Optimizing Outcomes in Clozapine Rechallenge Following Neutropenia: A Cohort Analysis

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ABSTRACT

Objective: Certain patients with treatment-refractory schizophrenia may be rechallenged with clozapine following previous neutropenia. Evidence guiding patient selection and the effectiveness of lithium and granulocyte-colony stimulating factor (G-CSF) in rechallenge is limited, and factors associated with successful outcomes are unclear.

Method: Outcomes were studied in patients rechallenged with clozapine at a tertiary referral center between January 2007 and December 2013, following 1 or more previous trials terminated due to neutropenia, defined as an absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L. Demographic characteristics, details of each clozapine trial including ANC, and coprescribed medication were extracted, and factors associated with rechallenge outcomes were examined.

Results: Nineteen patients underwent clozapine rechallenge following previous neutropenia; 4 (21%) experienced further neutropenia, 2 of which developed agranulocytosis. Compared to successfully rechallenged patients, unsuccessfully rechallenged patients were significantly older ($t = 2.10$, $P = .05$), experienced onset of neutropenia sooner ($W = 10.0$, $P = .03$), and were more commonly coprescribed valproate. In addition to 5 patients with benign ethnic neutropenia (BEN), 8 patients not of an ethnicity associated with BEN also had idiopathic low neutrophil counts at baseline; lithium and G-CSF coprescription facilitated successful rechallenge in these patients.

Conclusions: In this selected population, the initial neutropenia was unlikely to be related to clozapine in a substantial proportion of cases. This group was successfully rechallenged following careful consideration of the risks and benefits, and lithium and G-CSF contributed to allowing continued clozapine therapy. In addition to black patients, other ethnic groups can have persistently low ANC unrelated to clozapine.

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Clozapine is an antipsychotic with unique efficacy in treatment-refractory schizophrenia.[1] In the United Kingdom, clozapine is recommended in patients who have failed to respond to trials of at least 2 different antipsychotics at adequate doses.[2] However, first-line use is limited by its propensity to cause neutropenia[3] and potentially fatal agranulocytosis[4] in 3% and 0.8% of patients, respectively, and regular hematologic monitoring is mandatory for all patients receiving clozapine. Patients developing hematologic dyscrasia are excluded from further licensed treatment.

Nonetheless, in certain individuals for whom illness is severe and a good response to clozapine was observed, off-label rechallenge of clozapine may be attempted after careful consideration of the risks and benefits.[5] In particular, cases in which the original dyscrasia was likely due to factors other than clozapine may benefit from rechallenge. Coadministration of other drugs that interact with clozapine, or in themselves cause hematologic toxicity, may account for, or contribute to, some cases of neutropenia.[6] Benign ethnic neutropenia (BEN), shown to affect 5%[7] to over 25% of people of African and Middle Eastern ancestry,[8] has been recognized as a factor contributing to clozapine discontinuation in these populations.[9] The use of modified monitoring criteria for BEN populations[10] (Table 1) and coadministration of lithium[11] and granulocyte-colony stimulating factor (G-CSF)[12] have been used to augment leukocyte counts and avoid treatment interruption or discontinuation.

Due to the risk of agranulocytosis, patients and clinicians are understandably hesitant to undertake clozapine rechallenge, and rechallenge remains uncommon. The evidence base guiding practice is correspondingly sparse. The largest study consisted of 53 patients rechallenged in the United Kingdom over a 5-year period,[13] of whom 20 (38%) experienced a further dyscrasia, 9 of whom developed agranulocytoses. No clear risk factors for repeat dyscrasia were identified; however, the second dyscrasia was more severe, more prolonged, and occurred sooner. Kanaan and Kerwin[14] studied 25 rechallenges with coprescribed lithium and reported that only 1 (4%) had a second episode of neutropenia, suggesting that lithium improved the probability of success. A systematic review[15] including the 2 studies mentioned above reported 112 cases of rechallenge following neutropenia of which 34 (30%) failed, and 15 rechallenges following agranulocytosis, of which 12 (80%) experienced further dyscrasia.

Further evidence guiding the selection of patients for rechallenge based on their previous hematologic profile is therefore needed, as is evidence regarding the utility of treatments aimed at augmenting leukocyte counts. Observational studies of clozapine rechallenge offer important insights in this regard.

