

Atypical Weight Loss in Two Patients with Schizophrenia Treated with Clozapine: A Case Report

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Abstract

Clozapine is widely recognized as an effective antipsychotic medication for treatment-resistant schizophrenia, but it is typically associated with significant weight gain. This case report presents two unusual cases of patients with schizophrenia who experienced substantial weight loss while on long-term clozapine therapy. The first case involves a 35-year-old male who lost 21.3% of his initial body weight, and the second case describes a 54-year-old female who lost 30.2% of her initial weight, despite having comorbid hypothyroidism. Both patients showed improvement in psychiatric symptoms concurrent with the weight loss. Comprehensive investigations did not reveal other clear etiologies for the weight reduction. These cases challenge the conventional understanding of clozapine's metabolic effects and highlight the potential for atypical responses in some individuals. The report discusses possible mechanisms for this unusual phenomenon, including genetic factors and altered pharmacokinetics. It also emphasizes the need for individualized monitoring and management strategies in clozapine therapy. These findings contribute to the growing body of evidence suggesting that metabolic responses to clozapine may be more complex and varied than previously thought, underscoring the importance of personalized approaches in schizophrenia treatment.

Keywords

Schizophrenia, Clozapine, Weight Loss, Treatment-Resistant, Atypical Antipsychotics, Metabolic Effects, Case Report

1. Introduction

Schizophrenia is a severe chronic mental disorder that affects approximately 1%

of the population. It is manifested by such a wide range of symptoms as hallucinations, delusions, disorganized speech and behavior, cognitive impairments, and many others [1]. Treatment for schizophrenia almost always includes indefinite antipsychotic medication. Second-generation antipsychotics have become the mainstay of treatment because they are very effective in reducing psychotic symptoms, with less risk of extrapyramidal side effects compared to first-generation antipsychotics [2] [3].

Clozapine differs from the rest of the SGAs in being the most potent treatment for treatment-resistant schizophrenia. Clozapine is considered the prototype of atypical antipsychotics; it showed improved efficiency in those patients who had a poor response to the other antipsychotics [4]. Though very effective against this disorder, clozapine is not free from side effects at all, and it entails some management and monitoring. Weight gain is perhaps the most common and clinically significant of these, and it is well documented in the literature [5].

Antipsychotic-induced weight gain (AIWG) is a very well-established phenomenon, especially with SGAs like clozapine. From studies, it is evident that a good percentage of patients receiving treatment with clozapine showed considerable weight gain. [6] noted that 55%, 18%, and 12% of patients gained 10%, 15%, and 20% of their baseline weight during 12-week treatment with clozapine. This weight gain is usually associated with metabolic changes, such as dyslipidemia and insulin resistance, and increased risk for type 2 diabetes mellitus [7] [8].

Given that clozapine is well known to cause weight gain, reports of marked weight loss in patients treated with clozapine are few and fascinating. These atypical cases challenge our current knowledge regarding the metabolic effects of clozapine and further underscore the variability that can take place in individual treatment response. Whereas some studies have probed into the role of adjunctive medications, such as metformin, in attenuating clozapine-induced weight gain in obese patients [9], spontaneous weight loss in the absence of such interventions is a relatively rare phenomenon.

This case report presents two atypical cases of a 35-year-old male and a 54-year-old female diagnosed with schizophrenia and treated with clozapine, who had drastic weight loss contrary to the anticipated effect. These cases highlight how intricate interindividual variability can be in response to antipsychotics and, therefore, how important the development of personalized approaches in the management of schizophrenia is. In the following unusual presentations, we intend to add to the increasing literature regarding the effects of clozapine and probably delineate some factors that may influence treatment outcomes in some individuals.

2. Case Presentations

The section that follows presents two patients diagnosed with schizophrenia who suffered from atypical weight loss during the course of treatment with clozapine.

