Turkish Journal of Psychiatry 2021;32(2):137-141
https://doi.org/10.5080/u25185

Could Weight Loss During Clozapine Be an Indicator of Poor Response?: A Case Report

Burcu KÖK KENDİRLİOĞLU[1], Aytül GÜRSU HARİRİ[2]

SUMMARY

Even though effectiveness of clozapine on treatment resistant schizophrenia has been repeatedly demonstrated, it is also associated with many adverse effects including weight gain. Curiously, significant weight loss may occur in some patients. In this case report we discussed whether the observed weight loss could be a negative prognostic factor.

The 56 year-old male patient, followed up with the diagnosis of schizophrenia for 20 years, had persistent positive and negative symptoms despite concurrent use of different antiypsychotics. He was diagnosed with treatment-resistant schizophrenia and started on clozapine with dose titration to 500 mg/day over 3 months. He was observed to have lost 17.6% of his initial body weight after 7 months of therapy. The Positive and Negative Syndrome Scale (PANSS) score of the patient did not change significantly.

There are a few case reports in the literature on weight loss during clozapine therapy. Some proposed that the weight loss could be a sign of weak response to treatment which is based on the observation that the clinical response might be poor when there is a weight loss and no change in blood triglyceride levels is observed with the treatment.

There is a need for more case-control and preclinical studies to explain the mechanisms underlying weight loss and weak response to clozapine therapy in schizophrenia.

Keywords: Clozapine, schizophrenia, weight loss, poor response, triglyceride

INTRODUCTION

It is estimated that 20 to 30% of all schizophrenia cases are resistant to therapy (Lieberman et al. 2005, Agid et al. 2011). Clinical guidelines recommend clozapine as the first choice drug for management of treatment-resistant schizophrenia (Warnez and Alessi-Severini 2014). It has been demonstrated that 32% of the cases respond in the short term and 39% respond in the long term to clozapine (Siskind et al. 2017). An improvement of 16% in the score on the Positive and Negative Syndrome Scale (PANSS) is considered as clinically significant and it is reported that clozapine provides an improvement that exceeds 16% in PANSS (Hermes 2012).

Weight gain induced by antipsychotic agents including clozapine is a widely recognized side effect. Recent meta-analyses reported the prevalence of metabolic syndrome and obesity to be, respectively 32.5% and 49.4% in schizophrenia cases (Dayabandara et al. 2017). It is observed that female patients are more prone to weight gain and that one third of the patients started on clozapine are already obese (Covell 2004). A review on the metabolic effects of antipsychotics has pointed out that incidence of weight gain is 5 fold higher with clozapine or olanzapine use as compared to the other antipsychotic agents (Annamalai et al. 2017). Despite implications of various regions of the central nervous system, neurotransmitters, neuropeptides and genetic factors as being involved in these observations, the underlying mechanisms are still unclear (Rummel-Kluge et al 2010). Antipsychotics have been shown to affect the levels of leptin and adiponectin which play roles in regulating

Received: 16.09.2019, **Accepted:** 29.02.2020, **Available Online Date:** 31.01.2021

[1]Assist. Prof., Maltepe University Medical Faculty, Department of Psychiatry, İstanbul, [2]Prof., Retired, Turkey.

e-mail: kokburcu@gmail.com

hunger and energy mechanisms (Dayabandara 2017). Short and long term olanzapine use increases leptin and decreases adiponectin levels which is attributed to the direct impact of the medication rather than the secondary effect through weight gain (Dayabandara 2017).

Clozapine use, on the other hand, is also associated with a weight loss of 13.5-50% of total body weight in a small number of patients who did not have any physical disease as the possible underlying cause (Turgaraza 2016). The few available reports in the literature on serious weight loss due to clozapine use have given varying explanations for the phenomenon. Weight loss in three cases was attributed to improved mental state, better management of side effects and dietary interventions and exercise. (Lally and McDonald 2011, Appiani et al. 2011, Webster and Ingram 2013). Esophageal dysfunction following clozapine therapy was also implicated in the weight loss observed in some cases (McCarthy and Terkelsen 1994). The weight loss in three cases reported by Hanwella et al. (2010) was attributed to clozapine therapy per se with speculation on underlying genetic factors.

