

Key Words: Antipsychotic agents, schizophrenia, schizoaffective disorder, hospital readmission, patient readmission

Effectiveness of Clozapine use in Delaying Hospitalization in Routine Clinical Practice: A 2 year Observational Study

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ABSTRACT ~ Background: Previous naturalistic observational studies have produced mixed results concerning the effectiveness of clozapine on hospitalization, partly because the decision to place a patient on clozapine versus another antipsychotic has been confounded with the known efficacy of clozapine over other antipsychotics. **Objectives:** To examine the effectiveness of clozapine compared to other antipsychotic drugs in delaying hospitalization in routine clinical practice. **Experimental design:** Consecutive patients with schizophrenia or schizoaffective disorders registered to start on clozapine in one English mental health service over a six-year period were followed up for 2 years from the time of discharge (index admission). Time to hospitalization was used to compare patients started and discharged on clozapine (CG = 126) and those registered to start on clozapine but subsequently discharged on other antipsychotics (OAG = 34) using Kaplan-Meier survival analysis. **Principal observations:** There were more hospitalizations with OAG 13 [38%] than CG = 27 [21%]. Time to hospitalization (25th centile) was 299 days in CG and 136 days in OAG among patients who were successfully discharged from hospital ($\chi^2 = 4.80$, $df = 1$, $p = 0.043$). The time to hospitalization was delayed in CG versus other OAG when baseline differences in age, gender, marital status, previous forensic mental health service, case management and site of initiation were controlled [odds ratio (95% confidence intervals) = 1.87 (1.01, 4.33), $p = 0.048$]. **Conclusion:** Clozapine delays hospitalization in patients with treatment resistant schizophrenia if they are started on clozapine in the community or successfully discharged from hospital following their index admission. *Psychopharmacology Bulletin*. 2010;43(2):63-77.

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INTRODUCTION

Schizophrenia is estimated as the third leading cause of Years of Life lived with Disability (YLDs) worldwide in the age group of 15 to 44 years and seventh leading cause in all ages.¹ The use of antipsychotics in the management of this chronic illness is largely informed by randomised controlled trials (RCTs) looking at either symptom changes, tolerability or compliance measures. These studies may not always be reflective of patients in routine clinical practice, due to restrictive inclusion criteria. Despite good compliance with efficacious antipsychotics as many as 80% of patients with schizophrenia will relapse after five years and around 30% readmitted in 1 year following successful discharge.^{2,3} Amongst the RCTs of clozapine, many have been short to medium-term trials and have been criticised for concentrating on point changes in research scales such as positive and negative symptoms scales (PANSS) and brief psychiatric rating scales (BPRS), rather than clinically meaningful outcomes such as rehospitalization.⁴

In RCTs, clozapine has showed consistent improvements in positive and negative symptoms compared to other antipsychotic drugs, especially in treatment resistant schizophrenia.^{5,6} However, there still remains some uncertainty in relation to clozapine's effectiveness on important and clinical meaningful outcomes such as rehospitalization. A pragmatic open labelled RCT by Essock et al. showed marginal benefits of clozapine over other antipsychotic drugs in rehospitalization rates and an even more substantial benefit on time to rehospitalization.⁷ However even pragmatic RCTs can result in the exclusion of large numbers of patients with treatment resistant schizophrenia and it is possible that clozapine might be less effective in patients who are unable or least willing to give informed consent to participation in a RCT. Therefore the replication of the results of RCTs in observational studies of routine clinical practice involving complete samples of patients with treatment resistant schizophrenia are required.

