

Rechallenging With Clozapine Following Neutropenia: Treatment Options for Refractory Schizophrenia

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Clozapine, a second-generation antipsychotic, is the treatment of choice in refractory schizophrenia because of its proven efficacy over typical antipsychotics as well as other atypical antipsychotics (1). However, a major drawback to clozapine therapy is the increased risk of neutropenia and agranulocytosis (2). In patients who develop either of these serious side effects, clozapine is immediately discontinued. Unfortunately, trials of other antipsychotics often prove ineffective, and clinicians find themselves faced with the difficult decision of whether to rechallenge those patients with clozapine (3). Even more concerning for the clinician is the relative absence of any controlled data to suggest treatment options when clozapine cannot be used because of serious side effects, such as neutropenia or agranulocytosis. This case review highlights this particular aspect and provides some useful thinking points for clinicians and patients in this situation.

Efforts at rechallenge with clozapine have met with some success (4–9).

In a retrospective review of 53 cases of clozapine rechallenge in the United Kingdom and Ireland, 62% of the patients did not develop a blood dyscrasia on rechallenge (8). Of course, clozapine rechallenge is not without its risks. In the same retrospective review, it was found that among the 38% of cases who did develop a blood dyscrasia on rechallenge, in 85% of the cases, the blood dyscrasia

occurred more quickly and was more severe than with the initial trial of clozapine. In addition, in 65% of the cases in which patients developed a blood dyscrasia on rechallenge, the blood dyscrasia lasted longer after discontinuation of clozapine following rechallenge than when clozapine was first discontinued. Thus, when deciding whether to rechallenge a patient with clozapine, the clinician must carefully weigh the risks and benefits of a clozapine rechallenge. Here we present a patient with refractory schizophrenia who successfully tolerated a clozapine challenge 2 years after developing clozapine-induced neutropenia and failing to respond to a subsequent clozapine rechallenge. We propose that polypharmacy may have contributed to the initial episode of neutropenia as well as the failed clozapine rechallenge in our patient. We also discuss logical issues in medical decision making before considering clozapine rechallenges in patients.

Case Presentation

“S.P.” was a 55-year-old divorced African American man with a 30-year history of paranoid schizophrenia who was referred to our unit for medication adjustment after a 2-year gradual worsening of psychotic symptoms characterized by thought disturbance and behavioral disorganization. As a result of his worsening symptoms, 3 months before admission, S.P. went from living independently in a supervised care setting to requiring close supervision and help with activities of daily living. Two months before admission, he stopped bathing and washing his clothes and refused to socialize. S.P.’s relationship with his case manager, which had previously been good, deteriorated, and he began to refuse to let the case manager into his home. His neighbors complained of loud noises, objects being thrown on the floor; also, S.P. could be heard conversing with himself.

S.P. was hospitalized voluntarily; written consent was obtained before admission. Upon admission, he reported auditory hallucinations but no command auditory hallucinations or ever acting on the voice’s instructions. S.P. also possessed multiple well-organized and developed delusions, including persecutory delusions and delusions of grandeur, as well as some ideas of reference.

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Of importance, S.P.'s cognitive faculties were well conserved, allowing him to participate in his treatment. He demonstrated an understanding of the treatment plan to restart clozapine and was agreeable to it because he himself felt that he had a better quality of life when he was taking clozapine compared with the medication regimen he was placed on after developing neutropenia with the rechallenge. In cases such as S.P.'s, but in which the patient's cognitive faculties are not intact, treatment should proceed according to federal and state guidelines, on a case-by-case basis.

Past Psychiatric History

S.P.'s first psychiatric hospitalization occurred 30 years ago at the age of 25; however, medical records were only available from the preceding 14 years. It was noted that 14 years ago, he had been receiving 800 mg/day of clozapine for the management of his psychosis. From that time until 2 years before our hospitalization, S.P. was maintained with 750 mg/day of clozapine and 1500 mg/day of valproic acid. Although this medication regimen did not eliminate his symptoms, it did result in a marked improvement of functioning and allowed him to live and care for himself independently.