Clinical Points

- Neutropenia is a frequent reason for discontinuing clozapine, and there is often uncertainty over attempting rechallenge. This study suggests that with careful selection and support from a hematologist, some patients can be successfully rechallenged with clozapine following neutropenia.
- The circumstances of initial neutropenia should be carefully considered, including whether benign ethnic neutropenia (BEN), coprescribed medications, or medical conditions could have been responsible.
- In cases of BEN, lithium and G-CSF may aid rechallenge with clozapine. White patients can also present with a picture of persistent neutropenia identical to BEN.

Table 1. Clozapine Blood Monitoring Criteria in the United Kingdom and Ireland in Patients With and Without BEN[a]

	Normal Monitoring Criteria (No. of cells/L)	Modified BEN Monitoring Criteria (No. of cells/L)	Action Required
Green zone			
ANC	$>2.0\times10^9$	$>1.5\times10^9$	Continue treatment
WBC	$>3.5\times10^9$	$>3.0\times10^9$	
Amber zone			Continue treatment, sample blood twice weekly until counts stabilize or increase
ANC	1.5×10^9–2.0×10^9	1.0×10^9–1.5×10^9	
WBC	3.0×10^9–3.5×10^9	2.5×10^9–3.0×10^9	
Red zone			
ANC	$<1.5\times10^9$	$<1.0\times10^9$	Discontinue clozapine immediately
WBC	$<3.0\times10^9$	$<2.5\times10^9$	

[a]Based on references 10 and 18.
Abbreviations: ANC = absolute neutrophil count, BEN = benign ethnic neutropenia, WBC = white blood cell count.

The National Psychosis Unit (NPU) is a tertiary center admitting patients from across the United Kingdom for the management of treatment-refractory schizophrenia. A substantial proportion have previously discontinued clozapine due to hematologic adverse events and, therefore, form a unique population in which to study clozapine rechallenge. We report the outcomes of 19 adult inpatients selected for clozapine rechallenge following previous leukopenia or neutropenia and examine whether particular clinical characteristics are associated with outcome. We focus on the efficacy, safety, and tolerability of adjunctive measures including lithium and G-CSF.

METHOD

All admissions to the NPU between January 1, 2007, and December 31, 2013, were screened for inclusion. Inclusion criteria comprised at least 1 previous episode of clozapine therapy discontinued due to concurrent leukopenia and/or neutropenia and subsequent clozapine rechallenge on the unit. *Leukopenia* was defined as a white blood cell count (WBC) $<3.0\times10^9$/L, neutropenia as an absolute neutrophil count (ANC) $<1.5\times10^9$/L, and agranulocytosis as an ANC $<0.5\times10^9$/L. *Benign ethnic neutropenia* was defined as ANC consistently below the threshold of 1.5×10^9/L in people of African or Middle Eastern descent, with no evidence of increased susceptibility to infection and no alternative explanations for persistent neutropenia.[8]

Demographic information, psychiatric diagnosis, characteristics of each clozapine trial (duration, dose, neutrophil nadir, duration of neutropenia), alternative explanations for neutropenia (comorbid medical conditions, benign ethnic neutropenia, coprescription of drugs reported to have a definite or probable causal association with neutropenia and agranulocytosis[6,16]), and the use of adjunctive treatments (lithium and G-CSF) were extracted from the patient record. Ethnic group was classified according to guidelines from the Office for National Statistics, United Kingdom[17]: white, mixed, Asian (from any part of the Asian continent, including Chinese), black, and other ethnic group (including Arab).

Full blood counts during treatment and, where possible, complete historical blood counts were obtained. *Successful rechallenge* was defined as continued clozapine therapy until discharge from the unit, and *unsuccessful rechallenge* was defined as recurrence of leukopenia, neutropenia, or agranulocytosis prior to discharge. Blood tests during the follow-up period were performed in accordance with guidelines from the clozapine monitoring service[18] (weekly for the first 18 weeks and at 4-week intervals thereafter), with the exception that patients with a BEN-pattern receiving G-CSF had an increased frequency of monitoring (twice weekly or on alternate days) during the initial phase of treatment, on the advice of the hematologist.

The *t* test for independent and matched samples was used to compare differences in age and between- and within-group differences in ANC, and the Mann-Whitney test and Wilcoxon signed rank test were used to compare treatment duration between and within groups, respectively. Categorical variables were compared using the χ^2 test. All reported *P* values are 2-sided. Statistical analysis was undertaken using SPSS 22.[19]

Approval was obtained from the Drugs and Therapeutics Committee of the South London and Maudsley NHS Foundation Trust, and the study complies with the standards laid down in the Declaration of Helsinki.