Observational studies have produced mixed results, with some studies supporting the superiority of clozapine compared to other antipsychotics on rehospitalization, with others raising doubts.⁸⁻¹³ Due to lack of randomization in observational studies, selection bias is likely, as the decision to prescribe clozapine or another antipsychotic may be related to the prescribing physician's perception of treatment efficacy, adverse effects and cost of prescribing. Other studies have also included patients with organic mental disorders as a clinical indication for clozapine, a group of patients with a more refractory course of illness.¹¹ Most of these studies have also failed to control for some important baseline factors likely to affect future hospitalization such as level of previous hospital use and previous contact

with forensic services.¹⁰⁻¹³ Furthermore, these studies were performed in health systems with varying levels of access to free health care and a host of different treatment providers, which limit completeness of data, capture and introduce variability in prescribing practice, resulting in ascertainment and selection bias.

Our hypothesis was that clozapine would be associated with a longer time to next hospitalization compared to other antipsychotic drugs in patients with treatment resistant schizophrenia who are discharged from hospital on clozapine or started clozapine in the community.

MATERIALS AND METHODS

Study Design and Population

All consecutive patients registered on clozapine between 1st January 2000 and 22nd December 2006 within one local mental health service provider in the United Kingdom (Nottinghamshire Healthcare NHS Foundation Trust) with a diagnosis made by the treating psychiatrist of either schizophrenia or schizoaffective disorders (International Classification of Disease 10th revision (ICD-10) – F20 and F25) were included in this two year cohort study. The subjects were aged 18 to 65 years of age at time of clozapine registration. The recommendation by the national guidelines for England and Wales, the National Institute for Health and Clinical Excellence, on the use of clozapine in treatment resistant cases of schizophrenia, was closely adhered to in this service as the policy for routine clinical practice.^{14,15} Clozapine was considered when patients with a firm diagnosis of schizophrenia or schizoaffective disorder had failed to improve or could not tolerate two other antipsychotic drugs, one of which should be a second generation antipsychotic drug other than clozapine, provided that there was no medical contraindication to the prescription of clozapine. There was no restriction on its use because of cost. Patients were excluded from this current study if their primary diagnosis was not schizophrenia or schizoaffective disorder such as a psychosis or disturbed behaviour due to organic brain disease, substance misuse, learning disability, mood disorder or personality disorder.

Nottinghamshire Healthcare NHS Trust (NHNT) is a provider of mental health care to a defined geographical population of approximately 900,000 people with no alternative public provider of services and negligible uptake of private hospital admissions for patients with treatment resistant schizophrenia. The total inpatient bed capacity within the service was 310, for persons of working age in both acute and rehabilitation settings.

Routinely collected data was sought, retrospectively, from the service's pharmacy records and computerised patient database (Patient Information Management System [PIMS]). For clozapine to be prescribed in the United Kingdom all patients need to be registered with clozapine monitoring services before the first prescription is given. This register was also checked to ensure all eligible patients were captured in the study cohort. The study was exempted from patient consent by an independent ethics committee because it used anonymised and routinely collected data.

Allocation to Clozapine or Other Antipsychotic Drug Groups

The sample for the study consisted of all consecutive patients in NHNT with a clinical diagnosis of schizophrenia or schizoaffective disorder in acute or rehabilitation settings who were registered for clozapine use. Thus the decision to prescribe clozapine was not confounded by selection bias concerning the views of the prescriber on the likely effectiveness of clozapine or another antipsychotic drug in a given patient. Subjects discharged on clozapine treatment following discharge from the index hospital admission when clozapine was started made up the *clozapine group* (CG). Subjects registered but not started on clozapine, or clozapine was discontinued for any reason before discharge from hospital, made up the *other antipsychotic group* (OAG). All patients in the OAG group were prescribed an antipsychotic drug other than clozapine such as oral chlorpromazine, sulpiride, haloperidol, risperidone, olanzapine, quetiapine or amisulpride, or long acting injections such as haloperidol decanoate, flupenthixol decanoate, fluphenazine hydrochloride, zuclopenthixol acetate or piportil palmitate. Routine clinical practice was observed and not influenced by the investigators so premature stopping or non compliance to medication, flexible dosing and concomitant use of more than one antipsychotic all took place in the CG and OAG groups over the two year follow up period.

