

Reasons for admission to a general medical hospital for patients taking clozapine

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Abstract

Background: Clozapine is associated with a diverse range of side effects. In addition, patients prescribed clozapine commonly suffer with medical comorbidities.

Objectives: This study aimed to characterise patients prescribed clozapine who required medical admission, understand reasons for admission, identify areas for interventions to prevent future admission and describe clozapine management during the inpatient stay.

Design: We conducted a retrospective analysis of patients prescribed clozapine who were admitted to a general medical hospital in a 12-month period.

Method: Data were collected using electronic drug charts and notes.

Results: In total, 114 clozapine patients were hospitalised. Twenty-eight patients (25%) were admitted because of infection, 12 (11%) were elective admissions and 12 (11%) had gastrointestinal problems. Most patients admitted were Black (54%) and half were female. Few changes were made to clozapine dosing on admission or during the inpatient stay. Most patients had been taking clozapine for many years at the point of admission, the majority were able to continue taking it for the duration of their medical treatment and were discharged on the same dose they were taking prior to admission. Clozapine plasma concentrations were not consistently measured with only 18 (16%) patients having one or more plasma concentrations determined during their admission. The median clozapine plasma concentration on admission was 0.48 mg/L (nor-clozapine 0.21 mg/L), with a range of 0.09 to 3.9 mg/L. Three patients were admitted to the intensive care unit during their admission; all were discharged on clozapine. Four patients died; one from lung adenocarcinoma, one bowel obstruction, one cardiac arrest and one chest sepsis. In total, 27 patients (23%) had their clozapine stopped on admission, 6 (22% of this group) unintentionally.

Conclusions: Our study found that the most common reason for admission for patients taking clozapine was infection. Plasma concentrations were not measured routinely despite clozapine having a narrow therapeutic index and enhanced potential for toxicity in the medically unwell patient.

Keywords: antipsychotic, clozapine, liaison psychiatry, schizophrenia

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Introduction

Clozapine is the only antipsychotic with repeated, proven effectiveness in treatment-resistant schizophrenia and schizoaffective disorder.^{1,2} Benefits are also seen in other psychiatric indications including bipolar disorder.³ Not only effective for psychiatric symptom control, clozapine also reduces all-cause mortality.⁴ It is however

associated with many side effects, both in the short and long term. Furthermore, patients who are prescribed clozapine are likely to have already endured lengthy periods of psychotic illness and taken many other antipsychotic drugs,⁵ all of which are associated with their own side effects. Serious mental illness (SMI) itself is associated with higher odds of also suffering almost any

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other medical comorbidity,⁶ and there is strong evidence to support inequalities in medical care for patients with SMI.⁷

It is therefore possible that patients who take clozapine will require inpatient medical treatment at some point in their lives. It is also possible that clozapine itself may contribute directly to the need for a medical admission, either through acute toxicity (e.g. seizures, myocarditis) or more chronic effects (e.g. pneumonia, gastrointestinal obstruction, diabetes). Managing a complex drug such as clozapine safely during a medical admission can be challenging. Non-psychiatric professionals are unlikely to be familiar with clozapine in terms of its potential contribution to physical symptoms, and of the impact of physical symptoms on the safety of continuing clozapine. They might also be unaware that other antipsychotics do not substitute for clozapine.

The purpose of this retrospective descriptive analysis was to investigate why patients taking clozapine were hospitalised and to discover what happened to these patients once they were admitted.

Methods

All patients prescribed clozapine in any formulation on admission to King's College Hospital, a 950-bed medical facility, in a 12-month period from 2018 to 2019 were included. Patients were identified for inclusion using the hospital electronic prescribing system. Demographic, prescribing and clinical data were collected retrospectively using the general medical hospital electronic drug chart, electronic notes and the partnering mental health trust electronic notes systems. Different admission episodes for the same patients were included as separate events. Patients who newly started clozapine during admission episodes were excluded. Data on the length of time each patient had been taking clozapine for was gathered from the clozapine manufacturer's monitoring database. The length of the current episode of clozapine use was defined as the number of days from the start of uninterrupted registration with the manufacturer (interruptions of less than 6 weeks were disregarded) to the date of admission.

This study was approved by the Pharmacy Research and Audit Group at King's College Hospital, the Drug and Therapeutics Committee

Table 1. Demographic data.

