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Medical, Psychiatric, and Sociodemographic Predictors of Clozapine Initiation at an Academic Medical Center

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Background and Hypothesis: Clozapine is an effective yet underutilized treatment for treatment-resistant schizophrenia spectrum disorders. This study aimed to identify factors affecting clozapine prescribing patterns among patients with treatment-resistant schizophrenia and schizoaffective disorder at an academic medical center.

Study Design: This retrospective combined cohort and case-control study examined demographic, socioeconomic, medical and psychiatric characteristics to determine predictors of clozapine initiation. Eligible patients had a diagnosis of schizophrenia or schizoaffective disorder with at least two prior antipsychotic trials and were admitted to a University of Utah inpatient psychiatric facility (1/2014–3/2021). Patients who did and did not receive clozapine during the index hospitalization were compared in cohort and case-control study arms.

Study Results: Twelve percent (59/477) of the cohort received clozapine during the index admission. Among the cohort (n = 477), Black patients were twice as likely to receive clozapine than White and Hispanic patients (OR 2.18, 95% CI 1.20–3.97, p = 0.008). In the case-control analysis, patients with a greater number of previous psychiatric admissions (OR 1.14, p = 0.079) and antipsychotic trials (OR 1.40, p = 0.038) had greater odds of receiving clozapine. Homelessness was identified as a predictor against clozapine use (OR 2.77, p = 0.014).

Conclusions: This is the first study to identify homelessness as a predictor against clozapine use, which raises important clinical and ethical considerations. Our findings also add to the literature on clozapine prescribing discrepancies among ethnic-minority patients. Overall, clozapine remains underutilized as the gold-standard treatment for treatment-resistant schizophrenia-spectrum disorders, reinforcing a need to improve evidence-based prescribing.

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Schizophrenia is a costly and disabling mental illness which affects 1% of adults in the United States (1). Antipsychotic medication is the cornerstone of treatment for schizophrenia, with the aim of reducing symptoms and improving quality of life. However, one in three patients are treatment-resistant, meaning that they do not respond to traditional antipsychotic medications (2). Clozapine, a second-generation antipsychotic, is the gold-standard therapy for treatment-resistant schizophrenia. A trial of clozapine is recommended in patients who have failed adequate trials of two other antipsychotics per current guidelines (3–5). This recommendation is based on the superiority of clozapine to other antipsychotics in symptom reduction, time to discontinuation, number of psychiatric inpatient days, and overall healthcare costs (6–11).

Despite its effectiveness, clozapine is universally underutilized. A growing body of evidence suggests that the etiology of clozapine underutilization is multifactorial, with various patient, prescriber, and institutional-related barriers to use (12–14). Association with risk of agranulocytosis

HIGHLIGHTS

- Clozapine remains universally underutilized as the gold-standard therapy for treatment-resistant schizophrenia spectrum disorders.
- Among a cohort of hospitalized adults with treatment-resistant schizophrenia or schizoaffective disorder, only 12% of patients received clozapine.
- Black patients were twice as likely to be prescribed clozapine. Our findings add to a growing body of evidence of differential antipsychotic prescribing patterns among minority racial-ethnic groups.
- Patients who were homeless at the time of admission were significantly less likely to receive clozapine. Timely, effective treatment for the severely mentally ill may be necessary to alleviate symptoms that sustain homelessness.
- Clozapine prescribing rates and patterns are highly variable across the US; interventions to improve utilization may vary by region.

has indicated frequent monitoring of blood counts in patients who receive clozapine in the United States and Europe (3). This monitoring increases both patient and provider burden and may limit the use of clozapine (6, 15). In addition, prescribing rates and patterns are highly variable across the United States (16–18). Thus, interventions to improve clozapine utilization may vary by region.

Given these findings, the current study aimed to capture clozapine prescribing rates and patterns in patients admitted to University of Utah inpatient psychiatric facilities to facilitate interventions to increase clozapine use in patients with treatment-resistant schizophrenia-spectrum disorders.