The aim of this case report is to discuss whether a significant weight loss following clozapine therapy is a negative prognostic factor.

CASE

The 56-year old male patient, married and father of two, retired on grounds of disability, had been followed up for schizophrenia for 20 years. His initial complaints were reported to be related to positive symptoms of auditory hallucination and anxiety, with thought contents on anticipation of harm being done to his family, resulting in social isolation and retirement for not being able to continue working. At the time of consulting, he had a history of treatment with olanzapine (20 mg/day), aripiprazole (30 mg/day), biperiden (4mg/day), amisulpride (400 mg/day), zuclopenthixole (200 mg/2 weeks) and clonazepam (4 mg/day) over the course of 2 years. His persecutory and referential delusions had been exacerbated after owning up threatening expressions he had heard in the street. In his psychiatric examination, he was noted to appear older than his age; was conscious, cooperative and oriented; avoided eye contact; had normal psychomotor activity and normal speech with monotonous tone. His mood was dysphoric, affect limited; his thought contents indicated inner distress and restlessness which was attributed to the persecutory and referential delusions. Interviewing showed that he had negative symptoms of anhedonia and avolition.

It was learned that the patient's complaints persisted despite treatment for 20 years. The patient was diagnosed with treatment resistant schizophrenia and clozapine therapy was planned. The informed consent of the patient and his wife was obtained for the clozapine therapy. Body weight (BW) and the body mass index (BMI) were recorded and the haemogram, biochemical tests including the lipid profile and thyroid function tests were carried out before the start of the therapy. He was followed up with weekly controls on his haemogram, psychiatric condition and family consultation. Clozapine dosage was increased to 500 mg/day in 3 months.

During the course of therapy hypersalivation, constipation and weight loss were reported as adverse side effects. His initial BW of 85 kg and BMI of 29 kg/m^2 were respectively, 70 kg (-17.6%) and 24 kg/m^2 after 7 months of therapy (Table 1). Consultation with the internal diseases clinic provided the results of measurements including CRP, sedimentation, routine biochemical tests, haemogram, tumour markers, together with pulmonary radiography and abdominal ultrasonography which did not indicate any pathology to explain the weight loss. The patient was referred to the neurology clinic for complaint of dizziness. Cranial Magnetic Resonance Imaging (MRI) did not reveal any neurological pathology. Weight loss could not be attributed to having obsessive thoughts or compulsive behaviors such as engaging in heavy physical activities, sports or use of laxatives that could lead to weight loss. The psychiatric examinations and family visits for evaluating the response to the therapy indicated the persistence of the negative and positive symptoms, without any improvement in functionality. The PANNS score recorded at the start of the therapy had decreased by only 5 points (6.7%) at the end of 7 months of therapy (Table 1). Observing the lack of the expected response to clozapine, dose

Table 1. The Laboratory Test Results of the Patient at the Start and After 7 Months of Clozapine Therapy

	Before Therapy	After Therapy
Cholesterol mg/dL	225	242
LDL mg/dL	149	162
HDL mg/dL	35	38
Triglyceridemg/dL	202	206
Fasting Blood Glucose mg/dl	100	102
T3 pg/mL	2.91	2.93
T4 ng/dL	0.98	0.96
TSH uIU/mL	1.81	1.79
WBC K/ul	12900	9370
Body Weight (kg)	85	70
Body-Mass-Index (kg/m^2)	29	24
The PANSS* Score	P18 N23 G33	P16 N21 G32

*Positive and Negative Symptoms Scale
P: Positive Scale; N: Negative Scale; G: General Psychopathology Scale;
TSH: Thyroid-stimulating hormone; WBC: White blood cells;
T3: Triiodothyronine; T4: Thyroxine; LDL: Low-density lipoprotein;
HDL: High- density lipoprotein

increase was planned which was rejected by the patient as his weight loss had increased with each dose increase. Although amisulpride (400 mg/day titrated to 800 mg/day) was added to the therapy as the patient believed having had beneficial effect formerly, this was without effect on the positive and the negative symptoms and the changes in his BW.

