Evaluation Of Lipid Profiles In Psychiatric Patients Taking Olanzapine Drug In Khartoum State

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Abstract

Background: Psychiatric disorders are devastating and complex diseases involving alterations in mood, cognition, and behavior. The management of patients with psychiatric disorders consists of drug therapy and/or psychotherapy. Some of these drugs cause adverse metabolic complications, such as olanzapine, despite that olanzapine is one of the most effective drugs. The study aims to assess lipid profiles among psychiatric patients in Khartoum state.

Methods: This was a cross-sectional study, with fifty samples from known psychiatric patients as cases and fifty samples from healthy people as controls. The lipid profile parameters were measured by the enzymatic method using a spectrophotometric device. Data analysis was carried out through the statistical package for social science (SPSS).

Results: The statistical analysis of case study results showed that the mean and SD level of cholesterol (340 ± 41.9), triglycerides (284.6 ± 59.9), and LDL (274.9 ± 50) showed significant (P.value =0.00). HDL (26.8 4.5) showed a significant (P.value = 0.00) decrease in psychiatric patients when compared to healthy individuals.

Conclusion: olanzapine induces dyslipidemia in psychiatric patients. Dyslipidemia always occurs in the first month of treatment with all doses of drugs.

Keywords— Psychiatric disorders, Olanzapine, cholesterol, triglycerides, LDL, and HDL.

1- Introduction

People with severe mental illnesses such as schizophrenia, major depression, and bipolar disorder have a shorter lifespan that is approximately 20 %shorter than the General population and higher risks of suffering from various illnesses[(1,2)]. For instance, they tend to have a higher incidence of cardiovascular diseases(CVD) and mortality rate[(3)]. The high cardiovascular risk can be explained by modifiable risk factors for CVD including smoking [(4,5)], obesity [(6,7)], diabetes [(8)], Arterial hypertension [(9)], dyslipidemia [(10)], and metabolic syndrome [(11,12)].

Many Studies underlined the role of psychotropic drugs' Side effects in weight gain, diabetes mellitus, and dyslipidemia [(13,14)]. Certain psychiatric Patient populations such as patients with schizophrenia are at increased risk for dyslipidemia and obesity, due to poor diet and sedentary lifestyle, but these Conditions can be caused by some antipsychotic medications [(15,16)]. Clozapine and olanzapine, appear to be associated with hyperlipidemia, which may be associated with changes In body weight [(17,18,19)]. Further, newer antipsychotic agents tend to be less susceptible to weight gain and the development of dyslipidemia[(20)]. Psychiatric disorders are common in all countries where their prevalence has been examined, because of the combination of high prevalence, early onset, persistence, and impairment, mental disorders make a major contribution to the total disease burden[(21)]. In 2019, common mental disorders around the globe include depression, which affects about 264 million, bipolar disorder, which affects about 45 million, dementia, which affects about 50 million, and schizophrenia, and other psychoses, which affects about 20 million people[(22)]. Some factors can contribute to the development or progression of

mental disorders such as genetic, psychological, and environmental factors. [23] . Different risk factors may be present at different ages, with risk occurring as early as during the prenatal period [24]**.** Olanzapine is one of the most widely used second-generation antipsychotics (SGAs) for schizophrenia, bipolar disorder, and psychotic symptoms. Olanzapine can improve the main symptoms of psychosis, shows great acceptability, decreases all causes of discontinuation, and prevents future relapse[25]. Many studies suggested that olanzapine is one of the most efficacious antipsychotic drugs in patients with schizophrenia[26،27] olanzapine is associated with the highest level Of metabolic disturbances among Atypical antipsychotic drugs. [27,29,30,31]. These disturbances include weight gain, dyslipidemia, and type 2 diabetes[32], which increase the risk of cardiovascular disease, which is already a major clinical problem in Patients with severe mental disorders [33,34,35]. The underlying molecular pathways for these Side-effects are not yet established, although a CNS Mediated orexigenic action of antipsychotics has recently been shown [36,37]. One possible peripheral mechanism for drug Induced dyslipidemia, might be enhanced lipogenesis through increased enzymatic activity. Fatty acid synthase (FASN) And stearoyl-CoA desaturase (SCD) are two central Enzymes in fatty-acid biosynthesis[38].