METHODS

Patients

This retrospective combined cohort and case-control study was conducted at the University of Utah after approval by the University of Utah Institutional Review Board. The study population consisted of adult patients with a diagnosis of schizophrenia or schizoaffective disorder who were admitted to a University of Utah inpatient psychiatric facility (University of Utah Health Unit 5W or Huntsman Mental Health Institute, previously known as University Neuropsychiatric Institute) between January 1, 2014 to March 1, 2021 and who had had two or more previous antipsychotic trials according to medical record prescribing data. Patients were identified using the University of Utah's health system data repository (Enterprise Data Warehouse), International Classification of Diseases discharge diagnosis codes, and inpatient and outpatient prescription records. The study had no exclusion criteria.

Study Design

This study included cohort and case-control study arms. All eligible patient encounters were included in the cohort study arm to identify predictors of clozapine use. A case-control analysis was conducted to determine sociodemographic factors affecting clozapine prescription. Eligible case patients were defined as those who had been prescribed clozapine during the index hospitalization, whereas control patients had not. Patients were randomly selected from the cohort for age, gender, and race with a 1:1 control-to-case ratio.

Data Collection

Data were extracted automatically via the electronic medical record (EMR) for the cohort study arm. Additional clinical and sociodemographic variables contained in clinical text were manually extracted via retrospective chart review for the case-control study arm. Manual data were extracted by two independent raters. Where manually extracted data were discrepant, a third rater reviewed the chart to break the tie. All data were stored in a Research Electronic Data Capture database.

Demographic and socioeconomic data included age, gender, ethnicity, race, marital status, employment status, insurance type, county of residence, housing status, and distance from home address to the University of Utah to estimate access to services and urbanicity. Medical history included body mass index (BMI), HgbA1c and smoking status. Psychiatric history, including diagnosis, previous antipsychotic trials, number of psychiatric admissions before and after index admission, time to readmission, substance use history, and history of suicidal, self-injurious, or violent behaviors were collected. Index hospitalization-specific data included the presence of suicidal ideation or behavior at admission, adverse events, use of temporary hold, need for involuntary commitment, and use of medication over objection. Potential contraindications to clozapine use, such as history of seizure or myocardial infarction, were recorded. For the case-control study, adverse effects of clozapine were collected.

Statistical Analysis

Statistical analysis was conducted with the SAS System for Windows version 9.4 (Copyright © 2016, SAS Institute Inc.). For manually extracted variables, inter-rater reliability was calculated using Fleiss's kappa for multiple raters and ranged from 0.72 (for number of prior antipsychotic trials) to 0.92 (for history of substance use).

For both studies, *t*-tests were used to assess whether means of continuous variables differed between groups, and Chi-square tests were used to assess whether frequencies of categorical variables differed between groups. An alpha of 0.05 was selected a priori for assessing statistical significance. In the case-control study, logistic regression models were employed to evaluate whether clinical and demographic factors with univariable significance were associated with case status.

In the cohort study, visit data were assessed for missingness. Missing data were imputed using means (for continuous variables) or modes (for categorical variables) from existing data for each variable. Logistic regressions were used to identify clinical and demographic predictors of clozapine initiation treated as a binary variable. Linear mixed models controlling for clinical and demographic confounds that had univariable significance were used to evaluate associations between clozapine use treated as a predictor variable and key clinical outcomes such as length of stay, time to readmission, and number of readmissions. Models were refined by addition and removal of covariates to minimize the Aikake information criterion.

RESULTS

Cohort Study

In our linear mixed models of the associations of clinical outcomes with clozapine use, we identified 477

hospitalized patients who met criteria for treatment-resistant schizophrenia or schizoaffective disorder. Of this cohort, 59 patients received clozapine during the index hospitalization and 418 patients did not.

Clozapine recipients (CR) and non-recipients (CNR) were demographically similar. Participants were predominantly middle-aged (mean 50.86 ± 10.10 years for both groups, 50.52 ± 8.66 years CR, 50.90 ± 10.29 years CNR; $t = 0.27, p = 0.79$), male (61.64% for both groups, 64.41% CR, 61.24% CNR; $\chi^2 = 0.22, p = 0.64$), and Caucasian (87.21% for both groups, 84.75% CR, 87.56% CNR; $\chi^2 = 0.37, p = 0.54$), with no difference between CR and CNR groups for these characteristics (Table 1). Overall, 11.95% of patients were Hispanic and 2.73% were Black. Those who identified as Hispanic were similarly represented between groups (6.78% CR, 12.68% CNR; $\chi^2 = 1.71, p = 0.19$), whereas Black patients were disproportionately prescribed clozapine (8.47% CR, 1.91% CNR; $\chi^2 = 8.39, p = 0.0038$).