N = 114	
Age (mean), years	50
Female, <i>n</i> (%)	57 (50)
Ethnicity, <i>n</i> (%)	
Black	61 (54)
White	45 (39)
Mixed	1 (1)
Asian	2 (2)
Other	5 (4)
Diagnosis, <i>n</i> (%)	
Schizophrenia	87 (76)
Schizoaffective disorder	16 (14)
Other	11 (10)
Length of stay, median (range), days	3 (1–165)

at South London and the Maudsley NHS Foundation Trust (approval code DTC/2021/28).

Data were anonymised and stored on a password-protected computer.

Results

In total, 87 patients taking clozapine were admitted during the observation period, representing 114 separate hospitalisations (Table 1).

The most common presenting complaint on admission (19%) was some form of neurological complaint, including confusion, collapse and falls (Table 2) (for eight of these admissions, the cause was infection, and one cardiac). At the point of discharge, the most frequent primary diagnosis was an infection (25%). Of the cases of infection, 16 (57%) were respiratory, 8 (29%) were an abscess or other skin infection, 2 were urosepsis (7%), and the remaining 2 (7%) were infections of unknown origin.

The majority of patients were admitted from their own accommodation (42%, Table 3), but proportionally fewer were discharged there (36%). More patients were discharged to mental health inpatient care (36%) than were admitted from those locations (25%).

Table 2. Presenting complaint and final diagnosis.

	Presenting complaint on admission, <i>n</i> (%)	Diagnosis on discharge, <i>n</i> (%)
Elective admission	12 (11)	12 (11)
Drug/alcohol overdose	4 (4)	4 (4)
Psychiatric symptoms	8 (7)	15 (13)
Fall/collapse or neurological ^a	22 (19)	3 (3)
Respiratory ^b	18 (16)	3 (3)
Seizures	3 (3)	5 (4)
Trauma	9 (8)	9 (8)
Infection	11 (10)	28 (25)
Gastrointestinal ^c	11 (10)	12 (11)
Cardiac	3 (3)	7 (6)
Pain	3 (3)	0 (0)
Diabetes	2 (2)	2 (2)
Renal	6 (5)	8 (7)
Obstetrics & gynaecology	1 (1)	1 (1)
Endocrine	1 (1)	4 (4)
Cancer	0 (0)	1 (1)

^a'Fall/collapse or neurological' category included headache, confusion, collapse, reduced mobility, changes in consciousness and falls.
^b'Respiratory' included coughs and breathlessness.
^c'Gastrointestinal' included constipation, diarrhoea, nausea, abdominal pain and vomiting.

Intensive care

Of the total 114 admissions, 3 patients were admitted to intensive care, all within the first 24 h of admission. Presenting complaints were clozapine overdose and aspiration pneumonia, respiratory arrest and status epilepticus. Clozapine was temporarily withheld for the patient who took an overdose (plasma concentration on admission 3.9 mg/L) and continued with no treatment break for the other patients. All three patients survived and were discharged to their usual places of residence in 9 to 11 days.

Deaths

Four patients died during admission, two men and two women, aged between 50 and 79. All had a diagnosis of schizophrenia and had been taking clozapine for 612–9787 days. Mean dose on admission was 356 mg. Two patients were admitted from supported accommodation and two

from their own housing, and presenting complaints were respiratory for two patients (breathlessness, chest sepsis) and gastrointestinal for the other two (vomiting and abdominal pain). Clozapine was stopped on admission for all patients other than the patient presenting with breathlessness, for whom it was continued with no changes. It was subsequently retitrated for one of the patients presenting with abdominal pain. Diagnoses were lung adenocarcinoma, bowel obstruction, cardiac arrest, and chest sepsis. Three patients died 3 days after admission, the fourth after 38 days. None of these patients were admitted to critical care.

Clozapine plasma concentrations

In total, 18 patients had one or more plasma concentrations measured during their admission, 14 within the first 24 h. Median clozapine plasma concentration on admission was 0.48 mg/L

Table 3. Admission location and discharge destination.

	Admitted from, <i>n</i> (%)	Discharge destination, <i>n</i> (%)
Own accommodation	48 (42)	41 (36)
Supported accommodation	38 (33)	28 (25)
Mental health inpatient care	28 (25)	41 (36)
Died		4 (4)

Table 4. Clozapine data.

Length of current clozapine treatment episode, median, days (range)		3304 (13–10,478) (<i>n</i> = 80) ^a	
Clozapine management on admission, <i>n</i> (%)	No change		82 (72)
	Stopped (intentional)		21 (18)
	Stopped (unintentional)		6 (5)
	Dose increased		1 (1)
	Dose decreased		4 (4)
Clozapine dose, median (range), mg	Total cohort	On admission	300 (25–850)
		On discharge	300 (0–850)
	Male (<i>n</i> = 57)	On admission	350 (25–850)
		On discharge	325 (0–850)
	Female (<i>n</i> = 57)	On admission	300 (50–600)
		On discharge	300 (0–600)

^aData unavailable for 34 hospitalisations, representing 29 patients not under ongoing care with our trust.

