CASE REPORT

Eastern Journal of Medicine

East J Med 30(4): 672-677, 2025
DOI: 10.5505/ejm.2025.93685

Extreme Hypertriglyceridemia Following Clozapine Treatment: A Case of Twenty-Fold Increase

Tuba Ülkevan[1*], Seda Nur Kaya[1], Suheda Tapan[1], Saliha Yildiz[2]

[1]Department of Mental Health and Diseases, Van Yüzüncü Yıl University, Van, Turkey
[2]Department of Endocrinology and Metabolic Diseases, Van Yüzüncü Yıl University, Van, Turkey

ABSTRACT

Clozapine is a second-generation antipsychotic agent with established efficacy in patients with treatment-resistant schizophrenia. Among the most frequently reported adverse effects of clozapine are components of the metabolic syndrome, including central obesity, insulin resistance, impaired glucose metabolism, dyslipidemia and elevated blood pressure. It has been shown in several studies that clozapine use is associated with clinically relevant increases in serum triglyceride (TG) levels, ranging from 35% to nearly 100% over long-term treatment. In this case, an approximately twenty-fold increase in serum TG levels was observed following the initiation of clozapine therapy, rising from 73 mg/dL to 1686 mg/dL. Prior to clozapine administration, the patient was undergoing treatment for hyperlipidemia, and lipid parameters remained within normal limits. After initiating pharmacological treatment for hypertriglyceridemia, including statins, fibrates, and omega-3 fatty acids, clozapine was gradually tapered and replaced with aripiprazole. Subsequently, serum TG levels decreased to 604 mg/dL over a period of several months. The marked elevation in TG levels observed in our patient was considered to be associated with the patient's pre-existing history of hyperlipidemia. When evaluated in the light of the data obtained from this case, it can be suggested that the rate of lipid increase may be higher than expected in patients with a history of hyperlipidemia who are candidates for clozapine treatment; therefore, it may be recommended that lipid levels be monitored on a monthly basis during the early phase of treatment and at periodic intervals thereafter in such individuals.

Keywords: Clozapine, schizophrenia, hyperlipidemias, hypertriglyceridemia

Introduction

Schizophrenia is a severe, lifelong mental disorder affecting approximately 1% of the world population (1). The disease is characterised by positive, negative and cognitive symptoms and may lead to significant functional impairment. While many patients experience considerable improvement with antipsychotic therapy, approximately one-third of patients develop treatment-resistant schizophrenia (2).

Clozapine, a second generation antipsychotic, is known as the only antipsychotic drug with proven efficacy in patients with treatment-resistant schizophrenia (3). In addition, side effect rates including extrapyramidal symptoms and hyperprolactinemia are lower than other antipsychotic drugs (4). Among all antipsychotic agents, clozapine has been associated with the lowest rate of all-cause mortality (5). However, clozapine has serious side effects including neutropenia/agranulocytosis, myocarditis/cardiomyopathy, tachycardia and obsessive-compulsive symptoms (6–9). One of the most commonly reported adverse effects of clozapine is metabolic syndrome, which encompasses central obesity, insulin resistance, impaired glucose metabolism, dyslipidemia and elevated blood pressure (10,11). This syndrome is further characterized by clozapine-associated severe weight gain, hypercholesterolemia, hypertriglyceridemia, and hypertension (12). It has been shown in several studies that clozapine use is associated with clinically relevant increases in serum TG levels, ranging from 35% to nearly 100% over long-term treatment (13,14). Henderson et al. reported a 5-year naturalistic follow-up of 82 patients treated with clozapine, with 6-monthly laboratory monitoring. All patients were on clozapine, some also received valproate. TG(s) nearly doubled over the follow-up, while cholesterol rise was modest and nonsignificant (13).