A majority of both CR and CNR patients were unmarried (9.43% married for both groups, 6.78% CR, 9.81% CNR; $\chi^2 = 0.56$, $p = 0.46$) and unemployed (11.11% employed for both groups, 16.95% CR, 10.29% CNR; $\chi^2 = 1.32$, $p = 0.13$). Nearly all lived in Salt Lake County (94.5% for both groups, 91.49% CR, 97.50% CNR; $\chi^2 = 1.44$, $p = 0.23$). At the time of admission, 11% of CR and 21% of CNR patients were homeless ($\chi^2 = 2.86$, $p = 0.097$). A majority of both groups were publicly insured (88.26% for both groups, 83.22% CR, 87.56% CNR; $\chi^2 = 1.6$, $p = 0.21$), with 0% of CR and 3.83% of CNR ($\chi^2 = 2.34$, $p = 0.13$) uninsured at the time of admission.

Tobacco use was highly prevalent among the cohort, with current smoking history reported in 83% of CR and 86% of CNR ($\chi^2 = 0.28$, $p = 0.60$). One in four patients reported current alcohol use (23.69% for both groups, 16.95% CR, 24.64% CNR; $\chi^2 = 1.69$, $p = 0.19$). CR and CNR exhibited similar BMI (28.62 ± 7.41 kg/m^2 for both groups, 29.23 ± 6.14 kg/m^2 CR, 28.53 ± 7.59 kg/m^2 CNR; $t = -0.66, p = 0.51$) and hemoglobin A1c (HgbA1c) (5.94 ± 1.29% for both groups, 6.3 ± 1.68% CR, 5.87 ± 1.21% CNR; $t = -1.6, p = 0.11$).

On average, CR and CNR groups both had 5 psychiatric admissions preceding index admission (mean 5.19 CR, 4.95 CNR; $t = -0.31$, $p = 0.76$). Duration of index hospitalization was 13 days longer in the CR group, lasting an average of 29 versus 16 days ($t = -5.0$, $p < 0.0001$). After index hospitalization discharge, CR and CNR groups had a similar number of readmissions overall (3.52 ± 5.09 CR, 5.29 ± 10.23 CNR; $t = 1.09$, $p = 0.27$) and within 1 year of discharge (1.83 ± 3.18 CR, 2.53 ± 4.61, $t = 0.95$, $p = 0.34$). However, time to hospital readmission after index hospitalization was over 200 days longer in the CR group

TABLE 1. Sociodemographic, psychiatric, medical, and index admission characteristics among a hospitalized cohort of treatment resistant schizophrenia-spectrum patients who did and did not receive clozapine at index admission.

	All patients (n = 477) Mean (SD) or %	Clozapine recipients (n = 59) Mean (SD) or %	Clozapine non-recipients (n = 418) Mean (SD) or %	T or χ^2	p
Sociodemographic characteristics					
Age (years)	50.86 (10.1)	50.52 (8.66)	50.9 (10.29)	0.27	0.79
Gender (% male)	61.64	64.41	61.24	0.22	0.64
Race					
Caucasian	87.21	84.75	87.56	0.37	0.54
Hispanic	11.95	6.78	12.68	1.71	0.19
Black	2.73	8.47	1.91	8.39	0.0038
Married	9.43	6.78	9.81	0.56	0.46
Employed	11.11	16.95	10.29	1.32	0.13
Homeless	20.13	11.86	21.29	2.86	0.097
Salt Lake County resident	94.5	91.49	97.5	1.44	0.23
Insurance					
Public insurance	88.26	83.22	87.56	1.6	0.21
Uninsured	3.35	0	3.83	2.34	0.13
Psychiatric and social history					
Previous admissions (#)	4.98 (5.08)	5.19 (4.22)	4.95 (5.21)	−0.31	0.76
Substance use history					
Tobacco use	85.32	83.05	85.65	0.28	0.6
Alcohol use	23.69	16.95	24.64	1.69	0.19
Medical history					
BMI (kg/m^2)	28.62 (7.41)	29.23 (6.14)	28.53 (7.59)	−0.66	0.51
HgbA1c (%)	5.94 (1.29)	6.3 (1.68)	5.87 (1.21)	−1.6	0.11
Index admission					
LOS (days)	17.87 (19.32)	29.36 (25.16)	16.24 (17.79)	−5	<0.0001
Discharge to readmit (days)	293.62 (393.74)	472.48 (593.92)	268.64 (351.82)	−2.73	0.0067
Readmissions (#) total	5.05 (9.72)	3.52 (5.09)	5.29 (10.23)	1.09	0.27
Readmissions (#) within year after discharge	2.10 (3.54)	1.83 (3.18)	2.53 (4.61)	0.95	0.34