.Materials and methods:

2.1 Study design& population

Descriptive cross-sectional study. was conducted in the Khartoum States at Taha Baasher mental hospital during the period from September 2021 to October 2021.

This study includes 50 Sudanese psychotic patients taking olanzapine drug age range between (30 to 69) years old as the case group and 50 healthy Sudanese individuals as the control group from the same age. Diagnosis people with psychotic disorders are diagnosed according to the criteria outlined in the Diagnostic Clinical and based predominantly on the patient's history, observed behavior, and subjective reports, as well as the results of the mental status examination, diagnostic tests, including neuroimaging and electroencephalographic (EEG), genotypic, toxicologic, and serologic assessments, are usually performed only in certain patients who present with the first episode of psychosis or with psychotic symptoms associated with preexisting neurodegenerative diseases, other medical conditions, or substance abuse are at risk. [39].

2.2 Selection criteria :

Inclusion criteria:

Psychotic patients under olanzapine treatment were included in this study.

Exclusion criteria:

Newly diagnosed psychotic patients, undivided psychotic patients without treatment, psychotic patients using other treatments than olanzapine, and individuals with underlying diseases that may affect serum lipid levels were excluded.

2.3 Ethical consideration:

This study will be approved by the ethical committee of Alzaeim Alazhary University, MLSs college, and hospital administration with patients' guardians' consent considered for collection after explaining the objectives of the study.

2.4 Data collection:- Primary data was collected from the respondents in the form of a questionnaire and also from the analytical results of the patients who had undergone tests. **S**econdary data was collected from medical textbooks, medical journals, and internet websites.

2.5 Biochemical measurements:

An early morning venous blood sample was collected by using sterile, dry, plastic syringes and a tourniquet to make the veins more prominent. The puncture site was cleaned with 70% ethanol, and each volunteer provided a blood sample of 3 mL, which was collected in lithium heparin containers. The lithium heparin blood sample was centrifuged at 4000 rpm to obtain the plasma for lipid profile tests. All these samples were stored at (-4 c) until the analysis.

The lipid profile (plasma total cholesterol, triglycerides, LDL, and HDL) was estimated by an enzymatic method by using a spectrophotometric device A spectrophotometer consists of two instruments, namely a spectrometer for producing light of any selected color (wavelength) and a photometer for measuring the intensity of light. The standards and measurements of quality control of all materials and reagents used here were done according to standardized quality control measures.

2.6 Data analysis:-

The statistical analysis of the results was performed by using the Statistical Package for Social Sciences (SPSS) version 15.0 for Windows version 10 using a T-test for testing difference significance and a Pearson correlation test (r-value as the coefficient). A P value of 0.05 was considered statistically significant.

3. Results :

This study included 50 psychiatric patients as a case group and another 50 healthy subjects as a control group.

The results of the study showed a significant increase in cholesterol, TG, and LDL with a significant decrease in HDL in cases than the control group with a (P. Value = 0.00) as shown in **Table 1**.

In addition, we discovered no significant difference in the mean level of lipid profile between females and males in the case group, with P-values (0.07-0.3-0.5-0.09) for Cholestrol, TG, LDL, and HDL, as shown in Table 2.

The mean level of lipid profile between schizophrenia and depression showed that there was no significant difference with P-values (0.9-0.3-0.4-0.3) for Cholestrol, TG, LDL, and HDL, respectively, as shown in **Table 3.**

Also, the mean level of lipid profile between 15mg dose/day and 20mg dose/day showed that there was no significant difference with P-values (0.6-0.4-0.3-0.7) for Cholestrol, TG, LDL, and HDL respectively, as shown in **Table 4.**

Also, the correlation of lipid profile with the duration of treatment was insignificant as shown in **figure 1-4.**

Table (1): Statistical results of the mean, standard deviation, and P-value of the lipid profile in the case and control groups

variables	case group (N= 50)	Control group (N= 50)	P-value
Cholesterol mg/dl	340 ± 41.9	184 ± 19.9	0.000
TG mg/dl	284.6 ± 59.9	95.4 ± 15.7	0.000
LDL mg/dl	274.9 ± 50	66.4 ± 6.2	0.000
HDL mg/dl	26.8 ± 4.5	56.3± 8.7	0.000