2.1. Case 1: A 35-Year-Old Male

This 35-year-old Saudi male had a history of heavy smoking since adolescence and

a 16-year history of schizophrenia with a complicated clinical course of frequent relapses needing psychiatric hospitalization. His history was notable for medication nonadherence, which had contributed to the difficulties in managing his condition. Prior to starting clozapine, several antipsychotic medications, both oral and injectable, had been tried on the patient, but again with very poor response.

She was initially started on olanzapine 5 mg, twice a day, with valproic acid 200 mg twice a day. Her olanzapine dose was increased to 10 mg, twice a day, and augmentation with risperidone consta 37.5 mg injectable was done. Notwithstanding the above measures, her symptoms continued to be only partially controlled.

Because of the refractory nature of his illness, clozapine was introduced at a dosage of 100 mg twice a day. While this treatment with clozapine greatly improved the psychiatric condition of the patient, an incidental and progressive weight loss was noticed. The weight of the patient before the introduction of clozapine was 61 kg. By 2022, he weighed 48 kg, amounting to a loss of about 21% from the initial body weight.

Detailed investigations to find the possible causes for weight loss were essentially complete blood count, blood glucose levels, and thyroid function tests. All laboratory test results were unremarkable (Figure 1 and Figure 2). Of note, there were no medications being taken by the patient that could explain her significant weight loss.

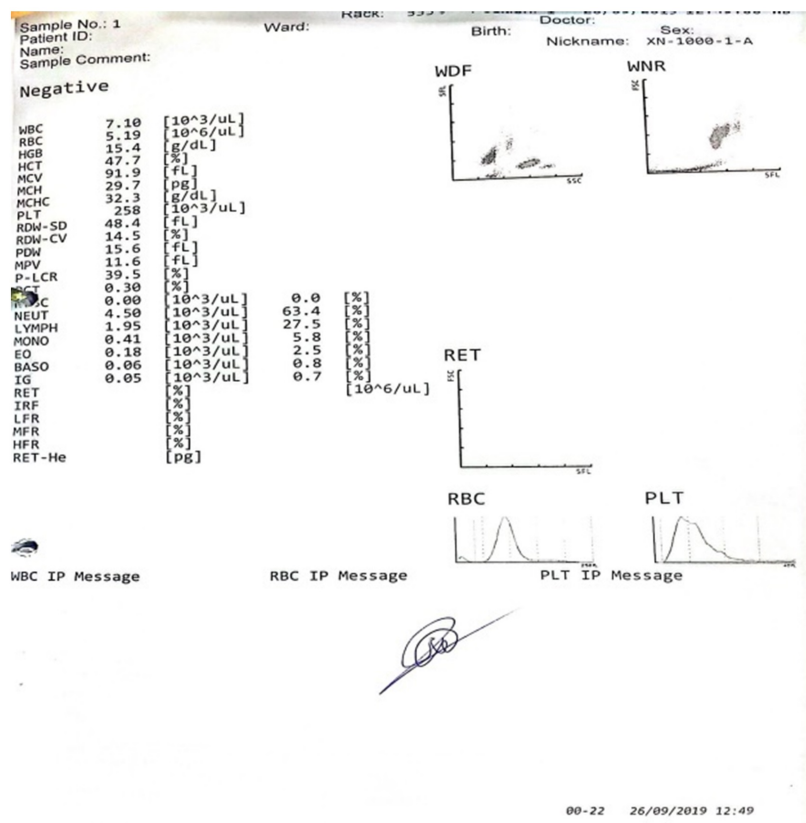


Figure 1. Complete blood count.