(nor-clozapine 0.21 mg/L), with a range of 0.09 to 3.9 mg/L. The median was lower in men (0.39 mg/L) compared with women (0.49 mg/L). Where the reason for taking a level was documented, it was either due to concerns that symptoms may be indicative of toxicity (myoclonic jerks, constipation, myocarditis, unsafe swallow) or suspicion of non-compliance. Of the 14 plasma concentrations recorded at admission, two were >1.0 mg/L and three were <0.3 mg/L. Of the patients presenting with high plasma concentrations, one was a result of a deliberate clozapine overdose, the other an incidental finding in a patient admitted due to confusion. Median length of stay for patients who had clozapine plasma concentration monitoring at some point during their admission was 15 days (range, 3–165 days).

Clozapine discontinuation

Twenty-seven patients (23%) had their clozapine stopped on admission (Table 4). For six of these, no reason was given and it appears to have been an unintentional omission. Of the 21 patients who had their clozapine intentionally stopped on admission, the majority were because of medical concerns [myoclonus and QT prolongation (1 patient), myocarditis (5 patients), unsafe swallow (1 patient), cardiomyopathy (1 patient), seizure (1 patient), high plasma concentrations (1 patient), heart failure (1 patient), dizziness (1 patient), bowel obstruction or constipation (3 patients), unresponsive (1 patient)]. The remaining five patients had either confirmed or suspected non-compliance prior to admission, and their clozapine was purposely not prescribed on admission. Where

clozapine was restarted, this was done so in line with local guidelines.³

In total, eight patients who had their clozapine stopped on admission (seven intentionally, one unintentionally) were not restarted on clozapine before discharge (Table 4). Of these, one patient refused to take clozapine during the acute medical admission, two patients died, one was diagnosed with clozapine-induced myocarditis, one with heart failure, three with infections (pneumonia, osteomyelitis and unknown origin) and one with sigmoid colitis.

Of the six patients whose clozapine was not restarted and were discharged, five were discharged to inpatient mental health services and one to supported accommodation with intensive community mental health support. For one patient, this was a change compared with the location they had been admitted from (previously in supported accommodation, discharged to mental health inpatient care).

Discussion

This retrospective study of patients taking clozapine who were admitted to a large London teaching hospital over the course of a year found the most common reason for admission was an infection. Most patients continued taking clozapine with no changes to dosing during admission. Proportionally more patients were discharged to inpatient mental health care, and fewer to their own homes or supported accommodation than were admitted from those locations.

Prescribers may worry particularly about the well known, but rare side effects of clozapine such as agranulocytosis or myocarditis that occur in the first few months of treatment, and indeed guidelines⁸ and mandatory blood test monitoring systems are used to identify these adverse effects quickly. In contrast to these safety protocols and clinical focus, our study found infection to be the most common single reason for admission for medical treatment in patients taking clozapine, accounting for 25% of admissions. Of these infections, the majority were respiratory. This predominance of pulmonary events leading to medical admission for patients taking clozapine echoes findings by others. Leung *et al.*⁹ performed a retrospective chart review of patients taking clozapine on admission to a general medical hospital in the United States, and also found that

respiratory conditions were the most reason for admission, with pneumonia the leading diagnosis within this category. We also showed that most patients had been taking clozapine for many years, rather than being recently started. In recent years, there has been an increasing interest in the suggestion that clozapine is directly immunomodulatory, with one group demonstrating a reduction in immunoglobulin levels in patients taking clozapine, with a greater effect in those taking long-term treatment.^{10–12} There is a linear correlation between a fall in immunoglobulins and the rate of infection,¹⁰ and many studies find patients on clozapine to be more susceptible to infection than those taking other antipsychotics.¹³ The presence of infection for patients taking clozapine can also affect the safety and tolerability of the drug. The release of cytokines during periods of infection may inhibit metabolism of clozapine, causing unpredictable increases in plasma concentration.¹⁴ Furthermore, patients admitted with lung infections who usually smoke may not be able to do so to the same extent (either because they cannot leave the hospital ward, or if they can, then the inhalation efficiency may be reduced, so the ‘dose’ of smoke itself may be lower than normal). Failure to reduce the dose of clozapine in patients who stop or reduce smoking can result in clozapine toxicity within days.¹⁵

