Clozapine Use Among People With Psychotic Disorders Who Experience Specific Indications for Clozapine

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Abstract

Objective: To examine rates of clozapine use among people with psychotic disorders who experience specific indications for clozapine.

Methods: Records data from 11 integrated health systems identified patients aged 18 years or older with recorded *International Classification of Diseases, Tenth Revision, Clinical Modification*, diagnoses of schizophrenia, schizoaffective disorder, or other psychotic disorder who experienced any of the 3 events between January 1, 2019, and December 31, 2019, suggesting indications for clozapine: a diagnosis of self-harm injury or poisoning, suicidal ideation diagnosed or in response to standardized assessments, and hospitalization or emergency department (ED) care for psychotic disorder despite treatment with 2 or more antipsychotic medications. Prescription dispensing data identified all clozapine use prior to or in the 12 months following each indication event. Analyses were conducted with aggregate data from each health system; no individual data were shared.

Results: A total of 7,648 patients with psychotic disorder diagnoses experienced at least 1 indication event. Among 1,097 experiencing a self-harm event, 32 (2.9%) had any prior clozapine use, and 10 (0.9%) initiated clozapine during the following 12 months. Among 6,396 with significant suicidal ideation, 238 (3.7%) had any prior clozapine use, and 70 (1.1%) initiated clozapine over 12 months. Among 881 with hospitalization or ED visit despite pharmacotherapy, 77 (8.7%) had any prior clozapine treatment, and 41 (4.7%) initiated clozapine over 12 months. Among those with significant suicidal ideation, rates of both prior clozapine treatment and subsequent initiation varied significantly by race and ethnicity, with rates among Hispanic and non-Hispanic Black patients lower than among non-Hispanic White patients.

Conclusions: Initiating clozapine treatment is uncommon among people with psychotic disorders who experience events suggesting clozapine is indicated, with even lower rates among Black and Hispanic patients.

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Clozapine is widely recommended as the preferred treatment for people with severe or treatment-resistant psychotic disorders.[1–3] The American Psychiatric Association's guideline for the treatment of people with schizophrenia[4] recommends clozapine for people with treatment-resistant symptoms (typically defined as significant symptoms despite treatment with 2 antipsychotic medications) and for those with a history of suicide attempt or substantial risk of suicidal behavior, regardless of treatment resistance. The UK National Institute for Health and Care Excellence[5] and Canadian practice guidelines[6] recommend offering clozapine to people with significant persistent symptoms despite treatment with 2 antipsychotic medications. Clozapine is the only medication approved by the US Food and Drug Administration (FDA) for reducing the risk of suicidal behavior in people with schizophrenia or schizoaffective disorder.[7] Evidence supports clozapine's superiority to other antipsychotic medications for reducing the risk of both hospitalization[8,9] and suicidal behavior.[7,10,11]

Actual use of clozapine falls far short of guideline recommendations.[2,12–14] While clozapine may be indicated for as many as one-third of people living with schizophrenia or schizoaffective disorder, fewer than

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Clinical Points

- Suicidal behavior, high risk of suicidal behavior, and treatment-resistant psychotic symptoms are all recommended indications for clozapine.
- Fewer than 10% of people experiencing a recommended indication for clozapine try clozapine in the following year.
- Rates of clozapine use are lower in Black and Hispanic than in non-Hispanic White patients.

5% receive clozapine treatment.[13] Among Medicaid recipients with a history of hospitalization despite prior treatment with 2 or more antipsychotic medications, clozapine accounted for only 5% of new medication trials.[14] Among veterans with schizophrenia or schizoaffective disorder and a history of suicide attempt, only 9% had any history of clozapine treatment.[15] Reported barriers to clozapine use include requirements for frequent laboratory monitoring, concern regarding serious side effects, and clinicians' lack of experience with and confidence in prescribing clozapine.[16–19] Wide geographic variation[13,20] suggests that clozapine use depends on local practice patterns or support for monitoring rather than on the prevalence of treatment-resistant schizophrenia.