DISCUSSION

The significance of this case report is in reflecting the possible association between weight loss, albeit seen infrequently, and the weak response to clozapine therapy. The relationship between weight gain and clozapine is also unclear, but some contributory mechanisms have been proposed. Investigating clozapine effects on receptors indicates that its affinity for the H1 (histamine 1) and 5-HT2C (5-hydroxythyripthamine/ serotonin 2C) receptor is more strongly associated with weight gain than its affinity for the 5-HT1A (serotonin 1A) and α-2 (alpha adrenergic 2) receptors.

Clinical studies show that polymorphism in the promoter region of the 5-HT2C receptor gene is associated with weight gain due to antipsychotics and that the clinical response to clozapine therapy partially depends on the polymorphisms of the subtypes of 5-HT2A and 2C receptors (Lally and McDonald 2011). Animal studies on 5-HT2C receptor knock-out rats showed development of hyperphagia and significant weight gain. Moreover, fenfluoramine, a partial agonist of the 5-HT2A/2C receptor was associated with hyperphagia and weight gain. It is also suggested that the serotonin receptor polymorphism in the gene as well as the promoter region is responsible for clinical response and weight loss (Nasrallah 2008). H1 receptor antagonism of antipsychotic agents may play a role in increasing appetite depending on their receptor affinity. Investigations on the 568 promoter gene variants of H1 and H2 receptors in schizophrenia cases also support the thesis that the various subtypes of histamine receptors affect differently the changes in clinical response and body weight (Stanton 1995, Czobor et al. 2002). In this context, one may speculate on a possible polymorphism in serotonin or histamine receptors in the case reported here. Absence of genetic investigation limits the evaluation of the case in this context.

Good response to clozapine therapy has been speculated to be associated with high triglyceride levels and weight gain. Triglyceride levels of unresponsive patients were demonstrated not to increase (Procyshyn et al. 2007). Hence, observing unaltered triglyceride levels in the case discussed here can be proposed as a negative prognostic factor for weak response to clozapine.

Using therapeutic doses of clozapine in patients resulted in increased leptin, triglyceride and insulin levels as well as symptoms of insulin resistance. Also, insulin and triglyceride levels were positively correlated with serum clozapine levels. It was concluded that the increases in insulin and triglyceride levels were the results of increasing serum clozapine levels. Although the increased leptin levels were attributed to hyperinsulinemia, a direct relationship between leptin and clozapine could not be demonstrated. The mean dose of clozapine therapy used was 400 mg/day but the data regarding the response to clozapine was not included (Melkersson and Dahl 2003). The reason for the stability in the triglyceride levels in the case discussed here could be due to insufficient increase in serum clozapine levels which might in turn have lead to an inadequate response to therapy. However, not having measured the serum clozapine levels in our patient presents a limitation to evaluating the case in this respect.

Apart from the reports that increased triglycerides and leptin levels are responsible for weight gain during clozapine therapy, evidence has been provided that the increase in leptin levels is correlated and the decrease in PANSS score which is an indicator of clinical response (Atmaca et al. 2003). Whereas a decrease in PANSS score of 16% is the minimum cut-off level for postive response to therapy (Hermes 2012), the change seen in the PANSS score in the case discussed here was insignificant, being only 5 points or 6.7% after seven months of therapy. The absence of increases in body weight, serum triglyceride levels, the PANSS score and the clinical response in the case discussed here could be attributed to an impaired leptin mechanism. We suggest that the serum leptin measures might be helpful to evaluate the response to therapy.