PSYCHIATRIC HOSPITAL LAB DEPARTMENT CHEMISTRY			
ID	THAMER SALEH	DATE	25/07/19 11:20:56
NO.	E002357 065	OPERATOR ID	fawaz1
TYPE	Ser/Pl	Comment	-001
AGE			
SEX			
DRAW DATE			
DRAW TIME			
PRE-DILUTED NO			
TEST	RATIO	RESULT	UNIT
GLUC		92	mg/dL
UREA		24.8	mg/dL
URIC ACID		4.9	mg/dL
CA		9.1	mg/dL
AST		14 L	U/L
ALT		3	U/L
CREATININE		1.1	mg/dL
			EXPECTED VALUE
			(70- 120)
			(10- 50)
			(2.0- 7.0)
			(8.0- 12.0)
			(15- 37)
			(0.0- 41)
			(0.5- 1.5)

Figure 2. Glucose levels test.

2.2. Case 2: 54-Year-Old Female

The second case is a 54-year-old Saudi female with a 15-year history of schizophrenia. Similar to the first patient, this case had a history of frequent relapses that mandated repeated psychiatric hospitalization, mainly related to poor compliance with prescribed treatments. Her medication history revealed her to be on different antipsychotics, both as a monotherapy and in combinations; however, the symptoms could not be controlled satisfactorily.

This patient was previously treated with full doses of haloperidol, olanzapine, paliperidone, and quetiapine in various combinations. As the patient failed to respond adequately to these medications, clozapine was introduced into her treatment plan quite gradually.

While her psychiatric symptoms improved significantly with clozapine therapy, there was a remarkable and progressive weight loss in the patient. She weighed 64.5 kg before commencing clozapine. In 2022, her weight was down to 45 kgs, amounting to nearly a 30% loss of pretreatment weight.

The patient had full investigations done, which included CBC, blood glucose levels, and thyroid function tests—results are shown in **Figure 3** and **Figure 4**. These investigations indicated the patient had hypothyroidism, a condition generally associated with weight gain rather than loss. Of note, he was not on any other medications that could have explained the weight loss described.

In both cases, the unintentional weight loss occurred in the setting of clozapine monotherapy with an agent known to cause significant weight gain [10] [11]. Both presentations are counter to the conventional knowledge of the metabolic effects of clozapine and point out that atypical responses might be seen in some individuals. In the absence of any other clear etiologies for the weight loss, especially against the background of extensive investigations performed, the strong likelihood exists that clozapine was having a direct or indirect effect in these cases.

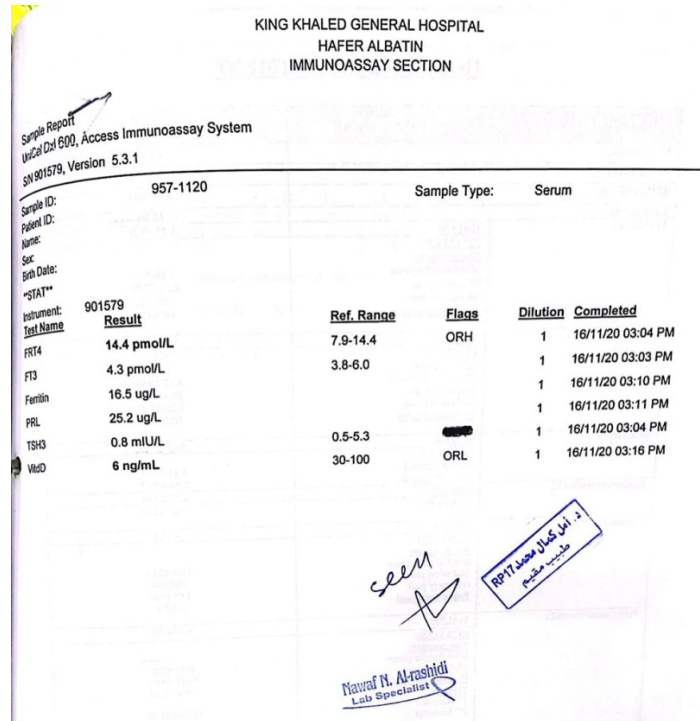


Figure 3. Thyroid function test.

