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Title: Demographic and clinical characteristics of patients who recommence clozapine following therapy interruptions

Short title: clozapine recommencement

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ABSTRACT
Objective: The proportion of patients who recommence clozapine after cessation, the time taken to resume clozapine post-cessation, and distinguishing demographic and clinical characteristics of this group have been poorly researched. We evaluated these in the current study.
Method: We retrospectively extracted selected demographic and clinical variables and clozapine treatment interruption and recommencement data up to December 2018 of a cohort of 458 patients who first commenced clozapine between 2006-2016. The study was conducted at three Australian health services.
Results: Of the 310 (69%) patients who had at least one interruption of clozapine treatment, 170 (54.8%) did not resume clozapine and 140 (45.2%) recommenced it after the first interruption. More than half of those who recommenced did so within a month and 80% by 12 months. Cox regression analysis revealed that age was found to be significantly associated with recommencement, with a 2% decrease in the likelihood of restarting after an interruption for each
year later that clozapine was initially commenced (HR=0.98 95%CI: 0.97, 0.997, p=0.02). Those who ceased clozapine due to adverse effects were less likely to restart than those who ceased due to noncompliance (HR=0.63 95%CI:0.41, 0.97, p=0.03). More time on clozapine prior to interruption increased the likelihood of restarting it, with each additional month on clozapine increasing this likelihood by 1% (HR=1.01 95%CI:1.01,1.02) p<0.001).

**Conclusion:** If the distinguishing demographic and clinical characteristics of the group identified in this study are corroborated through further research, this could further validate the need to identify treatment resistance and commence clozapine early in people with schizophrenia and provide appropriate interventions to those more at risk of permanent discontinuation of clozapine.

**KEY WORDS** – clozapine, therapy interruption, clozapine recommencement, treatment-resistant schizophrenia

**Data Availability Statement:** sharing of data would need permission of data custodians.

**Significant Outcomes**

- While interruption of clozapine treatment occurred commonly in clinical practice among people with schizophrenia more than half recommenced it. Eighty percent of the resumption occurred within 12 months.

- Some demographic and clinical characteristics such as younger age at commencing clozapine, having been treated with clozapine for a longer period, and not discontinuing clozapine due to adverse effects were associated with the group who resumed clozapine.

- Further investigations are warranted to evaluate whether there are differentiating clinical and demographic characteristics for the group of patients who recommence clozapine. Our findings support existing literature advocating for early identification of treatment resistance in schizophrenia and commencement of clozapine.

**Limitations**
Ours was a retrospective naturalistic study which collated data from electronic databases. The amount of information available for analysis was limited to the details entered in the databases.

- The length of follow up of patients was not uniform and varied from a minimum of 2 years to a maximum of 13 years.
- The study, while multisite, is from public mental health services of a metropolitan city in Western Australia limiting the generalisability to other settings.

**Introduction**

Clozapine is more efficacious than other antipsychotics in managing the symptoms of people with treatment-resistant schizophrenia (TRS).\textsuperscript{1,2} Furthermore, it is reported to have additional benefits such as reducing mortality,\textsuperscript{3} hospitalisation,\textsuperscript{4} suicide,\textsuperscript{5} aggression\textsuperscript{6} and psychosocial decline\textsuperscript{7} among people with this condition. However, discontinuation of clozapine treatment is common in clinical practice with a significant proportion of patients ranging from 20%-60% ceasing this treatment.\textsuperscript{8-17} Non-adherence and adverse effects were the two most common reasons reported for clozapine discontinuation in these studies. Older age at commencement of clozapine,\textsuperscript{9,10,12,15,16} African ethnicity,\textsuperscript{8,9,13,16,17} substance abuse,\textsuperscript{15} male gender,\textsuperscript{18} reduced treatment efficacy,\textsuperscript{19} and living in a deprived neighbourhood\textsuperscript{17} have been reported to be associated with clozapine discontinuation.

