BMJ Case Reports

TITLE OF CASE

Effective and Safe Use Of Intramuscular Clozapine In A Patient Presenting With Catatonia and Thrombocytopenia

SUMMARY

Clozapine is the most effective medication for the management of treatment-resistant schizophrenia and schizoaffective disorder, and its discontinuation can pose significant challenges in treatment. We present a patient with a diagnosis of schizoaffective disorder who was stable on clozapine for a decade until discontinuation due to thrombocytopenia. She experienced a relapse of her illness, presenting with psychotic and catatonic features with poor oral intake and physical health complications requiring a lengthy admission to the hospital. There was poor response to alternative antipsychotics and a full course of electroconvulsive therapy (ECT). Intramuscular (IM) clozapine was initiated due to catatonia and refusal to accept oral medications. After receiving ten doses of IM clozapine, she started accepting oral clozapine and made a full recovery within a few weeks. The low platelet count was persistent, and a bone marrow biopsy showed results consistent with Immune Thrombocytopenia being the cause of that low platelet count.

BACKGROUND

Clozapine is superior to other antipsychotics in chronic psychotic disorders such as schizophrenia and schizoaffective disorder that are resistant to other treatments.[1,2] Unfortunately, many patients discontinue treatment for a variety of reasons, often resulting in relapse. Adverse reactions are a common cause for discontinuation with haematological side-effects accounting for nearly half of these. [3-5] Furthermore, some patients are unable to accept oral formulations of clozapine due to being in a catatonic state, having swallowing difficulties, and suffering from gastrointestinal problems or perioperative status. Catatonia is a syndrome of psychomotor disturbances observed in mood disorders, schizophrenia and related psychotic disorders, neurodevelopmental disorders, and intoxication/withdrawal of certain psychoactive conditions. There is therefore a significant unmet medical need for alternative non-oral delivery routes for clozapine administration. This has prompted an increased interest in intramuscular (IM) clozapine because of its potential to prevent gaps in treatment for those patients who are non-concordant to oral treatment.[6]

We present in this case report, the successful use of IM clozapine to re-establish treatment in a previously stable patient. We will discuss her clinical presentation, course of clinical management, and outcome complicated by the challenging presentation of persisting low platelet count.

CASE PRESENTATION

A female patient in her early 40s with a known diagnosis of schizoaffective disorder was admitted involuntarily to the acute psychiatric inpatient unit due to relapse.

She was known to the mental health services since the age of 15 with a history of three involuntary psychiatric hospital admissions. At the age of 28, she was admitted to an acute psychiatric unit for 7 months and started on clozapine after a documented history of failure to respond to multiple antipsychotic medications. Following discharge, she remained stable in the community and fully functional for nearly 11 years until this admission. She had not experienced any major side effects with clozapine except constipation which was being managed with laxatives.

She had normal platelet counts (150–450 × 10^9/L) until seven years before the current admission after which the count kept fluctuating on the lower sides during routine blood monitoring. All the other blood parameters were normal. However, on one occasion the platelet count dipped to 43 ×10^9/L falling in the 'red' zone on FBC monitoring protocol (cut off platelets 50×10^9/L) while other haematological parameters including white blood cell (WBC) count and neutrophils remained within normal limits. Following this, clozapine was stopped and amisulpride was started as an alternative treatment. She quickly relapsed presenting with paranoia towards family members, experiencing auditory hallucinations (hearing voices unheard by others and responding to them), catatonic features, and self-neglect with refusal to eat and drink leading to her admission to an acute psychiatric hospital unit.

In the initial phase of acute psychiatric inpatient admission, she was tried on multiple antipsychotics like amisulpride, olanzapine, and aripiprazole at therapeutic doses. It was noted that thrombocytopenia continued during the first 6-month period in the hospital when she was being treated without a single dose of clozapine. During the period of admission, platelet count fluctuated between 30 to 150×10^9/L, mostly below 100×10^9/L.

