MEDDOCS Open Access Publisher

ISSN: 2637-8027

Journal of Psychiatry and Behavioral Sciences

Open Access | Original Paper

# Is Clozapine Really Under-Used? Investigating Clinical Practice in a Community Psychosis Team

***Carol Paton*[1,2]*; *Bimpe Idowu*[1]; *Victor Doku*[3]**

[1]*Oxleas NHS Foundation Trust, Dartford, Kent DA2 7WG, UK.*

[2]*Division of Psychiatry, Imperial College London, London, UK.*

[3]*Oxleas NHS Foundation Trust, Bexley ICMP, Erith Centre, Park Crescent, Erith, Kent A8 3EE, UK.*

***Corresponding Author(s): Carol Paton**

Oxleas NHS Foundation Trust, Dartford, Kent DA2 7WG, UK.

Email: Carol.Paton@nhs.net

Received: Oct 20, 2023

Accepted: Dec 08, 2023

Published Online: Dec 15, 2023

Journal: Journal of Psychiatry and Behavioral Sciences

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/



**Keywords:** Schizophrenia; Clozapine; Community mental health team.

## Abstract

**Introduction:** Clozapine is the most effective antipsychotic medication for treatment-refractory schizophrenia but is reported to be under-used in the UK, potentially compromising outcomes for patients. The report from the national audit of psychosis in early intervention services suggests that involving a mental health pharmacist to identify individuals who may benefit from clozapine treatment may increase prescribing of this medication.

**Methods:** We used experienced clinical pharmacists to identify patients with schizophrenia under the care of a single community mental health team who were not prescribed clozapine but were prescribed high-dose or combined antipsychotics, had been admitted in the last year or were dissatisfied with their mental health and reviewed their clinical records to determine if they may benefit from clozapine. Such pragmatic criteria are typical of those that might be used in routine clinical practice to identify patients who may have complex and/or refractory illness.

**Results:** 245 patients had a diagnosis of schizophrenia, 169 (69%) of whom were not prescribed clozapine. Of the 51 patients who might be considered using our broad criteria to be eligible for clozapine treatment, 3 were in the process of starting clozapine, 7 had been offered clozapine but consistently refused and 1 had a history of clozapine-induced agranulocytosis. Clozapine was not obviously immediately clinically indicated in the remaining 40.

**Conclusions:** The prevalence of clozapine use in this community psychosis team is consistent with the known prevalence of treatment-resistant schizophrenia suggesting that clozapine is not under-used. Further, the screening criteria used by the clinical pharmacists did not identify any patients who might obviously benefit from clozapine but had not yet been offered this treatment. Our methodology could be used by other clinical teams to explore their own use of clozapine and to identify pockets of under use.

**Cite this article:** Paton C, Idowu B, Doku V. Is Clozapine Really Under-Used Investigating Clinical Practice In A Community Psychosis Team. J Psychiatry Behav Sci. 2023; 6(2): 1089.

## Introduction

For patients with schizophrenia whose illness has not responded adequately to two antipsychotic medications used sequentially, clozapine is the most effective pharmacological treatment [1,2]. Compared with other antipsychotic medications, clozapine is associated with improved control of acute symptoms in patients with multi-episode illness [3] and lower relapse [4] and re-admission rates [4-6]. Use of this antipsychotic medication has also been found to reduce use of substances [7], and decrease suicidality [8] and aggression/violence [9]. Further, overall mortality risk is lower than with other antipsychotic medications [10-12]. Given these proven benefits it is clearly important that, as part of routine clinical practice, all patients with treatment-refractory schizophrenia are offered clozapine at the earliest opportunity [1,2].

However, it has been reported that clozapine is under-used [13] with only a third of eligible patients in the UK receiving this treatment [14]. Further, the national clinical audit of psychosis in England reported that only around half of patients under the care of early intervention services whose illness had not responded to two different antipsychotic medications had been offered clozapine and that this proportion had remained stable over the four consecutive audits conducted between 2018 and 2022 [15]. Such low levels of prescribing could potentially compromise clinical outcomes. The national audit of psychosis report includes as an 'idea for quality improvement' that involving a pharmacist to identify individuals who may benefit from treatment with clozapine may increase the proportion of eligible patients who are offered this treatment. We therefore sought to review the clinical records of selected patients with a diagnosis of schizophrenia, who might be considered using broad criteria to be eligible for treatment with clozapine, to determine if they had been offered this treatment or may currently benefit from it. We focused on patients under the care of a single community mental health team that provides borough-wide Intensive Case Management for Psychosis (ICMP) for residents of the London borough of Bexley.