Czobor et al. (2002) reported that weight gain is correlated with the response to clozapine or olanzapine treatments, but not with the response to haloperidol or risperidone treatments. The suggested correlation between weight gain and response to clozapine might explain the weak response in our case.

The weight loss reported in five cases on 400 or 500 mg/day clozapine treatment for resistant schizophrenia diagnoses was proposed to be an indicator of the poor response to therapy made possible by genetically based mechanisms (Thomas et al. 2009). Evaluating the persistence of the positive and negative symptoms and lack of improvement of functionality in the case discussed here, suggests that the weight loss is associated with the poor response to the 7-month therapy. However, significant weight loss by a patient on 500 mg/day clozapine was prevented by reducing the dose to 400 mg/day which maintained the satisfactory response to the treatment. It was proposed that the effect could be correlated with the clozapine dose or could be secondary to the gastrointestinal side effects of the drug or depends on genetically based factors. Clozapine dose reduction was recommended for coping with weight loss (Mutlu et al. 2020). In the case discussed here reducing clozapine dose was not considered on grounds of poor response.

Tungaraza (2016) reported the case of a patient with resistant schizoaffective disorder losing 26% of BW on treatment with clozapine dosage titrated to 500 mg/day. Despite the persistence of the psychotic symptoms, the cognitive functions related to organizational and management skills improved such that patient could limit food intake and lost weight which was not possible previously. Adding amisulpride to the therapy improved the psychotic symptoms and the weight loss phenomenon. In the case discussed here, an intentional limitation of dietary intake or any limitation of dietary intake due to the psychotic symptoms was not observed.

Dysphagia resulting in weight loss may be a side effect of treatment with either typical or atypical antipsychotics. Incidences of dysphagia have been reported to vary in the 0.43% to 2.08% range (Crouse Ericka et al. 2017). There are also case reports on weight loss due to dysphagia following clozapine therapy. Dysphagia was observed after clozapine dose escalation to 450 mg/day in 5 weeks in a patient with schizoaffective disorder, who lost 13.5 kg of body weight in 6 months after intentionally modifying his dietary habits to ingest fluid and soft foods in order to overcome this side effect. An esophageal pathology was not present and the problem was terminated by dose reduction to 350 mg/day, but data regarding the response to therapy was not reported (McCarthy and Terkelsen 1994). In general, presence of tardive dyskinesia, parkinsonism or anticholinergic side effects of drugs have been implicated as the causative mechanisms underlying dysphagia and weight loss. Particularly dose escalation in clozapine therapy might lead to esophageal dysfunction due to increased sensitivity of alpha-1-adrenergic and muscarinic acetylcholine receptors (McCarthy and Terkelsen 1994). Slowing down of gastrointenstinal movements by clozapine was also proposed to cause dysphagia (Osman and Devadas 2016). Dysphagia was not described by the patient and cholinergic symptoms were not observed in the case discussed here.

There were limitations in the management of the case reported here. Various sources have stated that the maximal dose of clozapine could be varied between 600 and 900 mg/day in cases of poor response (Subramanian et al. 2017). Not having escalated the dose maximally in the case discussed here limits the evaluation of the response to clozapine. Also, not having determined the serum levels of clozapine prevents an objective evaluation of the effectiveness of the therapy. Effective serum levels of clozapine have been reported in the literature to be 350–504 ng/ml (Perry 2001). Most of the previous reports on cases with weight loss after clozapine treatment have also not included the serum levels of the drug. In the case discussed here, the poor response to therapy may be attributed to serum clozapine being below the effective level.

Although generally weight gain is observed, clinicians should keep in mind that profound weight loss is possible during clozapine therapy. It is also important to follow up triglyceride levels and follow body weight in order to evaluate the clinical response. Measurement of leptin levels may also contribute to this objective. More case control studies and preclinical studies are needed for better understanding the mechanisms underlying the weight loss and the inadequate response to clozapine. Otherwise, is weight gain an inevitable outcome of the improvement with clozapine management?