Due to failure of response to these antipsychotics and having ruled out clozapine in causing thrombocytopenia, midway through the acute psychiatric unit admission, clozapine re-titration was attempted with fluctuating compliance and gradual improvement in her clinical presentation. Considering mood symptoms, lithium was added to the treatment regimen with some benefits. However, she refused clozapine on a few occasions and stopped eating and drinking. Due to poor hydration status, lithium was stopped. She became acutely unwell again with catatonic features, refusal to eat/drink due to catatonia, and further deterioration in physical health. ECT was planned and a single session was administered while she was in the acute psychiatric unit. However, she had to be taken to the emergency department of the nearby general hospital on two occasions due to a suspected urinary tract infection and autonomic instability with low blood pressure. A differential diagnosis of malignant catatonia was also considered.

At the general hospital, she remained under the care of Liaison Psychiatry Services. Moreover, she was referred to and further investigated by haematology for low platelets. All investigations were inclusive except bone marrow biopsy which remained undone due to her poor mental and physical health condition. She was further referred to gastroenterology to rule out hepatic and splenic causes of thrombocytopenia. While under the care of the Liaison Psychiatry team, she completed 12 sessions of ECT which led to minimal improvement. Oral clozapine was considered the next step in the treatment, and she was transferred back to the acute psychiatric ward after three months.

She continued to present unwell - paranoid, mute, refusing to eat and drink, and not engaging in meaningful therapeutic relationships. She was started on lorazepam 2 mg in divided doses to which she was intermittently compliant leading to some improvement in the catatonic features but features of negativism were prominent with her refusing to take oral clozapine. The patient lacked insight into her mental disorder and lacked the capacity to consent to treatment.

In her clinical history, it was established that clozapine was the only effective treatment for her condition, and the association of clozapine with low platelets was not clear. Following this, oral clozapine was recommended. Unfortunately, the patient was too unwell and could not take oral clozapine due to catatonia, thus posing challenges in a successful re-titration.

INVESTIGATIONS *If relevant*

All the blood investigations including WBC and neutrophil count were normal except for platelet count as described above. While in the general hospital, the patient also had special blood investigations to rule out any potential causes for thrombocytopenia including tests for antiphospholipid antibodies - b2 glycoprotein, Beta 2 microglobulin, cardiolipin antibodies, lupus anticoagulant, free light chains – kappa, lambda, and lactate dehydrogenase. Their levels were not considered clinically significant by haematology team. She had a normal abdomen ultrasound and a normal fibro scan. Finally, a bone marrow biopsy was completed which showed results consistent with a diagnosis of immune thrombocytopenia.

DIFFERENTIAL DIAGNOSIS *If relevant*

N/A

TREATMENT *If relevant*

Due to the complexity of her clinical presentation and management, a second opinion was sought from the Complex Psychosis Services Unit of the Kent and Medway NHS and Social Care Partnership Trust, a service specializing in the management of treatment-resistant psychotic disorders. A trial of IM clozapine was recommended. The risk of bleeding following IM injection administration in this patient with thrombocytopenia versus the benefit of improved mental status was carefully evaluated with input from haematology and deemed to be acceptable as her platelet counts were > 30 x 10^9/L. The local policy for IM clozapine prescription and administration was followed and input was taken from the multidisciplinary team including the pharmacy team.

The patient was prescribed oral clozapine with an option of administering IM clozapine (half the prescribed oral dose) when required (PRN) if the patient was refusing to take oral. During titration, she received a total of 10 doses of IM clozapine at varying doses of 6.25 mg on day 1 (equivalent to oral 12.5 mg) to 75 mg (equivalent to oral 150 mg) on day 15, all as single doses **(table 1).** Most of the administrations were under restraint and she was provided eyesight nursing support due to poor physical and mental state with regular review by the clinical team.

