Pharmacy Education (2024) 24(2) 23 - 31
https://doi.org/10.46542/pe.2024.242.2331

IAI SPECIAL EDITION

RESEARCH ARTICLE

Incidence of hypercholesterolaemia and hyperglycaemia in schizophrenic patients: Atypical antipsychotic medication and clinical variables

Woro Harjaningsih[1,2], Mustofa[3], Zullies Ikawati[2], Rahma Aqisfi Novyani[4], Natalia Sugianto[4]

[1] Doctoral Programme, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3] Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[4] Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia

Keywords
Atypical antipsychotic
Hypercholesterolemia
Hyperglycaemia
Schizophrenia

Correspondence
Zullies Ikawati
Department of Pharmacology and Clinical Pharmacy
Faculty of Pharmacy
Universitas Gadjah Mada
Yogyakarta
Indonesia
zullies_ikawati@ugm.ac.id

Abstract

Background: Atypical or second-generation antipsychotic drugs commonly used in the management of schizophrenia include risperidone. Risperidone is linked to the incidence of metabolic syndrome-related adverse effects. **Objective:** This study aims to investigate the correlation between the administration of risperidone therapy and the incidence of metabolic syndrome in outpatients diagnosed with schizophrenia. This inquiry involves an examination of relevant laboratory parameters, specifically cholesterol, blood glucose, and haemoglobin A1c (HbA1C) levels, alongside an evaluation of pertinent clinical variables that may exert an influence. **Methods**: This study adopted a cross-sectional approach to receiving risperidone therapy for a minimum of three months at Grhasia Mental Hospital in Yogyakarta, Indonesia. Sampling was executed using an accidental sampling technique, targeting patients who met the predefined inclusion criteria. **Results:** The study enrolled a total of 97 participants, comprising 58 males and 39 females. Subsequent statistical analyses failed to demonstrate any statistically significant associations between hyperglycemia and various factors, including the risperidone regimen (p = 0.574), risperidone dosage (p = 0.619), and the duration of risperidone therapy (p = 1.000). **Conclusion:** Risperidone has a long-term risk of causing hyperglycemia in people with schizophrenia; consequently, blood glucose and HbA1C levels must be monitored on a regular basis.

Introduction

Schizophrenia is a chronic and intricate mental health disorder characterised by a constellation of symptoms encompassing delusions, hallucinations, disorganised speech and behaviour, and cognitive impairments (Patel *et al*., 2014). Globally, it affects an estimated 24 million individuals, or approximately one in every 300 people (0.32%) (WHO, 2022). In Indonesia, the prevalence of schizophrenia is reported as 6.7 per 1000 households, signifying that 6.7 out of every 1000 households have members grappling with this condition. Notably, Yogyakarta Province exhibits the second-highest prevalence rate of schizophrenia in the nation, trailing only Bali (Ministry of Health Republic of Indonesia, 2019).

The pharmacological management of schizophrenia primarily relies on antipsychotic medications, categorised into two classes: first-generation antipsychotics, often referred to as 'typical' antipsychotics, and second-generation antipsychotics, known as 'atypical' antipsychotics. All antipsychotic drugs, whether typical or atypical, exert their therapeutic effects, particularly through the inhibition of dopamine D2 receptors (Bruijnzeel *et al*., 2014).

Conventional antipsychotics are associated with extrapyramidal symptoms, including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia. In contrast, atypical antipsychotics are generally less likely to induce extrapyramidal symptoms. However, they are known to carry cardiometabolic adverse effects, including weight gain, dyslipidaemia, and glucose dysregulation (Lally & MacCabe, 2015).

Despite its beneficial effects in the management of neuropsychiatric disorders, risperidone, as an atypical antipsychotic, is accompanied by side effects that induce metabolic disturbances in individuals with schizophrenia, particularly during short-term treatment, with these effects intensifying with long-term use (Delacrétaz *et al*., 2018). Extended utilisation of risperidone can result in metabolic syndrome-related complications, including weight gain, dyslipidaemia, increased adiposity, inflammation, glucose intolerance, insulin resistance, and an elevated risk of developing obesity, type 2 diabetes, and cardiovascular disease (Gonçalves *et al*., 2015). Notably, risperidone is associated with a 35% incidence rate of metabolic syndrome (Lee & Halter, 2017).