REFERENCES

Agid O, Arenovich T, Sajeev G et al (2011) An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry 72:1439–44.

Annamalai A, Kosir U, Tek C (2017) Prevalence of obesity and diabetes in patients with schizophrenia. World J Diabetes 8:390–6.

Appiani F, Carroll BT, Muñoz C et al (2011) Clozapine-induced weight loss? Ann Clin Psychiatry 23:225.

Atmaca M, Kuloglu M, Tezcan E et al (2003) Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. J Clin Psychiatry 64:598-604.

Covell N, Weissman E, Essock S (2004) Weight gain with clozapine compared to first generation antipsychotic medications. Schizophr Bull 30:229–40.

Crouse Ericka L, Alastanos JN, Bozymski KM et al (2017) Dysphagia with second-generation antipsychotics: A case report and review of the literature. Mental Health Clinician: Vol. 7 pp. 56-64.

CzoborP, Volavka J, Sheitman B et al (2002) Antipsychotic-induced weight gain and therapeutic response: a differential association. J Clin Psychopharmacol 22:244-51.

Dayabandara M, Hanwella R, Ratnatunga S et al (2017) Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat 13:2231–41.

Hanwella R, de Silva V, Wijeratne C et al (2010) Clozapine-associated weight loss. J Psychopharmacol 24:1127–9.

Hermes ED, Sokoloff D, Stroup TS et al (2012) Minimum clinically important difference in the positive and negative syndrome scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). J Clin Psychiatry 73:526-32.

Lally J, McDonald C (2011) Dramatic weight loss associated with commencing clozapine. BMJ Case Rep 8.

Lieberman JA, Stroup TS, McEvoy JP et al (2005) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators.Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209-23.

McCarthy RH, Terkelsen KG (1994) Esophageal dysfunction in two patients after clozapine treatment. J Clin Psychopharmacol 14:281-3.

Melkersson KI, Dahl ML (2003) Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacology (Berl) 170:157-66. Epub

Mutlu E, Özçelik Eroğlu E, Ayhan Y et al (2020) Weight loss associated with clozapine: a case report. Turk Psikiyatri Derg: 2020:31.

Nasrallah HA (2008) Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry 13:27–35 .

Osman M, Devadas V (2016) Clozapine-induced dysphagia with secondary substantial weight loss. BMJ Case Rep 2016: bcr2016216445.

Perry PJ (2001) Therapeutic Drug Monitoring of Antipsychotics. Psychopharmacol Bull 35:19-29.

Procyshyn RM, Wasan KM, Thornton AE et al (2007) Clozapine and risperidone enhancement study group. changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. J Psychiatry Neurosci 32:331-8.

Rummel-Kluge C, Komossa K, Schwarz S et al (2010) Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 123:225–33.

Siskind D, Siskind V, Kisely S (2017) Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can J Psychiatry 62:772–7.

Stanton JM (1995) Weight gain associated with neuroleptic medication: a review. Schizophr Bull 21:463-72.

Subramanian S, Völlm BA, Huband N (2017) Clozapine dose for schizophrenia. Cochrane Database of Systematic Reviews Issue 6.

Thomas N, Ravan JR, Jebaraj Pet al (2009) Clozapine producing weight loss: a case series with possible clinical implications – a hypothesis. J Postgrad Med 55:317

Tungaraza Tongeji E (2016) Significant weight loss following clozapine use, how is it possible? A case report and review of published cases and literature relevant to the subject. Ther Adv Psychopharmacol 6:335–42.

Warnez S and Alessi-Severini S (2014) Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry 14:102.

Webster A, Ingram L (2013) A weight off the mind: clozapine and profound weight loss. Aust NZ J Psychiatry 47:1212–13.