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Research Article

The Association Between Haloperidol and Clozapine and The Risk of Hyperglycaemia in Patients with Schizophrenia

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First- and second-generation antipsychotics such as haloperidol and clozapine are treatment options for schizophrenia; however, both have the potential for metabolic side effects, including hyperglycemia. This study aimed to analyse the association between using haloperidol or clozapine, either alone or together, and the occurrence of hyperglycemia in patients with schizophrenia. This study employed a cross-sectional design with retrospective data collection. A total of 154 medical records were obtained as the sample. The research variables consisted of an independent variable, namely the use of clozapine and haloperidol—whether administered as monotherapy or in combination; a dependent variable is blood glucose levels; and variables pertaining to the characteristics of the respondents. The research instruments comprised medical records, laboratory results, and a structured data collection sheet. Data analysis was conducted using the chi-square test, followed by calculation of the odds ratio, performed with RStudio 2024. The results showed there was no significant link between the type of therapy and the risk of hyperglycemia (OR = 1.243; 95% CI: 0.097–66.819).

Schizophrenia is a psychiatric disorder characterized by disturbances in behavior, emotions, perception, and thinking. This disorder often results in auditory hallucinations, paranoid or bizarre delusions, and disorganized thought processes. According to the Riset Kesehatan Dasar 2018 (Riskesdas), the prevalence of schizophrenia in Indonesia is 6.7 per 1,000 households, with East Java reporting a rate of 6.4 [1]. These findings indicate that schizophrenia remains a significant public health concern that requires attention from healthcare professionals.

Antipsychotic medication is the primary treatment for individuals with schizophrenia, aimed at managing psychotic symptoms. Antipsychotics are generally divided into typical (first-generation) and atypical (second-generation) categories. However, numerous studies have documented metabolic side effects linked to these treatments, especially atypical antipsychotics. A 2015 study using data from the FDA Adverse Event Reporting System (FAERS) found that 21.8% of patients treated with atypical antipsychotics experienced hyperglycaemia [2]. Additionally, a 2019 report highlighted weight gain and insulin resistance associated with second-generation antipsychotic use [3].

In Indonesia, second-generation antipsychotics are among the most commonly

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prescribed treatments [4]. Previous studies have mainly reported extrapyramidal symptoms as side effects, with hyperglycemia rarely documented [5], [6] However, other research has confirmed increased blood glucose levels in patients at a psychiatric hospital in South Sulawesi [7]. A similar study was conducted at a hospital in Semarang, which observed the effects of second-generation antipsychotics over four months. The findings showed increased blood glucose levels, although it was not statistically significant [8].

Routine blood glucose monitoring is essential since diabetes mellitus is a leading cause of death from non-communicable diseases. Given reports of hyperglycemia linked to antipsychotic use—particularly second-generation agents—this study aims to explore the occurrence of hyperglycemia further to improve the role of pharmacy professionals in monitoring adverse drug reactions.

This study was conducted at Dr. Radjiman Wediodiningrat Psychiatric Hospital in Lawang from January to March 2025. The main goal is to analyze the relationship between the use of typical and atypical antipsychotics and the risk of hyperglycemia in patients with schizophrenia. Additionally, this research investigates the association between patient characteristics and the use of clozapine or haloperidol, whether as monotherapy or in combination.

Results and Discussion

The respondent characteristics analyzed in this study included gender, age, blood glucose levels, SGOT, SGPT, creatinine, and urea levels. These variables were analyzed in RStudio to assess the association between patient characteristics and the type of antipsychotic therapy administered, using the Chi-square or Fisher's exact test as appropriate. The results of the analysis are presented in **Table 1**. A total of 154 schizophrenia patients met the inclusion criteria. The majority of patients received clozapine therapy, either as monotherapy or in combination (70.78%), compared to those who received haloperidol, either as monotherapy or in combination (29.22%).

Table 1. Association Between Respondents' Characteristics and Antipsychotic Therapy.