Risperidone use can result in hypercholesterolaemia, often known as dyslipidaemia. Risperidone raises total cholesterol levels due to the action of atypical antipsychotics, which cause shifts from Acetyl CoA to cholesterol. One of the main routes in turning Acetyl CoA into cholesterol is the lanosterol pathway and 7-dehydrocholesterol reductase (DHCR7), which has two roles in cholesterol production (Delacrétaz *et al*., 2018). Besides that, risperidone has been associated with metabolic syndrome-related adverse effects such as hyperglycaemia (Koller *et al*., 2003). Retrospective analyses have highlighted a higher prevalence of hyperglycaemia among individuals taking risperidone than those taking other antipsychotic medications (Ho *et al*., 2017). Furthermore, hyperglycaemia associated with risperidone treatment frequently manifests within the initial three months of use, with an average onset occurring at 3.9 years from the commencement of treatment (Van Winkel *et al*., 2008). Hypercholesterolaemia and hyperglycaemia-related issues can progress to cardiovascular disease, resulting in severe long-term morbidity and mortality (Casey, 2004).

It is worth noting that several factors in individuals with schizophrenia, including age, gender, duration of schizophrenia diagnosis, smoking habits, and dietary choices, can influence the incidence of hypercholesterolaemia and hyperglycaemia (Mordarska & Godziejewska-Zawada, 2017; Susanti & Bistara, 2018; Agaba *et al*., 2019; Campagna *et al*., 2019; Usman *et al*., 2020; Arania *et al*., 2021). However, there hasn't been sufficient investigation into the negative effects of hypercholesterolaemia and hyperglycaemia caused by risperidone use in Indonesia. Given the imperative nature of long-term or even lifelong therapy for individuals with schizophrenia to prevent relapse, there is a pressing need for research addressing the adverse effects stemming from hypercholesterolaemia and hyperglycaemia induced by risperidone use. The findings of this study are intended to serve as valuable research material for the ongoing monitoring of these side effects.

Methods

Research design

The ethical feasibility of this research has been registered with the Ghrasia Mental Hospital's Ethics Committee under the number No. 048/EC KEPKRSJG/VI/2022. This study adopts an observational approach, utilising a cross-sectional design. It focuses on individuals diagnosed with schizophrenia receiving outpatient care and undergoing risperidone therapy at Grhasia Mental Hospital in Yogyakarta. The sampling method employed in this study is incidental sampling. Subsequently, the researcher sought permission from the patient's family to include the patient as a research participant. Upon obtaining consent, a series of laboratory assessments, specifically temporary cholesterol measurements, random blood sugar analyses, and haemoglobin A1c (HbA1C) evaluations, were conducted on the selected patients at the Grhasia Mental Hospital Laboratory in Yogyakarta. Furthermore, a concise interview with the patient's family was conducted, complemented by a thorough review of the patient's medical records, to delineate the patient's demographic characteristics and medication history.

Material

This study recruited individuals receiving outpatient care at Grhasia Mental Hospital in Yogyakarta, specifically targeting those diagnosed with schizophrenia who were undergoing risperidone therapy. The eligibility criteria encompassed outpatients aged between 18 and 60 years who had been diagnosed with schizophrenia and had been consistently receiving antipsychotic therapy for a minimum of three preceding months. Patients who declined participation in the study were excluded from the research cohort.

Data analysis

Descriptive analysis was undertaken to examine patient demographics, disease characteristics, and patterns of risperidone therapy. To ascertain the correlation between risperidone therapy patterns (including regimen, dosage, and treatment duration) and the occurrence of hypercholesterolaemia and hyperglycaemia among patients, as well as the correlation with other variables (such as age, gender, duration of schizophrenia diagnosis, and the impact of schizophrenia, dietary habits, and smoking behaviour), the Chi-Square test was employed at a 95% confidence level. The ensuing discussion delves into the implications of schizophrenia, dietary factors, and smoking habits on developing hypercholesterolaemia and hyperglycaemia.

Results and Discussion

Patient demographic characteristics

Gender

This observed gender discrepancy can be attributed to men being 2.37 times more susceptible to developing schizophrenia than women. This heightened susceptibility among men may be attributed to their perceived higher life responsibilities and the increased stressors they encounter compared to women, who may demonstrate a greater capacity for accepting their circumstances (DiPiro *et al.*, 2020).