Previous research also suggests concerning racial disparities in clozapine use.[21] In studies of US health systems,[13,14] non-Hispanic White patients are more likely—sometimes more than twice as likely—to receive clozapine treatment than Black or Hispanic patients. In UK studies,[22,23] clozapine treatment was also twice as common among White as among Black patients. These consistent disparities are not accounted for by differences in severity of illness, type of health insurance, or treatment setting.[21] Racial and ethnic differences in clozapine treatment do not reflect racial or ethnic differences in clinical effectiveness or safety.[24] Rates of clozapine use in patients of African and Middle Eastern ancestry may have historically been suppressed by failure to account for benign ethnic neutropenia,[25,26] but revisions to US FDA monitoring guidelines in 2016 allowed tailoring of monitoring procedures.[26]

Here, we use comprehensive records data to examine clozapine use in 11 large integrated health systems across the United States. We extend previous research by focusing on patients with diagnoses of psychotic disorder and records documenting 3 specific indications for clozapine treatment: a self-harm event or suicide attempt, frequent or intense suicidal ideation, or a hospitalization or emergency care encounter for psychotic disorder despite adequate antipsychotic medication. For each specific event, we examine both prior and subsequent clozapine treatment. We examine 3 questions: Among people with psychotic disorder diagnoses experiencing each of these indication events, what proportion has any record of past or recent treatment with clozapine (so that new clozapine treatment would not be appropriate)? Among those with no prior clozapine treatment, what proportion initiates a trial of clozapine over the following year? How do those proportions vary by race and ethnicity?

METHODS

Setting

Data were extracted from records of 11 health systems participating in the Mental Health Research Network: Essentia Health, Harvard Pilgrim Health Care, HealthPartners, Henry Ford Health, Sutter Health, and the Colorado, Georgia, Northern California, Northwest, Southern California, and Washington regions of Kaiser Permanente. Participating health systems provide mental health and general medical care to a combined member or patient population of approximately 12 million in 11 states. Patients served are representative of each health system's geographic service area in terms of age, sex, race, and ethnicity.[27] Health plan members are enrolled or insured through employer-sponsored insurance, individual insurance, subsidized insurance exchange programs, Medicare, and Medicaid.

Data Sources

Each health system maintains a research data warehouse integrating data from electronic health records (EHRs), insurance claims, and pharmacy dispensing records,[28] including insurance claims submitted from external emergency departments (EDs) and hospitals. These records include demographic information, diagnoses and procedures for all inpatient and outpatient encounters either provided or paid for by each health system, and type and quantity of medication for all prescriptions dispensed or paid for by each health system. Race and ethnicity data in EHRs reflect patients' responses to questions regarding standard race categories and Hispanic ethnicity, most often asked at the time of an outpatient visit but sometimes entered directly by patients through the EHR patient portal. Patients reporting Hispanic ethnicity were considered in that category, and all others were considered in the first race category listed in health system databases. Race and ethnicity information may be unknown or missing because those questions were not asked or because a patient declined to respond. Analyses were conducted using aggregate data, with no sharing of individual-level information between health systems.

Study Sample

Records data were used to identify all patients aged 18 years or older in each participating health system who had recently recorded diagnoses of psychotic disorder and experienced any 1 of the 3 events between January 1, 2019, and December 31, 2019, for which guidelines[4–6] suggest that clozapine should be considered. Specific definitions for indication events included the following:

- A self-harm event, indicated by any coded *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), diagnosis indicating poisoning or injury with self-harm intent accompanied by a recorded diagnosis of schizophrenia (*ICD-10-CM* code F20), schizoaffective disorder (*ICD-10-CM* code F25), or other psychotic disorder (*ICD-10-CM* code F28 or F29) on the day of the self-harm event or in the prior 12 months. Diagnoses indicating self-harm included all poisoning diagnoses (*ICD-10-CM* codes T36 through T65) with modifiers indicating self-harm intent and all injury diagnoses with external cause codes indicating self-harm intent (X71 through X83). Previous research in these settings documents the accuracy of *ICD-10-CM* self-harm codes for identifying injuries and poisonings with self-harm intent.[29]
- Significant risk of suicidal behavior, indicated by an *ICD-10-CM* encounter diagnosis of R45.851 ("Suicidal ideations") OR a recorded response of "Nearly Every Day" to item 9 of the Patient Health Questionnaire-9 (PHQ-9) depression questionnaire regarding thoughts of suicide or self-harm[30] OR a recorded score 3 or higher (indicating active suicidal ideation with thoughts of method) on the current Suicidal Ideation subscale of the Columbia Suicide Severity Rating Scale (CSSRS),[31,32] each also accompanied by a recorded diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder on the day of the suicidal ideation event or in the prior 12 months. During the study period, the PHQ-9 and CSSRS were routinely administered in specialty mental health clinics in 7 of the participating health systems and administered routinely in primary care in 2 systems.
- Treatment-resistant psychotic symptoms, indicated by an inpatient admission or ED visit with a principal or primary diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder preceded by both dispensing of at least 60 days' supply of at least 2 different antipsychotic medications in the prior 24 months AND a recent enough dispensing of antipsychotic medication to suggest current use at the time of the hospitalization or ED visit (ie, number of days between dispensing and hospitalization or ED visit was no greater than 125% of the days' supply dispensed).

Patients with diagnoses of other psychotic disorder were included because that diagnosis is often recorded for some time after first presentation with psychotic symptoms,[33,34] a period during which clozapine treatment may be especially valuable.[35,36] Patients with any recorded diagnosis of seizure disorder, myocarditis, or cardiomyopathy (possible contraindications for clozapine treatment) in the 2 years prior to an indication event were excluded. Within each category of indication event, sampling included the first event for any individual patient in that category between January 1, 2019, and December 31, 2019. Analyses regarding patients with any indication event included the first event for any individual patient in any category between January 1, 2019, and December 31, 2019. Primary analyses did not require health system enrollment prior to the indication event, and sensitivity analyses considered only those enrolled in the participating health system for the prior 2 years.

Clozapine Use

For each individual indication event, all medication dispensing records prior to the event date and up to 12 months following the event date were used to identify any outpatient dispensings of clozapine. Four categories of clozapine use were defined:

- Any prior clozapine use, defined as any outpatient clozapine dispensing prior to the index event, including pharmacy dispensing and claims records extending back to 2000 in all health systems and earlier in some.
- Probable current clozapine use, defined as any outpatient clozapine dispensing in the 35 days prior to the index event. This 35-day interval accommodates a 28-day prescription (the maximum allowed for clozapine) plus a 25% allowance for partial adherence. Probable current use is a subset of (not distinct from) any prior use.
- Clozapine start, defined as no prior outpatient clozapine dispensing and any outpatient clozapine dispensing during the 12 months beginning on the day of the indication event.
- No clozapine use, defined as no record of outpatient clozapine dispensing prior to the indication event or during the 12 months after.

Data Analysis

Descriptive analyses computed proportions of patients in each of the 4 clozapine use categories listed above for each type of indication event, with exact 95% confidence limits for rates calculated by the Clopper-Person[37]

method. Additional analyses examined variation in rates of prior use and subsequent use across racial and ethnic groups. Heterogeneity of rates across racial/ethnic groups was examined with χ^2 statistics or Fisher exact test[38] (depending on sample size). In case of significant overall heterogeneity by race and ethnicity ($P < .05$), post hoc pairwise comparisons of rates for non-Hispanic White patients (the largest group) to each of the other groups were examined using χ^2 statistics or Fisher exact test (depending on sample size). Sensitivity analyses examined results in a subset of patients enrolled for at least 2 years before and 1 year after the indication event and examined alternative definitions of indication events. Analyses were conducted using SPSS version 22.

RESULTS

Across all 11 health systems, the above-described criteria identified 7,648 patients with recorded diagnosis of psychotic disorder experiencing 1 or more of the 3 indication events in 2019, with most identified by record of suicidal ideation. The numbers and characteristics of patients experiencing each event type are shown in Table 1.