RESULTS

One hundred forty-six patients were admitted over the study period, of whom 51 were rechallenged with clozapine. Nineteen of these patients had experienced previous clozapine-associated neutropenia that resulted in treatment discontinuation; all had primary *ICD-10* diagnoses of schizophrenia. Rechallenge was successful in 15 patients (79%) and unsuccessful in 4 (21%) (Table 2). Fourteen had undergone 1 previous trial of clozapine; 5 had undergone 2 previous trials, 4 of whom were successfully rechallenged. None of the patients selected for rechallenge had previous agranulocytosis, on the basis of evidence suggesting that rechallenge in this group is highly unlikely to succeed.[20]

Table 2. Patient Characteristics, Times to Neutropenia, and ANC Nadir on First and Rechallenge Exposures to Clozapine

Variable	All Patients (N = 19)	Successful Rechallenge (n = 15)	Failed Rechallenge (n = 4)
Patient characteristics			
Sex, n (%)			
Male	15 (79)	12 (80)	3 (75)
Female	4 (21)	3 (20)	1 (25)
Age at time of rechallenge, mean (SD), y	30.7 (7.4)	29.0 (5.7)	37.0 (10.4)
Ethnicity, n (%)			
White	12 (63)	9 (60)	3 (75)
Black	3 (16)	3 (20)	0
Asian	2 (11)	2 (13)	0
Mixed	1 (5)	1 (7)	0
Other	1 (5)	0	1 (25)
First exposure characteristics			
ANC nadir on first exposure × 10^9/L, mean (range)	1.26 (0.70–1.90)	1.33 (0.80–1.90)	1.08 (0.70–1.50)
Treatment duration, median (range), wk	28.6 (0.9–434.7)	28.6 (0.9–434.7)	34.6 (9.6–100.1)
Duration of break from clozapine treatment,[a] median (range), wk	99.6 (4.0–660.0)	94.0 (4.0–544.7)	146.1 (56.9–660.0)
Rechallenge characteristics			
ANC nadir on rechallenge × 10^9/L, mean (range)	NA	NA	0.56 (0.16–0.86)
Duration of follow-up[b]/time to neutropenia, median (range), wk	34.0 (3.0–88.4)	40.6 (8.0–88.4)	3.9 (3.0–5.7)
Duration of follow-up to at least: n (%)			
3 mo		14 (93)	NA
6 mo		13 (87)	
9 mo		8 (53)	
12 mo		5 (33)	
Treated with valproate on rechallenge, n (%)		3 (20)	3 (75)

[a]In patients with more than 1 previous trial, the duration between the end of the first and beginning of the most recent trials are reported.
[b]Follow-up is defined as time from reinitiation of clozapine until discharge from the ward or to recurrence of neutropenia.
Abbreviations: ANC = absolute neutrophil count, BEN = benign ethnic neutropenia, G-CSF = granulocyte-colony stimulating factor, NA = not applicable.

Table 3. Characteristics of the 4 Patients Failing Rechallenge

Patient	Age, y	Ethnic Group	Duration of First Exposure, wk	Duration of Rechallenge, wk	ANC Nadir on First Exposure, Cells × 10^9/L	ANC Nadir on Rechallenge, Cells × 10^9/L	Duration Neutropenia on Rechallenge, d	Concurrent Medication on Rechallenge
1	37	White	43	3	0.7	0.85	4	Lithium Sodium Valproate[b]
2[a]	51	White	100 10	3	1.5 0.9	0.16	9	Lithium Sodium Valproate[b] Amisulpride Spironolactone[b] Ramipril[b]
3	26	White	9	4	0.8	0.36	7	Lithium G-CSF
4	34	Other	26	5	1.3	0.86	19	Lithium Sodium Valproate[b] G-CSF

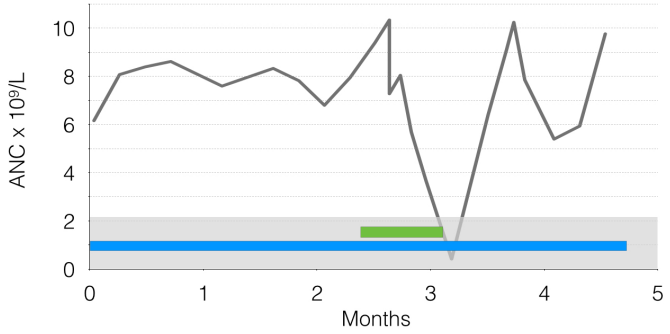
[a]This patient had 2 previous trials, both discontinued due to neutropenia.
[b]Known association with neutropenia.
Abbreviations: ANC = absolute neutrophil count, G-CSF = granulocyte-colony stimulating factor.