Table 1: Clozapine titration, both oral and IM clozapine		
Titration Day	Oral	IM (dose half of oral)
• **Day 1**		6.25 mg Lt gluteal (restraint +)
• **Day2**	25 mg	-
• **Day 3**		12.5 mg (restraint +)
• **Day 4**		25 mg (restraint -)
• **Day5**	50 mg	-
• **Day 6**	-	- (not given, too unwell)
• **Day 7**	-	37.5 mg (restraint+
• **Day 8**	-	50 mg (restraint -)
• **Day 9**	-	50 mg
• **Day 10**	-	50 mg (restraint +)
• **Day 11**	-	- (missed due to A & E visit)
• **Day 12**	100 mg	-
• **Day 13**	-	50 mg
• **Day 14**	-	50 mg
• **Day 15**	150 mg	-
• **Day 16**	-	75 mg (restraint +)
• **Day 17**	150 mg	-
• **Day 18**	150 mg	-
• **Day 19**	150 mg	-
• **Day 24**	450 mg (150 mg morning, 300 mg bed time)	-

The only reported side effect with IM clozapine was pain over the injection site. All the titration doses were prescribed at bedtime as the patient was refusing most oral medications in the morning time. After the second week of titration, the patient became regularly compliant with oral clozapine and IM clozapine was no longer required after the last dose on day 15. Furthermore, the oral clozapine dose was built up to 450 mg once daily. Given the low platelets, Full Blood Count monitoring was done twice a week. During the titration period, the platelet counts were as outlined below **(table 2).**

Table 2: Platelet count during Clozapine titration phase	
Day of titration	Platelet count ($n \times 10^9/L$)
Day 3	56
Day 6	54
Day 10	48
Day 17	47
Day 22	58

Throughout the admission, she was closely monitored and there were no symptoms or signs of abnormal bleeding.

Clozapine was built to 450 mg in divided doses on the fourth week, serum clozapine assay revealed clozapine 0.62 mg/L and norclozapine 0.34 mg/L. She had a maximum daily therapeutic dose of 500 mg in the past. However, further dose increment was not considered necessary due to significant clinical improvement.

OUTCOME AND FOLLOW-UP

Following titration and optimization of the clozapine dose, the clinical improvement was sustained over the next few weeks with significant remission of psychotic symptoms. Baseline BPRS was '72', and follow-up at 8 weeks was '6'. Her functioning returned to baseline. She also regained insight about mental disorder and capacity to consent to treatment and catatonia had completely resolved.

In the weeks preceding the discharge, her platelets continued to remain low with a few counts in the 20s, the lowest being 25×10^9/L.

During the treatment with both oral and IM clozapine, the inpatient psychiatry team was in regular touch with the haematology department and shared all the blood reports. There was no objection to the use of clozapine use because of low platelets.

At discharge, the patient was advised to visit the emergency department if she developed any symptoms of abnormal bleeding. She was discharged under the care of the community mental health team and a referral was made to the local haematological services for further opinion and clinical management.

DISCUSSION *Include a very brief review of similar published cases*

In this patient, a low platelet count was detected after five years of starting clozapine and there were periods both in the community and inpatient admission when the patient continued to have a low platelet count despite not being on clozapine. Furthermore, there was no clear association between clozapine dose and her platelet count. On reviewing the literature, thrombocytopenia is a very rare haematological side effect of clozapine as described in case reports and case series.[7-9] In a study conducted in Italy investigating the hematologic effects of clozapine; only 2 out of 2404 patients (0.08%) had thrombocytopenia and those two cases recovered spontaneously.[10] Indeed, current guidelines for clozapine monitoring in the United States do not require monitoring of platelets.[11]

Unfortunately, in this case, the ambiguity about the cause for low platelet at the initial phase of admission caused a significant delay in treatment with clozapine and this was further complicated by the patients' non-concordance due to catatonia and poor response to ECT. ECT is considered a standard and effective treatment for catatonia, however, in this case, there was no significant response to this treatment. This

presentation is similar to a patient described in another case study of a patient with ECT-resistant catatonia, who responded to a rechallenge of clozapine after failed trials due to adverse effects.[12]

Ultimately, the treating team not only considered re-commencing clozapine but also utilized the IM formulation safely in successfully establishing the patient on a therapeutic dose. In this process, liaison among the members of the multidisciplinary team including the nursing staff members who were involved in administration, consultation with the specialist services including pharmacy, haematology, and collaboration with the patient/carer were crucial factors for the successful treatment. However, IM clozapine is an unlicensed medicine in the UK and the prescriber must adhere to the guidance on non-licensed prescribing of the General Medical Council. The patient still needs to be registered with the appropriate monitoring system as the aim is to switch to oral clozapine.