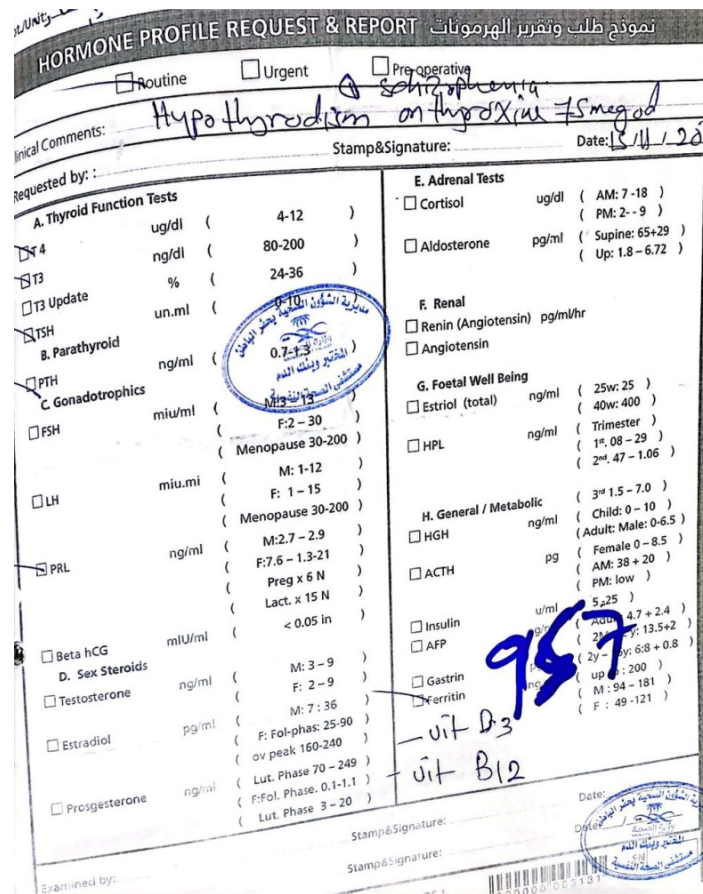


Figure 4. Results of investigations.

These peculiar cases underline the need for monitoring on an individual basis and further research into variables that may act to affect these very diverse responses to clozapine therapy. They also draw attention to the complex interplay between antipsychotic drugs, metabolic processes, and patient characteristics in the treatment of schizophrenia.

3. Methods

This section elaborates on the diagnostic criteria, monitoring practices, and investigations that were adopted in assessing and managing the two cases.

3.1. Diagnostic Criteria

The Manual of Mental Disorders (DSM-5) diagnosis of schizophrenia was considered in the two patients. These criteria included the presence of two or more characteristic symptoms such as delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms for a significant portion of time during one month, and some signs of the disorder persisting for at least six months. Also considered in the diagnosis was the marked impairment in social and occupational functioning of both patients.

Treatment-resistant schizophrenia was determined by the failure to have satisfactory clinical improvement with adequate trials of at least two antipsychotic agents, including at least one second-generation antipsychotic, at appropriate doses and duration, which had led to initiation of clozapine therapy [2].

3.2. Monitoring and Measurement Procedures

- **Weight Monitoring:** The weights of the patients were documented on a calibrated digital scale at regular intervals. The weight measurements were done at baseline—before the initiation of clozapine—then weekly during the first month, and monthly measurements thereafter. Patients were weighed in light clothing and without shoes to ensure consistency.

- **Psychiatric Symptom Assessment:** The severity and course of the psychiatric symptoms were assessed at baseline and during treatment by standardized rating scales, like the Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale. The assessment of the patients was performed once at baseline and regularly during the treatment period to track their response to therapy with clozapine.

- **Side Effect Monitoring:** Clozapine-induced side effects were regularly monitored in all patients with a focus on metabolic parameters. This included measurement of body mass index, waist circumference, and blood pressure at each follow-up visit.