Our study found that almost a quarter of patients (23%) had their clozapine stopped on admission. For nearly one in four of these patients, this omission was unintentional. For others, the decision was made based on concerns about their medical condition or because of a lack of certainty about concordance with clozapine. Clozapine is a drug that cannot be substituted by any other: no other drug can be expected to provide effective symptom control. Stopping clozapine almost always results in relapse. The difficulty of managing acutely psychotic patients in general medical environments, and the impact of psychotic symptoms on the ability of the patient to comply with necessary medical interventions, should not be underestimated. Maintaining continuity of treatment with clozapine is therefore imperative wherever possible. The ability to measure plasma concentrations of clozapine sufficiently rapidly to enable decision making about the next dose (*i.e.* within hours) would enable some patients to avoid a gap in treatment, where compliance could be confirmed. Turnaround times of 24 to 48 h (or longer, if assays are not run daily), as is usually the case with conventional laboratory assays, may

delay this decision making and impact on clinical care. Every effort must be made to avoid unintentional omissions, and specialist advice from experts in clozapine should be accessed to avoid unnecessary, albeit well-intentioned, cessation. Abrupt withdrawal of clozapine can cause problems beyond relapse, including withdrawal-associated psychosis, cholinergic rebound, catatonia, and serotonergic discontinuation symptoms.¹⁶ Conversely, it is essential that clozapine is discontinued in some circumstances. Patients with possible bowel obstruction, acute cardiac symptoms, or symptoms suggestive of toxicity (seizures, severe drowsiness) must have their clozapine stopped (and plasma concentrations measured) as these side effects can be fatal. These recommendations apply to patients during an inpatient stay as well as at the point of admission. Where clozapine is restarted during an admission, it is vital that the speed at which this is done is moderated by consideration of both the potential for toxicity, and the potential for psychiatric relapse. A wish for rapid attainment of pre-cessation dosing is understandable, especially if patients will require enhanced outpatient care (or even inpatient psychiatric admission) if retitration of the dose is not completed by the time of discharge. However, prescribers must take into account the risks associated with rapid dose escalation of clozapine where treatment breaks of 48 h or more have occurred, particularly when patients are also medically compromised. A loss of physiological tolerance to the common side effects of hypotension, tachycardia and drowsiness occurs quickly once plasma concentrations drop, resulting in severe adverse effects if clozapine is reinitiated at high doses without regard to retitration.¹⁷

Few changes were made to clozapine dosing, either on admission or during the inpatient stay. Clozapine plasma concentrations were not routinely measured. This is despite some of the reasons for admission potentially being caused by clozapine toxicity (seizures, collapse, gastrointestinal effects, cardiac symptoms). Furthermore, infection is known to cause clinically significant increases in clozapine plasma concentrations in some patients due to reduction in CYP1A2 enzyme activity during periods of inflammation.¹⁸ For this reason, monitoring of plasma concentrations during periods of severe infection and consideration of temporary dose reduction are recommended by many experts.¹⁹ It is also probable that a significant minority of patients may not be adherent to clozapine in the way their

clinicians believe them to be – in a local study, clozapine was not detected in 1.5% of samples sent for assay, despite patients being prescribed up to 900 mg,²⁰ implying that prescribers believed their patients to be compliant with clozapine when they were not. Sudden increases in clozapine plasma concentrations on restarting the drug at the assumed maintenance dose for the patient may result in significant side effects (e.g. seizure, tachycardia, hypotension), the consequences of which may be even more serious in a patient already medically unwell (and even potentially fatal^{17,21}). This study did not examine the reason for lack of monitoring of clozapine plasma concentrations. It is conceivable that admitting medical clinicians considered doing so but felt it to be unnecessary. It is perhaps more likely that non-psychiatric teams are not aware of the potential problems associated with clozapine toxicity or gaps in treatment. It is also possible that there may be a willingness to measure plasma concentrations, but it is curtailed by organisational barriers to monitoring. Lack of facilities to measure plasma concentrations rapidly severely inhibits the ability of the prescriber to make evidence-based dosing decisions. The advent of point-of-care testing machines that can provide clozapine assay results within minutes has the potential to revolutionise safe use of clozapine in patients who are medically unwell.²² We advocate routine testing of clozapine plasma concentrations for all patients who require medical inpatient care, but caution that results should be interpreted by clinicians with expertise in the use of clozapine.