Reasons for stopping clozapine were recorded as patient refusal, side effects, medical contra indications, non-response or unknown. Premature stopping of clozapine included stopping clozapine before discharge from hospital (allocated to OAG), or before rehospitalization (allocated to CG).

STATISTICAL METHODS

Power Calculation

We estimated an effect size of 1.86 on time to hospitalization in CG compared to OAG over two years follow up using available literature.⁷

A total of 183 subjects were needed (120 = CG, 63 = OAG), on the basis of a two-tailed test with $\alpha = 5\%$ and $1 - \beta = 80\%$. Differing numbers of subjects in CG and OAG were based on treatment discontinuation rate of 34% (observed in the literature) in a two-year follow up on patients started on clozapine (CG to OAG = 1:0.53).

Factors Affecting Hospitalization

Baseline factors known to affect hospitalization^{16,17} include demographic (age in years), gender (male vs female), race (White vs non White) and marital status- ever married vs never married), amount of time spent in hospital (in days) in the previous years preceding the index hospitalization and presence of forensic history (present vs absent), as well as intensive case management (Enhanced CPA vs. Non enhanced) following the index admission were all recorded. These were compared between the CG and OAG groups, and between hospitalized and non-hospitalized patients in the two-year follow up using independent t test, Mann Whitney U, Chi square as appropriate for parametric, non parametric and categorical variables.

67Nyakyoma,
Morris

Clozapine Registration in the Community

Clozapine registrations took place in both hospital and community, reflecting routine clinical practice.¹⁸ Community-initiated subjects were assigned *proxy* index discharge dates by imputing the average days (median/mean) between clozapine registration date and discharge date amongst the hospital initiated subjects. Patients started on clozapine while in hospital may have a worse prognosis in terms of hospitalization than those started on clozapine in the community so the site of clozapine initiation (hospital or community) was controlled in the analysis.

Analysis

We used Statistical Package for Social Sciences (SPSS) version 14 to analyse all data. The analysis was confined to patients who were either registered for clozapine treatment during the index hospital admission with successful discharge from hospital (index admission) or patients who were registered for clozapine in the community. This excluded hospital initiated patients who were not successfully discharged from index admission. The odds ratio for hospitalization in the follow-up period in the CG and OAG was calculated in an unadjusted analysis and in an adjusted analysis controlling for variables that differed