3.3. Investigations Performed

To assess the overall status of health and to find out the probable causes of weight loss observed in these patients, following investigations were carried out:

- **Complete Blood Count (CBC):** This was done to assess the general health status and monitor for possible hematological side effects of clozapine, including agranulocytosis.
- **Fasting Blood Glucose:** The test was done for the assessment of glucose metabolism and screening for possible diabetes mellitus, a metabolic complication associated with atypical antipsychotics [8].
- **Lipid Profile:** A comprehensive lipid panel was conducted to assess cholesterol and triglyceride levels, given the known effects of clozapine on lipid metabolism.
- **Thyroid Function Tests:** Thyroid-stimulating hormone (TSH) and free T4 were measured to evaluate thyroid functioning, as weight is greatly influenced by any thyroid disorder.
- **Liver Function Tests:** The tests were conducted both to evaluate hepatic function and to screen for possible hepatotoxicity in the course of treatment with clozapine.
- **Electrocardiogram (ECG):** This was done to monitor cardiac status and potential cardiovascular complications of clozapine.
- **CT Scan:** A CT scan was performed on the 35-year-old male patient to rule out intracranial pathology as the cause behind weight loss.

These full investigations were important in ruling out all other causes for the weight loss and for the general safety of continued therapy with clozapine. The results of these investigations, together with the continued clinical assessment, formed the basis for the evaluation and management of these atypical cases of clozapine-associated weight loss.

4. Results

This section summarizes the findings in both cases and compares these results to common responses to clozapine therapy.

4.1. Summary of Findings

4.1.1. Case 1: 35-Year-Old Male

This 35-year-old male patient had a significant, unintentional weight loss following the introduction of clozapine therapy. At the initiation of clozapine treatment, the patient had a weight of 61 kg. After 16 years of continuous treatment with clozapine, the patient's weight had decreased to 48 kg, corresponding to a loss of 13 kg or 21.3% of the initial weight. This weight loss occurred in the absence of concomitant medications or other medical conditions that could contribute to weight loss.

Laboratory investigations, including complete blood count, fasting blood glucose, and thyroid function tests, have been within normal limits. A CT scan did not reveal any intracranial pathology to explain the weight loss. Of note, his psychiatric symptoms did improve significantly with clozapine despite this atypical weight response, as depicted in **Figure 4**.

4.1.2. Case 2: 54-Year-Old Female

This weight loss was associated with considerable weight loss for the patient over the course of clozapine treatment. The patient weighed 64.5 kg prior to the introduction of clozapine. Her weight dropped to 45 kg after approximately 15 years of treatment. This was a decrease of 19.5 kg, or 30.2%, from her original body weight. This decrease was all the more significant in that the patient developed hypothyroidism over this period.

Laboratory investigations for this patient were all within normal limits, including the complete blood count and fasting blood glucose (**Figure 3** & **Figure 4**). Thyroid function tests confirmed the diagnosis of hypothyroidism that was being managed concurrent to this admission. The psychiatric symptoms of this patient improved significantly with clozapine therapy, much like the first case, while the unexpected weight loss persisted.

4.2. Comparison to the Typical Clozapine Response

These weight reductions in these two cases are in striking contrast to the typical metabolic effects associated with clozapine treatment. Clozapine is well-documented as causing significant weight gain in a large proportion of patients. Substantial weight gain in patients treated with clozapine has been earlier reported by a number of studies, including:

- 1) Leadbetter *et al.* [10] reported that 38% of patients had significant weight gain during a 16-week clozapine treatment study.
- 2) Umbricht *et al.* [11] described a sample of patients where 55%, 18%, and 12% gained 10%, 15%, and 20% of their baseline weight in the first 12 weeks of clozapine treatment, respectively.

Weight gain associated with the use of clozapine is usually part of other metabolic changes, including dyslipidemia and insulin resistance, an increased risk of type 2 diabetes mellitus [7] [8]. In our cases, though, not only did these patients fail to gain weight, but they were also suffering from extreme weight loss without any evidence of metabolic disturbance.