Unsuccessful Rechallenge

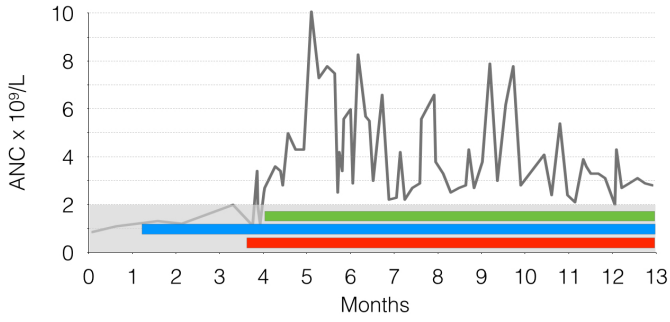
All 4 patients who were unsuccessfully rechallenged had pretreatment ANCs consistently above 2×10^9/L, thus not meeting criteria for benign neutropenia, all developed neutropenia below 1.0×10^9/L on rechallenge, and 2 developed agranulocytosis (Table 3). Clozapine dose range at neutropenia onset was 175–350 mg/d. Mean age for those unsuccessfully rechallenged was significantly higher than for those successfully rechallenged ($t = 2.10$, $P = .05$). Comparing unsuccessful and successful rechallenges, the difference in ANC nadir on first exposure was nonsignificant ($t = 1.4$, $P = .18$), and duration of initial exposure to clozapine was shorter, although this difference was not statistically significant ($U = 25.0$, $P = .67$). Among those unsuccessfully rechallenged, neutropenia on rechallenge occurred earlier (34.6 vs 3.9 weeks on first and rechallenge exposures respectively, $W = 10.0$, $P = .03$) and was more severe (ANC nadir 1.08×10^9/L vs 0.56×10^9/L on first and rechallenge

Figure 1. Illustrative Hematological Profiles of Failed (A) and Successful (B–D) Rechallenges[a]

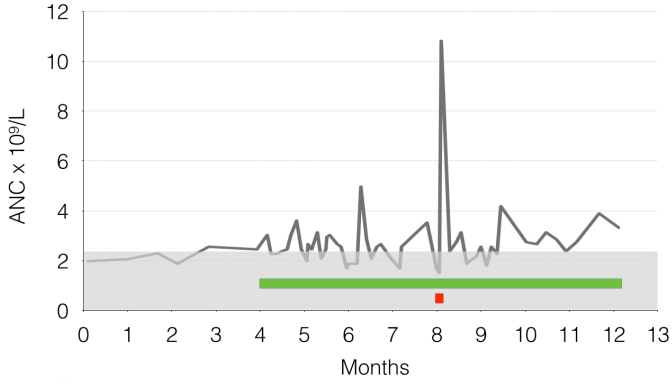
A. Patient Who Developed Agranulocytosis and Had Spontaneous Recovery (note ANC spike prior to neutropenia and rebound on recovery)



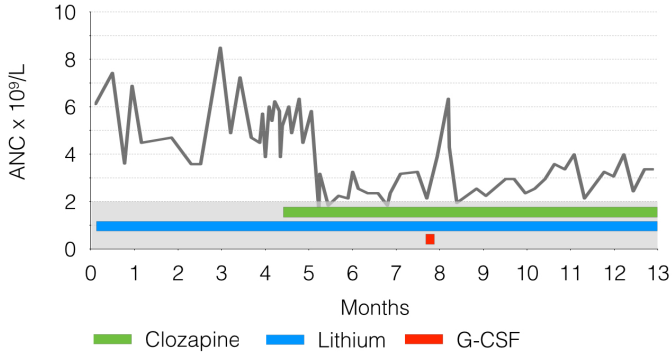
B. BEN Patient, Administered G-CSF on a Twice-Weekly Basis



