Outcome Following Clozapine Discontinuation: A Retrospective Analysis

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Background: Clozapine is uniquely effective in refractory schizophrenia, but treatment attrition is high. There has been minimal formal study of the outcomes of stopping clozapine, beyond published observations of the time period immediately after cessation. Our aim was to establish medium-term outcome in patients stopping clozapine in normal clinical practice.

Method: This study was a retrospective analysis of all subjects registered with Clozaril Patient Monitoring Service and treated in South London and Maudsley National Health Service (NHS) Trust who stopped clozapine between March 2002 and March 2005 after at least 1 year's treatment. Case note review was performed to determine relevant information for 1 year before and 1 year after discontinuation of clozapine, including subject details, reasons for stopping, and clinical outcome 1 year after discontinuation. The primary outcome measure was the Global Assessment of Functioning scale.

Results: Thirty-five patients met inclusion criteria. Twelve had died while receiving clozapine. Of those followed up for 1 year after cessation (N = 23), mean Global Assessment of Functioning scores fell by 15 points (95% CI = 6.6 to 24.3; p = .002). Days spent in hospital rose from a mean of 74.1 (SD = 137.3) to 119.8 (SD = 143.5) (p = .214).

Conclusion: Discontinuation of clozapine has a marked negative impact on clinical status. Death is a common cause of clozapine cessation.

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Clozapine is unequalled in its effectiveness in treatment-resistant schizophrenia[1]; it is effective even when other antipsychotics have failed.[2] Clozapine's unique place in the treatment of refractory schizophrenia is universally recognized by academic and government bodies.

Clozapine's role in refractory schizophrenia has led to substantial improvement in the quality of life of those receiving it. However, its unique effectiveness also presents problems. In particular, patients stopping clozapine are presumed to be unlikely to be as effectively treated with any other drug. Clozapine's varied and sometimes toxic profile dictates that cessation of clozapine treatment is a frequent event in clinical practice. As with other antipsychotics,[3] attrition from clozapine treatment is high.[4]

Little is known of the outcome of clozapine treatment cessation. Although in clinical practice relapse is very commonly observed on stopping clozapine, we could find nothing in the literature that systematically evaluated patients stopping clozapine. In the present study, our aim was to establish medium-term outcome in patients stopping clozapine in normal clinical practice.

METHOD

This study was approved by local Drug and Therapeutics Committees for the South London and Maudsley NHS Trust. In March 2006, all patients ever registered with Clozaril Patient Monitoring Service and treated in

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Table 1. Demographic and Clinical Characteristics of Study Population (N = 35)

Parameter	Study Subjects
Age at discontinuation, y	
Mean (SD)	46.7 (14.9)
Range	26–83
Gender, N (%)	
Male	26 (74.3)
Female	9 (25.7)
Diagnosis, N (%)[a]	
Treatment-resistant schizophrenia	26 (74.3)
Schizoaffective disorder	5 (14.3)
Psychotic depression	4 (11.4)
Years of psychiatric illness	
Mean (SD)	18.2 (12.8)
Range	3–45
Ethnicity, N (%)	
African Caribbean	15 (42.9)
White/Caucasian	14 (40.0)
Asian	6 (17.1)

[a]Prescriber diagnosis from case notes.

Table 2. Reasons for Discontinuation of Clozapine (N = 35)

Reason Recorded	N	%
Patient noncompliance	11	31.4
Neutropenia/agranulocytosis	6	17.1
Intolerable adverse effects	5	14.3
Prescriber decision	1	2.9
Patient deceased	12	34.3

Table 3. Documented Causes of Death During Clozapine Treatment (N = 12)

Cause of Death	N
Seizure	2
Unknown cause/not documented	2
Overdose of clozapine	1
Perforated gastric ulcer	1
Pulmonary embolism	1
Chronic bowel obstruction	1
Lung carcinoma	1
Stroke	1
Left ventricular failure due to hypertrophy	1
Bronchial pneumonia	1

South London and Maudsley NHS Trust were identified. All those who had taken clozapine for over 1 year and had discontinued treatment for any reason in the 3-year period between March 2002 and March 2005 were included in this study. Patients were required to have complete and accessible medical case notes confirming the discontinuation date. Patients not included were accounted for.