***Corresponding Author:** Tuba Ülkevan, Department of Mental Health and Diseases, Van Yüzüncü Yıl University, Faculty of Medicine, Bardakci, 65090 Tuşba/Van, Turkey
E-mail: tubaulkevan@hotmail.com, Phone: 0 (506) 349 11 67
ORCID ID: Tuba Ülkevan: 0000-0003-2907-5017, **Seda Nur Kaya:** 0009-0005-8431-3788, **Suheda Tapan:** 0000-0002-3809-4685, **Saliha Yildiz:** 0000-0001-5607-7259
Received: 12.05.2025, **Accepted:** 13.09.2025

In this case report, we present a patient with schizophrenia who experienced an approximately twenty-fold increase in serum TG levels following clozapine treatment—an elevation far beyond what has been reported in the literature. This case highlights the potential for extreme lipid abnormalities in clozapine-treated patients and underscores the importance of close monitoring in individuals with underlying risk factors.

Case Report

A 37-year-old single male patient, who had been residing in a care home for the past four years, was referred to the psychiatric outpatient department of the university hospital by the care home staff due to a 10-day history of food refusal, nonadherence to medication, reduced speech, and paranoid suspicion toward others.

According to the anamnesis and review of the medical records, the patient had been followed with a diagnosis of schizophrenia since 2015 and had experienced multiple hospitalizations. He had previously received antipsychotic treatments including amisulpride 800 mg/day, risperidone 4 mg/day, and quetiapine 200–800 mg/day. Additionally, he had a prior hospitalization lasting approximately 10 months due to prolonged food refusal, consumption of only water, and somatic delusions. He had also been diagnosed with hyperlipidemia and was receiving pitavastatin at a dose of 4 mg/day since 2021. It was noted that despite ongoing treatment with valproic acid 1250 mg/day, extended-release risperidone 50 mg every 15 days, and biperiden 1 mg/day, the patient continued to experience referential, persecutory, and somatic delusions, occasionally refusing to eat or speak due to these symptoms. The patient was referred to the outpatient psychiatry clinic due to a worsening of symptoms over the past 10 days and was subsequently admitted to the inpatient psychiatric unit.

After the patient was admitted to the clinic, the current risperidone dose was increased from 4 mg/day to 6 mg/day. PANSS (Positive and Negative Syndrome Scale) score was calculated as 73 on admission. At the time of admission, lipid parameters were within normal limits, except for a reduced level of HDL (High Density Lipoprotein) cholesterol. Laboratory results revealed a TG level of 73 mg/dL (reference range: 0–150 mg/dL), HDL cholesterol of 13 mg/dL (reference range: 35–55 mg/dL), LDL (Low Density Lipoprotein) cholesterol of 72 mg/dL (reference range: 0–100 mg/dL), and total cholesterol of 188 mg/dL (reference range: 0–200 mg/dL). In addition, metabolic parameters showed a glycated hemoglobin (HbA1c) of 5.5% (reference range: 4.4–5.7%) and a body mass index (BMI) of 23 kg/m² (normal range: 18.5–24.9 kg/m²). Although the patient used at least two antipsychotic treatments at an effective dose and duration, he did not benefit significantly from the treatments and was evaluated as treatment-resistant schizophrenia and was planned to be switched to clozapine treatment. The dose of clozapine was titrated up to 25 mg/day. As the patient had a prior history of hyperlipidemia, lipid profile was checked one month after clozapine initiation for monitoring purposes. While receiving clozapine at a dose of 150 mg/day, one month after the initiation of clozapine treatment, the patient's serum TG level increased to 736 mg/dL, HDL cholesterol was 30 mg/dL, LDL cholesterol was 210 mg/dL, and total cholesterol was 444 mg/dL. The patient was referred to the Department of Endocrinology and Metabolic Diseases, where it was recommended to add omega-3 fatty acids 1440 mg/day and fenofibrate 550 mg/day to the existing pitavastatin regimen, along with regular monitoring of TG levels. Following the initiation of clozapine treatment, a reduction in persecutory, referential, and somatic delusions was observed. The patient resumed eating, and the PANSS score decreased to 50. The patient was discharged on the 41st day of hospitalization, with a recommendation to continue follow-up at the Endocrinology and Metabolic Diseases outpatient clinic. At the time of discharge, the patient had gained only 1.1 kg, and the HbA1c level was measured at 5.6%. One month after discharge, the patient's serum TG level was measured at 1416 mg/dL. Given that the patient's TG level had increased approximately 20-fold from baseline, a gradual tapering and planned discontinuation of clozapine treatment was considered. According to the Naranjo Adverse Drug Reaction Probability Scale, the patient's hypertriglyceridemia scored 5 points, indicating a "probable" adverse drug reaction associated with clozapine. Clozapine treatment was tapered and discontinued within seven days, while aripiprazole was initiated simultaneously at 5–10 mg/day. During follow-up, the aripiprazole dose was gradually increased, and the patient's final antipsychotic treatment consisted of aripiprazole 20 mg/day. During follow-up conducted by the Department of Endocrinology and Metabolic Diseases, the patient underwent plasmapheresis. However, two months later, the serum TG level increased to 1686 mg/dL. Consequently, metformin 1700 mg/day and acetylsalicylic acid