Approximately 2 years before our admission in an effort to improve cognitive functioning, in particular, mild memory deficits, S.P. was started with donepezil. Within a month after starting donepezil, he began to experience declines in WBC count and absolute neutrophil count; the lowest level WBC count, recorded 1 month after S.P. began taking donepezil, was 4.0×10^3 cells/ml, an absolute neutrophil count of 1620/ml and a hematocrit of 29.9%, down from a WBC count of 6.1×10^3 cells/ml, with an absolute neutrophil count of 2556/ml, and a hemocrit of 32.5% at the start of treatment.

It is worth noting that although our patient was African American, the previously normal absolute neutrophil count of 2556/ml was inconsistent with benign ethnic neutropenia, which is defined as an absolute neutrophil count below 1500/ml at *baseline*, in the absence of a history of susceptibility to infection, in persons of African descent and some ethnic groups in the Middle East (10). Patients with treatment-resistant schizophrenia who also have benign ethnic neutropenia present a particular challenge to treatment providers (11, 12). In fact, there is concern that clozapine is underused in African Americans who might otherwise benefit from clozapine treatment owing to benign ethnic neutropenia, which has prompted discussion about revising the guidelines of clozapine use to account for benign ethnic neutropenia in African Americans (11).

The absolute neutrophil count of 1620 in our patient led to discontinuation of both clozapine and donepezil. Although the accepted recommendation is to discontinue clozapine in patients with an absolute neutrophil count of 1500/ml or less (13), at the time that the decision to discontinue clozapine was made, the patient was not under our care. S.P.'s treatment provider at the time discontinued clozapine out of concern for likely progression to neutropenia and possibly agranulocytosis. He continued taking 1500 mg/day of valproic acid. Four days after clozapine was discontinued, risperidone was introduced and titrated up to 6 mg/day. Before starting risperidone, S.P. had a WBC count of 5.9×10^3 cells/ml and an absolute neutrophil count of 2300/ml.

A week later, S.P. had a WBC level of 5.79×10^3 cells/ml and an absolute neutrophil count of 2762/ml. The following day, clozapine was added to risperidone and titrated gradually over the course of 20 days up to 500 mg/day. He remained taking risperidone with clozapine, and 6 weeks later, his WBC count was 3.23×10^3 cells/ml with an absolute neutrophil count of 904/ml. The next day, the patient's WBC count was 3.4×10^3 cells/ml, and his absolute neutrophil count was 850/ml. Of note, these results were obtained from different laboratories. The low WBC count and absolute neutrophil count prompted discontinuation of clozapine. The patient's WBC count as well as his absolute neutrophil count began to normalize by the following day (a WBC count of 4.6×10^3 cells/ml and an absolute neutrophil count of 1500/ml).

Over the next 2 years, the dose of risperidone was increased to 8 mg/day and subsequently decreased to 6 mg/day after reports of stiffness and slight extrapyramidal symptoms. In an effort to treat S.P.'s increasingly refractory psychosis, olanzapine was added to the drug regimen and titrated up to a dose of 25 mg/day. In other efforts to treat his worsening psychosis, he was also treated with quetiapine up to a maximally tolerated dose of 400 mg/day, but none of these manipulations manifested as an improvement in S.P.'s symptoms.

Throughout, his dose of valproic acid remained 1500 mg/day. However, before admission, in anticipation of the clozapine rechallenge, valproic acid was tapered down to 750 mg/day. Upon admission, S.P.'s medication regimen consisted of olanzapine, 25 mg/day; valproic acid, 750 mg/day; and risperidone, 6 mg/day.

Hospital Course

Valproic acid was tapered by 250 mg decrements every 2 days and discontinued 1 week after admission. S.P.'s olanzapine dose was also tapered and discontinued 1 week after admission. Lithium carbonate, 300 mg/day, was started 1 week after admission. Ten days later, the patient's WBC count was 8.83×10^3 cells/ml, and his absolute neutrophil count was 4901/ml, up from admission, when his WBC count was 6.83×10^3 cells/ml and his absolute neutrophil count was 3339/ml.

Clozapine was started 3 days later at 12.5 mg/day, then 12.5 mg/b.i.d., followed by 25 mg/day increments up to a therapeutic dose of 300 mg/day. Once a daily dose of 100 mg of clozapine was reached, risperidone was tapered off in 1 mg decrements every 2 days. The dose of clozapine was eventually increased to 325 mg/day in anticipation of discharge and a likely increase in smoking, which would decrease serum clozapine levels. At the time of discharge, S.P.'s serum clozapine level was 520 ng/ml.