Respondent characteristics	Antipsychotic Therapy		*p-value*
	Clozapine (n=109)	Haloperidol (n=45)	
Gender			
Female	26 (16,9)	28 (18,2)	0,014[a]
Male	83 (53,9)	17 (11,0)	
Age (years)			
17-40	70 (45,5)	15 (9,7)	0,001[a]
41-65	39 (25,3)	30 (19,5)	
SGOT			
Normal	92 (59,7)	39 (25,3)	0,913[a]
Abnormal	17 (11,0)	6 (3,9)	
SGPT			
Normal	84 (54,5)	39 (25,3)	0,258[a]
Abnormal	25 (16,2)	6 (3,9)	
Creatinine			
Normal	90 (58,4)	29 (18,8)	0,026[a]
Abnormal	19 (12,3)	16 (10,4)	
Urea			
Normal	106 (68,8)	44 (28,6)	1,000[b]
Abnormal	3 (1,9)	1 (0,6)	

[a]: Chi-square test

[b]: Fisher's exact test

The analysis revealed a statistically significant association between gender and type of antipsychotic therapy (p-value = 0.014). Male patients were more likely to receive clozapine, while female patients tended to be prescribed haloperidol. This may be explained by pharmacokinetic and pharmacodynamic differences, whereby the presence of estrogen and progesterone influences clozapine metabolism and distribution, resulting in higher plasma concentrations in females [9]. Furthermore, females are more susceptible to weight gain, and there are reports, albeit inconsistent, of a higher incidence of leukopenia and neutropenia in women [10]. However, a limitation of this study is the lack of analysis on adverse effects, such as weight gain.

A significant association was also found between age group and type of therapy (p-value = 0.001), where patients aged 17–40 years were more likely to receive clozapine, while those aged above 40 years were more frequently treated with haloperidol. This is supported by meta-analyses indicating that younger patients may derive greater benefits from clozapine, with better tolerance of side effects and higher treatment adherence and monitoring compliance [11]. Similarly, other studies have shown that haloperidol is more commonly recommended for elderly patients, due to its lower anticholinergic effects and the ability to be administered at lower doses to minimize the risk of extrapyramidal symptoms [12].

Another significant association was observed for creatinine levels (p-value = 0.026), with patients on clozapine tending to have normal levels compared with those on haloperidol. Other studies have confirmed this finding, reporting that haloperidol use is associated with an increased risk of acute kidney injury (AKI), with an incidence rate of 20.3 per 1000 person-years [13]. However, no further analysis of clozapine's effects on renal function was performed in that study. Additional research found that haloperidol monotherapy was not directly associated with AKI, but the concurrent use of other medications might contribute to an increased AKI risk[13]. The use of antipsychotics may lead to focal necrosis in the renal cortex and medulla, resulting in thickening of the glomerular capillary basement membrane and potentially triggering AKI [14].

In contrast, no statistically significant associations were found for SGOT (p-value = 0.913), SGPT (p-value = 0.258), or urea (p-value = 1.000) with the type of antipsychotic therapy used. Both clozapine and haloperidol, whether administered as monotherapy or in combination, were predominantly associated with normal liver enzyme and urea levels. These findings are consistent with prior studies documenting transient elevations in transaminases during the initial phase of clozapine or haloperidol therapy, typically not requiring discontinuation [15], [16]. Similarly, urea levels were generally within normal limits and did not indicate impaired renal function. Nevertheless, routine liver function monitoring is recommended, especially during the early phase of antipsychotic treatment.

Referring to **Table 2**, the combinations suspected to carry a high risk of hyperglycemia are: clozapine alone; clozapine with risperidone (32.5%), clozapine with valproic acid (5.8%), clozapine with olanzapine (3.9%), and clozapine with quetiapine (3.2%). Impaired insulin secretion is attributable to clozapine binding to muscarinic M3 receptors on pancreatic β-cells, thereby reducing glucose-stimulated insulin secretion (GSIS). This peripheral mechanism directly precipitates hyperglycemia and can occur independently of weight gain. When clozapine is combined with other antipsychotics that also have muscarinic affinity, inhibition along the M3 pathway is further amplified, leading to a greater reduction in insulin secretion. Another mechanism involves weight gain induced by olanzapine, quetiapine, and risperidone through H1 and 5-HT2C antagonism. These effects increase appetite, blunt satiety, and activate the hypothalamic AMPK axis, promoting weight gain and insulin resistance. Other studies have shown that clozapine can increase hepatic glucose production and impair β-cell function, contributing directly to hyperglycemia [3], [18], [19]. In addition, valproate combination therapy can increase appetite and body weight and promote insulin resistance; thus, combining valproate with

clozapine raises the overall metabolic burden and further increases the risk of hyperglycaemia [3], [20].

