studies have

shown that muscarinic antagonism not only affects insulin secretion directly, but also alters autonomic balance by lowering parasympathetic activity, which further worsens the regulation of glucose metabolism(19)

D. β Cell dysfunction

Atypical antipsychotics such as olanzapine, clozapine, and aripiprazole has been shown to affect the function of pancreatic β cells through various molecular mechanisms. Olanzapine can trigger endoplasmic reticulum (ER) stress in β cells leading to impaired insulin secretion; This ER stress reduction has been shown to improve β cell function. In addition, aripiprazole is associated with β cell dysfunction through modulation of the serotonergic system on the islet of Langerhans, where changes in the 5-HT pathway contribute to a decrease in the cell's ability β secrete insulin. Meanwhile, clozapine has been shown to interfere with glucose-stimulated insulin secretion (GSIS) by utilizing the serotonin pathway, primarily through increased 5-HT and activation of 5-HTR3A receptors as well as 5-HTR2A receptor antagonism in β cells. Chronic use of clozapine worsens glucose intolerance as well as decreases the number of pancreatic β cells by directly damaging β cells(10,20).

E. Peripheral Metabolism

Atypical antipsychotics (especially olanzapine and clozapine) causes metabolic syndrome through GLP-1 receptor agonists (GLP-1RAs) that work to counteract these effects. Atypical antipsychotics are known to trigger weight gain, dyslipidemia, insulin resistance, and type 2 diabetes, as they affect a variety of neuroendocrine pathways including as well as interfere with the regulation of insulin, leptin, ghrelin, cortisol, and other metabolism-related hormones. GLP-1RAs such as liraglutide, exenatide, semaglutide, and dulaglutide work by increasing insulin secretion only when blood glucose levels are high, slowing gastric emptying, decreasing glucagon secretion, and affecting appetite regulation centers in the brain, particularly in the hypothalamus and nucleus accumbens, resulting in reduced food intake and improved glycemic control. This effect not only plays a role in blood sugar levels, but also lowers body mass index, waist circumference, as well as visceral fat, which ultimately reduces cardiometabolic risk. In preclinical studies, the administration of GLP-1RAs was shown to protect test animals from acute hyperglycemia due to olanzapine, as well as to reduce weight gain and improve antipsychotic-induced glucose intolerance. Clinical studies in schizophrenic patients who received olanzapine or klozapine showed that liraglutide was able to improve glucose tolerance, lose an average weight of about 7 kg, and shrink waist circumference compared to placebo. However, after therapy was discontinued,

most of the metabolic benefits were reduced, although the relative weight loss still persisted over a period of one year. In addition, Exenatide also showed similar benefits in open-label trials, where some patients achieved $\geq 5\%$ weight loss as well as improvements in fasting HbA1c and glucose. However, at long-term follow-up (12 months), this positive effect decreased, suggesting the importance of continuous monitoring and the possible need for long-term therapy (21).

Conclusion

Antipsychotic treatment in adults is consistently associated with an increased risk of glucose dysregulation, which often emerges within the first months to years of therapy. However, the precise onset of glucose dysregulation remains uncertain, thereby underscoring the importance of early monitoring and the implementation of preventive strategies.

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