The patient's CBC and differential were monitored weekly. Throughout the course of treatment, the patient's WBC count and absolute neutrophil count remained within normal limits. At the time of discharge, the patient's WBC count was 9.37×10^3 cells/ml, and his absolute neutrophil count was 5453/ml.

We also evaluated the patient's symptoms with the Positive and Negative Syndrome Scale (PANSS) (14). Unfortunately, a PANSS score was not obtained upon admission because we began using the PANSS to follow S.P.'s symptoms only after initiating clozapine. After 1 week of taking clozapine, the patient's score on the PANSS was 93. At the time of discharge, his score on the PANSS was

56, demonstrating a marked improvement in symptoms with clozapine treatment. Over 6 months after these events and at the time of writing this report, S.P. continues taking clozapine 350 mg/day and lithium 300 mg/day, is much improved (a PANSS score of 45), and has robustly healthy blood counts (a WBC count of 9.27×10^3 cells/ml and an absolute neutrophil count of 5683/ml).

Discussion

We present a case of a patient who developed neutropenia after 12 years of clozapine therapy, which in itself is atypical for a clozapine-induced blood dyscrasia (5). To the best of our knowledge, there have been only four case reports of neutropenia or agranulocytosis at 5 or more years of treatment with clozapine (6, 7, 15, 16). The greatest reported risk of developing neutropenia or agranulocytosis with clozapine is during the first 6 months of treatment (5). The cumulative incidence of either clozapine-induced agranulocytosis or neutropenia at more than 1 year of treatment is less than 1% (5).

In three of the four reported cases of late-onset neutropenia or agranulocytosis, the patients were taking additional psychotropic medications that carry a risk for blood dyscrasia (17, 18), namely valproic acid, haloperidol, or risperidone. This raises the question of whether the neutropenia or agranulocytosis in those cases was truly clozapine-induced or the result of synergistic effects on hematopoiesis, which led to an increased risk for neutropenia or agranulocytosis. The decision to restart clozapine in our patient was arrived at after careful consideration of the medication regimens that the patient was on, both when he initially developed neutropenia and when he received the clozapine rechallenge. We had reason to believe that the neutropenia in both cases may be attributable to adjunctive use of other psychotropics with clozapine.

When our patient first developed neutropenia, he was taking valproic acid as well as clozapine for seizure prophylaxis. The use of valproic acid as an adjunct to clozapine is used by some clinicians as a secondary prophylaxis against clozapine-induced seizures (2, 19, 20). Valproic acid is a first-line agent for the treatment of clozapine-induced seizures because clozapine-induced seizures are quite diverse, including tonic-clonic, myoclonic, and atonic seizures, and valproic acid provides a broad spectrum of coverage (19). Unfortunately, valproic acid carries a risk of neutropenia (17, 18) and has been shown to increase serum clozapine levels when used adjunctively with clozapine (21), so the combination of clozapine and valproic acid may have placed our patient at higher risk for developing neutropenia. Consistent with this, there is a case report of neutropenia after 3 years of clozapine treatment, which is outside the 6-month window of greatest risk, in which the patient was taking a combination of valproic acid and clozapine (22). In addition, there is a case report of neutropenia in a patient who was taking clozapine and valproic acid, whose neutropenia resolved with discontinuation of the valproic acid (23). It may be that in some pa-

tients the combination of clozapine and valproic acid confers a greater risk of developing later-onset neutropenia.

