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# Clozapine discontinuation in early schizophrenia: a retrospective case note review of patients under an early intervention service

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***Abstract***

**Aim:** Research in patients with treatment-resistant schizophrenia has demonstrated that clozapine discontinuation is associated with poor outcomes. There is, however, a paucity of research investigating the impact of clozapine discontinuation specifically in younger patients with more recent onset schizophrenia. A case note review was therefore conducted to ascertain medium-term prognoses in patients with treatment-resistant schizophrenia under an early intervention service (EIS) following clozapine discontinuation.

**Methods:** The case notes of 25 patients under the care of Birmingham EIS who discontinued clozapine were examined retrospectively. Reasons for discontinuation were recorded. Clinical outcomes including total duration of inpatient or home treatment admission, antipsychotic dose, number of alternative antipsychotics prescribed and adverse events were recorded for both the year before and the year after stopping clozapine. Statistical comparisons of pre- and post-discontinuation clinical outcomes determined whether discontinuation had negative effects.

**Results:** There was no significant difference between the pre- and post-discontinuation clinical status following clozapine discontinuation. More than half (56%) of patients remained stable after stopping clozapine. Mean inpatient or home treatment stay rose from 29.7 to 62.6 days ($p = 0.155$), total antipsychotic dose from 50.1% of British National Formulary (BNF) limits to 60.5% ($p = 0.627$), number of alternative antipsychotics prescribed from 1.28 to 1.80 ($p = 0.186$), number of hospital/home treatment episodes from 0.20 to 0.44 ($p = 0.083$) and number of adverse events from 0 to 0.20 ($p = 0.059$). Non-compliance was the main reason for discontinuation (44%, $n = 11$).

**Conclusions:** This is the first clozapine discontinuation study specifically considering EIS patients. Discontinuation did not lead to significant effects on 1 year outcomes, though the study is underpowered. These findings may be used to inform future prospective cohort discontinuation studies.

***Keywords:*** clozapine, discontinuation, first-episode psychosis, outcomes, schizophrenia

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## Introduction

Clozapine has been long established as the mainstay antipsychotic therapy for treatment-resistant schizophrenia.[1] While 'first generation' antipsychotics were being shown to precipitate debilitating extra-pyramidal side effects including parkinsonism, tardive dyskinesia and akathisia,[2] clozapine was novel in showing that antipsychotic efficacy and motor side effects could be dissociated.[3] However, it was withdrawn shortly after introduction due to agranulocytosis-related deaths in a small cluster of users.[4] Despite these concerns, clozapine's superior side-effect profile and antipsychotic efficacy in treatment-resistant schizophrenia

led to its reintroduction on a restricted basis involving rigorous blood monitoring regimes as a requisite for prescribing.[5]

The first episode of schizophrenia normally occurs in the late teens through to early twenties.[6] Given that early and effective management of early schizophrenia has been linked to improved long-term outcomes,[7] it is important that treatment of this group is optimal. The effectiveness of clozapine in managing treatment-resistant early schizophrenia has been demonstrated. Indeed, research has demonstrated response rates of 75% in first-episode schizophrenia patients treated with clozapine after treatment with two atypical antipsychotics.[8] Current NICE guidelines state that clozapine should be considered after the failure of two trials of antipsychotic medication of adequate duration.[9]

While the efficacy of clozapine is well established, its toxic nature has been associated with a wide range of adverse effects. Research has reported significant rates of agranulocytosis,[10] seizures,[11,12] intestinal obstruction,[13] diabetes,[14] myocarditis,[15] thromboembolism and cardiomyopathy[16] in clozapine users. Furthermore, adherence to frequent blood monitoring can be challenging; a 12-year retrospective study concluded that non-concordance with either treatment or mandatory blood monitoring was the most common reason (55.3%) for discontinuation, followed by adverse effects (25.2%).[17] Up to half of users discontinue clozapine.[18,19] A number of authors have investigated patient outcomes following discontinuation, with rather pessimistic findings: polypharmacy,[20] psychotic relapse,[21,22] increased antipsychotic resistance,[23] reduction in Global Assessment of Functioning score[20] and an increase in days spent in hospital[24,25] have been reported. However, the average duration of illness prior to commencing clozapine in the majority of discontinuation studies is in the order of several years. Therefore, while their findings are relevant to those with chronic schizophrenia, they may be less applicable to patients with schizophrenia of more recent onset.