Table (2): Statistical results of the mean, standard deviation, and P-value of the lipid profile in the case group by gender

	male (27)	female (23)	p-value
Cholesterol mg/dl	349 ± 56.5	329.4 ± 61	0.07
TG mg/dl	298.4 ± 49.1	268.3 ± 51	0.3
LDL mg/dl	268.5 ± 4.1	282.5 ± 4.9	0.5
HDL mg/dl	26.5 ± 43.4	27.2 ± 38.3	0.09

Table (3): Statistical results of the mean, standard deviation, and P-value of the lipid profile in the case group based on diagnosis

	schizophrenia (25)	depression (25)	P-value
Cholesterol mg/dl	334.2 ± 65	345.9 ± 55.8	0.9
TG mg/dl	285.4 ± 55.9	283.8 ± 43.2	0.3
LDL mg/dl	282 ± 4.4	267.9 ± 4.6	0.4
HDL mg/dl	27.3 ± 41.3	26.4 ± 42.4	0.3

Table (4): Statistical results of mean, SD, and P-value of lipid profile in the case group according to the dose of treatment

	15 mg/day (28)	20 mg/days (22)	p value
Cholesterol mg/dl	338.2 ± 44.9	342.3 ± 38.6	0.6
TG mg/dl	287.8 ± 63.3	280.5 ± 56.6	0.4
LDL mg/dl	279.7 ± 53.1	268.8 ± 46.2	0.3
HDL mg/dl	26.2 ± 4.3	27.5 ± 4.7	0.7

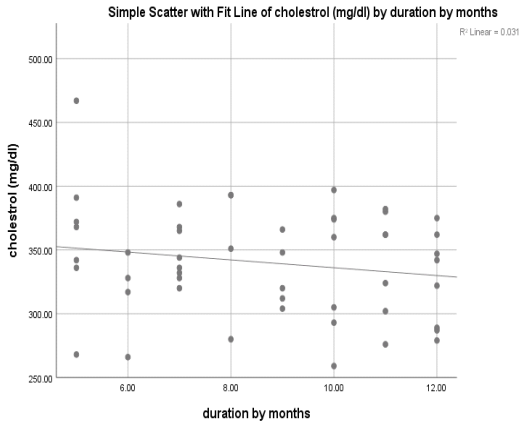

Figure 1: Correlation between cholesterol and duration of treatment in a case study R= - 0.117 (negative correlation). P. value= 0.21.

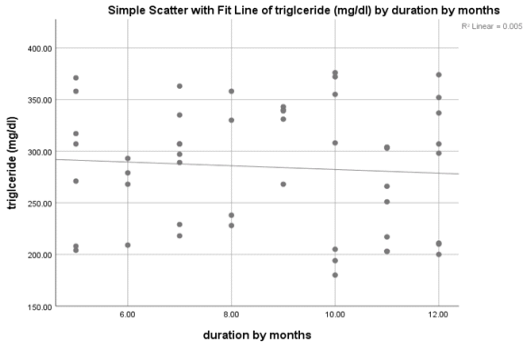

Figure 2: Correlation between TG and duration of treatment in the case study R= - 0.072 (negative correlation). P. value= 0.61.

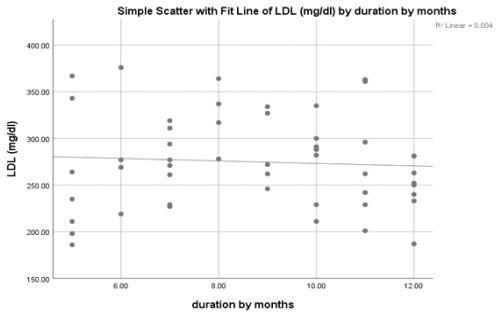

Figure 3: Correlation between LDL and duration of treatment in the case study. R= - 0.065 (negative correlation). P. value= 0.65.