## Method

All patients with an ICD-10 [16] diagnosis of schizophrenia (F20) on the caseload of a single community mental health team, that provides Intensive Case Management For Psychosis (ICMP), were identified from the Trust electronic patient record system (RIO) [17] in November 2022. Patients with other diagnoses in the ICD-10 F20-29 category (schizotypal disorder, schizoaffective disorder, brief psychotic disorders and delusional and other non-mood psychotic disorders) were excluded.

For each patient, the following information was collected; age, sex, ethnicity, antipsychotic medication and regimen (whether combined or high dose), whether the patient had been admitted to an acute psychiatric bed in the last year, and where documented, DIALOG [18] scores as described below.

DIALOG is a scale consisting of eleven questions, each rated on a Likert scale of 1 (totally dissatisfied) to 7 (totally satisfied) with a score of 4 being neutral [18]. The first eight questions constitute a Patient-Related Outcome Measure (PROM) and the last three a Patient-Related Experience Measure (PREM). Two questions; 'how satisfied are you with your mental health' (a PROM) and 'how satisfied are you with your medication' (a PREM) are particularly relevant to assessing the patient's perceptions of the effectiveness of pharmacological treatment. Where available, DIALOG scores documented in the last year for these 2 items were collected. Scores of 1-3 on each item were taken to indicate dissatisfaction.

### Selection of clinical records for further review

Patients who were not prescribed clozapine were identified. Prescription of combined antipsychotics, high dose antipsychotics, an admission to an acute adult psychiatric ward in the last year and patient dissatisfaction with their mental health or medication might be considered to suggest complex and refractory illness that may benefit from further review; such pragmatic criteria are typical of those that might be used in routine clinical practice to identify patients who may have complex and/or refractory illness. We therefore used these broad criteria to identify patients whose clinical records were further scrutinized to determine if treatment with clozapine may potentially be indicated; clinical judgements were made by BI and CP, both of whom are experienced specialist mental health pharmacists.

Ethical approval is not required for such audit-based quality improvement initiatives [19].

## Results

Two hundred and forty-five patients with a diagnosis of schizophrenia were identified as being on the caseload of Bexley ICMP, 76 (31%) of whom were prescribed clozapine, 89 (36%) were prescribed oral antipsychotic medication other than clozapine and 80 (33%) were prescribed an antipsychotic Long-Acting Injection (LAI). The demographic characteristics of these three sub-groups are shown in **Table 1**. Almost three-quarters (n=181; 74%) of patients overall were 31 to 60 years of age, with those prescribed oral antipsychotics other than clozapine being younger than those prescribed an LAI who were in turn younger than those prescribed clozapine. Statistical tests were not conducted as we are describing the sample, not testing a hypothesis.

DIALOG scores were not available for the majority of patients, and when available not all of the questions had been consistently completed. Scores for 'how satisfied are you with your mental health' were documented for 53 patients, 9 of whom had a score of 1-3 indicating dissatisfaction. Scores for 'how satisfied are you with your medication' were documented for 56 patients, 4 of whom had a score of 1-3 indicating dissatisfaction.

With respect to the other categories used as proxy measures for complex and refractory illness, 5 patients were prescribed high-dose antipsychotic regimens, 12 combined antipsychotics that did not include clozapine and 21 had been admitted to an acute psychiatric ward in the last year, giving a total of 51 patients whose clinical records were reviewed to determine if they might benefit from treatment with clozapine. As can be seen in **Table 2**, seven of these patients had been offered clozapine but consistently refused, preparations were being made to start clozapine in a further three and one patient had a history of clozapine-induced agranulocytosis. In the remaining 40 cases, treatment with clozapine was not considered to be indicated at this point in time; the reasons for this can be seen in **Table 2**.