It is important that further research into clozapine discontinuation outcomes in such patients is conducted. Patients with treatment-resistant schizophrenia who have failed multiple antipsychotic trials are likely to need to remain on clozapine.[26] In contrast, it is less apparent whether or not patients with early treatment-resistant schizophrenia should remain on clozapine long term. It could be argued that the unwanted toxic effects caused by long-term use coupled with strict blood monitoring, which may be even more impractical in the younger, more mobile patient population, might justify a trial of discontinuing clozapine.

Birmingham and Solihull Early Intervention Service (EIS) diagnoses and treats individuals aged between 16 and 35 years who have experienced a first episode of psychosis. It was the first such UK service and led to the subsequent implementation of similar services countrywide. The service aims to reduce delay in access to treatment, thus minimizing the duration of untreated psychosis. It provides medical and psychological therapies and also delivers vocational interventions working in partnership with non-statutory services. Birmingham EIS is commissioned to provide care for up to 3 years, though some patients remain with the service for a longer period of time. The majority of patients are then transferred to other community mental health services, though a significant minority are discharged back to primary care.

Patients identified as having treatment-resistant schizophrenia who are prescribed clozapine may still be in their first episode of illness or may have developed treatment resistance during a subsequent relapse. They are likely to be substantially earlier in the course of their illness at the time of clozapine commencement than cases in the established literature on clozapine discontinuation.

The central aim of this study is to establish the direction and size of clinical effect associated with clozapine discontinuation in EIS patients with treatment-resistant schizophrenia and to indirectly compare these findings with the available literature on clozapine discontinuation in patients with longer-term illness. Such evidence would assist clinicians and patients in making more informed decisions about whether to continue clozapine longer term. Moreover, given that clozapine discontinuation has not been previously investigated specifically in an EIS cohort, findings would be valuable in generating hypotheses to guide further investigation.

## Methods

### *Study design*

The study design was a retrospective case note review examining differences in mental health

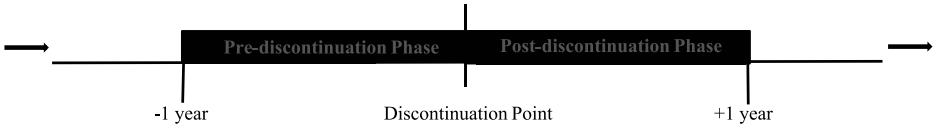


**Figure 1.** A patient timeline highlighting the point at which clozapine is discontinued, the 1-year period prior to discontinuation, the 'pre-discontinuation phase', and 1-year period after discontinuation, the 'post-discontinuation phase', in relation to which all clinical outcomes were measured.

status of EIS patients before and after clozapine discontinuation. Approval for the study was obtained from Birmingham and Solihull Mental Health Foundation Trust (BSMHFT) Research and Innovation department and the University of Birmingham Population Sciences and Humanities Internal Research Ethics Committee. Informed consent for study participation was not required for the study as the scope was restricted to a retrospective case note review.

### *Sample*

The study population was sampled from BSMHFT EIS. Pharmacy records were used to identify all EIS patients who had discontinued clozapine between January 2009 and December 2013. Medical records were screened to identify all patients who met inclusion criteria, namely a duration of clozapine prescription of at least 3 months and patients having remained off clozapine for the duration of the follow-up period. A 3-month threshold was selected to allow sufficient time for clozapine to exert a therapeutic effect.[27] There were no other exclusion criteria.

### *Data collection*

Medical records of patients who met the inclusion criteria were accessed through RiO (electronic patient record system) and trust manual case notes. Demographic and clinical characteristics including gender, ethnicity, diagnosis, age at the point of discontinuation and duration of treatment prior to commencing clozapine were collected. Clinical outcomes were recorded with reference to the period 1 year before and one year after discontinuation of clozapine, the 'pre-discontinuation phase' and 'post-discontinuation phase' respectively (see Figure 1).