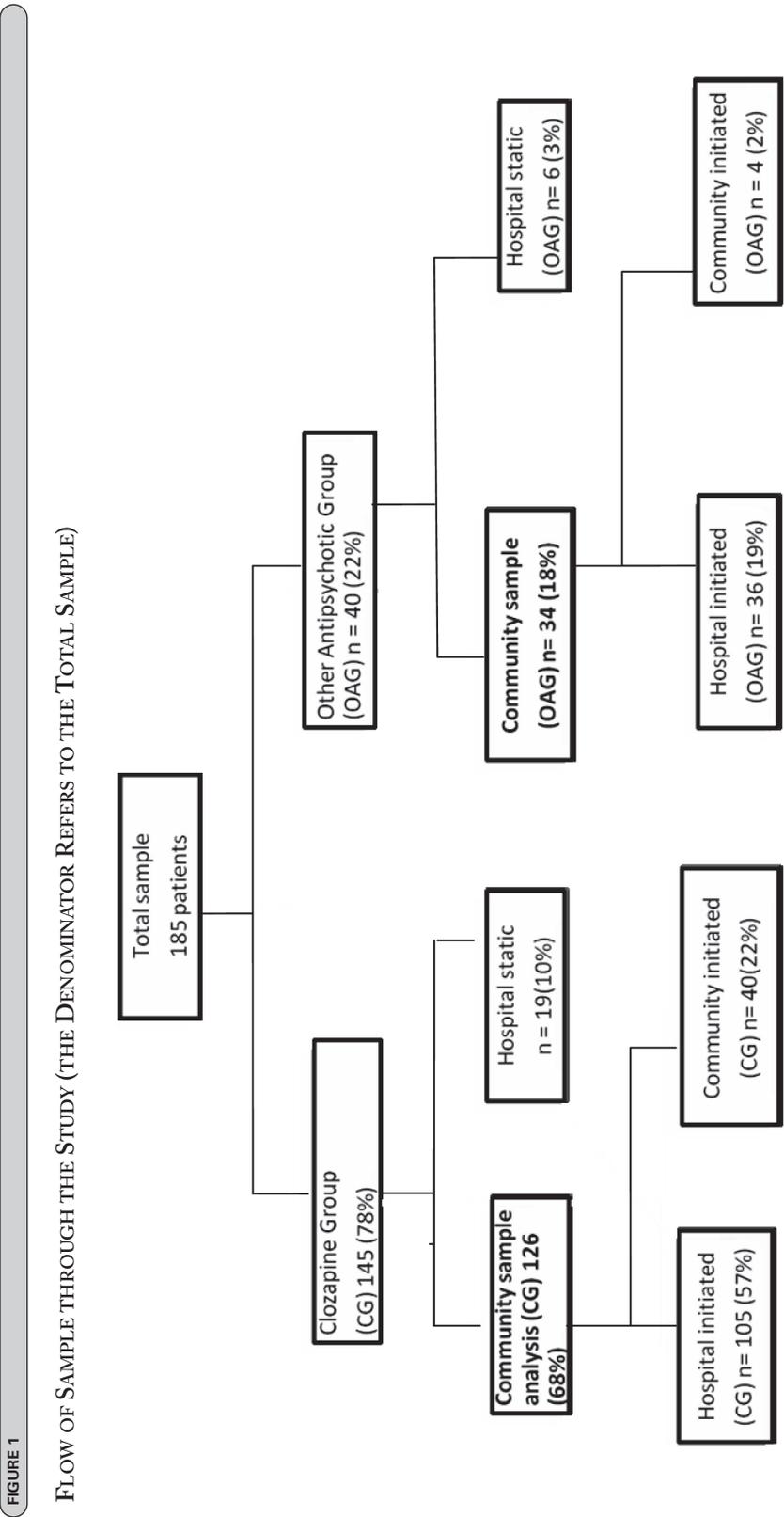
between the two groups at baseline and variables other than medication that were associated with hospitalization in the sample (odds ratio, 95% confidence interval). Time to hospitalization (in days) was compared between CG and OAG using the Kaplan-Meier method of survival analysis (log rank test, $p \leq 0.05$). Cox regression analysis was used to calculate time to hospitalization between CG and OAG to adjust for variables that differed between the two groups at baseline and variables other than medication that were associated with hospitalization in the sample.

RESULTS

The sample consisted of 185 patients with a diagnosis of either schizophrenia ($n = 174$) or schizoaffective disorder ($n = 11$). A further 26 patients were registered for clozapine treatment but were excluded from the sample because they did not have schizophrenia or schizoaffective disorder (25 with organic psychosis and one with emotional unstable personality disorder). A total of 11 (6%) patients registered for clozapine could not be considered because there was insufficient demographic or diagnostic information to ascertain their eligibility for inclusion.

Figure 1 shows how the sample was derived. There were 145 patients in the clozapine group (CG) and 40 patients in the other antipsychotics group (OAG). Of the 185 clozapine registered patients with schizophrenia or schizoaffective disorder in the sample 178 (96%) started on clozapine and 7 (4%) never started clozapine and were allocated to the OAG. Discontinuation of clozapine occurred in 48 (27%) patients in the 178 patients who started clozapine in the two year follow up period. In 33 patients the discontinuation occurred within the index admission, or equivalent period in the community (median clozapine length of treatment in the OAG was 25.5 days [IQR 7.5–68.25]). These subjects made up the total OAG ($n = 40$, 22%). There were no OAG subjects who had clozapine restarted in the follow-up period. Of the remaining 145 subjects, 15 (10%) patients had discontinued clozapine after discharge from hospital or equivalent period in the community (median clozapine length 246 days [IQR 71–335]). The reasons for stopping clozapine were only recorded in 19 (40%) out of 48 patients; seven were for side-effects, four for agranulocytosis, three for neutropenia and five out of patient preference. There were no recorded cases of stopping clozapine because the clinician or patient thought that the drug was not efficacious.