Abbreviation: LOS, length of stay.

(472.48 ± 593.92 days CR, 268.84 ± 351.82 days CNR; $t = -2.73$, $p = 0.0067$).

Subgroup analysis revealed that Black patients were twice as likely to receive clozapine (OR 2.18, 95% CI 1.20–3.97, $p = 0.0084$) (Table 2). There was a trend, which did not achieve statistical significance with our sample size, towards an inverse relationship between homelessness and receiving clozapine (OR 0.70, 95% CI 0.46–1.07, $p = 0.097$) (Table 2). Unemployment (OR 1.40, 95% CI 0.94–2.10, $p = 0.086$) and receiving public insurance (OR 1.54, 95% CI 0.88–2.69, $p = 0.12$) had no apparent effect on clozapine prescription.

Case-Control Study

To further explore predictors of clozapine prescription, we identified 40 hospitalized patients who were prescribed clozapine (cases) and 47 patients who were not prescribed clozapine (controls) after matching for age, gender, and race. All patients met criteria for treatment-resistant schizophrenia or schizoaffective disorder.

CR and CNR had similar sociodemographic characteristics. The majority of CR and CNR at time of index admission were unmarried (10% vs. 6.38% married; $\chi^2 = 0.38$, $p = 0.54$) and unemployed (12.50% vs. 10.64% employed; $\chi^2 = 0.074$, $p = 0.79$) (Table 3). A vast majority of all patients lived within the local urban county (98% CR, 92% CNR; $\chi^2 = 1.44$, $p = 0.23$). Accordingly, there was no difference in proximity to the index psychiatric hospital (10.79 ± 4.71 miles CR vs. 17.10 ± 38.02 miles CNR; $t = -1.04$, $p = 0.30$). CR and CNR had similar rates of homelessness based on EMR flagging system (15% vs. 21.28%; $\chi^2 = 0.57$, $p = 0.45$). However, manual review of charts revealed a substantially lower rate of homelessness in the CR group compared to the CNR group (5% CR vs. 21% CNR; $\chi^2 = 9.96$, $p = 0.0016$). There was no difference between groups in public insurance rate (92% CR and CNR; $\chi^2 = 0.03$, $p = 0.86$), and few patients lacked health insurance (0% CR vs. 2.13% CNR; $\chi^2 = 0.86$, $p = 0.35$).

Past psychiatric history did reveal notable differences between CR and CNR groups. CR had more past antipsychotic trials (4.78 ± 1.87 CR vs. 3.70 ± 1.60 CNR; $t = 2.88$, $p = 0.0050$) and nearly twice as many previous psychiatric admissions as CNR (5.13 ± 4.73 CR vs. 2.79 ± 3.02 CNR; $t = 2.79$, $p = 0.0066$). Cases and controls had similarly high rates of historical medication non-adherence (70% vs. 65.96%; $\chi^2 = 0.16$, $p = 0.69$). No differences between groups were found for prior suicide attempts (37.5% vs. 42.55%; $\chi^2 = 0.23$, $p = 0.63$), self-injurious behavior (20% vs. 25.53%; $\chi^2 = 0.37$, $p = 0.54$), violent behavior (35% vs. 27.66%; $\chi^2 = 0.054$, $p = 0.46$) or incarceration (40% vs. 34.04%; $\chi^2 = 0.33$, $p = 0.57$).