These findings are all the more remarkable given that both patients had clinical improvement in psychiatric symptoms, consistent with the known efficacy of clozapine in treatment-resistant schizophrenia [4], thus an atypical weight response cannot explain a decrease in the therapeutic effect of clozapine in these cases.

The alternative common causes for such a weight loss are not contributory in these patients. All investigations in the male were within the range of normal, and he was not on any other medications that could account for the weight loss. The female's hypothyroidism would actually be expected to contribute to weight gain rather than loss, so her weight reduction is all the more remarkable.

These cases illustrate how individual responses to clozapine can vary, particularly in its metabolic effects. They also point out that person-specific monitoring and management strategies with respect to clozapine therapy should be adopted,

as atypical responses may occur even in those whose symptoms are well controlled.

5. Discussion

The cases presented in this report highlight a highly atypical response to clozapine treatment in two patients with schizophrenia, marked by significant weight loss rather than the expected weight gain. This unusual outcome challenges the typical understanding of clozapine's effects and prompts a detailed exploration into the underlying causes and implications for clinical practice. Clozapine, a second-generation antipsychotic, is conventionally associated with weight gain, primarily due to its impact on appetite and metabolism. However, the weight loss observed in these patients deviates significantly from this norm, warranting a closer examination of potential metabolic disruptions.

One possible mechanism for this weight loss could be alterations in metabolic processes. While clozapine is known to generally increase appetite and contribute to weight gain, it may also affect the body's metabolism in ways that could lead to weight loss. Changes in basal metabolic rate or variations in how the body processes and utilizes nutrients could be factors in this deviation. Investigating these metabolic aspects could reveal whether clozapine is causing an unusual disruption in the metabolic pathways of these patients.

Furthermore, clozapine's impact on neurotransmitters involved in appetite regulation, such as serotonin, dopamine, and histamine, might be contributing to the reduced appetite observed in these cases. An imbalance or disruption in these neurotransmitters could interfere with normal hunger signals, leading to decreased food intake and subsequent weight loss.

Additionally, gastrointestinal side effects associated with clozapine, such as nausea or diarrhea, could play a role in the weight loss by impairing nutritional intake and absorption. If these patients experienced significant gastrointestinal symptoms, it is plausible that these symptoms contributed to their reduced weight through decreased food consumption and malabsorption of nutrients.

Overall, the atypical weight loss observed in these patients emphasizes the need for a more nuanced understanding of clozapine's effects and underscores the importance of monitoring and managing potential side effects in clinical practice.

6. Closer Look at Unusual Weight Loss

The weight lost by both patients is all the more remarkable because there is an equally well-recognized association of weight gain with clozapine. Clozapine-induced weight gain is usually ascribed to its action on histamine H1 receptors, serotonin 5-HT_{2C} receptors, and its potential to modify leptin and ghrelin levels, hence influencing appetite and metabolism (Wirshing *et al.*, 1999; Allison & Casey, 2001) [2] [3]. The fact that our patients significantly lost weight may indicate other mechanisms underlying the response or individual peculiarities that modulate the effect of the drug.

7. Possible Mechanisms

Several mechanisms underlying such unusual weight loss in these cases may be explained:

1) Genetic Factors: Gressier *et al.* [4] have suggested that genetic variability may determine the response to clozapine and the induced increase in weight. Perhaps our patients have genetic polymorphisms that change their metabolic response to clozapine, producing weight loss instead of weight gain.

2) Altered Pharmacokinetics: Interindividual differences in the metabolism of clozapine, presumably by genetically regulated cytochrome P450 enzymes, might cause different pharmacokinetic profiles that would differently influence weight change.

3) Smoking Interaction: In the 35-year-old male patient, his heavy smoking might interact with the metabolism of clozapine. It is known that smoking induces CYP1A2 that is responsible for the metabolism of clozapine and may lead to altered effects [11].