Table 1 shows the demographic and clinical variables of the sample. The mean age of study participants was 36.4 years (18–60 years), with 143 (77%) men and 42 (23%) women. The ethnicity groups included



Note: The main survival analysis was carried out in the community samples highlighted in bold.

CLOZAPINE DELAYS HOSPITALIZATION

TABLE 1

BASELINE CHARACTERISTICS OF CLOZAPINE (CG) AND OTHER ANTIPSYCHOTICS (OAG) GROUPS

	CLOZAPINE GROUP (N = 145)	OTHER ANTIPSYCHOTICS GROUP (N = 40)	STATISTICAL TEST (TWO-TAILED)
Age (s.d.)	35.6 (11.5)	39.3 (11.4)	$t = -1.83$, $df = 183$, $p = 0.068$
Male (%)	111 (77)	32 (80)	$\chi^2 = 3.51$, $df = 1$, $p = 0.061$
Ever Married (%)	27 (19)	7 (18)	$\chi^2 = 0.03$, $df = 1$, $p = 0.871$
Previous forensic contact (%)	30 (21)	15 (38)	$\chi^2 = 4.81$, $df = 1$, $p = 0.028$
2 year pre index hospitalisation (%)	117 (81)	35 (88)	
No. days in hospital (IQR) range	20 (0–96) 0–730	14 (0–131) 0–578	$U = 2034$, $z = -0.061$, $p = 0.951$
Enhanced CPA (%)	62 (43)	11 (28)	$\chi^2 = 3.06$, $df = 1$, $p = 0.08$
Community initiated clozapine registration (%)	40 (28)	4 (10)	Fisher's exact test, $p = 0.021$

Abbreviation: Enhanced CPA = enhanced care programme approach (multidisciplinary case management).

white 143 (77%), black 23 (12%), South Asian 11 (6%), oriental 2 (1%) and mixed/others, 6 (3%). Information recording on PIMS were 100% reliable for diagnoses, demographic data and admission episodes when compared with twenty randomly selected set of medical case notes. This audit also showed the use of clozapine to be consistent with NICE guidelines.^{14,15} Compared to CG, OAG patients showed trends for being slightly older, more often male, and less likely to be on intensive case management (enhanced care programme approach) (Table 1). OAG patients were significantly more likely to have had previous contact with forensic services prior to the index admission, and significantly more likely to be hospital-initiated (Figure 1 & Table 1).

Of the 185 patients in the study, 126 (87%) in the CG and 34 (85%) in the OAG were discharged to the community or started clozapine in the community. Thus the main analysis was carried out in a sample of 160 (86%) patients. The remaining 25 (14%) patients were never discharged from hospital following the index admission where their registration for clozapine started (hospital static group). This group had more subjects