**Table 1:** Demographic characteristics and antipsychotic medication regimen: patients with a diagnosis of schizophrenia under the care of a single community mental health team.

| Demographic characteristics and prescriptions for high-dose and/or combined antipsychotics | | Antipsychotic medication regimen prescribed n (% of each characteristic) | | | |
|---|---|---|---|---|---|
| | | Oral n=89 | LAI n=80 | Clozapine n=76 | Total N=245 |
| Age (years) | 21-30 | 13 (62) | 5 (24) | 3 (14) | 21 |
| | 31-40 | 17 (33) | 22 (42) | 13 (25) | 52 |
| | 41-50 | 20 (32) | 19 (30) | 24 (38) | 63 |
| | 51-60 | 20 (30) | 18 (27) | 28 (42) | 66 |
| | >60 | 19 (49) | 16 (37) | 8 (19) | 43 |
| Sex | Male | 59 (35) | 52 (31) | 57 (34) | 168 |
| | Female | 30 (39) | 28 (36) | 19 (25) | 77 |
| Ethnicity | White/White British/White Other | 53 (34) | 44 (28) | 61 (38) | 158 |
| | Black/Black British | 24 (46) | 18 (35) | 10 (19) | 52 |
| | Asian/Asian British | 4 (4) | 7 (9) | 3 (4) | 14 |
| | Mixed | 2 (2) | 6 (8) | - | 8 |
| | Other | 3 (3) | 3 (4) | 1 (1) | 7 |
| | Not documented | 3 (3) | 2 (3) | 1 (1) | 6 |
| Antipsychotic medication regimen prescribed | Combined antipsychotics | 4 (4) | 8 (10) | 23 (30) | 35 |
| | High-dose antipsychotics | 1 (1) | 4 (5) | 3 (4) | 8 |

**Table 2:** Findings from review of 51 clinical records of patients not currently prescribed clozapine who met broad criteria that may suggest complex and/or refractory illness that warrants a trial of clozapine.

| Clinical factor suggesting clozapine may be indicated | N | Findings from review of clinical records | |
|---|---|---|---|
| | | Clozapine not currently indicated (n) | Clozapine indicated (n) |
| High-dose antipsychotic regimen | 5 | • Prescription regimen started during admission to an acute ward. Dose reduction now indicated (2)<br>• Consta and oral risperidone combination. Consider switch to paliperidone (2) | • Offered clozapine but consistently refuses (1) |
| Combined antipsychotics not including clozapine | 12 | • Incomplete switch. Needs review (2)<br>• Low dose quetiapine added for sleep (2)<br>• Current antipsychotic dose sub-therapeutic but limited by prolactin-related side effects. Switch indicated (2)<br>• Second antipsychotic (aripiprazole) added to mitigate metabolic and/or prolactin-related side effects (2)<br>• Recent psychology intervention has been effective. Antipsychotic regimen needs review (1) | • Offered clozapine but consistently refuses (2)<br>• Team currently preparing to start clozapine (1) |
| Admission to an acute mental health ward in the previous year | 21 | • Use of drugs and alcohol are the major destabilising factor (7)<br>• Response to antipsychotic medication, but intentional non-adherence including to LAI preparations (5)<br>• Unintentional non-adherence. Practical support needed to take medication (2)<br>• Admission secondary to patient-negotiated dose reduction (2)<br>• Social support needed (2)<br>• Currently responding well to new psychology intervention (1) | • Team currently planning to start clozapine (1)<br>• Clozapine agranulocytosis (1) |
| Dissatisfied with mental health (DIALOG score of 1-3 on item) | 9 | • Social circumstances are main driver of dissatisfaction (3)<br>• Intervention to treat depression indicated (2)<br>• Dose limiting side effects with current LAI (symptomatic hyperprolactinaemia). Switch indicated (1)<br>• Use of drugs and alcohol are the major destabilising factor (1) | • Offered clozapine but consistently refuses (2) |
| Dissatisfied with current medication (DIALOG score of 1-3 on item) | 4 | • May benefit from an increased in (the currently low) antipsychotic LAI dose (1) | • Offered clozapine but consistently refuses (2)<br>• Team are currently preparing to start clozapine (1) |

## Discussion

We used the pragmatic approach of reviewing the clinical records of patients with a diagnosis of schizophrenia whose prescription, recent admission history and/or poor perceptions of their own mental health suggested complex and refractory illness and therefore potential eligibility for clozapine treatment. This patient-centred approach enabled a more detailed clinical understanding of the quality of prescribing decisions that cannot be obtained from studies based on prescribing data and epidemiological estimates alone; in contrast to these studies that have suggested marked under-use of clozapine [13,14], we did not identify any patients who could obviously benefit from treatment with clozapine who had not been offered this medication. Indeed over a third of patients under the care of Bexley ICMP were either prescribed clozapine or had consistently refused to consider this treatment option. However, a limitation of our methodology is that we did not scrutinize the clinical records of all patients under the care of the team who were prescribed antipsychotic medication other than clozapine so cannot exclude sub-optimal control of symptoms in those patients who did not meet our broad criteria for complex and refractory illness.