In this patient, no significant serious side effects were reported except pain on the injection site. A summary of studies found no significant serious side effects due to IM clozapine in comparison with oral clozapine except for pain at the injection site. Other injection-related known side effects of IM clozapine are tachycardia and hypotension in the short term and the development of nodules on long-term use.[13]

In another study, eleven patients were prescribed intramuscular clozapine at five UK sites: 2 medium-secure units, 2 high-secure hospitals, and a locked rehabilitation unit, no serious side effects were recorded other than pain/nodule at the injection site. Out of 11 patients who were offered oral/IM choice, three accepted oral, and the remaining eight received intramuscular clozapine. Overall, nine patients were successfully established on oral clozapine with significant improvement in their clinical presentations.[14]

In a case series, it was highlighted that IM clozapine was safely used in acute medical settings in two patients, one with co-morbid liver abscess and the other admitted to the Intensive Treatment Unit with severe injury after a suicidal jump.[15] Another study of IM clozapine usage in the UK showed that, among 39 patients prescribed IM clozapine, 19 received at least one injection, whereas 20 accepted oral clozapine when given an enforced choice between the two. Thirty- six (92%) patients successfully initiated oral clozapine after intramuscular prescription; three never transitioned to oral.[16] Overall, it is indicated for patients for whom clozapine has a definite indication and benefit, either for initiation or restarting in those who were previously on clozapine but discontinued treatment and as a maintenance treatment for those refusing oral treatment.

In this context, it is important to reflect that clozapine is grossly underutilized in the United Kingdom and only a third of eligible patients are receiving the treatment despite good effectiveness and safety profile.[17]

Despite the clear benefit of intramuscular clozapine and its established place in pharmacotherapy of treatment-resistant schizophrenia, it is important to stress that the current formulation is unlicenced and caution must be exercised until a licensed preparation becomes available for clinical use.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- Careful and timely clinical evaluation is crucial before attributing rare side effects with clozapine as this might lead to the premature decision to stop the medication and delay treatment.
- The clinical decision to prescribe unlicensed medicine might be cautiously considered by a psychiatrist in a challenging clinical situation when no other effective treatment options are available, and the benefit to the patients outweighs the risk.
- However, any such challenging clinical decisions should be backed by scientific evidence, and input from the multidisciplinary team, and adherence to relevant guidelines and policies should be strictly followed.
- Close physical monitoring in the acute inpatient psychiatric unit and liaison with the general hospital medical team help to build up confidence in treating patients with clinical presentation complicated by comorbid physical health problems.

REFERENCES

1. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin. 1997;14(1):1–20.

2. Rey Souto D, Pinzón Espinosa J, Vieta E, Benabarre Hernández A. Clozapine in patients with schizoaffective disorder: A systematic review. Revista de Psiquiatría y Salud Mental (English Edition). 2021 Jul 1;14(3):148–56.

3. Blackman G, Oloyede E, Horowitz M, Harland R, Taylor D, MacCabe J, et al. Reducing the Risk of Withdrawal Symptoms and Relapse Following Clozapine Discontinuation-Is It Feasible to Develop Evidence-Based Guidelines? Schizophr Bull. 2022 Jan 21;48(1):176–89.

4. Legge SE, Hamshere M, Hayes RD, Downs J, O'Donovan MC, Owen MJ, et al. Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. Schizophr Res. 2016 Jul;174(1–3):113–9.

5. Davis MC, Fuller MA, Strauss ME, Konicki PE, Jaskiw GE. Discontinuation of clozapine: a 15-year naturalistic retrospective study of 320 patients. Acta Psychiatrica Scandinavica. 2014 Jul;130(1):30-9.

6. Bhattacherjee S, Young A, Ahuja N, Allen S. Should intramuscular clozapine be adopted into mainstream clinical practice?. The British Journal of Psychiatry. 2021 Jul;219(1):357-8.