Age

These findings align with the National Institute of Mental Health's assertion that the onset of schizophrenia frequently occurs between the ages of 16 and 30 years subsequent to the initial episode of psychosis. Furthermore, corroborating evidence from prior research conducted at the Atma Husada Mahakam Samarinda Regional Mental Hospital in Indonesia indicates that 55.3% of schizophrenia cases were recorded in individuals aged between 25 and 45 years (Farizah *et al*., 2020). This pattern can be attributed, in part, to the multifaceted nature of the adult life stage, characterised by significant physical, intellectual, and social role transformations, rendering it susceptible to a range of psychological health disorders, including schizophrenia (Sefrina, 2016).

Length of schizophrenia

It is imperative to underscore that schizophrenia, characterised as a chronic condition, mandates prolonged and, in certain cases, lifelong therapeutic interventions. This is primarily attributable to the inherent propensity of schizophrenia symptoms to resurface intermittently (Andari, 2017).

Comorbidity

It is noteworthy that schizophrenia is frequently associated with comorbid medical conditions, including but not limited to diabetes, hypertension, and dyslipidaemia. Consequently, the selection of antipsychotic medications must be undertaken with meticulous consideration of the patient's comorbidity profile (Heald *et al*., 2017).

Antipsychotic pattern

According to the findings, more patients received combination therapy at a dose of ≤ 2mg/day (Table I). Typically, the initial dosage of risperidone ranges from 1 to 2 mg per day, with the option for gradual escalation to a range of 6 to 8 mg per day (Chisholm-Burns, 2016). The majority of patients are also on long-term risperidone medication. Notably, the average duration of risperidone usage stood at 4.12 years, with the shortest treatment duration documented at three months and the longest extending to 14 years. According to research, schizophrenia is a mental condition that lasts a long period, possibly even throughout the patient's life, and relapses frequently occur, extending the duration of the disorder (DiPiro *et al.*, 2020).

Table I: Patient demographic characteristics and antipsychotic pattern

Patient characteristic		Number of patients	Percentage (%)
Gender	Male	58	57.79
	Female	39	42.21
Age (years)	18-45	69	71.13
	46-60	28	28.87
Length of schizophrenia (years)	≤10	45	46.39
	>10	52	53.61
Comorbidity	Hypertension	10	10.31
	Without comorbid	87	89.69
Regimen	Single	21	21.65
	Combination	76	78.35
Dosage	≤ 2 mg/daily	51	52.58
	>2 mg/daily	46	47.42
Length of therapy	≤ 1 year	18	18.56
	>1 year	79	81.44

Results of bivariate analysis between regimen, dosage, duration of risperidone therapy and incident of hypercholesterolaemia and hyperglycaemia

Table II presents the bivariate analysis outcomes, indicating that no statistically significant correlation was observed between the regimen, dose, or duration of risperidone medication and the occurrence of hypercholesterolaemia ($p > 0.05$).

Table II: Bivariate analysis between regimen, dosage, duration of risperidone therapy and incidence of hypercholesterolaemia and hyperglycaemia

Variable	Yes		No		*p*	RR (95%CI)
	n	%	n	%		
Hypercholesterolaemia						
Regimen						
Single	7	33.33	14	66.67	0.561	0.768 (0.398-1.481)
Combination	33	43.42	43	56.58		
Total	40		57			
Dosage						
≤ 2 mg/daily	20	39.22	31	60.78	0.826	0.902 (0.561-1.450)
>2 mg/daily	20	43.48	26	56.52		
Total	40		57			
Length of therapy						
≤ 1 year	6	35.29	11	64.71	0.782	0.830 (0.416-1.659)
>1 year	34	42.50	46	57.50		
Total	40		57			
Hyperglycaemia						
Regimen						
Single	0	0.00	21	100.00	0.574	0
Combination	4	5.26	72	94.74		
Total	4		93			
Dosage						
≤2 mg/daily	3	5.88	48	94.12	0.619	2.706 (0.292-25.109)
>2 mg/daily	1	2.17	45	97.83		
Total	4		93			
Length of therapy						
≤ 1 year	0	0.00	17	100.00	1.000	0
>1 year	4	5.00	76	95.00		
Total	4		93			

For the purposes of this study, the term "*single regimen*" encompasses both the use of risperidone alone and its combination with typical antipsychotics. Meanwhile, the term "*combination regimen*" encompasses the use of risperidone in combination with atypical antipsychotics and its concurrent administration with both typical and atypical antipsychotics. It should be noted that the inclusion of other atypical antipsychotics such as clozapine, aripiprazole, and quetiapine in combination with risperidone is associated with an elevated risk of hypercholesterolemic events, given that these atypical antipsychotics are recognised for their propensity to induce hypercholesterolemic side effects (Meyer & Koro, 2004).