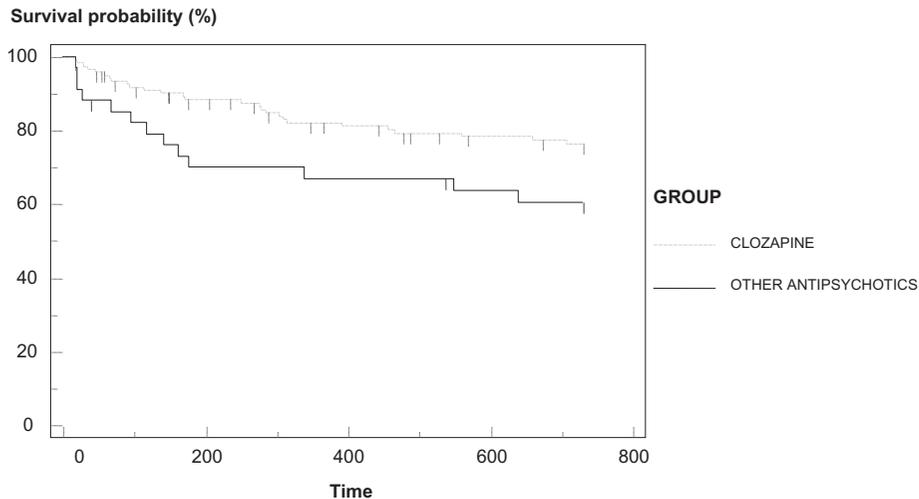
with previous forensic contact than those making up our analysis (12/25 (48%) versus 33/160 (21%), two-tailed $\chi^2 = 8.80$, $df = 1$, $p = 0.003$) but otherwise they did not differ in all other demographic and clinical features.

A total of 137 (86%) of the patients were followed up for a full two-year period, or up to the time to hospitalization in the follow-up period. The remaining 23 (14%) were followed up between 6 and 23 months and were censored at the end of the follow-up period in the survival analysis as they were not hospitalized (Figure 2). The number of patients completing two-year follow-up did not differ between the CG and OAG groups. Forty (25%) patients were readmitted to hospital in the two-year follow up period. Marital status was the only independent factor associated with hospitalization (ever being married were 13/40 (33%), in hospitalized versus 19/120 (16%) in the not hospitalized two-tailed $\chi^2 = 5.06$, $df = 1$, $p = 0.025$).

Patients in OAG were more likely to be hospitalized than CG in the two year follow-up period (OAG 13 [38%], CG = 27 [21%], unadjusted analysis Wald = 3.91, $df = 1$, odds ratio (95% confidence intervals) = 2.27 (1.01, 5.10) $p = 0.048$). When the analysis was adjusted for age,

FIGURE 2

TIME TO REHOSPITALISATION IN PATIENTS ALLOCATED TO CLOZAPINE AND OTHER ANTIPSYCHOTIC AGENTS



Number at risk

Group: CLOZAPINE	126	103	89	81	78
Group: OTHER ANTIPSYCHOTICS	34	23	22	20	19

gender, marital status, community initiation, enhanced care programme approach and previous contact with forensic mental health services, there was a trend for hospitalization to be more likely in OAG than CG (Wald = 3.40, df = 1, odds ratio (95% confidence intervals) = 2.29 (0.95–5.52) $p = 0.065$). Most of these hospitalizations occurred in the first year of follow-up (OAG 11 [32%], CG = 21 [17%]). Premature discontinuation of clozapine in the CG was not associated with earlier hospitalization in the two-year follow-up period (Fisher's exact two-tailed $p = 0.752$).

Time to rehospitalization in the OAG was less than half of that in CG; 25th centile time-to-hospitalization was 136 days in OAG and 299 days in CG (log rank $\chi^2 = 4.80$, df = 1, $p = 0.043$, Figure 2). When a Cox regression analysis controlled for differences between the CG and OAG at baseline and marital status, time to hospitalization remained significantly longer in CG than OAG (Wald = 3.91, df = 1, odds ratio (95% confidence intervals) = 1.87 (1.01, 4.33), $p = 0.048$).