C. White Patient With Low Baseline ANC (spike represents administration of G-CSF following red result[b])



D. White Patient Who Developed a Drop in Mean ANC 4 Weeks After Commencing Clozapine but Was Able to Continue Treatment With Lithium and a Single Administration of G-CSF



[a]0 on the ordinal axis indicates time of admission; note different scale in Figure 1A.
[b]See Table 1 for monitoring and discontinuation criteria.
Abbreviations: ANC = absolute neutrophil count, BEN = benign ethnic neutropenia, G-CSF = granulocyte-colony stimulating factor.

exposures respectively), though this was nonsignificant ($t = 1.7$, $P = .19$). The median time to recovery of neutrophils following rechallenge was 8 days (range, 4–19). Three of 4 patients failing rechallenge (75%) were prescribed valproate on rechallenge, compared with 3 of 15 (20%) who were successfully rechallenged ($\chi^2 = 4.42$; $P = .07$). All other coprescribed drugs associated with neutropenia are outlined in Table 3.

Patient 1 had spontaneous recovery of ANC on discontinuation of clozapine. Patient 2 developed agranulocytosis and required hospital admission for treatment of febrile neutropenia, and ANC recovered. Patient 3 received G-CSF on developing neutropenia and continued to receive clozapine, in line with a plan agreed upon with hematologists. Despite this, agranulocytosis developed, at which point clozapine was discontinued, and the patient transferred to a general hospital. Further G-CSF was administered, and the patient made a good recovery. Patients 1, 2, and 3 demonstrated a characteristic profile of a spike in ANC within a fortnight prior to neutropenia onset and a rebound leukocytosis following resolution (patient 2 shown in Figure 1A).

Patient 4 experienced protracted neutropenia and leukopenia on week 5 of treatment, after which clozapine was discontinued and G-CSF administered 19 days after the onset of neutropenia. A robust granulopoietic response was observed (peak ANC of 15.2 and WBC of 17.7). Due to continued severe psychotic symptoms, a further rechallenge with clozapine was reattempted 4 months later following hematologic consultation, with concurrent G-CSF cover (not shown in Table 3). The response to G-CSF was, however, attenuated (ANC range, 2.03–5.38; WBC 2.86–6.74), and ANC continued a downward trend. Rechallenge was abandoned after 25 days, and ANC normalized following discontinuation of clozapine treatment.

Successful Rechallenge

Following hematologic consultation, 5 of the 15 successfully rechallenged patients (33%) were diagnosed with BEN; their ethnicities were black (n = 3), Asian (n = 1), and mixed (n = 1). For these patients, the use of modified monitoring criteria[10] was agreed upon with the clozapine monitoring service prior to clozapine initiation, accompanied by an initially increased frequency of blood monitoring (twice a week for the first 12 weeks). In all cases, other agents known to cause neutropenia were discontinued prior to initiation, and a trial of lithium augmentation was initiated at a therapeutic dosage (> 0.4 mmol/L 12 hours postdose) and continued in all but 1 patient.

Despite the use of lithium and BEN monitoring criteria, the baseline pre-clozapine ANC in 2 patients frequently fell below 1.0×10^9/L and was too low to permit initiation and maintenance of clozapine. G-CSF was therefore administered on a twice-weekly

basis prior to and throughout clozapine treatment to allow continued dispensing of clozapine by the monitoring service (Figure 1B). Lenograstim 105 μg twice weekly (Granocyte, Chugai Pharmaceutical, Tokyo, Japan) and filgrastim 150 μg twice weekly (Neupogen, Amgen, Vienna, Austria) were administered subcutaneously in either case; further details of the G-CSF administration protocol are described in a previously published case report.[12] No significant side effects of G-CSF were reported.

Though their ethnicity precluded a formal diagnosis of BEN, 8 of the 15 successfully rechallenged patients (53%) demonstrated a similar pattern of constitutionally low neutrophil counts that preceded clozapine treatment, with fluctuating pre-clozapine neutrophil counts whose lower limit frequently neared, or breached, the lower threshold of 2.0×10^9/L. Seven were white, and 1 was Asian. Alternative reasons for neutropenia were excluded, and, where possible, other drugs associated with neutropenia were discontinued. Six patients received lithium for ANC augmentation, and 4 had a plan agreed upon with a hematologist for G-CSF administration in the event of a neutropenia in the amber or red range. Two patients received a single dose of G-CSF following an amber or red neutropenia result and were able to continue treatment (Figure 1C).