According to prior research, combined risperidone therapy correlates to a higher likelihood of developing hypercholesterolaemia than risperidone monotherapy. Notably, polytherapy has been associated with a greater prevalence of metabolic syndrome (50.0% *vs*. 34.3%, $p = 0.015$) relative to antipsychotic monotherapy (Correll *et al*., 2007).

Furthermore, this study's outcomes are consistent with previous schizophrenia research, demonstrating that risperidone is associated with metabolic abnormalities, including obesity and hypercholesterolaemia, at a higher rate than aripiprazole. After one year of treatment, a substantial increase in body weight was observed in both groups, amounting to 9.2 kg for aripiprazole and 10.5 kg for risperidone (Vázquez-Bourgon *et al*., 2022).

Table II provides an overview of the bivariate analysis outcomes, which did not yield a statistically significant correlation ($p > 0.05$) between the regimen, dose, or duration of risperidone medication and the prevalence of hyperglycaemia. It is noteworthy that the concurrent administration of risperidone with other atypical antipsychotics, such as clozapine, aripiprazole, and quetiapine, which are recognised for their potential to induce hyperglycaemic side effects, can elevate the risk of hyperglycaemia (Lindenmayer *et al*., 2001). Conversely, typical antipsychotics are associated with a lower risk of hyperglycaemia than atypical antipsychotics (Holt, 2019). Specifically, one study found that the combination of risperidone, particularly when combined with clozapine, resulted in the highest blood sugar deterioration, affecting 26.7% of individuals, compared to risperidone monotherapy, affecting 15% (Riawan *et al*., 2022).

A systematic review assessing the risk of diabetes in patients treated with risperidone or olanzapine, in comparison to those not receiving antipsychotics, indicated that higher doses of risperidone (i.e. doses in the upper third of the daily dosing range for specific subgroups, with a mean dose of 2.7 mg), were associated with an increased likelihood of developing diabetes (OR 1.68, 95% CI 1.07-2.65) (Bernardo *et al*., 2021).

Regarding the duration of risperidone therapy, the findings of this study revealed that 4 out of 80 patients (5.00%) who had been on risperidone for more than a year exhibited hyperglycaemia. Among these individuals, one patient with the highest blood sugar level (334 mg/dL) had been on risperidone for nine years, followed by another patient with a blood sugar level of 289 mg/dL who had been using risperidone for seven years. Additionally, two patients with blood sugar levels of 249 mg/dL and 238 mg/dL had been on risperidone for three years. These observations indicate that the duration of risperidone therapy has an impact on the incidence of hyperglycaemia. Hyperglycaemia onset varies when using risperidone, with new onset typically occurring within the first three months of use and persisting for an average of 3.9 years (Van Winkel *et al*., 2008).

Correlation of other variables (age, sex, onset of diagnosis of schizophrenia, dietary and smoking habits with the prevalence of hypercholesterolaemia and hyperglycaemia

The results presented in Table III indicate that this study did not identify any statistically significant associations ($p > 0.05$) between diverse variables, including age, gender, onset of schizophrenia, dietary habits, smoking behaviours, and the incidence of hypercholesterolaemia and hyperglycaemia.

Table III: Correlation of other clinical variables (age, sex, onset of diagnosis of schizophrenia, dietary and smoking habits with the prevalence of hypercholesterolaemia and hyperglycaemia

Variable	Yes		No		*p*	RR (95%CI)
	n	%	n	%		
Hypercholesterolaemia						
Age (years old)						
18 - 45	26	37.68	43	62.23	0.374	0.754 (0.467-1.216)
46-60	14	50.00	14	50.00		
Total	40		57			
Gender						
Male	23	39.66	35	60.34	0.861	0.910 (0.564-1.467)
Female	17	43.59	22	56.41		
Total	40		57			
Length of schizophrenia (years)						
≤ 10	17	37.78	28	62.22	0.662	0.854 (0.527-1.385)
>10	23	44.23	29	55.77		
Total	40		57			
Dietary habit						