Most studies have observed that discontinuation of clozapine occurs early during treatment.\textsuperscript{8,10,12,15,16,17,19} Termination of clozapine can be associated with rebound cholinergic overactivity, intractable psychosis, increased mortality, hospitalisation, compulsory treatments, and poorer functioning.\textsuperscript{14,20-24} Evidence for effectiveness of alternate antipsychotics after cessation of clozapine in patients with TRS is lacking and recommencing clozapine could be the safest and most effective intervention in many instances.\textsuperscript{23,24}

**Aims of the Study:** Identifying the demographic and clinical characteristics of the patients who restart clozapine after cessation could assist clinical practice. However, research so far has focused on the prevalence of clozapine discontinuation and distinguishing characteristics of this group. To our knowledge, no study has compared the characteristics of patients who resumed clozapine after a therapy interruption to those with sustained discontinuation. The aim of this study was to ascertain the proportion of patients who recommenced clozapine after the first
interruption of treatment, the time taken to resume clozapine, and compare selected clinical and demographic characteristics of the group who restarted clozapine with those who ceased clozapine.

Method
This retrospective cohort study was carried out among the patients who were commenced on clozapine for the first time from 1 January 2006 to 31 December 2016. The study was carried out at three metropolitan public mental health services in Perth, Western Australia, namely, Bentley Health Service (BHS), Fremantle Health Service (FHS), and Peel and Rockingham Kwinana Health Service (PaRK). Approval for the study was obtained from the Western Australian Department of Health Human Research Ethics Committee and local clinical governance committees.

Patients who were commenced on clozapine at these health services were registered on the Clozapine Central Registry and their haematological indices (white cell count and neutrophils) and clozapine dose were recorded on the electronic database every seven days for first 18 weeks and 28 days then onwards. If clozapine treatment was interrupted for any reason, the treating clinicians completed a structured termination report (checklist) of the reasons for discontinuation and this was entered into the electronic database. If clozapine was recommenced following interruption of treatment, this was recorded in the register.

In March 2020 the list of patients who were commenced on clozapine for the first time during the 11-year study period was collected from the Clozapine register of these health services. Demographic characteristics such as age and gender, and parameters related to clozapine prescription such as the date of commencing, ceasing, and recommencing clozapine therapy, and the dose of clozapine prescribed before the first therapy interruption were collated. Further, the reasons for therapy interruption entered in the termination report were collected and grouped into the following themes previously reported in the literature: a) non-adherence (non-compliance and personal choice to cease), b) adverse effects, c) inadequate efficacy, d) deceased, e) unspecified (reason not entered in the database). While the study inclusion deadline for commencement of clozapine ended on 31 December 2016, data on treatment interruptions and recommencements was collected for a further two years until 31 December 2018. Outcome was defined as recommencement of clozapine following the first interruption.

Statistical Methods
Data were summarised using means and standard deviation (SD) or counts and percentages or medians and first to third quartiles [Q1,Q3] as appropriate. Differences in age between males and
females were investigated using Student’s T test. Median follow-up time was estimated using reverse Kaplan-Meier approach where the status indicator variable is reversed. Cox proportional hazard regression models were used to investigate associations between demographic and clinical characteristic of the patients and recommencement of clozapine following interruption. Unadjusted and adjusted effects (multivariable model including all variables investigated) have been reported. Tests of the proportional hazards assumption based on Schoenfeld’s residuals were performed and identified violation for the clozapine dose prior to interruption. To address this issue a time varying coefficient model involving the interaction of time and clozapine dose was used. Analyses were conducted using Stata 16 and significance was set at p<0.05.

Results

Four hundred fifty-eight patients were registered in the clozapine database during the 11-year study period across the three health services. Two patients ceased without ever taking a dose of clozapine and were excluded due to the absence of information that could contribute to the analysis. Of the remaining, 214 (47%) patients were from BHS, 123 (27%) from FHS, and 119 (26%) from PaRK. Of the total, 314 (69%) were males. The mean age of the sample was 42.8 (SD13.6) years and the mean age at commencement of clozapine was 35.6 (SD13.7) years. Median follow up time was 7.9 (95% CI 6.6, 8.5) years. The median time the sample of patients were on clozapine was 1277 (256, 2629) days.