The remaining 2 of the 15 successfully rechallenged patients (13%) were white and did not have an ANC at baseline consistent with chronic neutropenia. Both were prescribed lithium. One patient had a sustained drop in baseline ANC 4 weeks after clozapine initiation, as shown in Figure 1D.

Additional coprescribed medications in the 10 patients without BEN were lamotrigine (n = 2), valproate (n = 3), amisulpride (n = 2), and aripiprazole (n = 1). Of these, lamotrigine and valproate are associated with neutropenia.

DISCUSSION

In this series, which is the third largest of clozapine rechallenge in adults, we have shown that in a selected group of inpatients with severe treatment-refractory illness, 15 of 19 patients (79%) were successfully reestablished on clozapine therapy following previous treatment-emergent leukopenia or neutropenia. This is higher than the findings of Dunk and colleagues[13] reporting successful rechallenge in 62% of patients (32 of 52), and comparable to the 96% success rate (24 of 25 patients) reported previously by our unit.[14] We believe that these results demonstrate the importance of carefully selecting patients who have a relatively reduced risk of neutropenia based on their previous history and optimizing rechallenge with adjunctive treatments.

The mechanisms of clozapine-induced neutropenia and agranulocytosis remain uncertain.[21] A unitary process may exist whereby neutropenia progresses inevitably to agranulocytosis if clozapine is not terminated.[21] An alternative hypothesis posits 2 distinct mechanisms, 1 leading to agranulocytosis and another to persistent neutropenia but not agranulocytosis.[6]

Given that the hematologic outcomes on rechallenge are likely to reflect the cause underlying discontinuation in earlier trials, we hypothesize the following categories based on the rechallenge outcomes observed in our cohort: (1) clozapine-induced agranulocytosis, or neutropenia that would otherwise have progressed to agranulocytosis, with a characteristic pattern and time course; (2) persistent neutropenia that does not progress to agranulocytosis that may be related to clozapine but also to the coprescription of other agents; and (3) idiopathic, persistent neutropenia (not restricted to those with ethnicity associated with BEN) unrelated to clozapine or other agents. We suggest that groups 2 and 3 can be considered for rechallenge with specialist input.

Factors Associated With Unsuccessful Rechallenge

Consistent with established findings that age is a risk factor for clozapine-induced dyscrasia,[3,4] patients who developed neutropenia on rechallenge were significantly older. Similar to the finding by Dunk et al,[13] patients who failed rechallenge had a more severe and rapid onset of subsequent neutropenia, suggesting an immune-mediated mechanism.

Three of 4 patients developing neutropenia on rechallenge showed a spike in ANC in the fortnight preceding dyscrasia, a phenomenon that was found to be a sensitive but nonspecific predictor of agranulocytosis.[22] A possible mechanism is the production of endogenous granulopoietic factors that initially compensates for the incipient fall in granulocytes. The response to G-CSF was attenuated in 2 patients who failed rechallenge, in comparison to BEN patients whose granulopoietic response did not diminish despite successive administrations or G-CSF. This suggests that attenuation in response to G-CSF is an indicator of injury to the granulocyte precursors in the bone marrow and that clozapine should be discontinued immediately.

Factors Associated With Successful Rechallenge

Successful rechallenge was associated with a shorter median duration of first exposure to clozapine: one explanation might be that these patients failed their first trial early in treatment due to constitutionally low neutrophils and not clozapine toxicity. Over half of the successfully rechallenged patients were white and, therefore, ineligible for BEN criteria but nonetheless had consistently low pre-clozapine ANC. This is consistent with previous studies[9] that suggest that ANCs at the lower end of the population distribution in otherwise asymptomatic individuals are a common reason for clozapine discontinuation and do not necessarily indicate clozapine toxicity. Therefore, correctly identifying this hematologic pattern is critical in selecting patients who are likely to be successfully rechallenged. Four of 5 patients who had undergone more than 1 previous trial were successfully rechallenged, suggesting that multiple trials are not necessarily associated with unsuccessful rechallenge.

Treatment With Lithium and G-CSF

All of the patients who developed neutropenia on rechallenge were prescribed lithium, suggesting that, in these

patients, lithium does not protect against clozapine-induced neutropenia. Similarly, responses to G-CSF were attenuated in patients who failed rechallenge, also arguing that G-CSF is not protective against clozapine-induced neutropenia in these patients.