Variable	Yes		No		*p*	RR (95%CI)
	n	%	n	%		
High cholesterol	17	42.50	23	57.50	0.998	0.949 (0.588-1.533)
Low cholesterol	23	40.35	34	59.65		
Total	40		57			
Smoking habit						
Smoking	19	41.30	27	58.70	1.000	1.003 (0.623-1.614)
No smoking	21	41.18	30	58.82		
Total	40		57			
Hyperglycaemia						
Age (years old)						
18 - 45	3	4.35	66	95.65	1.000	1.217 (0.132-11.211)
46-60	1	3.57	27	96.43		
Total	4		93			
Gender						
Male	2	3.45	56	96.55	1.000	0.672 (0.099-4.575)
Female	2	5.13	37	94.87		
Total	4		93			
Length of schizophrenia						
≤10	2	4.54	42	95.45	1.000	1.205 (0.177-8.206)
>10	2	3.77	51	96.23		
Total	4		93			
Dietary habit						
High glucose	3	6.82	41	93.18	0.326	0.277 (0.030-2.567)
Low glucose	1	1.89	52	98.11		
Total	4		93			
Smoking habit						
Smoking	2	4.35	44	95.65	1.000	1.109 (0.163-7.555)
No smoking	2	3.92	49	96.08		
Total	4		93			

These findings align with existing literature suggesting that women aged over 45 years tend to exhibit higher total cholesterol levels compared to men of the same age (Chang *et al*., 2002). Additionally, the findings indicated that hypercholesterolaemia was more prevalent among schizophrenic patients who had used risperidone for over a year, affecting 34 out of 80 patients (42.5%), in comparison to those who had used risperidone for less than a year, affecting 6 out of 17 patients (35.3%). These findings corroborate recent research suggesting that risperidone is associated with metabolic abnormalities, including obesity and hypercholesterolaemia, at a higher rate than aripiprazole. Both groups exhibited substantial increases in body weight after one year of treatment, with aripiprazole users gaining 9.2 kg and risperidone users gaining 10.5 kg (Vázquez-Bourgon *et al*., 2022). Regarding dietary habits, hypercholesterolaemia was more common in patients who frequently consumed high-cholesterol foods, affecting 17 out of 40 patients (42.5%), compared to those who rarely consumed such foods, affecting 23 out of 57 patients (40.4%). These findings support the notion that diet plays a substantial role in total cholesterol levels, with higher consumption of fatty foods leading to elevated cholesterol levels. Individuals who consume a diet rich in saturated fats, including meats, butter, cheese, and ice cream, are at risk of experiencing elevated cholesterol levels (Dewi *et al*., 2015). Aside from that, hyperglycaemia was reported by 3 out of 44 (6.82%) schizophrenia patients who frequently consumed sugary meals and 1 out of 53 (1.89%) schizophrenia patients who rarely consumed sugary foods. Individuals with a frequent high-sugar diet exhibited a higher prevalence of hyperglycaemia than those with infrequent high-sugar consumption. An unbalanced diet can lead to unstable blood sugar levels (Susanti & Bistara, 2018). The study also noted that hypercholesterolaemia was more common among

patients who smoked, affecting 19 out of 46 patients (41.3%), compared to non-smokers, which affected 21 out of 51 patients (41.2%). These findings align with several other studies, which have shown that smokers are at a higher risk of hypercholesterolaemia, with relative risks (RR) ranging from 1.4 (95% CI 1.3-1.6), p = 0.010 (Febriani & Febriani, 2018), and RR = 2.5 (95% CI 1.6-4.0) (Mamat & Sudikno, 2010). Additionally, 2 out of 46 (4.35%) schizophrenia patients who smoked and 2 out of 51 (3.92%) schizophrenia patients who did not smoke experienced hyperglycaemia. Individuals who smoke exhibited a higher prevalence of hyperglycaemia compared to non-smokers. These findings are consistent with a study in Port Harcourt, Nigeria, which found that individuals who smoke or have smoked have a 1.9 times higher likelihood of developing hyperglycaemia than non-smokers (Nyenwe *et al*., 2003). According to the American Diabetes Association, cigarette smoking can elevate blood sugar levels, increasing the risk of diabetes mellitus among frequent smokers. Studies have also indicated that smoking contributes to the development of insulin resistance, accelerating the transition from normoglycemia to impaired glucose tolerance, ultimately resulting in a higher risk of pre-diabetes among smokers (Campagna *et al*., 2019).