The majority of patients (54%) were Black, which reflects the population with treatment-resistant schizophrenia in this part of South East London.²³ Half of the patients were female, which is in line with data on hospital admissions in England in 2018 to 2019, where 55% patients were women.²⁴ It is in contrast however to the proportion of female patients taking clozapine in our trust, where 33% of patients taking clozapine are female. It should further be noted that the national statistic includes a large proportion of women admitted to maternity services, a scenario only relevant in one of the cases in our study. It appears therefore that women were over-represented in the admissions for patients taking clozapine in our data set. There are sex differences in the metabolism of clozapine, with women on average attaining 17% higher plasma concentrations on the same dose compared with men.²⁵ We also found higher plasma concentrations on average in

female patients compared with males in our study. This has been shown to lead to a higher body mass index and blood glucose concentrations in women,¹⁵ leading to an increased risk of diabetes²⁶ and presumably other risks associated with increased body weight. Our data do not prove that all admissions observed were linked to clozapine use, either through acute toxicity or chronic adverse effects, but the known differences in metabolism of clozapine in women and our observed differences in numbers of admissions compared with prescribing rates of clozapine in women warrants further investigation.

Across England as a whole, the age group with the highest number of hospital admissions during the study time period was 70 to 74 years, in contrast to the mean age of the patients in this study (50 years). This may be a reflection of the ongoing morbidity and mortality gap for patients with schizophrenia, an illness associated with an average of 14.5 years of potential life loss.²⁷ It is also possible that maintaining patients on clozapine becomes more difficult with advancing age, as multimorbidity and polypharmacy make adverse drug reactions more likely.

Finally, it is worthy of note that our study describes what might be considered a high number of admissions to a single hospital for patients who were taking clozapine. King's College Hospital serves a local population that broadly encompasses the London borough of Southwark. Our study found a total of 58 'local' patients taking clozapine admitted over the course of a year, which represents 20% of the total number of patients in Southwark who are prescribed clozapine ($n=294$). This could be interpreted as one in five patients who take clozapine requiring medical hospital admission during the course of a year. This has two implications: one, that mental health teams that care for patients who take clozapine should be alert to the likelihood of physical illness, particularly respiratory infection, and ensure patients are monitored appropriately and contributory risks modified wherever possible; two, that non-specialist medical clinicians working in general hospitals should expect to see patients taking clozapine frequently. Access to specialist advice regarding the use of clozapine in medically unwell patients is vital, as well as increasing awareness of medical complications of clozapine to internists.

In summary, our study found that the main reason for admission to medical inpatient care for patients taking clozapine was infection. Most patients had

been taking clozapine for many years (median 9 years) at the point of admission, the majority were able to continue taking it for the duration of their medical treatment and were discharged on the same dose they were taking prior to admission. Drug plasma concentrations were not measured routinely despite clozapine having a narrow therapeutic index and enhanced potential for toxicity in the medically unwell patient. We recommend that all patients taking clozapine who are admitted to hospital for medical treatment should have a plasma concentration measured at least at admission, and then as clinically indicated. Clozapine should only be stopped if it is absolutely necessary to do so, and when it is necessary to do so, prescribers must ensure that it is stopped. Prescribers and patients should be aware of the association of clozapine with increased rates of infection, minimise risk factors for this where possible, and ensure timely access to treatment.

Limitations

Data were collected retrospectively from electronic notes systems and are therefore inherently limited to the quality of the notes available. One advantage of our study was that these data were gathered by hand, by expert clinicians familiar with the informatics systems held by both mental health and general medical trust, reducing the likelihood of missed or incorrectly classified data. We did not gather data on medication interactions, or the potential impact of newly started medications during the inpatient admission on the safety and tolerability of clozapine. Further examination of these details may be instructive for improving the safe use of clozapine by non-specialist prescribers. We did not have a comparison group of patients taking non-clozapine antipsychotics – this should be the basis of future work. Our data are from one single hospital in London, limiting the generalisability of the conclusions.

Declarations

Ethics approval and consent to participate

This study involves human participants and was approved by the following institutional boards: Pharmacy Research and Audit Group, King's College Hospital NHS Foundation Trust; Drug and Therapeutics Committee, South London and Maudsley NHS Foundation Trust, reference number DTC 2021/28. Consent to participate was not obtained as this was a retrospective analysis

that did not involve intervention or randomisation and was therefore not applicable to this article (NHS Health Research Authority).

Consent for publication

Not applicable; this submission does not contain individual patient data.

Author contributions

Siobhan Gee: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Vasco Almeida: Data curation, Writing – original draft.

Adam Hughes: Data curation, Writing – review & editing.

Isabel McMullen: Project administration, Supervision, Writing – review & editing.

David Taylor: Methodology, Writing – review & editing.

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Competing interests

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Availability of data and materials

Primary data are not available due to restrictions on patient confidentiality.

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