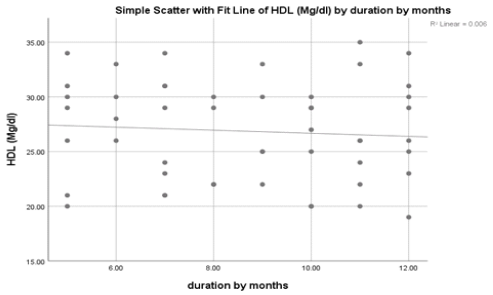

Figure 4: Correlation between HDL and duration of treatment in the case study

R= - 0.075 (negative correlation). P.value= 0.60.

4. Discussion

Psychiatric patients are severe neuropsychiatric illnesses have a high morbidity and mortality rate due to dyslipidemia in conjunction with cardiovascular disease (CVD) relapse[40,41]. It has been shown that olanzapine, a second-generation antipsychotic drug, is a major contributor to dyslipidemia among patients with schizophrenia [42,43,44]. However, the clinical features of olanzapine-induced dyslipidemia remain unclear because of inconsistent data among previous studies. Although some clinical randomized trials have reported increased serum triglyceride (TG) levels in schizophrenic patients on olanzapine therapy, the changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) remain a matter of dispute [45,46,47,48,49]. Dyslipidemia is a well-established risk factor in the pathogenesis of CVD, including coronary heart disease (CAD), and acute coronary syndrome (ACS). [50].

Olanzapine induces dyslipidemia, There is one possible peripheral mechanism for olanzapine drug Induced dyslipidemia, which might be enhanced lipogenesis through increased enzymatic activity. Fatty acid synthase (FASN) And stearoyl-CoA desaturase (SCD) are two central Enzymes in fatty-acid biosynthesis[51].

This was a cross-sectional study aimed to measure levels of lipid profile (Cholestrol, Triglycerides, LDL, HDL) among Sudanese patients with psychotic disorder taking olanzapine as treatment, psychotic patients enrolled in this study. The results of the present study provide evidence that psychotic patients had higher levels of cholesterol, triglycerides, and LDL than the reference values. In contrast, the level of HDL is lower than the reference values. These findings agree with the study reported that there were Significant increases in triglyceride, cholesterol, and LDL-C, and significant decreases in HDL-C were observed. [52].

Our study also reported that there is no significant difference between the two genders, which disagrees with the study conducted by Zhou XM and his colleagues reported that olanzapine has adverse effects on lipid profile in Female over Male patients. This difference may be due to the small sample size and the use of different instruments. [80]

We reported that there was no significant difference in the Duration of treatment and dose. This agreed with a previous study [53] that reported no significant difference in TG, LDL, and HDL of the cases group with time. The only alterations being observed with statistical significance in Total cholesterol. This difference may be attributed to Environmental factors. They also reported that there was no significant dose-dependent as we did.

In the previous meta-analysis of 21 studies on the impact of olanzapine on lipid profiles in schizophrenia patients, we showed that the clinical symptoms of dyslipidemia were defined by an increase in TG, TC, and LDL-C, with no significant changes in HDL-C. Furthermore, when we examined the effects of olanzapine medication duration on patients with schizophrenia's lipid profiles, we found that 4 weeks of olanzapine treatment led to aberrant serum lipid levels. The effect of olanzapine on altering serum levels of lipids might endure synchronously even if the course of olanzapine therapy was prolonged. Intriguingly, there was a substantial rise in TC level in the TC 24-week group after the data of McDonnell et al. [53] were excluded (P = 0.005). The mean fasting serum TC levels significantly decreased from baseline to endpoint [54] according to an evaluation of the research. Given that the long-term diet control was not covered in the trial and that its design included an initial period of stabilization on oral olanzapine before random assignment to therapy, McDonnell's group's conclusion may be contested. In this study, the correlation between lipid profiles and duration of treatment in the case study of olanzapine-induced dyslipidemia did not depend on duration (see figure (1,2,3,4)).

The previous study done by Rong Li *et al* demonstrated the influence of olanzapine on serum lipids after 4 weeks of treatment and may be beneficial clinically to monitor the plasma lipid levels on time and help guide appropriate interventions if necessary. Of note, two studies concluded that TG levels increased significantly after 2–3 weeks of olanzapine treatment and found the increase in TG levels to occur before the weight gain and other lipid levels changes,[45,56]. However, their relatively small sample sizes of 13 and 15 patients, make it difficult to generalize their findings to a broader clinical population of patients on olanzapine. More extensive studies will be required to validate the findings.