72

Nyakyoma,
Morris

DISCUSSION

Main Findings

This study showed that in routine clinical practice patients with treatment resistant schizophrenia or schizoaffective disorders registered for clozapine treatment, in line with NICE guidelines,^{14,15} spend twice as long in the community when clozapine is continued beyond discharge than when an alternative antipsychotic is introduced. This difference in the two treatment groups remained significant after factors known to affect hospitalization were considered. Such a difference seems clinically significant and may be economically important as the extra cost of clozapine and its monitoring may be offset by economic savings from reduction in hospital bed usage. Cost gains have been reported from reductions of hospital days in cost effectiveness studies of clozapine treatment,^{19–21} although these reductions were not statistically significant in studies where hospital days have been the primary outcome.^{22,23}

Our findings were limited to patients who were successfully discharged following clozapine initiation in hospital. Patients who remained in hospital throughout the six-year study period were not included as part of an intention to treat analysis. Given that our hospital static subjects were more likely to have previous forensic contact, the delayed discharge in our study population may not reflect a lack of

treatment response alone because issues of residential placement and future risk management may also delay discharge.²⁴

Comparison with Other Studies

The effectiveness of clozapine in our observational study is in line with the results of previous pragmatic RCT by Essock et al.⁷ In the latter study the overall intention to treat analysis showed that clozapine was also associated with a longer time to rehospitalization than treatment as usual, but the difference was not statistically significant. However, an analysis confined to patients who were successfully discharged from hospital showed a similar result to our current study with clozapine being more effective than treatment as usual with risperidone and first generation antipsychotic drugs.

Our study conforms to the general trend of lower hospitalization rates seen with clozapine treatment seen both in the UK²⁵ and abroad,^{7-10,12} suggesting that the effectiveness of clozapine is generalizable from our study to other services in the UK and internationally. A large prospective cohort study from Finland⁸ involved 2230 consecutive admitted adults with schizophrenia or schizoaffective disorders, with clozapine having the lowest adjusted relative risk of rehospitalization to oral haloperidol (RR = 0.53 [0.41 to 0.69]), only second to perphenazine depot (RR = 0.45 [0.32 to 0.65]). The study included olanzapine and risperidone amongst the second generation antipsychotics as well as oral first generation antipsychotic drugs such as haloperidol, chlorpromazine, thioridazine and levomepromazine, and depot perphenazine. A one year follow up by Conley et al.¹⁰ in the USA showed patients on clozapine (n = 41) to have longer non-significant time to rehospitalization (246 days) compared to; olanzapine (n = 103, 175 days), risperidone (n = 149, 157.5 days) and fluphenazine decanoate (n = 59, 161.5 days) and haloperidol decanoate (n = 59, 140.5 days).

The findings in some observational studies have not been in favour of clozapine when examining time to rehospitalization as an outcome, against specific antipsychotic agents. Hence, two studies performed in Taiwan and Croatia^{11,13} showed other specific antipsychotic agents such as risperidone and haloperidol were similar to clozapine in terms of time to rehospitalization. In these studies clozapine use was restricted to treatment resistant schizophrenia with a relatively poorer outcome whereas the use of other antipsychotic drugs was not restricted. Therefore these studies were open to indication bias that might have underestimated the effectiveness of clozapine.

Study Strengths and Limitations

This was the first observational study which looked at the effectiveness of clozapine in reducing time to hospitalization in patients with treatment resistant schizophrenia who meet clinical threshold for clozapine use, minimising the potential indication bias seen in some previous studies. Almost all patients who were eligible were included and unlike a RCT there were no exclusions of patients who were unwilling or unable to consent who may have had a worse prognosis compared to those who consent in RCTs. The design involved the use of readily available data through routine data collection of computerised records with perfect agreement with data from medical case notes in a retrospective audit. There was very little loss of follow-up data (six per cent) and the use of a hard outcome data point recorded with great accuracy (rehospitalization) resulted in a study with high internal validity and clinical relevance.

This study considered routine clinical practice in one UK health service provider so there are limitations on its generalizability. Our findings may not be reflective of clozapine use in other health settings and indeed other countries where clinical guidelines on clozapine use and, level of free hospital and community resources may be different. Our study used time to hospitalization as an outcome that could be measured accurately from routine data collection. However, there are other outcome measures of clinical interest which influence antipsychotic prescribing such as symptom control, side effects, compliance and quality of life measures that were not considered here.