For eight patients the first termination of clozapine treatment was due to death and they were excluded from further analysis. One hundred and thirty-eight (31%) patients had no interruption of clozapine treatment from commencement until the study endpoint. Three hundred ten (69%) patients had at least one interruption of clozapine treatment. Of these patients, 170 (54.8%) did not resume clozapine and 140 (45.2%) recommenced clozapine during the study period. The demographic and clinical characteristics and reasons for cessation of clozapine of the patients who recommenced clozapine and those who did not are shown in Table 1. The probability of recommencing clozapine and time taken to restart are shown in Figure 1. Of the 140 patients who recommenced clozapine, 74 (52.9%) restarted it within 1 month and 112 (80%) by 12 months. Sixty-two (44.3%) of those who resumed clozapine continued it until the endpoint of the study, while some had multiple interruptions of treatment.

The results of univariate and multivariable cox regression analysis of time to restarting clozapine following first interruption are presented in Table 2. Age was found to be significantly associated with a 2% decrease in the likelihood of restarting after an interruption for each year later that clozapine was initially commenced (HR=0.98, 95%CI:0.97, 0.997, p=0.02).

Examination of potential non-linearity using fractional polynomials detected no evidence of a non-linear association for age, indicating that a linear relationship was appropriate. The greater
the period on clozapine treatment prior to interruption the higher the likelihood of restarting, with each additional month on clozapine increasing the likelihood of restarting by 1% (HR=1.01 95%CI: 1.006, 1.02, p<0.001). The significant interaction of time and clozapine dose prior to interruption, included to address the violation of the assumption of proportional hazards, indicated the relationship between clozapine dose and recommencement varied over time. At the time of interruption, the clozapine dose was not significantly associated with restarting (HR=1.01, 95%CI: 0.98, 1.04, p=0.6). However, the hazard ratio for clozapine dose was found to increase by 2% for each subsequent year (HR=1.02 95%CI: 1.004, 1.03, p=0.01) such that by 2 years post interruption, the likelihood of restarting was significantly associated with dose. At this time each 25mg increase in dose corresponded to a 4% increase in the likelihood of restarting (HR=1.04 95%CI: 1.01, 1.07). In those who ceased clozapine due to adverse effects, the likelihood of restarting was 47% lower than those who ceased due to noncompliance issues (HR=0.63, 95%CI: 0.41, 0.97, p=0.03). No significant association was found with gender (p=0.37) nor location of service (p=0.46) and recommencing clozapine.

Discussion
To our knowledge, this retrospective, naturalistic study is the first one to focus on ascertaining the proportion of patients who recommenced clozapine after a therapy interruption and also examined the demographic and clinical characteristics of the group who resumed treatment with clozapine. Only few researchers have reported the proportion of patients who recommenced clozapine after discontinuation. Encouragingly, almost half of the patients in our population resumed clozapine therapy following their first therapy interruption, which compares favourably with Davis et al. and Krivoy et al. who reported resumption rates of 16% and 18% respectively, but is not as impressive as the recommencement rate of 71% reported by Gee et al. These authors have not reported the time taken to recommence clozapine, and the length of follow up of patients in the different studies varied. Our observation that more than 50% of those who resumed clozapine treatment did so within a month and 80% by 12 months indicates that length of follow up alone is unlikely to explain the considerable differences in rates of resumption of clozapine described in the different studies. It is possible that other methodological differences and differences in clinical practice at various settings could also have played a role in accounting for the discrepancies in observed rates. Termination of clozapine treatment can be associated with a variety of adverse outcomes. Recently, Luyx et al. evaluated the comparative effectiveness and safety of antipsychotics in patients with schizophrenia who discontinued clozapine through a nationwide Finnish registry study. The authors observed that recommencing clozapine was the best option, or among the top best option, and was consistently associated
with the best outcomes such as lower risk of psychiatric hospitalisation and treatment failure and mortality, compared with no antipsychotic use and or use of other antipsychotics. While our study was not designed to test the efficacy of recommencing clozapine, it is reassuring to note that a significant proportion of patients recommenced clozapine and continued the treatment after discontinuing it initially.