While the mechanism of olanzapine-induced dyslipidemia remains unknown, several factors have been implicated. First, olanzapine antagonizes the 5-hydroxytryptamine and histamine H1 receptors in the hypothalamus,[57,58], and promotes adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in the central nervous system[59]. This in turn results in increased food intake, dyslipidemia,

and obesity[60]. Dyslipidemia may be a secondary reaction to olanzapine-induced weight gain or obesity. Our study only revealed changes in four lipid parameters and did not explore the relationship between lipid profile and body weight. More studies such as meta-analyses or large-scale clinical trials could be conducted to discuss this issue in the future. Besides, the concentrations of circulating leptin and ghrelin were also significantly increased in schizophrenic patients on olanzapine and correlated with increased food intake[61,62]. Second, olanzapine-induced insulin resistance inhibits the activity of lipoprotein lipase, thereby slowing the catabolism of LDL and increasing plasma LDL-C levels[63,64]. In addition, insulin resistance stimulates sterol regulatory element binding protein-1c (SREBP-1c), which enhances the production of very low-density lipoprotein in the liver and consequently increases plasma TG levels[65,66]. Third, the molecular mechanisms underlying olanzapine-associated lipid dysregulation are partly understood. Olanzapine enhances lipogenesis directly in the liver by regulating the expression of AMPK, SREBP-1c, or peroxisome proliferation-activated receptors in the liver and disturbing the transcription of genes regulating lipid metabolism[67,68,69].

Finally, we found an insignificant difference in the mean level of lipid profile according to diagnosis, which agreed with a study conducted by (Moteshafi H, et al)[82]. Antipsychotics may have direct and immediate effects on lipid levels beyond obesity effects. Olanzapine has an impact on hyperlipidemia in psychiatric patients at all doses.

Conclusion :

This study concluded that olanzapine drugs induce dyslipidemia in psychiatric disorders (schizophrenia, depression) characterized by a significant increase in cholesterol, triglycerides, and LDL, and a significant decrease in HDL. Dyslipidemia always occurs after treatment during the first month and, to some extent, exhibits a time-dependent effect. Hence, there is an urgent need for physicians to manage olanzapine-induced dyslipidemia in patients with schizophrenia to prevent the development of CVD in this population.

References :

1- Heald A. Physical health in schizophrenia: A challenge for antipsychotic therapy.European Psychiatry 2010;25(2): S6-S11.

2- De Hert M, Correll CU, Bobes J, et al . Physical illness in patients with severe mental disorders. I. Prevalence, the impact of medications and disparities in health care. World Psychiatry 2011;10(1):52-77.

3- Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prevention of Chronic Diseases 2006;3(2): A42.

4- Bobes J, Arango C, Garcia-Garcia M, Rejas J. Healthy lifestyle habits and 10-year cardiovascular risk in schizophrenia spectrum disorders: An analysis of the impact of smoking tobacco in the CLAMORS schizophrenia cohort. Schizophrenia Research 2010;119(1-3):101-109.

5- Ucok A, Polat A, Bozkurt O, et al. Cigarette smoking among patients with schizophrenia and bipolar disorders. Psychiatry in Clinical Neuroscience 2004;58(4):434-437.

6- Fagiolini A, Frank E, Scott JA, et al. Metabolic syndrome in bipolar disorder: Findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disorders 2005;7:424-430.

7- Hennekens CH, Hennekens AR, Hollar D, et al. Schizophrenia and increased risk of cardiovascular disease. American Heart Journal 2005;150(6):1115-1112.

8- Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disorders 2004;6(5):368-373.

9- Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls.Schizophrenia Research 2005;80(1):45-53.

10- Nasrallah HA. An overview of common medical comorbidities in patients with schizophrenia. Journal of Clinical Psychiatry 2005;66(Suppl. 6):3-4.

11- Cohn T, Prud'homme D, Streiner D, et al. Characterizing coronary heart disease risk in chronic schizophrenia: High prevalence of the metabolic syndrome. Canadian Journal of Psychiatry 2004;49(11):753-760.