*Duration on antipsychotic treatment prior to clozapine.* The number of days receiving antipsychotic treatment prior to commencing clozapine was measured. This allowed exploration of the clinical impact that duration of ineffectively treated psychiatric illness has on post-discontinuation clinical outcome.

*Exposure to clozapine.* Maximum recorded plasma clozapine level, maximum clozapine dose for the treatment period and total duration on clozapine prior to stoppage were recorded. In addition to ensuring that clozapine treatment was in the therapeutic range, this allowed investigation of the impact that varying levels of clozapine exposure may have on post-discontinuation clinical outcome.

*Reason for discontinuation.* In order to explore treatment acceptability, we allocated patients' reasons for discontinuing clozapine into the following categories:

1. non-compliance with clozapine treatment or blood monitoring regime;
2. agranulocytosis/neutropenia;
3. other adverse effects;
4. patient choice.

*Clozapine prescribed for the pre-discontinuation phase.* We recorded if patients had been prescribed clozapine for the whole of the pre-discontinuation phase as a binary (yes/no) variable. This allowed us to address a significant confounder; that not all patients will have been prescribed clozapine for the entire pre-discontinuation phase.

*Total inpatient/home treatment days stay.* This outcome comprised the total time duration under inpatient and home treatment care within the pre- and post-discontinuation phases. Home treatment was defined as acute psychiatric care received in the patient's residence, without which hospital admission would result. Measurement of inpatient/home treatment stay represents an effective proxy to mental health status and has been used in a comparable way by similar studies.[20,24,25] Number of inpatient/home treatment episodes was also recorded as a binary variable.

*Total antipsychotic dosage.* The British National Formulary (BNF) total antipsychotic dosage ready reckoner[28] was used to convert antipsychotic dosages into percentage of maximum recommended daily antipsychotic dose as per BNF guidelines. Total antipsychotic dosage provides an indication of treatment resistance and polypharmacy.[29] This was measured at the start of the pre-discontinuation phase and the end of the post-discontinuation phase.

*Alternative antipsychotics.* The number of antipsychotic medications other than clozapine that were prescribed within the pre- and post-discontinuation phases was recorded. This provided a further measure of treatment resistance and polypharmacy.[30]

*Adverse events.* The number of adverse events within the pre- and post-discontinuation phases was recorded. An adverse event was defined as an 'untoward' or 'serious' incident according to the BSMHFT incident reporting system.[31] An untoward incident is defined as any event that has given or may give rise to actual or possible injury, or to property loss/damage. A serious incident is defined as an event that results in death or causes/has the potential to cause such serious harm that it may place life in jeopardy.

### Statistical analyses

Statistical analysis was performed using SPSS for Windows version 22 (SPSS, Inc.; Chicago, USA). All testing was carried out at a 5% significance level. In keeping with a similar study,[20] mean differences between pre- and post-discontinuation phase values were calculated for all clinical outcomes. Pre- and post-discontinuation clinical values were compared using the Wilcoxon signed-rank test. To explore factors associated with post-discontinuation clinical status, we performed several multiple regression analyses. Multiple regression models were created with each of the following outcomes as a dependent variable: total inpatient/home treatment stay in the post-discontinuation phase; total antipsychotic dose at the end of the post-discontinuation phase; the number of inpatient or home treatment admissions in the post-discontinuation phase; the number of alternate antipsychotics prescribed in the post-discontinuation phase; and the number of adverse events in the post-discontinuation phase. In every multiple regression model, the independent variables were: ethnicity; gender; age at the point of discontinuation; maximum clozapine dose; maximum recorded plasma clozapine level; total duration on clozapine prior to stoppage; duration of antipsychotic treatment prior to clozapine; and clozapine prescribed for the whole of the pre-discontinuation phase (binary variable). Lastly, using the same independent variables, we performed a binary logistic regression analysis in which the dependent variable was inpatient or home treatment episode in the post-discontinuation phase as a binary outcome (i.e. yes/no).