The decision to discontinue valproic acid in our patient, despite the risk for seizure upon restarting clozapine, came after a careful review of the facts surrounding clozapine-induced seizures, the risk involved, and the recommended management of that risk. The risk of clozapine-induced seizures is dose related: there is a 1% risk at doses less than 300 mg/day, 2.7% at 300–600 mg/day, and 4.4% at doses greater than 600 mg/day (24). Our patient was taking 350 mg/day of clozapine upon discharge, putting him at low risk for a seizure event. The recommendations regarding the use of anticonvulsants in patients taking clozapine suggest that anti-convulsants are indicated for patients with evidenced clozapine-induced seizures, as a form of *secondary* prophylaxis (19, 20). To the best of our knowledge, valproic acid was being used as a *primary* prophylaxis in our patient; there were no documented seizures in him. Recommendations for primary prophylaxis of clozapine-induced seizures are limited to careful monitoring, especially in those with a prior history of seizure and those at higher dosages and slow titration of clozapine dosage (19). In light of the possibility that the combination of clozapine and valproic acid may put patients at greater risk for late-onset neutropenia, for the patients who do experience a seizure while taking clozapine, two other anticonvulsants, lamotrigine and gabapentin, are viable alternatives since they do not affect the pharmacokinetics of clozapine (19). Also, please see the review by Wong and Delva of the management of clozapine-induced seizure for further recommendations (19).

Another important consideration in our patient's case is that when he first developed neutropenia, it was 1 month after the addition of donepezil to his medication regimen. Although donepezil has been reported to cause a number of hematological side effects, including anemia, thrombocytopenia, and ecchymosis (17), it has not been shown to cause neutropenia. However, donepezil is metabolized by the P450 isoenzymes 2D6 and 3A4 (25), which are also responsible for the metabolism of clozapine (26). The addition of donepezil may have led to increased serum levels of clozapine and placed our patient at greater risk for clozapine-induced neutropenia. Unfortunately, serum levels of clozapine were not obtained before and after initiation of donepezil in our patient, so this conclusion is speculative.

At the time of the first clozapine rechallenge, our patient was still taking valproic acid. In addition, after discontinuation of clozapine, risperidone was introduced, which itself also carries a risk of neutropenia and agranulocytosis (18). Moreover, risperidone has been shown to increase serum levels of clozapine (27). Therefore, the combination of clozapine and risperidone at the time of the first rechallenge may have placed our patient at increased risk for developing neutropenia. Consistent with this, there have been three case reports of neutropenia or agranulocytosis in patients treated with clozapine and risperidone (6, 15, 28), with two of three cases being late-onset neutropenia. Notably, in one of the cases of late-onset neutropenia with

clozapine and risperidone, neutropenia resolved upon discontinuation of the risperidone (6).

When the patient first came into our care, our first goal for treatment was to eliminate the increased risk of developing neutropenia that is associated with clozapine use in conjunction with other psychotropic medications. In anticipation of restarting clozapine, the patient's valproic acid was tapered down from 1500 mg/day to 750 mg/day before admission. The taper was continued during the patient's hospital course, and valproic acid was discontinued before initiation of clozapine treatment. Unfortunately, we cannot know whether the discontinuation of valproic acid alone would have led to an increase in WBC count because we also gave our patient lithium carbonate, which is known to increase WBC count, before restarting clozapine, only 2 days after discontinuing valproic acid.

Lithium's co-administration with clozapine has been suggested as a means of preventing neutropenia on clozapine rechallenge and has met with some success (16, 29–31). In our patient, the addition of lithium led to a 2.0×10^3 cells/ml increase in WBC count and a 1600/ml increase in absolute neutrophil count. Current thinking about the mechanism for the lithium-induced increase in WBC count supports direct granulocyte stimulation (32) and/or stimulation of granulocyte macrophage colony-stimulating factors (33). Some authors have raised the possibility that lithium may result in only a demargination of cells rather than a true increase in WBC count (34); however, research by Tisman et al. (35) from the early 1970s demonstrated that lithium-induced leukocytosis is due to genuine increases in blood granulocyte pool and not demargination of marginated leukocytes.