12- Yumru M, Savas HA, Kurt E, et al. Atypical antipsychotics related metabolic Syndrome in bipolar patients. Journal of Affective Disorders 2007;98(3):247-522.

13- Arango C, Bobes J, Aranda P, et al. CLAMORS Study Collaborative Group. A comparison of schizophrenia outpatients treated with Antipsychotics with and without metabolic syndrome: Findings from the CLAMORS Study. Schizophrenia Research 2008;104(1-3):1-12.

14-Bowden CL, Calabrese JR, McElroy SL, et al . A randomized, placebo-controlled 12-month trial of Divalproex and lithium in Treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Archives of General Psychiatry 2000;57(5):481-489.

15- Cormac I, Ferriter M, Bening R, Saul C. Physical Health and health risk factors in a population of long-Stay psychiatric patients. Psychiatr Bull 2005; 29:18-20.

16- Phelan M, Stradins L, Morrison S. Physical health of people with severe mental illness. BMJ 2001; 322:443-4.

17- Perez-Iglesias R, Mata I, Pelayo-Teran JM, et al . Glucose and Lipid disturbances after 1 year of antipsychotic treatment in a drug-naïve population. Schizophr Res 2009; 107:115-21.

18- Reist C, Mintz J, Albers LJ, et al. Second-generation antipsychotic expo-Sure and metabolic-related disorders in patients with Schizophrenia. J Clin Psychopharmacol 2007; 27: 46-51.

19- Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. Psychoneuroendocrinology 2003; 28(Suppl 1):9-26.

20- Uzun S, Kozumplik O, Mimica N, et al . Nuspojave psihofarmaka. Zagreb: Medicinska na-Klada, 2005.

21-Hyman S, Chisholm D, Kessler R, et al. Mental Disorders. In: Jamison DT, Breman JG, Measham AR, et al., editors. Disease Control Priorities in Developing Countries. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 31. Co-published by Oxford University Press, New York.

22-World Health Organization. Mental Disorders". World Health Organization20 July 2020. Report

23-Arango C, Díaz-Caneja CM, McGorry PD, et al. “Preventive strategies for mental health”. The Lancet. Psychiatry. July 2018;5 (7):591-604

24-World Health Organisation. "Risks To Mental Health: An Overview Of Vulnerabilities And Risk Factors".int. 2012. Report.

25-Leucht, S., Corves, C., Albert, D., et al. Second-generation versus first-generation antipsychotic drugs for Schizophrenia: a Meta-analysis., 2009;373, 31–41. Doi: 10.1016/S0140-6736(08)61764-X

26-Leucht, S., Cipriani, A., Spinelli, L., et al. . Comparative efficacy and tolerability of 15 antipsychotic drugs in Schizophrenia: a multiple-treatments meta-analysis.,2013; Lancet 382, 951–962.Doi: 10.1016/S0140-6736(13)60733-3

27-Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., et al. Comparative efficacy and tolerability of 32 oral Antipsychotics for the acute treatment of adults with multi-episode Schizophrenia: a systematic review and network meta-analysis,2019; Lancet 394(10202), 939–951. Doi: 10.1016/S0140-6736(19)31135-3

28-Allison DB, Casey DE. Antipsychotic-induced weight Gain: a review of the literature. Journal of Clinical Psychiatry .2001; 62 (Suppl. 7), 22–31.

29-Lamberti JS, Olson D, Crilly JF, et al . Prevalence of the metabolic syndrome among patients receiving clozapine. American Journal of Psychiatry, 2006;163,1273–1276.

30-Nasrallah HA. Metabolic findings from the CATIE Trial and their relation to tolerability. CNS Spectrums, 2006; 11(Suppl. 7), 32–39.

31-Smith RC, Lindenmayer JP, Bark N, et al . Clozapine, Risperidone, olanzapine, and conventional antipsychotic Drug effects on glucose, lipids, and leptin in schizophrenic Patients. International Journal of Neuropsychopharmacology, 2005;8, 183–194.

32-Consensus Statement (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity). Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care, 2004;27,596–601.

33-Brown S. Excess mortality of schizophrenia. A Meta-analysis. British Journal of Psychiatry, 1997;171, 502–508.

34-Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of Patients with schizophrenia. American Journal of Psychiatry, 2004; 161, 1334–1349.