The choice of our comparison group may have exaggerated the effectiveness of clozapine as the reasons for stopping clozapine in both CG and OAG was not always revealed. It is possible that clinicians might stop clozapine if they perceived it to be ineffective and to expose patients to higher medical risk from side-effects such as agranulocytosis. Therefore the clozapine group would be open to selection bias as it would exclude patients who are not expected to respond well to clozapine who may also respond poorly to any antipsychotic drug. While such selection bias cannot be ruled out, the short course of clozapine treatment, less than eight weeks, in most of our comparison group suggests treatment non response was unlikely to be the reason for discontinuation of clozapine.²⁶ The OAG consisted of patients taking a number of different antipsychotic agents, potentially increasing variability in outcome and possibly reducing the chance of a sustained treatment effect in those patients who had a number of changes of antipsychotic agent. The former would reduce the chances of demonstrating the effectiveness of clozapine while latter may inflated the effect size of clozapine.

Our study did not measure the reported effects of sudden clozapine discontinuation reported in some studies.^{27,28} This effect was only likely to impact the four (10%) of the OAG patients whose clozapine treatment started in the community. However, similar clinical thresholds for discharge apply in routine clinical practice whether the patient is taking clozapine or other antipsychotic agents, suggesting that any residual symptoms in the hospital initiated OAG who stopped clozapine would not have significantly differed from the hospital initiated clozapine group, who were maintained on clozapine.

The potential nursing and clinical time associated with the administration of clozapine during follow up was not measured in our study. The Essock et al.⁷ study found little impact when this factor was controlled. It is possible that the decision to discharge a patient on clozapine might be perceived as a reason for the need for more intensive follow up because of medical risks of treatment or less follow-up because the clinicians perceive clozapine to be more effective than other antipsychotic agents so less nursing and clinical follow-up is required. Our study was not a randomized controlled trial so there is a danger that the provision of after care services and decisions on readmission might have been biased by the knowledge whether a person was taking clozapine or not. The expectancy effect of a more optimistic outcome with clozapine treatment might be conveyed by clinicians and nursing staff to patients who in turn tolerate their symptoms better and do not seek re-hospitalization. More exploration is required from future studies.

Our study did not look at differing treatment doses or number of concomitant antipsychotics and other psychotropic medication used in the two groups. There is a possibility of confound from additional treatment and this might differentially effect treatment groups²⁹ although there is little evidence so far that concomitant medication delays or increases time to re-hospitalization.

Research Implications

Larger prospective multicentre observational studies looking at the effect of clozapine use to prolong community stay in routine clinical practice should be undertaken so that the results can be seen to be generalizable and due to clozapine rather than service organisation. These studies would carry more authority if complete datasets were obtained from services which captured virtually all patients in a defined geographical area as we have employed in the current study. Furthermore it is important that there are clear guidelines for clozapine and other antipsychotic use which do not introduce indication bias into the study, strength of the current study and a limitation of other studies.

CONCLUSION

Clozapine use in our study was effective in delaying hospitalization once patients were successfully discharged. Patients who were more likely to benefit were those in-patients who had no history of forensic contact. In general, our study supports the National Institute for Health and Clinical Excellence guidelines in the United Kingdom on the management of schizophrenia^{14,15} which emphasize on the use of clozapine as soon as patients have had non-satisfactory clinical response to two or more antipsychotics, one of which should be a non clozapine second generation antipsychotics. ❖

COMPETING INTERESTS

Neither author has any competing financial or non-financial interests to report.

AUTHORS' CONTRIBUTION

KN first conceptualised the study, collected the data, carried out the analysis and wrote the first draft of the paper. RM advised on the design, supervised the data collection and analysis, and commented on all drafts of the paper.

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