Tabel 2. Frequency of Clozapine and Haloperidol Use (Monotherapy vs Combination)

Mono/Combination therapy	Antipsychotic Therapy	
	Clozapine (n=109)	**Haloperidol (n=45)**
Monotherapy	3 (1,9)	2 (1,3)
Combination		
Atypical Antipsychotic		
Risperidone	50 (32,5)	0 (0,0)
Aripiprazole	4 (2,6)	0 (0,0)
Olanzapine	6 (3,9)	3 (1,9)
Quetiapine	5 (3,2)	0 (0,0)
Typical Antipsychotic		
Trifluoperazine	26 (16,9)	0 (0,0)
Chlorpromazine	0 (0,0)	9 (5,8)
Benzodiazepine		
Lorazepam	20 (13,0)	28 (18,2)
Diazepam	14 (9,1)	0 (0,0)
Clobazam	3 (1,9)	1 (0,6)
Anticholinergic		
Trihexyphenidyl	16 (10,4)	0 (0,0)
SSRI		
Fluoxetine	3 (1,9)	0 (0,0)
Tetracyclic antidepressant		
Maprotiline	0 (0,0)	1 (0,6)
Mood stabilizer		
Lithium Carbonate	2 (1,3)	0 (0,0)
Valproic Acid	9 (5,8)	0 (0,0)
Divalproex Sodium	0 (0,0)	6 (3,9)
Antihistamine		
Cetirizine	1 (0,6)	0 (0,0)
Vitamine		
Folic Acid	5 (3,2)	6 (3,9)
Hepatoprotector		
Curcuma	5 (3,2)	0 (0,0)

Haloperidol combinations that may increase the risk of hyperglycemia include haloperidol plus chlorpromazine (5.8%), haloperidol plus divalproex sodium (3.9%), haloperidol plus olanzapine (1.9%), and haloperidol plus maprotiline (0.6%). Haloperidol itself—a first-generation antipsychotic with prominent D2 receptor blockade—has a lower metabolic liability, and therefore does not substantially affect appetite or directly provoke hyperglycemia. However, the risk increases when combined with other agents. Specifically, chlorpromazine adds M1 and H1 antagonism, which can increase appetite and body weight and is associated with a heightened tendency toward type 2 diabetes mellitus. Moreover, co-administration with haloperidol can augment sedation, potentially reducing physical activity and thereby increasing hyperglycemia risk. A similar pattern is observed with olanzapine, which carries a high risk of glucose dysregulation via H1/5-HT2C antagonism, insulin resistance, and peripheral effects on pancreatic β-cells. Combination with divalproex sodium is

associated with weight gain and insulin resistance, leading to worsened glucose control when used alongside antipsychotics, owing to an increased total metabolic load. Maprotiline can also promote weight gain and insulin resistance. It has a strong affinity for histamine H1 receptors (akin to sedating antihistamines). H1 blockade within the hypothalamus reduces anorexigenic (histaminergic) signaling, increasing appetite; the accompanying sedation lowers energy expenditure. 5-HT2C and α1-adrenergic antagonism further diminishes satiety signaling and increases food intake. α1 blockade contributes to sedation/fatigue and reduced energy expenditure—phenomena collectively known as psychotropic-drug-related weight gain. Additional metabolic–hormonal alterations with maprotiline include increased ghrelin, reduced adiponectin, and worsening insulin resistance [20], [21].

Referring to **Table 3**, the association between antipsychotic therapy and hyperglycemia events shows that three respondents developed hyperglycemia in the clozapine combination group and one respondent in the haloperidol combination group. Among those receiving olanzapine combinations, all cases of hyperglycemia occurred in patients who were also taking risperidone. In the haloperidol group, the hyperglycemia patient received the haloperidol–lorazepam combination

Table 3. Association Between Antipsychotic Therapy and Risk of Hyperglycemia

Antipsychotic Therapy	Risk of Hyperglycemia		p-value	OR (CI95%)
	Hyperglycemia	Normal Blood Glucose		
Clozapine Monotherapy/ combination	3 (1,9)	106(68,8)	1,000[a]	1,243 (0,097-66,819)
Haloperidol Monotherapy/ combination	1(0,6)	44(28,6)		
Total	4	150		

[a]: Fisher's exact test

Based on the results, exposure to clozapine therapy, whether as monotherapy or in combination, was associated with a 1.24-fold increase in the risk of hyperglycemia compared with haloperidol monotherapy or combination therapy (OR = 1.243; 95% CI: 0.097–66.819). However, this risk was not statistically significant, indicating that both clozapine and haloperidol have a similar likelihood of causing hyperglycemia. Blood glucose level in the clozapine combination group is 111 ± 27mg/dL and haloperidol combination group is 121 ± 33mg/dL. In this study, most patients had normal blood glucose levels. These findings align with previous research reporting elevated blood glucose levels during short-term haloperidol use, although the increase was not statistically significant. Furthermore, low-dose, limited use of haloperidol appears to be safe for glucose regulation [21]. Other studies have shown that clozapine, even at low doses, can lead to elevated HbA1c levels after two months of treatment. However, this condition is not always linked to weight gain or insulin resistance and is often reversible [22]. Similar findings were reported regarding the risk of metabolic syndrome associated with clozapine use.