CR and CNR had a similar pattern of current and prior substance use. Tobacco use was highly prevalent (87.5% vs. 91.49%; $\chi^2 = 0.37$, $p = 0.54$). Also common were current alcohol use (17.5% vs. 21.28%; $\chi^2 = 0.20$, $p = 0.66$) and other substance use (37.5% vs. 29.79%; $\chi^2 = 0.58$, $p = 0.45$). Most patients reported a lifetime history of any substance use disorder (68% CR vs. 55% CNR; $\chi^2 = 1.35$, $p = 0.25$).

CR and CNR had similar biomarkers of metabolic health, including BMI (29.22 ± 6.10 kg/m^2 vs. 27.65 ± 5.54 kg/m^2; $t = 1.24$, $p = 0.22$) and hemoglobin A1c (6.27 ± 1.68% vs. 5.68 ± 0.74%; $t = 1.37$, $p = 0.18$).

During the index admission, patients who received clozapine had on average a 10-day longer hospital course (25.99 ± 22.97 days CR vs. 16.05 ± 12.80 days CNR; $t = 2.54$, $p = 0.013$). No other parameters during the index hospitalization differed between groups. At the time of index admission, one in three patients had suicidal behavior or ideation (27.5% vs. 34.04%; $\chi^2 = 0.43$, $p = 0.51$). While half of patients were voluntary on admission ($\chi^2 = 0.17$, $p = 0.68$), 44% of CR and 55% of CNR received a petition for involuntary commitment ($\chi^2 = 1.17$, $p = 0.28$) and 38% of patients in each group were involuntarily committed ($\chi^2 = 0.0058$, $p = 0.94$). About 15% in both groups required involuntary treatment ($\chi^2 = 0.00020$, $p = 0.99$) during the index hospitalization. CR patients exhibited a trend towards a higher rate of serious adverse events throughout hospitalization, but this difference failed to achieve statistical significance (7.50% CR vs. 2.13% CNR; $\chi^2 = 1.42$, $p = 0.23$).

Overall, we identified three key predictors of clozapine prescription using logistic regression analysis. Patients with a greater number of previous psychiatric admissions (OR 1.14, 95% CI 0.98–1.32, $p = 0.079$) and antipsychotic trials (OR 1.40, 95% CI 1.00–1.96, $p = 0.038$) were more likely to receive clozapine (Table 4). Homelessness was identified as a negative predictor of clozapine use, with homeless patients having reduced odds of receiving clozapine during the index admission (OR 2.77, 95% CI 1.24–6.19, $p = 0.014$).

DISCUSSION

This retrospective study examined the use of clozapine among hospitalized adults diagnosed with treatment-resistant schizophrenia or schizoaffective disorder. We

TABLE 2. Predictors of clozapine initiation at index admission among the cohort.

	B	SE	DF	Wald χ^2	*p*	OR	95% CI
Black	0.78	0.3	1	6.95	0.0084	2.18	1.20–3.97
Employed	0.34	0.2	1	2.94	0.086	1.40	0.94–2.10
Homeless	−0.35	0.21	1	2.76	0.097	0.70	0.46–1.07
Public insurance	0.43	0.28	1	2.41	0.12	1.54	0.88–2.69

TABLE 3. Sociodemographic, psychiatric, medical, and index admission characteristics among clozapine recipients (cases) and non-recipients (controls).