Distribution of patients according to HbA1C levels

According to HbA1C readings, approximately 47% of patients in this study had pre-diabetes and more than 10% had diabetes (Table IV).

Table IV: Distribution of patients according to HbA1C levels

HbA1C levels (%)	Category	Number of patients	Percentage (%)
< 5.7	Normal	18	40.91
5.7 – 6.4	Pre-diabetic	21	47.73
≥6.5	Diabetic	5	11.36
Total		**44**	**100.00**

Research conducted by Guo *et al*. in 2011 reported that risperidone had a more pronounced impact on elevating HbA1c levels than olanzapine or clozapine. In addition, patients taking risperidone at or above the FDA-recommended daily dose of 2 mg/day had a significantly greater likelihood of developing HbA1c levels exceeding 6.0 compared to those using aripiprazole or ziprasidone. Almost half of the patients in this study received risperidone at a dose of > 2 mg/day, with the remainder receiving a dose of ≥ 2 mg/day. It is important to note that while HbA1c levels above 6.0 do not invariably signify the onset of diabetes mellitus, risperidone can substantially influence glycaemic control and the risk of developing diabetes, particularly at higher cumulative dosages (Guo *et al*., 2011). However, it is crucial to consider the risk of diabetes in the context of antipsychotic treatment and implement measures to prevent, screen for, and manage diabetes if it ensues (Holt, 2019).

Conclusion

Risperidone, as an atypical or second-generation antipsychotic drug, poses a long-term risk of inducing hyperglycaemia in individuals with schizophrenia; therefore, regular monitoring of blood glucose and HbA1C levels is imperative.

Acknowledgements

The authors wish to extend their heartfelt gratitude to the director and the entire staff of Grhasia Mental Hospital in Yogyakarta, Indonesia, for their invaluable support and assistance in facilitating the data collection for this study. Furthermore, it is worth noting that this article was presented at the 2023 Annual Scientific Conference of the Indonesian Pharmacist Association.

Source of funding

The Lecturer Research Grants 2022 from the Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.

References

Agaba, D. C., Migisha, R., Namayanja, R., Katamba, G., Lugobe, H. M., Aheisibwe, H., Twesigomwe, G., & Ashaba, S. (2019). Prevalence and associated factors of metabolic syndrome among patients with severe mental illness attending a tertiary hospital in Southwest Uganda. *BioMed Research International,* **2019**, 1–8. https://doi.org/10.1155/2019/1096201

American Diabetes Association. (2018). 4. Lifestyle management: Standards of medical care in diabetes—2018. *Diabetes Care*, **41**(1), 38–50. https://doi.org/10.2337/dc18-S004

Andari, S. (2017). Religious based social services on rehabilitation of schizophrenic patients. *Jurnal PKS,* **16**(2), 195–208.

Arania, R., Triwahyuni, T., Esfandiari, F., & Nugraha, F. R. (2021). The relationship between age, gender and education

level and the incidence of diabetes mellitus at the Mardi Waluyo Clinic, Central Lampung. *Jurnal Medika Malahayati*, **5**(3), 146–153. https://doi.org/10.33024/jmm.v5i3.4200

Bernardo, M., Rico-Villademoros, F., García-Rizo, C., Rojo, R., & Gómez-Huelgas, R. (2021). Real-world data on the adverse metabolic effects of second-generation antipsychotics and their potential determinants in adult patients: A systematic review of population-based studies. *Advances in Therapy*, **38**(5), 2491–2512. https://doi.org/10.1007/s12325-021-01689-8

Bruijnzeel, D., Suryadevara, U., & Tandon, R. (2014). Antipsychotic treatment of schizophrenia: An update. *Asian Journal of Psychiatry*, **11**, 3–7. https://doi.org/10.1016/j.ajp.2014.08.002

Campagna, D., Alamo, A., Di Pino, A., Russo, C., Calogero, A. E., Purrello, F., & Polosa, R. (2019). Smoking and diabetes: Dangerous liaisons and confusing relationships. *Diabetology & Metabolic Syndrome*, **11**(1), 85. https://doi.org/10.1186/s13098-019-0482-2

Casey, D. E. (2004). Dyslipidemia and atypical antipsychotic drugs. *The Journal of Clinical Psychiatry*, **65**(suppl 18), 27v35. https://www.psychiatrist.com/read-pdf/5244/

Chang, H.-Y., Yeh, W.-T., Chang, Y.-H., Tsai, K.-S., & Pan, W.-H. (2002). Prevalence of dyslipidemia and mean blood lipid values in Taiwan: Results from the nutrition and health survey in Taiwan (NAHSIT, 1993-1996). *The Chinese Journal of Physiology*, **45**(4), 187–197.