## Results

### Subjects

In total, 166 patients were identified who had discontinued clozapine between January 2009 and December 2013. Of these, 28 had been on clozapine for longer than 3 months before discontinuation and did not restart clozapine within the study period. Thus, 28 patients met our inclusion criteria. Of these, two had died while on clozapine from causes not obviously related to clozapine. One other had incomplete records, but was known to be alive at the end of the study period. These were excluded from the analysis. The study population therefore consisted of 25 subjects, all of whom had diagnoses of schizophrenia, schizoaffective disorder or unspecified non-organic psychosis. Demographic and clinical characteristics of the study cohort are presented in Table 1.

Reasons for discontinuation are detailed in Table 2. Patient non-compliance was the most common reason for discontinuation (44%, $n$ = 11). Adverse effects included weight gain, nausea and vomiting, constipation and palpitations. Only one subject discontinued due to the development of neutropenia.

On average, the maximum clozapine dose taken by patients was 404.5 mg (SD = 169.9, range = 150–950), duration on clozapine prior to stoppage was 531.6 days (SD = 454.8, range = 94–1578) and maximum clozapine plasma level was 0.73 mg per litre (SD = 0.49, range = 0.146–1.891). These values are consistent with clozapine therapeutic ranges.[32] The average duration of antipsychotic treatment prior to commencing clozapine was 529.4 days (SD = 320.6, range = 172–1306). Maximum clozapine level data were missing for four patients. All other outcomes were obtained for all patients.

**Table 1.** Demographic characteristics of the study population ($n = 25$).

| Parameter | Study subjects |
|---|---|
| Age at discontinuation | |
| Mean (SD) | 25.8 (4.6) |
| Range | 19–35 |
| Duration of prior antipsychotic treatment – days Mean (median) | 605 (446) |
| Gender, *n* (%) | |
| Male | 18 (72) |
| Female | 7 (28) |
| Ethnicity, *n* (%) | |
| Caucasian | 8 (32) |
| Asian | 10 (40) |
| Afro-Caribbean | 4 (16) |
| Mixed race | 3 (12) |

### *Clinical outcomes*

No adverse events were recorded during the pre-discontinuation phase. There were no 'serious' adverse events recorded for the post-discontinuation phase. In total, 56% (95% CI 36.5–75.5) of patients did not experience relapse in the post-discontinuation phase. From the pre-discontinuation phase to the post-discontinuation phase, the mean inpatient/home treatment stay increased by 33.0 days, mean number of psychotic relapses by 0.24 and the mean number of adverse events by 0.20. With respect to antipsychotic dosage and polypharmacy, mean percentage of maximum recommended antipsychotic dose increased by 10.3% (see Figure 2). Eleven patients saw a reduction in dosage after discontinuation, while 13 experienced an increase (see Table 3). Two patients received no antipsychotic treatment after stopping clozapine and remained off antipsychotic medication at the end of the post-discontinuation phase, though one of these had undergone a course of electroconvulsive treatment for catatonic symptoms. The mean number of alternative antipsychotics prescribed rose by 0.52 (see Figure 3). While 10 patients were prescribed the same number of alternative antipsychotics after discontinuation, 9 were prescribed more and 6 were prescribed fewer. There were no statistically significant differences between pre-discontinuation and post-discontinuation clinical outcomes (see Table 4).

**Table 2.** Reasons for discontinuation ($n = 25$).

| Reason for discontinuation | *n* | % |
|---|---|---|
| Patient non-compliance | 11 | 44 |
| Agranulocytosis/neutropenia | 1 | 4 |
| Other adverse effects | 9 | 36 |
| Patient decision | 4 | 16 |

Multiple regression analyses showed that none of the independent variables were significant in predicting any of the post-discontinuation clinical outcomes. Similarly, the logistic regression analysis showed that these independent variables were not significant in predicting inpatient or home treatment admission.

## Discussion

With respect to the mean difference between clinical outcomes, there was a trend towards deterioration in each clinical outcome, but none of these results was statistically significant. It is likely that the lack of significance is a reflection of the study's limited power; however, it is also quite possible that there was no overall difference between pre- and post-discontinuation clinical status. Therefore, while our findings may have limited implications in clinical practice, they hold value in directing future larger-scale studies and hypothesis generation.