Table 1: Timeline of Triglyceride Levels and Interventions

Day	Triglyceride (mg/dL)	Interventions
0	73	Clozapine started; Pitavastatin 4 mg/day (baseline)
30	736	TG rise → + Omega-3 (1440 mg/day), Fenofibrate (550 mg/day)
41	-	Discharge
71	1416	TG 1416 mg/dL → Clozapine tapered off; Aripiprazole 5–10 mg/day started; Plasmapheresis
130	1686	TG 1686 mg/dL → + Metformin (1700 mg/day), Acetylsalicylic acid (300 mg/day)
160	604	TG improved to 604 mg/dL

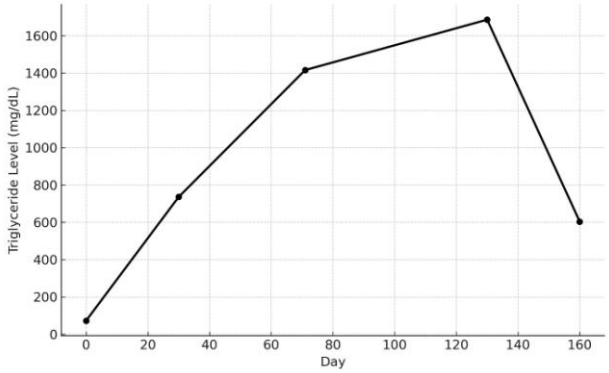

Fig. 1. Changes in serum triglyceride levels over time

300 mg/day were added to the treatment regimen. One month after these additions, the TG level decreased to 604 mg/dL. Figure 1 illustrates the changes in serum triglyceride levels over time, while Table 1 summarizes the timeline of triglyceride levels and corresponding intervention.

Discussion

Cardiometabolic comorbidities represent the primary cause of premature mortality among individuals with schizophrenia (15). Although the majority of studies have focused on weight gain and glucose intolerance, recognizing and managing hyperlipidemia in patients with schizophrenia remains crucial, given its long-term contribution to cardiovascular mortality (16). Clozapine remains one of the few effective treatment options for patients with treatment-resistant schizophrenia (13,17). Therefore, a comprehensive understanding of its associated metabolic side effects is essential.

In a study evaluating patients who had been treated with clozapine or typical antipsychotics for at least one year, the mean serum TG level in the clozapine group was found to be 264 mg/dL, and severe hypertriglyceridemia (defined as >500 mg/dL) was observed in three patients receiving clozapine treatment (18). Similarly, in a study evaluating patients who had been treated with clozapine or typical antipsychotics for at least six months, an average increase of 41% in serum TG levels was reported in the clozapine group (19). Also an acute, marked elevation in TG levels after clozapine initiation was reported by Kumar and Sidana (2017), who described a patient with an increase from 69 mg/dL to 458 mg/dL within two weeks (20). In contrast to these previously reported findings, our patient experienced a far more extreme and rapid twenty-fold increase in TG levels, highlighting the unique clinical significance of this case.