Of the successful rechallenges, 4 of the 5 BEN patients and 8 of the remaining 10 patients received lithium, suggesting that lithium has utility in increasing ANC and avoiding treatment discontinuation. Two BEN patients received regular G-CSF and 3 white patients received single doses of G-CSF, indicating that G-CSF can also play a role in facilitating uninterrupted treatment with clozapine.

However, lithium may compromise neutrophil function,[23,24] and no studies have investigated the rate of infection in lithium treatment. Furthermore, the use of G-CSF in allowing continued clozapine therapy is contentious. In addition to commonly reported acute side effects such as bone pain[25] in patients receiving G-CSF following chemotherapy, the safety of long-term treatment with G-CSF is unknown. Osteopenia[26] and splenic enlargement[27] have been described, and we recommend monitoring of bone density and spleen size in long-term G-CSF use.

Implications for Clinical Practice and Future Research

Our findings suggest that current concepts of BEN are too narrow and lead to unnecessary discontinuation of clozapine in those with a picture of idiopathic neutropenia. Absolute neutrophil counts of $0.5–1.5 \times 10^9$/L, defined hematologically as *mild to moderate neutropenia* are not associated with a significantly increased risk of infection.[28] Consideration should therefore be given to the use of lowered thresholds for patients of other ethnicities, following hematologic evaluation. The use of definitions such as chronic idiopathic neutropenia[29] may aid this process. Future approaches to differentiating clozapine-induced neutropenia from incidental neutropenia unrelated to clozapine may include consideration of dynamic trends in ANC relative to an individual's baseline pre-clozapine ANC, rather than the absolute counts relative to an arbitrary threshold.

We could not clearly identify a subset of patients who develop a milder form of clozapine-induced neutropenia, although the trend in 1 case (Figure 1D) did support the existence of such a pattern. Further work is necessary to identify whether clozapine can cause a milder neutropenia or induces fluctuations in ANC.

When possible, other drugs associated with neutropenia were stopped prior to rechallenge. However, 3 of 4 patients failing rechallenge (75%) were coprescribed valproate, compared to 3 of 15 (20%) who were successfully rechallenged. Clozapine in combination with valproate has been associated with a greater risk of neutropenia than either drug alone,[30] and a case of treatment-emergent neutropenia with clozapine and valproate that resolved on withdrawal of valproate has been reported.[31] When rechallenge is considered, the potential role of valproate in contributing to neutropenia should be borne in mind.

The requirement for hematologic monitoring has led to a greater awareness of clozapine-induced neutropenia. However, other serious medical complications such as cardiomyopathy, ileus, or diabetic ketoacidosis are reported to have caused more deaths than agranulocytosis[32] and deserve equal emphasis. Future research should examine the relative risks of all complications, not only hematologic, as well as the circumstances in which rechallenge may be appropriate. Finally, the benefits of clozapine in reducing suicide[33] and overall mortality[34,35] must be balanced against these risks.

Limitations

Clozapine rechallenge is a rare occurrence, and the small number of cases reported here reflects this. The statistical analyses and conclusions in relation to the unsuccessful rechallenge group should therefore be interpreted with caution. A further limitation of this study arises from its retrospective observational design. Follow-up ended when patients were discharged from the service, with a median duration of follow-up in successfully rechallenged patients of 41 weeks. It is therefore possible that some of these individuals developed neutropenia after discharge. However, other rechallenge studies with longer follow-up found a median time to dyscrasia of 5.5 weeks,[13] suggesting that most dyscrasia occurs soon after restarting clozapine.

The severity of psychosis in our patient group did not permit a drug-free period prior to clozapine initiation. Therefore, other antipsychotics associated with neutropenia such as olanzapine and risperidone[6] may have contributed to the persistent pre-clozapine neutropenia observed in some patients. It remains extremely difficult to demonstrate that a given drug contributes to dyscrasia when prescribed in conjunction with clozapine, and case reports have been conflicting.[36]

The highly selected patient group and setting may limit the generalizability of our findings; patients with BEN or other benign neutropenia may be overrepresented in our sample, and not all centers will have experience in using G-CSF. Definitions of ethnic groups are imprecise,[37] and the categories used in this study overlook the significant diversity that exists within populations.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), ramipril (Altace and others), risperidone (Risperdal and others), spironolactone (Aldactone).

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