	Cases Clozapine recipients (n = 40) Mean (SD) or %	Controls Clozapine non-recipients (n = 47) Mean (SD) or %	T or χ^2	p
Sociodemographic characteristics				
Age (years)	52.45 (7.78)	52.7 (8.98)	−0.14	0.89
Race				
Caucasian	87.5	95.74	1.98	0.16
Hispanic	5	8.51	0.41	0.52
Black	7.5	4.26	0.42	0.52
Married	10	6.38	0.38	0.54
Employed	12.5	10.64	0.074	0.79
Homeless (flag)	15	21.28	0.57	0.45
Homeless (manual)	5	31.91	9.96	0.0016
Salt Lake County resident	97.5	91.49	1.44	0.23
Distance from HMHI (miles)	10.79 (4.71)	17.1 (38.02)	−1.04	0.3
Insurance				
Public insurance	92.5	91.49	0.03	0.86
Uninsured	0	2.13	0.86	0.35
Psychiatric and social history				
Previous admissions (#)	5.13 (4.73)	2.79 (3.02)	2.79	0.0066
Previous antipsychotic trials (#)	4.78 (1.87)	3.7 (1.6)	2.88	0.005
Past suicide attempt	37.5	42.55	0.23	0.63
History of self-injurious behavior	20	25.53	0.37	0.54
Past medication non-adherence	70	65.96	0.16	0.69
History of violent behavior	35	27.66	0.054	0.46
History of incarceration	40	34.04	0.33	0.57
Substance use history				
Tobacco use	87.5	91.49	0.37	0.54
Alcohol use	17.5	21.28	0.2	0.66
Current substance use	37.5	29.79	0.58	0.45
Lifetime substance use disorder	67.5	55.32	1.35	0.25
Medical history				
BMI (kg/m^2)	29.22 (6.1)	27.65 (5.54)	1.24	0.22
HgbA1c (%)	6.27 (1.68)	5.68 (0.74)	1.37	0.18
Index admission				
LOS (days)	25.99 (22.97)	16.05 (12.8)	2.54	0.013
Suicidal behavior present on admit	27.5	34.04	0.43	0.51
Voluntary on admit	48.72	53.19	0.17	0.68
Petition for involuntary commitment	43.59	55.32	1.17	0.28
Involuntary commitment	37.5	38.3	0.0058	0.94
Involuntary treatment	15	14.89	0.0002	0.99
Serious adverse events	7.5	2.13	1.42	0.23

Abbreviation: HMHI, psychiatric hospital.

TABLE 4. Independent variable's effect on clozapine initiation, controlled by age, gender and race.

	B	SE	DF	Wald χ^2	p	OR	95% CI
Previous admissions (#)	0.13	0.075	1	3.08	0.079	1.14	0.98–1.32
Previous AP trials (#)	0.34	0.17	1	4.31	0.038	1.40	1.00–1.96
Homelessness	1.02	0.41	1	6.03	0.014	2.77	1.24–6.19

Abbreviation: AP, antipsychotic.

conducted a comprehensive analysis of medical, psychiatric, and sociodemographic factors influencing clozapine initiation during psychiatric hospitalization within a single academic healthcare institution over a 7-year period. Our analysis incorporated both cohort and case-control study designs, combining the benefits of each approach to identify general associations and specific sociodemographic predictors of interest. We found that race, homelessness, and number of prior psychiatric admissions and antipsychotic trials modified clozapine prescribing patterns. Our findings also revealed the underutilization of clozapine among eligible patients.

The first important outcome was how housing status impacted clozapine prescribing patterns. Patients who were homeless at time of hospitalization, as determined by manual search, were less likely to be prescribed clozapine than stably housed individuals. To our knowledge, housing status has not been previously described as a predictor against clozapine initiation, which raises important ethical and clinical considerations. Prescribers may be less likely to prescribe clozapine to homeless patients due to anticipated medication non-adherence or loss to follow-up. However, previous studies of clozapine prescribing barriers consistently find that prescribers overestimate adverse effects, the likelihood of non-adherence, and the burden of monitoring requirements for patients (12–14, 19). Clinicians also underestimate patient satisfaction with clozapine treatment (14, 20). It must also be considered that severe, poorly controlled mental illness and delay to effective treatment increase the likelihood of homelessness, while clozapine treatment may be necessary to alleviate symptoms that sustain homelessness. In this sense, consideration of early clozapine initiation in eligible patients is particularly important in this patient population.