Chisholm-Burns, M. A. (Ed.). (2016). *Pharmacotherapy Principles & Practice, Fourth Edition*. McGraw-Hill Education.

Correll, C. U., Frederickson, A. M., Kane, J. M., & Manu, P. (2007). Does antipsychotic polypharmacy increase the risk for metabolic syndrome? *Schizophrenia Research*, **89**(1), 91–100. https://doi.org/10.1016/j.schres.2006.08.017

Delacrétaz, A., Vandenberghe, F., Gholam-Rezaee, M., Saigi Morgui, N., Glatard, A., Thonney, J., Solida-Tozzi, A., Kolly, S., Gallo, S. F., Baumann, P., Berney, S., Zulauff, S. V., Aubry, J.-M., Hasler, R., Ebbing, K., von Gunten, A., Conus, P., & Eap, C. B. (2018). Early changes of blood lipid levels during psychotropic drug treatment as predictors of long-term lipid changes and of new onset dyslipidemia. *Journal of Clinical Lipidology*, **12**(1), 219–229. https://doi.org/10.1016/j.jacl.2017.10.002

Dewi, S. S., Nur Lathifah Mardiyati, S. G., & Elida Soviana, S. G. (2015). *The relationship between fiber intake and cholesterol levels in outpatients with coronary heart disease at Dr. Hospital. Moewardi Surakarta* [Thesis Diploma, Universitas Muhammadiyah Surakarta]. https://eprints.ums.ac.id/37871/

DiPiro, J. T., DiPiro, C. V., Ellingrod, V. L., & Schwinghammer, T. L. (2021). *Pharmacotherapy Handbook, Eleventh Edition*. McGraw-Hill Education.

Farizah, N. A., Fitriany, E., & Nugrahayu, E. Y. (2020). The relationship between social function and quality of life of outpatient schizophrenia patients at the Atma Husada Mahakam Samarinda Regional Mental Hospital. *Motiva*: *Jurnal Psikologi*, **2**(2), 43–50. https://doi.org/10.31293/mv.v2i2.4436

Febriani, D., & Febriani, B. (2018). The effect of lifestyle on hypercholesterolemia. *The Open Public Health Journal,* **11**(1), 526–532. https://doi.org/10.2174/1874944501811010526

Gonçalves, P., Araújo, J. R., & Martel, F. (2015). Antipsychotics-induced metabolic alterations: Focus on adipose tissue and molecular mechanisms. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology,* **25**(1), 1–16. https://doi.org/10.1016/j.euroneuro.2014.11.008

Guo, Z., L'italien, G. J., Jing, Y., Baker, R. A., Forbes, R. A., Hebden, T., & Kim, E. (2011). A real-world data analysis of dose effect of second-generation antipsychotic therapy on hemoglobin A1C level. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **35**(5), 1326–1332. https://doi.org/10.1016/j.pnpbp.2011.03.020

Heald, A., Pendlebury, J., Anderson, S., Narayan, V., Guy, M., Gibson, M., Haddad, P., & Livingston, M. (2017). Lifestyle factors and the metabolic syndrome in Schizophrenia: A cross-sectional study. *Annals of General Psychiatry*, **16**(1), 12. https://doi.org/10.1186/s12991-017-0134-6

Ho, B. L., Lee, W. Y., Chou, Y. C., Chen, Y. C., & Chou, Y. H. (2017). Risk of metabolic syndrome and hyperglycaemia among users of typical and atypical antipsychotics: A retrospective cohort study. *Journal of clinical pharmacy and therapeutics*, **42**(4), 464–471.