4) Thyroid Function Interaction: The 54-year-old female patient has hypothyroidism, thus complicating the case. Although hypothyroidism itself results in weight gain, its interaction with clozapine could result in unpredictable effects on metabolism.

5) Dopamine System Modulation: Particularly the modulation of the dopamine system, which is unique to clozapine, may result in alteration of reward processing and eating behavior in some patients [12].

8. Differential Diagnosis

Although thorough workups to a large extent excluded common causes for weight loss, differential diagnoses such as:

1) Malabsorption Disorders: The patient did not make any complaint of gastrointestinal symptoms, although occult malabsorption could be a cause of weight loss.

2) Occult Malignancy: The initial investigations turned out normal, but an underlying malignancy cannot be completely excluded without proper and extensive tests as a cause for weight loss.

3) Eating Disorders: The possibility of eating disorders having developed secondarily to psychotic symptoms or as an independent illness should be borne in mind [13].

4) Hypermetabolic Condition: The presence of undiagnosed hypermetabolic condition may potentially explain weight loss. This is perhaps less likely since the male patient's thyroid function test results are within normal limits.

The weight loss in our cases is starkly different from the existing literature on clozapine metabolic effects. Most studies, including those by [6] [10], reported significant weight gain in many patients treated with clozapine. Our findings are much more in line with case reports of weight loss with clozapine, hence the need to go further with efforts in identifying factors that could signal these individual

differences in metabolic response to the medication.

The concept of pharmacogenetic variability in clozapine response as discussed by Gressier *et al.* [4] might offer a potential framework to make meaning of these atypical cases. However, on the basis of the magnitude and constancy of weight loss in our patients, other factors in addition to genetic variability may be at work.

9. Limitations of the Study

Several limitations of this study should be acknowledged:

1) Sample Size: As a case report of only two patients, the generalizability of these findings is limited.

2) Retrospective Nature: The retrospective analysis of these cases may have led to incomplete data collection, particularly regarding detailed metabolic parameters over time.

3) Lack of Pharmacogenetic Testing: Without specific genetic testing, we cannot definitively ascertain the role of genetic factors in these atypical responses.

4) Limited Long-term Follow-up: More extended follow-up would be beneficial to assess the stability of the weight loss and any long-term health implications.

5) Absence of Control Group: The lack of a control group of clozapine-treated patients without weight loss limits our ability to identify specific factors associated with this atypical response.

Despite these limitations, the case reports are of immense value in metabolic atypia during clozapine treatment and illustrate the need for careful individualized follow-up and management in patients with schizophrenia being treated. Further research, more elaborately designed using prospective studies and appropriately powered, with wide genetic and metabolic profiling, is necessary to delineate the mechanisms underlying these atypical responses in the treatment with clozapine.

10. Clinical Implications

The atypical weight loss seen in these cases of clozapine therapy has important clinical implications that might influence strategies for the management of patients and requires close considerations for a clinician prescribing clozapine.

11. Potential Impact on Patient Management

11.1. Individualized Monitoring Protocols

These cases highlight the need for very individualized monitoring algorithms for clozapine-treated patients. Guidelines currently underscore monitoring for weight gain and metabolic syndrome, but clinicians must remain alert for idiopathic severe weight loss. Weight measurement and metabolic screening must take place at more frequent intervals than otherwise indicated, at least in the first months of treatment and in atypical responders.

11.2. Nutritional Assessment and Support

In the case of undesired weight loss in clients due to clozapine, detailed nutritional

assessments could be indicated. One can liaison with dieticians and ensure that adequate caloric intake and balanced nutrition are provided to the patient. The monitoring becomes imperative if the weight loss is rapid or massive.

11.3. Chronic Adjustments to Concurrent Medication

In those with a heavy weight loss, medications may need to be reviewed and changed by clinicians, at the same time, which themselves contribute to or exacerbate weight loss. This is particularly relevant for patients with comorbid conditions that mandate multiple medications.