The second factor revealed in the present study was how clozapine prescribing patterns differ across racial-ethnic groups. Black patients were more likely to be prescribed clozapine, accounting for 8% of CR despite representing 3% of the total cohort. Caucasian or Hispanic race, alternatively, did not alter clozapine initiation. The existing data on racial-ethnic disparities in antipsychotic prescribing is mixed, with an interesting divide between the use of clozapine and other antipsychotics, which complicates the interpretation of our findings. Multiple studies report an overuse of antipsychotics in Black patients (21–23). In comparison to Caucasian patients, Black patients with schizophrenia are more likely to receive oral and long-acting injectable first-generation antipsychotics and oral second-generation antipsychotics (23, 24). On the other hand, the majority of studies on clozapine use have demonstrated *underutilization* in ethnic minority groups. In a 2020 systematic review, all 16 studies reported clozapine underutilization in minority patients as compared to Caucasian patients in the US (25). This prescribing discrepancy remained after controlling for length of hospital stay, institutional setting, and disease severity. An additional systematic review that included international studies of clozapine prescribing disparities drew similar conclusions (26). Our current results are consistent with the literature on antipsychotic prescribing patterns, yet contradict the general consensus on clozapine prescribing patterns in minority patients. The reason for this is unclear, though confounding by medical comorbidity may play a role. A greater incidence of benign ethnic neutropenia (BEN), cardiovascular and metabolic comorbidities have been proposed as contributors to underutilization among Black and African-American patients (27, 28). It is worth noting that no analyses accounted for BEN in the aforementioned systematic review studies. Although we did not specifically control for these potential confounders, post-hoc analysis of our data found no difference in contraindications to clozapine, including history of neutropenia, diabetes, and cardiovascular disease, between recipients and non-recipients. The impact of comorbidities on clozapine prescribing patterns across racial-ethnic groups remains unclear, and is an area of research ripe for investigation.

Our study found no relationship between clozapine initiation and history of suicide attempt, violent behavior, or substance use. This is unexpected given that clozapine is FDA-approved for reducing suicidal behavior in schizophrenia-spectrum disorders. There is also some evidence for clozapine in reducing aggressive behavior (29, 30) and potential benefits in patients with comorbid substance use disorders (31, 32). Prescribers may be unaware of these indications for clozapine use, and could be a point of intervention.

The present study revealed clozapine underutilization among all patients despite eligibility. Just 12% of the cohort received clozapine during the index admission. In our case-control study arm, clozapine initiation was correlated with a greater number of prior psychiatric admissions and antipsychotic trials. Specifically, cases had an average of five previous admissions and five medication trials preceding clozapine initiation. Of note, some patients had been prescribed clozapine among prior medication trials. It may be fruitful for future research to investigate how prior trials of clozapine affect the likelihood of a future retrial. It is feasible that nonadherence due to adverse effects may reduce the likelihood of a retrial, whereas cessation of clozapine for other reasons could conceivably increase the likelihood of a retrial. Our findings agree with existing literature indicating that clozapine is underutilized and its prescription onset delayed in the US. Stroup et al. (16) reported that 5.5% of patients with treatment-resistant schizophrenia were prescribed clozapine in a retrospective study using national Medicaid claims data from 2002 to 2005, while Baries et al. (17) found a 1%–11% clozapine prescription rate across states using 2011–2012 data. Moreover, Howes et al. found an average of five antipsychotic trials before initiation of clozapine, causing a mean delay of 4 years (2). These findings are important to emphasize since patients who receive clozapine earlier in the disease course are more likely to respond. A large Danish database study found that a greater number of previous antipsychotic trials and admissions prior to clozapine initiation were independent predictors of negative clinical outcomes (33). Treatment-resistant schizophrenia patients who initiated clozapine earlier than 2.8 years in the disease course had an 82% response rate, while patients initiated after 2.8 years had a 31% response rate (34). This suggests a critical successful treatment window with clozapine.

There are several limitations to consider in interpreting these findings. The retrospective nature of the study and reliance on ICD-10 coding for diagnosis of treatment-resistant schizophrenia or schizoaffective disorder introduces inherent limitations. Exclusion of patients who had previously trialed clozapine and did not receive a retrial due to inefficacy or intolerance would have improved study validity. Additionally, this study focused on clozapine initiation during the index admission only; outcomes such as symptom response to clozapine and outpatient medication adherence, while important, were beyond the scope of the present analysis. Common comorbidities among minority patients were not taken into account in the analysis. Finally, patients were selected from a single academic institution in a geographic region with limited racial-ethnic diversity, which may limit the generalizability of these findings.

CONCLUSIONS

Overall, clozapine remains underutilized as the gold-standard treatment for treatment-resistant schizophrenia-spectrum disorders at our academic institution. Those who were prescribed clozapine had a higher number of prior psychiatric admissions and antipsychotic trials that exceeded the threshold for clozapine initiation per current guidelines, reinforcing a need to improve guideline- and evidence-based prescribing. Our findings also identify differential clozapine prescribing patterns in minority and homeless patients, introducing potential areas of intervention for clinical practice and healthcare policies.

AUTHOR AND ARTICLE INFORMATION

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