To our knowledge, this is the first clozapine discontinuation study to look specifically at an EIS cohort. Previous research indicates that discontinuation of clozapine in patients with more chronic illness leads to increased polypharmacy,[20] increased hospital stay,[24] increased rates of relapse,[21,22] a reduction in quality of remission,[33] and increased frequency of acute withdrawal-related phenomena including rebound and supersensitivity psychosis.[34,35] Conversely, there is very limited evidence suggesting that clinical status remains unaffected after discontinuation.[25]

With regards to reasons for discontinuation in this study, non-compliance and adverse effects unrelated to neutropenia made up the majority of cases. Current approaches to improve adherence include supervised medication taking, interventions to reduce and manage adverse effects and improving transport to phlebotomy clinics/arranging home visits.[36] Alternative strategies may be explored in mental health

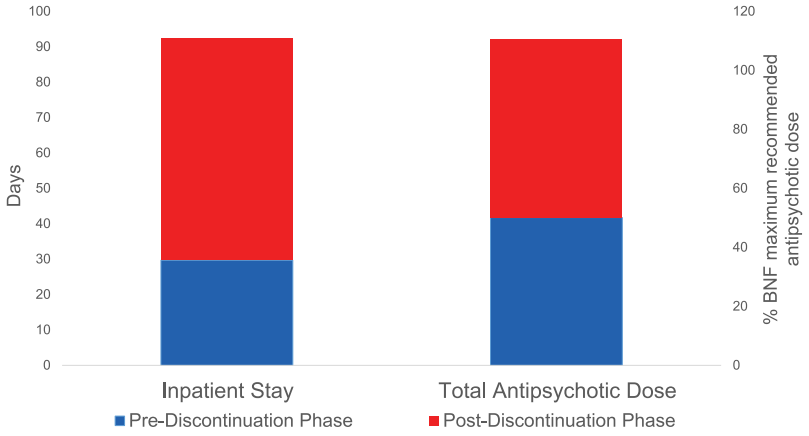


**Figure 2.** Stacked bar chart illustrating the increase in mean inpatient stay and mean total antipsychotic dose from the pre-discontinuation phase to the post-discontinuation phase.

**Table 3.** The number of patients who experienced a positive rank, negative rank and tie for each clinical outcome.

| Clinical outcome | Better | Worse | No change |
|---|---|---|---|
| Inpatient/home treatment days stay | 7 | 4 | 14 |
| Percentage of max. recommended antipsychotic dosage | 13 | 11 | 1 |
| No. hospital/home treatment admissions | 9 | 3 | 13 |
| No. alternative antipsychotics | 9 | 6 | 10 |
| No. adverse events | 4 | 0 | 21 |

Better – indicates an improvement in clinical outcome after they stopped clozapine = positive rank.
Worse – indicates a worse clinical outcome after they stopped clozapine = negative rank.
No change – indicates that the patient experienced no change after stopping clozapine = tie.

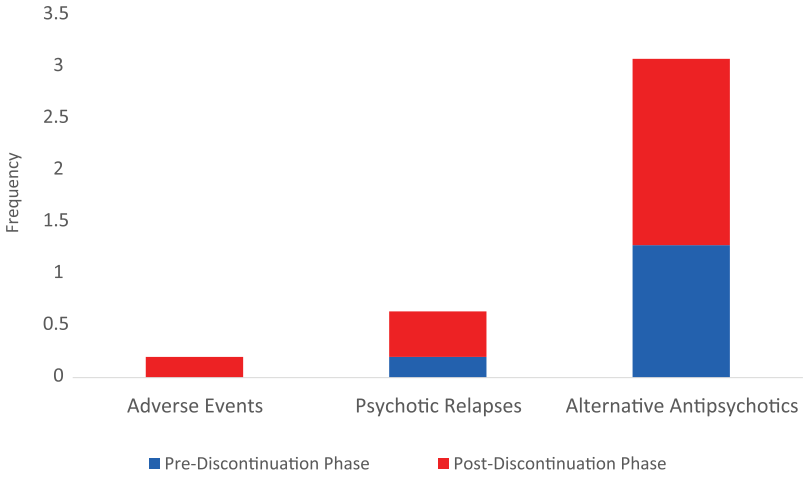


**Figure 3.** Stacked bar chart illustrating the increase in mean number of adverse events, psychotic relapses and alternative antipsychotics prescribed from the pre-discontinuation phase to the post-discontinuation phase.