**Demographic characteristics and antipsychotic medication prescribed**

Almost two-thirds of patients who were 30 years of age or younger were prescribed oral medication other than clozapine while antipsychotic LAIs were used more often in patients' age 31 to 50 years and clozapine in those age 41 – 60 years. Such a pattern of use is not unexpected; an oral antipsychotic is usually the treatment of choice early in the course of the illness, with a switch to a LAI in more established illness, particularly where adherence is sub-optimal and then to clozapine where the illness has proven to be refractory to other evidence-based pharmacological strategies.

First-episode patients can manifest treatment-refractory illness [20] and delays to starting clozapine are a well-documented clinical problem [21]. We therefore cannot exclude delays to clozapine treatment in younger patients under the care of Bexley ICMP but caution is required in interpreting our data due to the small numbers in some age categories.

There were apparent gender differences in the use of clozapine with this medication being prescribed for a third of men with a diagnosis of schizophrenia compared with only a quarter of women. Treatment-refractory illness may be more common in men than in women [22] and this is a potential explanation for our finding. However, Wesley et al [22] reported that, compared with a man, the odds of a women with treatment-resistant schizophrenia being prescribed clozapine was 0.66 and concluded that there may be some gender bias in routine prescribing decisions.

Over a third of White patients under the care of the team were prescribed clozapine, compared with fewer than a fifth of Black patients with the latter more likely to be prescribed an oral antipsychotic other than clozapine. One potential explanation for this finding is that the relatively high prevalence of benign ethnic neutropenia in people of African descent [23] leads to the perception that clozapine is more difficult to use and so seen as a 'last resort' rather than a strategy to consider as soon as a treatment-refractory illness is evident.

**Why might clozapine not be immediately clinically indicated where the antipsychotic regimen is non-standard, the patient has recently relapsed or is dissatisfied with their mental health?**

There is limited evidence to support the use of high-dose or combinations of antipsychotic medication that do not include clozapine and therefore clinical guidelines caution against the routine use of these strategies [1,2]. We found that high dose was likely to be inadvertent rather than an indicator of complex and refractory illness; for example risperidone LAI was combined with oral risperidone resulting in a high total dose of risperidone but if the equivalent dose of paliperidone (which has a higher licensed maximum dose) was to be prescribed, the prescription would no longer be high dose. Where combined antipsychotics were prescribed, reasons included the addition of very low dose quetiapine to aid sleep or the addition of aripiprazole to lower prolactin or mitigate metabolic side effects. Psychotic symptoms per se were reasonably well controlled in these patients. Where the patient had relapsed in the last year resulting in a hospital admission, non-adherence to antipsychotic medication (including LAIs), patient-negotiated antipsychotic dosage reductions to the bottom of/below the recommended range, or ongoing problematic use of drugs and alcohol were considered to be the major drivers in the majority of cases; restarting standard antipsychotic medication and/or limiting access to substances during admission led to improved symptom control in all cases. There is some evidence to support the effectiveness of clozapine in reducing substance use [7]and that, once treatment has been established, attrition rates are lower than with previously prescribed antipsychotic medication [24]. However, these potential, numerically modest, benefits must be weighed against the complexity of establishing and maintaining treatment with clozapine in patients whose lifestyle may be chaotic and whose illness is not refractory to standard antipsychotic medication.

As well as causing potentially serious side effects such as agranulocytosis, pneumonia and severe constipation, clozapine can also cause bothersome side effects such as weight gain, hypersalivation, sedation and nocturnal enuresis. [25]. This side effect burden is greater than that associated with other antipsychotic medication so it is important to establish that the illness has failed to respond to two other antipsychotic medications before offering clozapine.

With respect to those patients who were dissatisfied with their medication or mental health, two themes were identified from the clinical records. The first relates to social circumstances such as poor housing and restricted access to children; issues that cannot be solved by medication. The second relates to the use of doses of antipsychotic medication that are below or near the bottom of the licensed range; the clinical team were working with these patients to encourage acceptance of a higher dose or switch to an alternative antipsychotic medication. For example, in one patient the dose of paliperidone LAI that was acceptable to the patient was very low and limited by prolactin-related side effects. A switch to aripiprazole LAI would be the logical next step, rather than considering clozapine at this point.