Patients' medical records (case notes and hospital computer records) were reviewed and relevant information collected. We recorded patient demographics, antipsychotic prescribed immediately before and after clozapine, number of antipsychotics prescribed during 1 year postdiscontinuation, reason for discontinuation, duration of illness, length of treatment of clozapine, and last recorded clozapine dose and plasma level. All relevant information was collected for a period of 1 year before discontinuation and 1 year after discontinuation. Inpatient stay during 1 year before and 1 year after discontinuation was also noted. Global Assessment of Functioning (GAF)[5] scores were assigned (following careful examination of case notes) and recorded for each patient at 1 year and at 1 month before discontinuation and at 1 month and at 1 year after discontinuation.

Statistical tests were performed using SPSS for Windows, version 13.0 (SPSS, Inc.; Chicago, Ill.). Comparison of means was assessed using the Student t test, and 95% confidence intervals were calculated. When comparing more than 2 mean values, 1-way analysis of variance was employed. Categorical measures were compared using the χ^2 test.

RESULTS

Subjects

In total, 1196 patients had received clozapine, 559 of whom had taken clozapine for more than a year. Overall, 654 had discontinued, 114 of whom had taken clozapine for more than a year, and 42 of these subjects stopped clozapine between March 2002 and March 2005. Thus, 42 patients met inclusion criteria, and their medical records were reviewed. Of these patients, 7 had incomplete records. Three of these were known to have died while on clozapine (2 lung cancer, 1 cause unknown), but few other details were available. The other 4 left the trust before completing 52 weeks of postclozapine treatment; 3 of these were known to be alive at the time of loss to follow-up. The study cohort was therefore 35 patients. Demographic and clinical characteristics of these subjects are shown in Table 1.

The reasons noted for discontinuation from clozapine are detailed in Table 2. Mean duration of clozapine treatment overall was 3.4 years (SD = 1.8, range = 1.1–8.3 years). Mean duration of treatment was not significantly different in those who died while taking clozapine (3.8 years, SD = 3.8) compared with those completing 1 year's postclozapine treatment (3.2 years, SD = 3.1) (p = .294).

Deceased Patients

Twelve of the 35 patients died. These patients had a mean age of 57.4 years (SD = 15.6, range = 36–83), compared with a mean age of 40.8 years (SD = 11.0, range = 26–67) for those who lived. Difference in mean age was 16.6 years (95% CI = 7.5 to 25.7, p = .001). No other subject parameter was associated with death as the reason for discontinuation (gender [p = .429], ethnicity [p =.636], duration of illness [p = .129], inpatient stay [p = .995], clozapine plasma level [p = .463], and duration of treatment [p = .304] had no association). Cause of death is given in Table 3.

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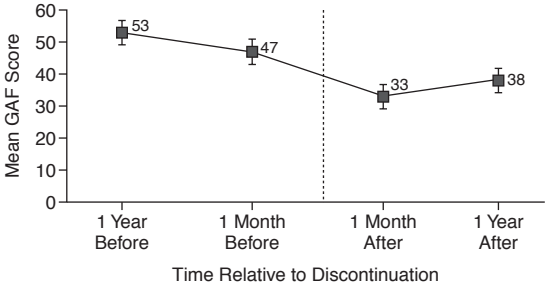
Table 4. Antipsychotics Prescribed Immediately After Discontinuing Clozapine and Mean Inpatient Stay for Each Medication in the Year Following Clozapine Discontinuation (N = 23)

Antipsychotic Prescribed	N	Mean Inpatient Stay, d
Amisulpride	1	0
Aripiprazole	2	93
Haloperidol	1	0
Olanzapine	6	128
Quetiapine	3	227
Conventional depot	4	118
Polypharmacy	5	130
None	1	0

Figure 1. Effect of Clozapine Discontinuation on Functioning (N = 23)



Abbreviation: GAF = Global Assessment of Functioning.

Hospital Stay

For the 23 subjects completing 12 months of treatment after clozapine discontinuation, change in hospital bed days was not statistically significant. Mean number of days spent in hospital in the year before discontinuation was 74.1 (SD = 137.3) compared with a mean of 119.8 days (SD = 143.5) in the 12 months following discontinuation (p = .214).

Antipsychotic Prescribing Following Discontinuation of Clozapine

After stopping clozapine, 1 subject (4%) received no antipsychotic in the following year, 5 (22%) received 1 antipsychotic, 9 (39%) received 2 antipsychotics, 6 (26%) received 3 antipsychotics, and 2 (9%) received 4 antipsychotics. The median number of antipsychotics used following clozapine was 2 (range = 0–4) in the 23-patient cohort. Ten patients (43.5%) were treated concurrently with 2 or more antipsychotics in the year following clozapine discontinuation.