11.4. Psychoeducation and Behavioral Interventions

Patients and their caregivers should be informed that atypical responses to clozapine, such as weight changes, are potential possibilities. Interventions targeting behavioral change to promote healthy eating habits and maintaining proper weight could be of potential benefit, either gaining or losing weight.

11.5. Pharmacogenetic Testing Should Be Considered

In view of the potential involvement of genetic factors in clozapine response and metabolic effects, pharmacogenetic testing may be a worthwhile consideration in atypical responses. It may provide very useful insights into individual variations in drug metabolism and guide personalized treatment strategies.

12. Things for the Clinician to Consider When Prescribing Clozapine

12.1. Full Baseline Assessment

Clinicians should undertake a general medical and physical examination, as well as metabolic parameters, in detail before initiation of clozapine. After garnering this detailed profile, the clinician will be in a better position to accurately follow-up changes over time.

12.2. Vigilance for Atypical Responses

When monitoring for the common side effects of clozapine, such as weight gain and metabolic syndrome, there is an obligation on the part of the clinician to remain aware of atypical such as undue weight loss. Early corrective measures may be initiated with atypical response recognition.

13. Balancing Efficacy and Side Effects

In those patients where the psychiatric benefits from clozapine are very good, but the medication induces alarming weight loss, the clinician is challenged with making an appropriate balance between therapeutic efficiency and possible health risks. When considering dosage adjustment or a change in treatment, great care should be exercised, taking into account the total risk-benefit profile for each patient.

13.1. Interdisciplinary Collaboration

Such atypical responses in patients on clozapine are better managed interdisciplinarily. Interdisciplinary approaches will ensure all dimensions of care and monitoring through coordination among psychiatrists, primary care physicians, endocrinologists, and dietitians.

13.2. Personalized Education for the Patient

The handouts and literature, as well as face-to-face education, must give importance to this atypical response to clozapine so that they recognize unusual variations in themselves and report such strange changes immediately.

14. Monitoring Strate

Since metabolic effects could be time-dependent, clinicians should have more extended period monitoring strategies beyond the period of acute management. This is very essential considering cases presented here in which weight balance went on for an extended period.

With that, such patients with an abnormal drug response should be considered, therefore, for recruitment into research studies or registries if available. This will help to add to the growing corpus of knowledge about individual variation to clozapine response and, importantly, has implications for informing future guidelines.

These cases herald the need for a paradigm shift in how we approach metabolic monitoring in clozapine therapy. While vigilance for weight gain and metabolic syndrome remains important, the clinicians have to be prepared for atypical responses such as unexpected weight loss. This nuanced approach to the care of patients will help optimize treatment outcomes yet minimize potential risks associated with clozapine therapy in the management of schizophrenia.

15. Conclusion

Clozapine represents a second-generation antipsychotic that is generally accepted as an effective treatment for resistant schizophrenia. It, however, usually significantly induces weight gain and metabolic disturbances. The case report presents two unusual cases of patients with schizophrenia who experienced substantial weight loss while on long-term clozapine therapy, opposite to the expected metabolic effects. The first is a 35-year-old male patient who lost 21.3% of his initial weight, and the second is a 54-year-old female patient who lost 30.2% of her initial weight in the presence of hypothyroidism. Coinciding with weight loss, there were improvements in psychiatric symptoms for both patients. Full investigation did not demonstrate another clear etiology for weight reduction. These cases challenge the conventional understanding of clozapine's metabolic effects and indicate the probability of atypical responses in some subjects. The report discusses the possible mechanisms by which such an unusual phenomenon may take place, through genetic factors or pharmacokinetics, for example. It finally stresses that

clozapine therapy requires individual monitoring and management strategies. These findings add to a growing literature that suggests metabolic responses to clozapine are considerably more complex and heterogeneous than appreciated to date, lending further impetus to the need for individualized approaches in the treatment of schizophrenia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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