We observed that those who ceased clozapine due to adverse effects were significantly less likely to restart clozapine than those who ceased it due to noncompliance issues. Non-adherence due to unspecified reasons is the most common cause for clozapine discontinuation identified in most studies.\textsuperscript{8-18} Discontinuation of antipsychotic treatment is common among people with schizophrenia, and is multifactorial in origin and not unique to those treated with clozapine.\textsuperscript{26-28} Adverse effects are common among people treated with clozapine and patients and clinicians are likely to be reluctant to recommence clozapine in the presence of significant side effects. However, while adverse effects are ubiquitous with clozapine treatment, fortunately, life-threatening side effects such as myocarditis, cardiomyopathy and agranulocytosis requiring cessation of clozapine are rare.\textsuperscript{29-31} In many instances medical reasons which eventuated in interruption of clozapine treatment do not warrant permanent cessation of the medication.\textsuperscript{32} While it might be clinically appropriate not to rechallenge patients with clozapine in some instances, such as among those recently experiencing myocarditis or agranulocytosis, clinicians should provide appropriate psychoeducation to patients discontinuing clozapine and encourage resumption of treatment where it is safe to do so.\textsuperscript{32,33}

Older age at commencing clozapine treatment was found to be significantly associated with a lower likelihood of recommencing clozapine after an interruption. Other authors have observed that older age of starting clozapine was associated with increased risk of discontinuation.\textsuperscript{9,10,12,15,16} Among patients with TRS, in nearly three quarters of patients, treatment resistance and indication for commencing clozapine occurs early in the course of illness.\textsuperscript{34,35} Furthermore, some researchers have reported greater efficacy for clozapine if it is commenced early once treatment resistance is identified.\textsuperscript{34-36} All these indicate the need for a concerted effort by clinicians, health services and policy makers to commence clozapine early in people with TRS. However, despite recommendations of treatment guidelines of schizophrenia to identify treatment resistance early and commence clozapine\textsuperscript{37}, in clinical practice, unfortunately, initiation of clozapine treatment is unduly delayed, often by many years.\textsuperscript{38,39}

We found that the longer the patients stayed on clozapine the more likely they were to recommence clozapine after an interruption. It is recommended that clozapine dose is titrated up slowly and an adequate dosage of clozapine to achieve a minimum plasma level of 350 ng/ml is often required to achieve therapeutic benefit.\textsuperscript{40} It is possible that in this study those who stayed
on clozapine for a longer period had a greater chance to experience its efficacy and hence were more willing to consider recommencing clozapine after treatment interruptions. Our observation that while at the time of interruption, the clozapine dose was not significantly associated with the risk of restarting, but that this became a relevant factor with the progression of time post-cessation is interesting. It is possible that immediately after cessation of clozapine factors other than efficacy might determine decision to recommence. In the long run, having been treated with a higher dose and possibly having a better response with optimal dose had a positive effect on the decision to recommence clozapine. Some of the serious adverse effects such as myocarditis and neutropenia are likely to occur early during treatment\textsuperscript{29,30} and it is possible that some patients who experienced these or other adverse effects in the early stages of treatment were either unwilling to recommence clozapine or clinicians did not recommend recommencing clozapine for these patients.

Being a retrospective naturalistic study, there were several methodological constraints and limitations in this study. We relied on data available in the Clopine databases at the health services and therapy termination reports completed by the treating medical team and clinicians to collate information. Inclusion of other baseline clinical, psychosocial or other variables such as the duration of psychosis, duration of treatment with other antipsychotics, comorbidities, previous history of noncompliance with other antipsychotics, living environment, ethnic and educational background, support network etc could have added further value to the study. The amount of information available for analyses was limited to the details entered in the databases and omissions and bias of the entered data cannot be excluded. However, registering all patients who commenced on clozapine in the database and entering the dates of commencement, haematological monitoring parameters, dose of clozapine and reasons for therapy interruption were part of the mandatory clozapine monitoring protocol practised at these health services. Some patients who were commenced on clozapine during the study period at these services could have moved to a different service and their clozapine status would not have been captured through these databases. A nation-wide study using clozapine central registries will provide a more accurate picture. Reason for therapy interruption was completed by the medical team involved in the patient’s care. This avoided the need for research staff to retrospectively form an opinion regarding the cause of discontinuation gleaned from the often limited information in the medical records. Due to the selection of patients from public health services the results of this study may not be generalisable to patients seen in private practice. However, most of the patients with treatment resistant schizophrenia treated with clozapine are managed by the public mental health services in Western Australia. Our moderate study sample size was comparable or larger

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than the other studies which ascertained the rate of recommencement of clozapine after interruption of treatment. However the sample size precluded examination of potential interactions such as an age effect on the dose relationship with restarting clozapine and for some categorical variables resulted in small numbers in some categories. The follow up period in this study is at the higher end of the period of follow up among clozapine discontinuation and recommencement studies. Our sample of patients had a preponderance of males which is in keeping with the higher prevalence of TRS and clozapine use among males documented by some reviewers.