services to increase compliance, such as capillary blood monitoring[37,38] and improved management of clozapine-induced metabolic syndrome.[39]

**Table 4.** Pre-discontinuation and post-discontinuation averages for each clinical outcome. There is an increase in value across all clinical outcomes after patients stopped clozapine, suggestive of a deterioration in mental health. There was found to be no statistically significant difference between pre- and post-discontinuation values.

| Clinical outcome | Pre-discontinuation | Post-discontinuation | *p*-value* |
|---|---|---|---|
| | Mean | Mean | |
| Inpatient/home treatment days stay | 29.7 | 62.6 | 0.155 |
| Percentage of max. recommended antipsychotic dosage | 50.1 | 60.5 | 0.627 |
| No. alternative antipsychotics prescribed | 1.28 | 1.8 | 0.186 |
| No. hospital/home treatment admissions | 0.20 | 0.44 | 0.083 |
| No. adverse events | 0 | 0.20 | 0.059 |

*Significance of Wilcoxon signed-rank test statistic on comparison of pre-discontinuation and post-discontinuation values.

Studies of discontinuation in more chronic illness[17,19] similarly show that non-compliance and adverse effects are the primary reasons for discontinuation. A concerning finding in these studies has been that death is the reason for discontinuation in a significant number of patients on clozapine[20]; in one study the average age of death on clozapine was 48 years.[17] In contrast, only two patients in this EIS cohort died while taking clozapine, both from causes not known to be related to clozapine usage. An explanation for this observation is that EIS patients who are relatively early in the course of their illness inherently have reduced exposure to clozapine's toxicity and are therefore less likely to develop downstream pathologies that may take years to manifest. Interestingly, rates of neutropenia/agranulocytosis as a reason for discontinuation were low in this EIS study as compared to the wider literature. This is intriguing given that the risk of neutropenia reportedly decreases with age.[40]

An important finding in this study was that a notable share of patients did not deteriorate in the year after stopping clozapine. This may indicate that there is a variable prognosis for EIS patients who stop clozapine. While many EIS patients who have responded positively to clozapine may need to remain on the drug in the long term, there may be a separate population who, despite having initially met the criteria for clozapine therapy, will have an inherently more favourable prognosis enabling them to substitute clozapine for an alternative antipsychotic regime. This treatment strategy could reduce morbidity associated with long-term clozapine therapy while maintaining a good level of recovery. The variable prognosis suggested by the results and unsuitability of the regression model in predicting post-discontinuation outcome warrant the need for investigation of other factors that may predict who can safely stop clozapine.

## Study limitations

There are significant limitations to this study.

A major limitation is that it does not distinguish between patients discontinuing clozapine who have had a good therapeutic response to clozapine and those who have not. However, the average duration of clozapine was 531.6 days for all patients and 404 days for patients whose condition did not apparently deteriorate after stopping clozapine, indicating that clozapine treatment had been continued in the latter group beyond just a therapeutic trial.

A further drawback relates to the time frame in which clinical outcomes were measured. Outcomes were recorded for the 1-year period pre- and post-discontinuation. However, their spread within those years was not recorded for all outcomes. Previous research has produced results suggestive of a withdrawal effect immediately after stoppage[20]; the study design did not allow an examination of this feature of clozapine discontinuation, other than by measuring duration of

inpatient or home treatment stay. Moreover, it did not allow for a direct comparison of EIS patients who stop clozapine and those who do not. Furthermore, the success of outcome measurement was reliant upon the accuracy, completeness and accessibility of patients' notes, introducing potential for measurement bias.

## Conclusion

In conclusion, this retrospective case note review found that discontinuation of clozapine in EIS patients does not universally have an adverse effect on clinical status. These findings add to the smaller collection of evidence supporting 'life after clozapine', and will be useful in directing appropriately powered prospective cohort studies comparing EIS patients who discontinue clozapine and those who do not.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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