In summary, the broad pragmatic criteria that we used did not identify patients with refractory illness who might benefit from treatment with clozapine but rather exposed the many other clinical and service-related factors that psychiatrists face in their everyday practice.

**Why might conclusions regarding under-use of clozapine differ?**

Our finding that around a third of patients with a diagnosis of schizophrenia under the care of Bexley ICMP were prescribed clozapine is consistent with the estimate that around a third of patients with schizophrenia will have a treatment-refractory illness [26]. Previous research that has reported on the under-use of clozapine has used population estimates of the prevalence of treatment-refractory schizophrenia along with data from monitoring services relating to the number of patients receiving clozapine leading to the suggestion that if clozapine was always used where indicated, 0.2% of the adult population in the UK would be prescribed this medication [14]. Applying this estimate to the adult population of Bexley borough, which is approximately 200,000, [27] the optimal number of patients treated with clozapine would be expected to be 400. When the total number of patients prescribed clozapine under the care of any clinical team in Bexley borough is extracted directly from the monitoring service [28], this yields 110; just over a quarter of the estimated optimal number.

However, using the more modest median point prevalence of schizophrenia of 0.46% [29], it can be estimated that 920 people living in the borough will currently have schizophrenia, 276 of whom are likely to have a treatment-refractory illness. Bexley ICMP provides care for the vast majority of community-based patients with schizophrenia and has 245 patients with this diagnosis on their current caseload. Relatively small numbers of patients with schizophrenia will of course be under the care of early intervention and community resettlement teams or will be inpatients in rehabilitation or forensic facilities. But even when accounting for patients with schizophrenia whose care is provided by other mental health teams, and using the more conservative estimate of 0.46% for illness prevalence, our data suggest that fewer than half of people likely to have schizophrenia in the local catchment area are currently in contact with mental health services. We therefore suggest that clozapine may not be under-used in this community mental health team but rather there may be a relatively large number of people with schizophrenia who are under the sole care of their GP or who are living undiagnosed in the community.

In summary, by looking in more detail at the clinical records of patients with schizophrenia who might be considered using broad pragmatic criteria to be eligible for clozapine treatment, there was a sound clinical rationale for not offering clozapine at the present time in the majority. In the remainder, clozapine treatment was currently being considered or had been offered and consistently refused. We did not find clozapine to be under-used in this community team that provides intensive case management for psychosis and it is possible that it is not under-used in other services. Our methodology could be used by other Trusts to examine the use of clozapine within individual clinical teams and provide local reassurance that this medicationis not being under used.

**Strengths and limitations**

- We used pragmatic criteria to identify patients with complex and/or treatment-refractory schizophrenia who may be eligible for treatment with clozapine. Our criteria are typical of those that may be used in routine clinical practice.

- We did not scrutinize the clinical records of patients who did not meet our criteria and so cannot exclude the possibility that there were patients in this group whose symptoms were not optimally controlled and who may therefore benefit from treatment with clozapine.

**About the authors: Carol Paton** is a pharmacist at Oxleas NHS Foundation Trust, Joint Head of the Prescribing Observatory for Mental Health at the Centre for Quality Improvement, Royal College of Psychiatrists, UK, and an Honorary Research Fellow at the Division of Psychiatry, Imperial College London, UK. **Bimpe Idowu** is a senior pharmacist at Oxleas NHS Foundation Trust **Victor Doku** is Consultant Psychiatrist at Oxleas NHS Foundation Trust and Honorary Lecturer in Psychiatry at the Faculty of Life Sciences and Medicine, Kings College London**.**

**Data availability:** Data relating to demographic characteristics, diagnosis, dialogue scores and hospital admissions were extracted from pre-set fields in routine clinical records. These data are not publicly available as they contain information that could compromise privacy. Data relating to whether clozapine was considered to be indicated or not were based on the judgement of BI and CP after scrutiny of narrative accounts in the clinical records; such data are confidential and therefore not available for sharing.

**Author contributions:** C.P. and B.I. designed the study and were responsible for data collection and analysis. All authors (C.P., B.I., and V.D.) contributed to interpreting the data, drafting the paper and revising it critically for academic content. All authors approved the final version and are accountable for its contents.

**Declaration for interest:** CP, BI and VD have nothing to declare.

**Funding:** No funding was received for this work.

**Ethics statement:** Ethical approval is not required for audit-based quality improvement initiatives

**Acknowledgements:** The authors would like to thank Pinder Thind from the Informatics reporting team at Oxleas NHS Foundation Trust for extracting routinely collected data from RIO.

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