35- Osborn DP, Levy G, Nazareth I, et al . Relative risk of cardiovascular and cancer Mortality in people with severe mental illness from the United Kingdom’s General Practice Research Database.Archives of General Psychiatry, 2007;64, 242–249.

36-Kim SF, Huang AS, Snowman AM, et al . From the Cover: Antipsychotic Drug-induced weight gain mediated by histamine H1Receptor-linked activation of hypothalamic AMP-kinase.Proceedings of the National Academy of Sciences USA, 2007;104,3456–3459.

37-Kroeze WK, Hufeisen SJ, Popadak BA, et al . H1-histamine receptor affinity Predicts short-term weight gain for typical and Atypical antipsychotic drugs. Neuropsychopharmacology, 2003; 28, 519–526.

38- Audun O. Vik-Mo, Astrid B. Et al . Increase expression of lipid biosynthesis genes in peripheral

blood cells of olanzapine–treated patients. International Journal of Neuropsychopharmacology, 2008; 11, 679–684.

39-Jeffrey A. Lieberman, M.D., and Michael B. First, M.D.psychotic disorders, The New England Journal of Medicine, 2018;379:270-280.

40- Curkendall, S. M., Mo, J., Glasser, D. B., Rose Stang, M. & Jones, J. K. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *J. Clin. Psychiatry***65**, 715–720, 10.4088/JCP.v65n0519 (2004).

41- Ryan MC, Thakore JH. Physical consequences of schizophrenia and its treatment: The metabolic syndrome. *Life Sci.* 2002;**71**:239–257. doi: 10.1016/s0024-3205(02)01646-6.

42- Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. *Lancet Psychiatry.* 2015;**2**:452–464. doi: 10.1016/s2215-0366(15)00115-7.

43-Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment–pharmacological mechanisms. *Pharmacol. Ther.* 2010;**125**:169–179. doi: 10.1016/j.pharmthera.2009.10.010.

44-Misawa F, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: A cross-sectional study. *BMC Psychiatry.* 2011;**11**:118. doi: 10.1186/1471-244x-11-118.

45- Huang TL, Chen JF. Serum lipid profiles and schizophrenia: Effects of conventional or atypical antipsychotic drugs in Taiwan. *Schizophr. Res.* 2005;**80**:55–59. doi: 10.1016/j.schres.2005.05.001.

46-Ou JJ, et al. Comparison of metabolic effects of ziprasidone versus olanzapine treatment in patients with first-episode schizophrenia. *Psychopharmacology.* 2013;**225**:627–635. doi: 10.1007/s00213-012-2850-6.

47-Salvato Balbao, M. *et al.* Olanzapine, weight change, and metabolic effects: A naturalistic 12-month follow up. *Ther. Adv. Psychopharmacol.***4**, 30–36, 10.1177/2045125313507738 (2014).

48-Chiu CC, Chen CH, Chen BY, Yu SH, Lu ML. The time-dependent change of insulin secretion in schizophrenic patients treated with olanzapine. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2010;**34**:866–870. doi: 10.1016/j.pnpbp.2010.04.003.

49- Gautam S, Meena PS. Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics. *Indian J. Psychiatry.* 2011;**53**:128–133. doi: 10.4103/0019-5545.82537.

50- Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: Guidelines and new therapies. *Atherosclerosis.* 2018;**277**:483–492. doi: 10.1016/j.atherosclerosis.2018.06.859.

51-Audun O. Vik-Mo, Astrid B. Et al . Increase expression of lipid biosynthesis genes in peripheral blood cells of olanzapine–treated patients. International Journal of Neuropsychopharmacology, 2008; 11, 679–684.

52-Huang J, Hei G-R, Yang Y, et al. Increased Appetite Plays a Key Role In Olanzapine-Induced Weight Gain in First-Episode Schizophrenia Patients. Front. Pharmacol. 2020; 11:739. Doi:10.3389 /fphar. 2020.00739.

53-Zhou XM, Hu MR, Gong MY, et al . Sex-differential effects of olanzapine vs. Aripiprazole on glucose and lipid metabolism In first-episode schizophrenia, Arch Clin Psychiatry. 2019;46(2):33-9.