Previous reports have shown that switching from clozapine to risperidone can normalize TG levels in affected patients (21). A network meta-analysis by Pillinger et al. demonstrated that aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone are associated with more favorable metabolic and lipid outcomes compared to clozapine and olanzapine (22). In our case, clozapine was tapered and replaced with aripiprazole, which is supported by recent evidence indicating a more favorable metabolic profile and potential improvement in lipid parameters (23). Recent meta-analytic evidence indicates that pharmacological strategies for antipsychotic-induced dyslipidemia are variably effective, with antipsychotic switching or add-on

approaches showing the most consistent improvements in TG and HDL cholesterol. Among off-label agents, metformin demonstrated particular efficacy in reducing TG and total cholesterol, whereas approved lipid-lowering agents were less effective in this population (24). Furthermore, TG levels exceeding 500 mg/dL warrant the initiation of fibrates or omega-3 fatty acids (25). In severe or refractory cases, switching to an antipsychotic with a more favorable metabolic profile may be warranted. In line with these findings, our patient benefited from fibrates, omega-3 fatty acids, and metformin, in addition to switching to aripiprazole, reflecting a stepwise, evidence-based management strategy.

There is no single, clearly defined mechanism underlying the diverse metabolic and therapeutic effects of clozapine. Proposed mechanisms for its metabolic side effects include a predisposition to obesity among individuals with schizophrenia due to a sedentary lifestyle, increased appetite and food intake resulting from clozapine's antagonism of histamine H1 and serotonin 5-HT2C receptors, as well as suppression of insulin secretion and the development of insulin resistance (26,27). Hyperlipidemia may arise either as a consequence of weight gain or as a direct pharmacological effect of antipsychotics. The underlying mechanism for clozapine-induced dyslipidemia, beyond increased food intake, remains unclear, and no specific receptor targets have been reliably identified (28). However, several studies have demonstrated that certain antipsychotic-induced metabolic side effects may occur independently of weight gain (29,30). In addition, recent evidence suggests that inflammatory pathways, endocrine alterations, underlying disease, dietary habits and genetic polymorphisms affecting lipid metabolism may predispose certain patients to more severe metabolic disturbances during clozapine therapy (28,31). Prior to the initiation of clozapine treatment, the patient had been receiving pitavastatin for hyperlipidemia, and his serum TG levels were within the normal range at the time of admission. In our case, the patient did not exhibit significant weight gain during clozapine treatment, suggesting that mechanisms other than adiposity may have contributed to the marked hypertriglyceridemia observed. This elevation in TG levels observed during follow-up may be attributable to the patient's pre-existing history of hyperlipidemia. Notably, TG levels decreased to 604 mg/dL approximately 12 weeks after clozapine discontinuation. However, despite switching to aripiprazole and initiating multiple lipid-lowering agents, TG levels initially continued to rise, suggesting that factors beyond clozapine exposure may have contributed to the persistent hypertriglyceridemia. This underscores the need to consider both drug-related and patient-specific variables when evaluating severe metabolic disturbances.

Taken together, these findings suggest that the rate of lipid elevation may be higher than expected in patients with a history of hyperlipidemia who are scheduled to receive clozapine treatment. Therefore, closer monitoring of lipid levels is recommended in this patient population. According to the National Institute for Health and Care Excellence (NICE) guidelines, lipid profiles should be assessed at baseline, after 3 months, and annually thereafter, with more frequent monitoring (every 3–6 months) in patients with pre-existing dyslipidemia or abnormal results (32). In light of our observations, it may further be recommended that lipid levels be monitored on a monthly basis during the early phase of treatment and at periodic intervals thereafter in such individuals. The rarity of such a dramatic, twenty-fold TG increase highlights the need for heightened clinical vigilance, reminding clinicians that although uncommon, severe lipid disturbances of this magnitude may occur and require timely intervention.

References

1. Saha S, Chant D, Welham J, McGrath. A Systematic Review of the Prevalence of Schizophrenia. PLoS Med 2005; 2: e141.
2. Diniz E, Fonseca L, Rocha D, Trevizol A, Cerqueira R, Ortiz B, et al. Treatment resistance in schizophrenia: a meta-analysis of prevalence and correlates. Brazilian J Psychiatry 2023; 45: 448-458.
3. De Hert M, van Eyck D, De Nayer A. Metabolic abnormalities associated with second generation antipsychotics: fact or fiction? Development of guidelines for screening and monitoring. Int Clin Psychopharmacol 2006; 21: 11-15.
4. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. Hist Psychiatry. 2007;18(1):39–60.
5. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry 2020; 19: 61-68.