7. Rakesh KM, Innamuri RT, Kattula D. Clozapine and Thrombocytopenia: Case Report & Literature Review. Indian Journal of Psychiatry. 2022 Mar;64(Suppl 3):S672.

8. Durst R, Dorevitch A, Fraenkel Y. Platelet dysfunction associated with clozapine therapy. South Med J 1993;86(10):1170-2. [CrossRef] 5. Mihaljevi-Peles A, Jakovljevic

9. Kate N, Grover S, Aggarwal M, Malhotra P, Sachdeva MS. Clozapine associated thrombocytopenia. Journal of Pharmacology and Pharmacotherapeutics. 2013 Jun;4(2):149-51.

10. Lambertenghi Deliliers G. Blood dyscrasias in clozapine treated patients in Italy. Haematologica 2000;85(3):233-7)

11. Whiskey E, Dzahini O, Ramsay R, O'Flynn D, Mijovic A, Gaughran F, MacCabe J, Shergill S, Taylor D. Need to bleed? Clozapine haematological monitoring approaches a time for change. International clinical psychopharmacology. 2019 Sep 1;34(5):264-8.

12. Dima A, Abdelsamie A, Clark-Castillo R, Webb-Wilson H, Shergill SS, Stanton B, Gaughran F, Whiskey E, Nettis MA. Overcoming Obstacles to Clozapine Treatment: A Case of Clozapine Rechallenge in ECT-Resistant Schizophrenia With Catatonic Features. Journal of Clinical Psychopharmacology. 2022 Mar 28:10-97.

13. Munzar B, Nemets B. Clinical experience with intramuscular clozapine. Cureus. 2021 Sep 25;13(9).

14. Henry, R., Massey, R., Morgan, K., Deeks, J., Macfarlane, H., Holmes, N., & Silva, E. (2020). Evaluation of the effectiveness and acceptability of intramuscular clozapine injection: illustrative case series. BJPsych Bulletin, 44(6), 239-243.

15. Gee, S., McMullen, I., Wyke, C., Yeoh, S. Y., & Taylor, D. (2021). Intramuscular clozapine in the acute medical hospital: Experiences from a liaison psychiatry team. SAGE Open Medical Case Reports, 9, 2050313X211004796.

16. Casetta, C., Oloyede, E., Whiskey, E., Taylor, D. M., Gaughran, F., Shergill, S. S., ... & MacCabe, J. H. (2020). A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis. The British Journal of Psychiatry, 217(3), 506-513.

17. Whiskey E, Barnard A, Oloyede E, Dzahini O, Taylor DM, Shergill SS. An evaluation of the variation and underuse of clozapine in the United Kingdom. Acta Psychiatrica Scandinavica. 2021 Apr;143(4):339-47.

PATIENT'S PERSPECTIVE

'Before coming to the hospital last year, I was doing good for nearly a decade. I was taking Clozapine and it was very effective. I was working part-time and managing myself independently. My clozapine was stopped because I was told it was causing low platelets. After stopping clozapine, I became quite unwell. I was admitted to the hospital and moved from one unit to another which was very frustrating and tiring. I was not able to go home and see my family. I understand it was because my treatment was complicated. I think, when I was in the hospital, I was feeling too overwhelmed and frustrated. I don't remember much but I was very confused. So, I was not taking Clozapine following which I was also given ECT. I remember I was given injection of clozapine when I was refusing oral Clozapine. It was painful; I don't think I'd have that injection clozapine again. However, I do understand that it helped me to go back to clozapine tablets which I am taking regularly now. I am quite excited about going home because it has been a long time. I went on home leave for Christmas, it went well. I was helping my dad to cook. After discharge, I will attend appointment with the haematologist in hospital. I need to watch for symptoms of abnormal bleeding and go to emergency if there is any concern. I have a chronic mental illness and I need to continue taking oral Clozapine. I will engage with the community team and attend the clozapine clinic regularly. I'd also like to go back to my work soon. I want to participate in recovery activities because I have been away from hospital for a long time. Thank you for all the support.'

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