The proposed mechanism involves clozapine's antagonistic action on M3 muscarinic receptors, which may cause β-cell dysfunction in the pancreas. Additionally, clozapine increases plasma catecholamine levels, thereby promoting gluconeogenesis and glycogenolysis. It also disrupts the regulation of leptin, ghrelin, and GLP-1, which is vital for insulin homeostasis [23]. Conversely, other studies recommend the early initiation of oral antidiabetic agents alongside clozapine to reduce the risk of prediabetes and prevent weight gain, given clozapine's metabolic effects, including impaired peripheral insulin signaling and pancreatic β-cell dysfunction. Metformin is advised to counteract insulin resistance, or liraglutide, a GLP-1 receptor agonist, may improve glycemic control, supporting

early intervention [24], [25] (Jain & Lai, 2024; Siskind et al., 2016). The limitation of this study is that it did not analyze the duration of antipsychotic use. As a result, patients receiving treatment for longer periods—who are relatively more stable—were pooled with those in the early phase of treatment, particularly during the first three months, when metabolic risk is typically higher. Random blood glucose (RBG) was used per the hospital's pharmacovigilance policy; however, it is strongly influenced by pre-test food intake, acute stress, intercurrent infection, and physical activity. This high variability introduces measurement error and may statistically obscure the true association. Moreover, RBG reflects momentary glycemic status rather than chronic exposure to subacute metabolic changes (e.g., those mediated by H1/5-HT2C antagonism). Recommendation. Future analyses should prioritize HbA1c as the primary outcome and/or implement repeated measurements at baseline and at regular 3-month intervals.

Conclusion

In this study, clozapine was associated with a slightly higher risk of hyperglycemia; however, the difference was not statistically significant. The findings suggest that treatment with either haloperidol or clozapine is generally safe for liver and kidney function, as indicated by normal SGOT, SGPT, and urea levels. Additionally, the study showed that clozapine was more often prescribed to male patients and those aged 17–40 years, while haloperidol use was linked to an increased risk of elevated creatinine levels.

Material and Methods

This study employed an observational cross-sectional design. Data was collected retrospectively from medical records of schizophrenia patients who received haloperidol or clozapine therapy, either as monotherapy or in combination. This study was ethically approved with an Ethical Clearance (EC) letter issued by the Health Research Ethics Committee of Dr. Radjiman Wediodiningrat Psychiatric Hospital, Lawang, with reference number TK.02.04/D.XXXVII.3.6/14178/2024**.**

Population and Sample

The total population during the period from January to March 2025 comprised 154 medical records. The sampling technique used was purposive sampling, with inclusion criteria as follows: diagnosed with schizophrenia, aged between 17 and 65 years, and received haloperidol or clozapine therapy (either as monotherapy or in combination) for a minimum duration of one month. Exclusion criteria included a history of diabetes mellitus, long-term use of corticosteroids, or incomplete medical records. The sample size was equal to the total population studied.

Research Instrument

The instruments used in this study included the Electronic Medical Record (EMR) system and a data collection sheet containing the medical record number, type of antipsychotic therapy received, age, gender, concurrent medications, random blood glucose level, SGOT, SGPT, creatinine, and urea levels. Statistical analysis was performed using RStudio version 2024**.**

Statistical Analyses and Data Visualization

Data were classified into categorical variables and presented as percentages in tabular form. Gender was categorized as male or female; age was grouped into two ranges: 17–40 years and 41–65 years. Random blood glucose (RBG) was considered normal if within the range of 70–199 mg/dL; SGOT and SGPT were considered normal at ≤ 40 U/L; creatinine was categorized as normal within 0.6–1.2 mg/dL; and urea was considered normal within 10–50 mg/dL.

An analysis of the relationship between patient characteristics and the use of clozapine versus haloperidol was conducted using the chi-square and Fisher's exact tests**.** The hypotheses were H_0: There is no association between patient characteristics and the use of clozapine compared to haloperidol; H_1: There is an association between patient characteristics and the use of clozapine compared to haloperidol.

An analysis was also conducted to examine the relationship between the use of clozapine versus haloperidol and the incidence of hyperglycemia using a 2x2 contingency . The relationship was tested using Fisher's exact test**,** with the hypotheses H_0: There is

no association between the use of clozapine compared to haloperidol and the incidence of hyperglycemia; H_1: There is an association between the use of clozapine compared to haloperidol and the incidence of hyperglycemia. This analysis was followed by the calculation of the Odds Ratio (OR)

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