6. Mijovic A, MacCabe JH. Clozapine-induced agranulocytosis. Ann Hematol. 2020; 99: 2477-2482.
7. Yuen JWY, Kim DD, Procyshyn RM, White RF, Honer WG, Barr AM. Clozapine-induced cardiovascular side effects and autonomic dysfunction: A systematic review. Front Neurosci 2018; 12: 203.
8. Kim DD, White RF, Barr AM, Honer WG, Procyshyn RM. Clozapine, elevated heart rate and QTc prolongation. J Psychiatry Neurosci 2018; 43: 71-72.
9. Kim DD, Barr AM, Lu C, Stewart SE, White RF, Honer WG, et al. Clozapine-associated obsessive-compulsive symptoms and their management: a systematic review and analysis of 107 reported cases. Psychother Psychosom 2020; 89: 151-160.
10. Kim DD, Barr AM, Fredrikson DH, Honer WG, Procyshyn RM. Association between serum lipids and antipsychotic response in schizophrenia. Curr Neuropharmacol 2019; 17: 852-860.
11. Whitney Z, Procyshyn RM, Fredrikson DH, Barr AM. Treatment of clozapine-associated weight gain: A systematic review. Eur J Clin Pharmacol 2015; 71: 389-401.
12. Sepúlveda-Lizcano L, Arenas-Villamizar V V, Jaimes-Duarte EB, et al. Metabolic adverse effects of psychotropic drug therapy: a systematic review. Eur J Investig Heal Psychol Educ 2023; 13: 1505-1520.
13. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry 2000; 157: 975-981.
14. Gaulin BD, Markowitz JS, Caley CF, Nesbitt LA, Dufresne RL. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999; 156: 1270-1272.
15. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World psychiatry 2017; 16: 163-180.
16. Cleeman JI. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) 2001; 2486-2497.
17. Lahti M, Tiihonen J, Wildgust H, et al. Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. Psychol Med 2012; 42: 2275-2285.
18. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Heal Pharm 1996; 53: 2079-2081.
19. Spivak B, Lamschtein C, Talmon Y, et al. The impact of clozapine treatment on serum lipids in chronic schizophrenic patients. Clin Neuropharmacol 1999; 22: 98-101.
20. Kumar M, Sidana A. Clozapine-induced acute hypertriglyceridemia. Indian J Psychol Med 2017; 39: 682-684.
21. Dufresne RL, Ghaeli P. Elevated serum triglycerides with clozapine resolved with risperidone in four patients. Pharmacother J Hum Pharmacol Drug Ther 1999; 19: 1099-1101.
22. Pillinger T, Mccutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatr. 2020; 7: 64-77.
23. Wei T, Jiang L, Zhang R, Su H, Sun Z, Sun J. A systematic review and meta-analysis of the effects of combined aripiprazole on glycolipid metabolism in schizophrenia. Front Psychiatry 2025; 15: 1496986.
24. Kanagasundaram P, Lee J, Prasad F, et al. Pharmacological interventions to treat antipsychotic-induced dyslipidemia in schizophrenia patients: a systematic review and meta analysis. Front psychiatry 2021; 12: 642403.
25. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27: 596-601.
26. Procyshyn RM, Wasan KM, Thornton AE, et al. Changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. J Psychiatry Neurosci 2007; 32: 331-338.
27. 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.
28. Yuen JWY, Kim DD, Procyshyn RM, Panenka WJ, Honer WG, Barr AM. A focused review of the metabolic side-effects of clozapine. Front Endocrinol (Lausanne) 2021; 12: 609240.
29. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry 2008; 13: 27-35.

30. Fernø J, Vik-Mo AO, Jassim G, et al. Acute clozapine exposure in vivo induces lipid accumulation and marked sequential changes in the expression of SREBP, PPAR, and LXR target genes in rat liver. Psychopharmacology (Berl) 2009; 203: 73-84.
31. Li N, Cao T, Wu X, Tang M, Xiang D, Cai H. Progress in genetic polymorphisms related to lipid disturbances induced by atypical antipsychotic drugs. Front Pharmacol 2020; 10: 1669.
32. National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in adults: prevention and management (Clinical guideline CG178). London: NICE; 2014 (updated 2020).