54- McDonnell DP, Kryzhanovskaya LA, Zhao F, Detke HC, Feldman PD. Comparison of metabolic changes in patients with schizophrenia during randomized treatment with intramuscular olanzapine long-acting injection versus oral olanzapine. *Hum.Psychopharmacol.* 2011;**26**:422–433. doi: 10.1002/hup.1225.

55-Rong Li,[1] Yiqi Zhang *et al.* Effects of olanzapine treatment on lipid profiles in patients with schizophrenia: a systematic review and meta-analysis, Sci Rep. 2020; 10: 17028. Published online 2020 Oct 12. doi: 10.1038/s41598-020-73983-4 ,PMCID: PMC7552389 PMID: HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/33046806"33046806

56-Chiu C-C, Chen K-P, Liu H-C, Lu M-L. The early effect of olanzapine and risperidone on insulin secretion in atypical-naive schizophrenic patients. *J. Clin. Psychopharmacol.* 2006;**26**:504–507. doi: 10.1097/01. jcp.0000237947.80764.d9.

57- Martin-Gronert MS, et al. 5-HT2A and 5-HT2C receptors as hypothalamic targets of developmental programming in male rats. *Dis. Models Mech.* 2016;**9**:401–412. doi: 10.1242/dmm.023903.

58-Kirk SL, Glazebrook J, Grayson B, Neill JC, Reynolds GP. Olanzapine-induced weight gain in the rat: role of 5-HT2C and histamine H1 receptors. *Psychopharmacology.* 2009;**207**:119–125. doi: 10.1007/s00213-009-1639-8.

59- Manu P, et al. Weight gain and obesity in schizophrenia: Epidemiology, pathobiology, and management. *Acta Psychiatr. Scand.* 2015;**132**:97–108. doi: 10.1111/acps.12445.

60- Lopez M, Tena-Sempere M. Estradiol effects on hypothalamic AMPK and BAT thermogenesis: A gateway for obesity treatment? *Pharmacol. Ther.* 2017;**178**:109–122. doi: 10.1016/j.pharmthera.2017.03.014.

61- Sentissi O, Epelbaum J, Olie JP, Poirier MF. Leptin and ghrelin levels in patients with schizophrenia during different antipsychotics treatment: A review. *Schizophr. Bull.* 2008;**34**:1189–1199. doi: 10.1093/schbul/sbm141.

62-Murashita M, et al. Olanzapine increases plasma ghrelin level in patients with schizophrenia. *Psychoneuroendocrinology.* 2005;**30**:106–110. doi: 10.1016/j.psyneuen.2004.05.008.

63- Melkersson K. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release in vitro. *Eur. Neuropsychopharmacol.* 2004;**14**:115–119. doi: 10.1016/s0924-977x(03)00072-5.

64- Yan H, Chen JD, Zheng XY. Potential mechanisms of atypical antipsychotic-induced hypertriglyceridemia. *Psychopharmacology.* 2013;**229**:1–7. doi: 10.1007/s00213-013-3193-7.

65- Postic C, Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: Lessons from genetically engineered mice. *J. Clin. Invest.* 2008;**118**:829–838. doi: 10.1172/jci34275.

66- Ferre P, Foufelle F. SREBP-1c transcription factor and lipid homeostasis: Clinical perspective. *Horm. Res.* 2007;**68**:72–82. doi: 10.1159/000100426.

67- Polymeropoulos MH, et al. Common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol supports a key role of lipid homeostasis in schizophrenia. *Schizophr. Res.* 2009;**108**:134–142. doi: 10.1016/j.schres.2008.11.025.

68- Jassim G, et al. Acute effects of orexigenic antipsychotic drugs on lipid and carbohydrate metabolism in the rat. *Psychopharmacology.* 2012;**219**:783–794. doi: 10.1007/s00213-011-2397-y

69- Oh, K. J. *et al.* Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. *Am. J. Physiol. Endocrinol. Metab.***300**, E624–E632, 10.1152/ajpendo.00502.2010 (2011).

70-Moteshafi, H., Zhornitsky, S., Brunelle, S. Et al. Comparing Tolerability of Olanzapine in Schizophrenia and Affective Disorders. Drug Saf 35, 819–836 (2012).