Despite the clinical benefit of the coadministration of lithium and clozapine for prevention of neutropenia, it is not without its risks. There are case reports of adverse neurological effects, including tremors, involuntary movements, and seizures (16, 34, 36, 37), as well as case reports of agranulocytosis (38, 39), in patients taking clozapine and lithium. However, the adverse neurological effects reported in most cases were transient and occurred only during initiation of lithium treatment (16, 36, 40); in other cases, the picture was complicated by polypharmacy and the possible contribution of other medications, including haloperidol (16) and serotonergic agents (40). Similarly, one of the two cases of agranulocytosis reported was complicated by haloperidol, as well as a number of anticonvulsants that themselves carry a risk of blood dyscrasia in that patient's medication regimen (39). Additionally, a recent retrospective chart analysis of 25 patients who were treated with lithium during a clozapine rechallenge found only a single case of agranulocytosis, a rate lower than the estimated risk of developing neutropenia or agranulocytosis on clozapine rechallenge alone (30). Thus, although there is some risk of adverse neurological side effects and agranulocytosis, the risk is either transient or minimal, and the risk that does exist is best approached with careful observation during the period in which lithium treatment is initiated and vigilant blood count monitoring throughout.

Another means of increasing WBC count in patients taking clozapine, proposed in the last decade, is the use of granulocyte colony-stimulating factor (3, 29). Granulocyte colony-stimulating factor, which is believed to both induce neutrophil maturation and enhance neutrophil activity (41), has traditionally been used to treat chemotherapy-induced neutropenia (41, 42). The introduction of granulocyte colony-stimulating factor onto the psychiatric scene came by way of its use as treatment for drug-induced agranulocytosis, to decrease the episode of granulocytosis following discontinuation of the offending drug (29), in some cases clozapine (43).

However, there have been a few case reports of using granulocyte colony-stimulating factor to symptomatically treat neutropenia in a patient with clozapine-induced neutropenia (44–46) as well as a report of multiple cases of patients who developed clozapine-induced neutropenia who were successfully treated with a combination of clozapine and granulocyte colony-stimulating factor (47). Although the most common side effect of granulocyte colony-stimulating factor is bone pain, there is concern about a possible causal relationship between the use of granulocyte colony-stimulating factor in the long term and the development of acute myeloid leukemia (48), which is relevant to its use as a long-term adjunct to clozapine. Additionally, treatment with granulocyte colony-stimulating factor is quite costly and invasive (41, 42), requiring daily/weekly subcutaneous injections. So although granulocyte colony-stimulating factor presents an exciting new option for use in the prevention of clozapine-induced neutropenia or agranulocytosis, there are many limitations to extending its use in more patients. It was owing to these very concerns that we chose not to use granulocyte colony-stimulating factor in the management of our patient.

A final note on our treatment plan: we maintained the patient with risperidone while we initiated clozapine so that the patient would not be without antipsychotic coverage. However, we tapered the patient off of risperidone once the patient's clozapine dose reached 100 mg/day so as to avoid a possible blood dyscrasia from the combination of clozapine and risperidone.

Our patient responded well to the treatment course outlined here without any further episodes of neutropenia. At the time of writing this article, the patient reports a significant reduction in the frequency of his auditory hallucinations, as well as in their duration and interference with his daily functioning. He also reports feeling much less anxious and endorses fewer delusions. Moreover, he has been able to return to his independent living facility and care for himself. Thus, while restarting our patient with clozapine in the face of a failed clozapine rechallenge was not without risks, clozapine proved to be *critical* to managing this patient's symptoms and allowing him to live and care for himself independently.

We believe that this case has useful clinical practice points for the treatment of patients with relatively unyielding forms of schizophrenia. The case demonstrates the im-

portance of careful consideration of the possible contribution of other medications when a patient taking clozapine presents with late-onset neutropenia. Discontinuation of clozapine in a treatment-resistant patient with schizophrenia often results in relapse, and this might be prevented if the clinician is able to identify a causative agent other than clozapine; medication regimens should be carefully evaluated for other medications with the potential to cause neutropenia. This case also emphasizes the need for careful monitoring in a patient taking clozapine when new medications are introduced that carry a risk for developing a blood dyscrasia and/or result in increased serum levels of clozapine. Should a blood dyscrasia develop, we believe that the prudent approach is that the last medication to be introduced into a patient's medication regimen should be the first to be tapered off, as we successfully did with the case presented here. We also believe that the role of lithium as an agent to increase neutrophil counts needs to be explored further and may prove beneficial to patients with clozapine-induced neutropenia. Finally, this case, more generally, highlights the need for rational pharmacotherapy in treating patients with longstanding psychotic illness, whose clinical pictures are often complicated by multiple pharmacologic interventions and for whom we have limited well-validated treatments.

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