In conclusion, our study highlights that resuming clozapine treatment after an interruption is common and the majority of those who recommence do so without much delay. Some demographic and clinical characteristics could potentially assist clinicians in understanding the likelihood of patients recommencing clozapine after interruptions. Given the high prevalence of clozapine discontinuation and a lack of substantial evidence for effectiveness of alternate treatments for patients with TRS who discontinue clozapine, further methodologically sound research scrutinising the proportion of the people with TRS who recommence clozapine and their characteristics are warranted. If the findings of our study are corroborated through other studies, it would further validate the need for interventions such as identifying treatment resistance early, commencing clozapine without delay, and psychoeducation of those who are vulnerable for sustained discontinuation to become part of clinical practice in schizophrenia.

References:


Table 1. Demographic and clinical characteristics of those who ceased clozapine therapy (N=310)

<table>
<thead>
<tr>
<th></th>
<th>Did not recommence</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=140</td>
<td>n=170</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Male</th>
<th>97 (69.3%)</th>
<th>113 (66.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age started Clozapine (years)</td>
<td>32 (11.9%)</td>
<td>38.2 (15.4%)</td>
</tr>
<tr>
<td>Service Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHS (reference)</td>
<td>64 (45.7%)</td>
<td>86 (50.6%)</td>
</tr>
<tr>
<td>FHS</td>
<td>34 (24.3%)</td>
<td>46 (27.1%)</td>
</tr>
<tr>
<td>PaRK</td>
<td>42 (30%)</td>
<td>38 (22.3%)</td>
</tr>
<tr>
<td>Months to first interruption</td>
<td>12.8 [3.3, 32.1]</td>
<td>3.9 [0.9, 15.2]</td>
</tr>
<tr>
<td>Clozapine dose (mg) †</td>
<td>300 [200, 400]</td>
<td>200 [125, 300]</td>
</tr>
<tr>
<td>Reason for Ceasing Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-compliance (reference)</td>
<td>95 (67.9%)</td>
<td>87 (51.5%)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>29 (20.7%)</td>
<td>63 (37.3%)</td>
</tr>
<tr>
<td>Inadequate efficacy</td>
<td>1 (0.7%)</td>
<td>10 (5.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (10.7%)</td>
<td>9 (5.3%)</td>
</tr>
</tbody>
</table>

†Dose prior to ceasing.

Data are n(%) or mean(sd) or median[Q1,Q3]

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**Table 2** Univariate and Multivariable Cox regression of time to restarting clozapine (N=310)

<table>
<thead>
<tr>
<th>Service Location</th>
<th>Univariate Cox Regression</th>
<th>Multivariable Cox Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95%CI</td>
</tr>
<tr>
<td>Male</td>
<td>1.11 (0.78, 1.59)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age started Clozapine</td>
<td>0.98 (0.96, 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FHS</td>
<td>1.07 (0.70, 1.62)</td>
<td>0.76</td>
</tr>
<tr>
<td>PaRK</td>
<td>1.40 (0.95, 2.07)</td>
<td>0.09</td>
</tr>
<tr>
<td>Months to first interruption</td>
<td>1.01 (1.01, 1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reason for Ceasing Clozapine</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>Non compliance (reference)</td>
<td>0.51</td>
<td>(0.34, 0.78)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>0.14</td>
<td>(0.02, 1.01)</td>
</tr>
<tr>
<td>Inadequate efficacy</td>
<td>1.27</td>
<td>(0.73, 2.18)</td>
</tr>
<tr>
<td>Other</td>
<td>1.02</td>
<td>(0.99, 1.05)</td>
</tr>
</tbody>
</table>

*Note: Dose prior to ceasing.*

Figure 1: Kaplan Meier Curve for time to restarting clozapine after first interruption.
Figure 1: Kaplan Meier Curve for time to restarting clozapine after first interruption.