A wide range of drugs was prescribed following clozapine discontinuation. Medication prescribed immediately after discontinuation of clozapine was found not to have a significant association with inpatient hospitalization in the year following discontinuation (p = .672). Details are provided in Table 4.

Global Assessment of Functioning Scores

When GAF scores were compared for 1 year before and 1 year after discontinuation of clozapine, it was found that 16 patients were more ill in the year after discontinuation compared with 1 year before discontinuation. Five people were documented as improved following discontinuation, and no change in functioning was recorded for 2 patients. GAF scores were significantly lower 12 months after stopping clozapine (Figure 1): the mean difference was 15 points (95% CI = 6.6 to 24.3, p = .002). In those who stopped clozapine because of reasons other than poor compliance (mainly adverse events, N = 12), mean GAF scores fell from 51 to 33 (mean change = 18 points, 95% CI = 5.7 to 31.6, p = .009). Among those stopping clozapine due to noncompliance (N = 11), there was no statistically significant change in mean scores (55 to 44, mean change = 11 points, 95% CI = –2.2 to 26, p = .09).

DISCUSSION

This retrospective study of patients discontinuing clozapine after more than 1 year of continuous treatment found that the most common reason for stopping clozapine was death. The 2 other major reasons for stopping clozapine were patient noncompliance and adverse effects (usually blood disorders). In those who received follow-up for 1 year after stopping clozapine, polypharmacy was commonplace, and GAF scores were significantly lower than during clozapine treatment. Most subjects' condition worsened substantially after stopping clozapine, especially those who stopped clozapine for reasons other than noncompliance.

With over one third of our subjects dying while taking clozapine, and at such a young age, clozapine has to be suspected as the possible cause of, or contributory factor to, some of these deaths. Arguably, 7 of the 12 deaths could be at least in some part attributed to clozapine. Two of the deaths were associated with seizures—a well-known side effect of clozapine.[6,7] One subject died of a pulmonary embolism; a possible association between clozapine and pulmonary embolism has been suggested.[8,9] Chronic bowel obstruction was linked to 1 death. Constipation is a common side effect of clozapine, and there are reported incidences of clozapine causing death by bowel obstruction.[10,11] Two deaths were conceivably related to clozapine's adverse effect on metabolic profile[12–14]: 1 death was due to stroke and another to left ventricular failure associated with left ventricular hypertrophy. Finally, 1 death was due to bronchial pneumonia—an adverse event occasionally linked to clozapine-related hypersalivation.[15] Additionally, 1 patient's documented cause of death was clozapine overdose—an event directly related, of course, to clozapine treatment. Despite these observa-

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tions, there is evidence from other sources that clozapine reduces mortality, largely by reducing the risk of suicide.[16,17] Nonetheless, there is clearly scope for preventing deaths in those taking clozapine—for example, by providing adequate anticonvulsant treatment and by monitoring and treating metabolic adverse effects. Indeed, it might be argued that the most important finding of this study (which set out to uncover medium-term outcome) was that preventable death is a common occurrence in those stabilized on clozapine.

In this study, stopping clozapine clearly worsened global functioning, and clinicians appeared to struggle to find a suitable replacement antipsychotic. This dilemma is illustrated by the fact that 17 patients (74%) received 2 or more antipsychotics in the year following clozapine discontinuation. Ten patients (43.5%) were also treated concurrently with 2 or more antipsychotics after clozapine discontinuation. Interestingly, no statistically significant difference was found in inpatient days in the year before clozapine discontinuation compared with the year after, although numerically there was a mean increase of 45.7 days in the year following clozapine stoppage. The lack of statistical significance is possibly related to the limited power of this retrospective study: only 23 patients provided data for the whole study period.

Various observations point to the possibility of withdrawal or rebound symptoms with clozapine.[18] One month after stopping clozapine, the mean GAF scores decreased from 47 to 33 and thereafter increased to 38 eleven months later. This course is somewhat suggestive of a withdrawal effect. The small reduction in GAF scores in the month before stopping clozapine may reflect hitherto undetected noncompliance in some subjects.

To our knowledge, this is the first study that has attempted to establish medium-term outcome in patients stopping clozapine. Our results clearly indicate that death is a common cause of clozapine discontinuation. In those who are switched to alternative drug treatment, global functioning worsens in the year following discontinuation. Larger studies with a follow-up period of several years would provide more useful data on outcome following clozapine discontinuation.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel).

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