Holt, R. I. G. (2019). Association Between Antipsychotic Medication Use and Diabetes. *Current Diabetes Reports*, **19**(10), 96. https://doi.org/10.1007/s11892-019-1220-8

Koller, E. A., Cross, J. T., Doraiswamy, P. M., & Schneider, B. S. (2003). Risperidon-associated diabetes mellitus: A pharmacovigilance study. *Pharmacotherapy*, **23**(6), 735–744. https://doi.org/10.1592/phco.23.6.735.32178

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *British Medical Bulletin,* **114(**1), 169–179. https://doi.org/10.1093/bmb/ldv017

Lee, P. G., & Halter, J. B. (2017). The pathophysiology of hyperglycemia in older adults: Clinical considerations. *Diabetes Care*, **40**(4), 444–452. https://doi.org/10.2337/dc16-1732

Lindenmayer, J. P., Nathan, A. M., & Smith, R. C. (2001). Hyperglycemia is associated with the use of atypical antipsychotics. *The Journal of Clinical Psychiatry*, **62**(23), 30–38. https://www.psychiatrist.com/read-pdf/8374/

Mamat & Sudikno. (2010). Factors associated with HDL cholesterol levels (Analisis Data of The Indonesian Family Life Survey 2007/2008). *Gizi Indonesia,* **33(**2), 143–149. https://doi.org/10.36457/gizindo.v33i2.90

Meyer, J. M., & Koro, C. E. (2004). The effects of antipsychotic therapy on serum lipids: A comprehensive Review. *Schizophrenia Research,* **70**(1), 1–17. https://doi.org/10.1016/j.schres.2004.01.014

Ministry of Health Republic of Indonesia. (2019). *Basic health research, Distribution of schizophrenia/psychosis prevalence in Indonesia*. https://databoks.katadata.co.id/datapublish/2019/10/08/persebaran-prevalensi-skizofreniapsikosis-di-indonesia

Mordarska, K., & Godziejewska-Zawada, M. (2017). Diabetes in the elderly. *Menopause Review*, **16**(2), 38. https://doi.org/10.5114/pm.2017.68589

Nyenwe, E. A., Odia, O. J., Ihekwaba, A. E., Ojule, A., & Babatunde, S. (2003). Type 2 diabetes in adult Nigerians: A study of its prevalence and risk factors in Port Harcourt, Nigeria. *Diabetes Research and Clinical Practice*, **62**(3), 177–185. https://doi.org/10.1016/j.diabres.2003.07.002

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: Overview and treatment options. *Pharmacy and Therapeutics*, **39**(9), 638–645.

Riawan, H., Kristanto, C. S., & Ikawati, Z. (2022). Comparison of risperidone-based antipsychotic therapy regimens against extrapyramidal syndrome, cognitive function, and metabolic disorders in schizophrenia patients. *Majalah Farmaseutik*, **18**(2). https://doi.org/10.22146/farmaseutik.v1i1.60346

Sefrina, F. (2016). The relationship between family support and social functioning in outpatient schizophrenia patients. *Jurnal Ilmiah Psikologi Terapan*, **4**(2), 140-160.

Susanti, S., & Bistara, D. N. (2018). Relationship between eating patterns and blood sugar levels in diabetes mellitus sufferers. *Jurnal Kesehatan Vokasional*, **3**(1), Article 1. https://doi.org/10.22146/jkesvo.34080

Usman, J., Rahman, D., & Sulaiman, N. (2020). Factors associated with the incident of diabetes mellitus in patients at RSUD Haji Makassar. *Jurnal Komunitas Kesehatan Masyarakat*, **2**(1), 16–22.

Van Winkel, R., De Hert, M., Wampers, M., Van Eyck, D., Hanssens, L., Scheen, A., & Peuskens, J. (2008). Major changes in glucose metabolism, including new-onset diabetes, within three months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. *The Journal of Clinical Psychiatry*, **69**(3), 472–479. https://doi.org/10.4088/jcp.v69n0320v

Vázquez-Bourgon, J., Ortiz-García de la Foz, V., Gómez-Revuelta, M., Mayoral-van Son, J., Juncal-Ruiz, M., Garrido-Torres, N., & Crespo-Facorro, B. (2022). Aripiprazole and risperidone present comparable long-term metabolic profiles: Data from a pragmatic randomized controlled trial in drug-naïve first-episode psychosis. *International Journal of Neuropsychopharmacology*, **25**(10), 795–806. https://doi.org/10.1093/ijnp/pyac033

WHO. (2022). *Schizophrenia*. https://www.who.int/news-room/fact-sheets/detail/schizophrenia