Among 7,648 patients experiencing any indication event, 288 (3.8%) had any record of previous clozapine use, and an additional 98 (1.3%) filled at least 1 prescription for clozapine in the 12 months after the event. Patterns of prior and subsequent clozapine use by type of indication event are shown in Table 2. Rates of prior clozapine use (8.7%) and clozapine initiation (4.7%) were approximately twice as high for patients identified by ED or hospital encounter than for those identified by self-harm diagnosis or record of suicidal ideation. Between 0.5% and 2.0% of patients with each indication had a clozapine prescription filled in the prior 90 days.

Figure 1 shows variation in rates of clozapine use before each type of indication event by patient race and ethnicity, with counts and rates shown in Supplementary Tables 4 and 5. Among patients identified by self-harm diagnosis and by ED or inpatient care, variation across racial and ethnic groups in prior clozapine use was not statistically significant. Among patients identified by record of suicidal ideation and those experiencing any indication event, rates of prior clozapine use varied significantly across racial and ethnic groups. Among those identified by record of suicidal ideation, post hoc pairwise comparisons of non-Hispanic White patients to other racial/ethnic groups found that rates of prior clozapine use were significantly lower in non-Hispanic Black patients ($\chi^2 = 29.70$, $df = 1$, $P < .001$), significantly lower in Hispanic patients ($\chi^2 = 3.92$, $df = 1$, $P = .048$), and not significantly different in other groups. Among those experiencing any indication event, post hoc pairwise comparisons of non-Hispanic white patients to other racial/ethnic groups found that rates were significantly lower in non-Hispanic Black patients ($\chi^2 = 33.76$, $df = 1$, $P < .001$), significantly lower in Hispanic patients ($\chi^2 = 4.49$, $df = 1$, $P = .034$), and not significantly different in other groups.

Figure 2 shows variation in rates of clozapine initiation during the 12 months after each type of indication event, limited to patients with no record of clozapine use prior to the indication event. Among patients identified by self-harm diagnosis and by ED or inpatient care, variation in rates of clozapine initiation across racial and ethnic groups in clozapine initiation was not statistically significant. Among patients experiencing suicidal ideation and those experiencing any indication event, rates of clozapine initiation varied significantly across racial and ethnic groups. Among those experiencing significant suicidal ideation, post hoc pairwise comparisons of the rate of prior clozapine use in non-Hispanic White patients to rates in other racial/ethnic groups found that rates were significantly lower in non-Hispanic Black patients (Fisher exact $P = .0019$) and not significantly different in other groups. Among those experiencing any indication event, post hoc pairwise comparisons of the rate of prior clozapine use in non-Hispanic White patients to rates in other racial/ethnic groups found that rates were significantly lower in non-Hispanic Black patients (Fisher exact $P = .0003$) and not significantly different in other groups.

Sensitivity analyses examined rates of prior clozapine use and clozapine initiation limited to patients who were continuously enrolled in the participating health system for at least 2 years prior to and 1 year after the indication event. Results (Supplementary Tables 1 and 2) were similar to those in the full sample.

Additional sensitivity analyses (Supplementary Table 3) examined alternative definitions for indication events: hospitalization coded with schizophrenia or schizoaffective disorder as primary diagnosis (ie, not including those with ED visit not accompanied by hospitalization), suicidal ideation identified by visit diagnosis, and suicidal diagnosis identified by standard questionnaires. Results using these alternative definitions were similar to those of the primary analyses.

DISCUSSION

Using records data from 11 large integrated health systems, we find that fewer than 2% of patients experiencing an event suggesting an indication for clozapine treatment had any record of starting clozapine during the following 12 months. Fewer than 4% had any record of prior clozapine treatment, demonstrating that

Table 1.

Patients Experiencing Specific Events Suggesting Indications for Clozapine Treatment

	Self-harm (total n = 1,097)	Suicidal ideation (total n = 6,396)	Hospitalization or ED visit (total n = 881)	Any event (total n = 7,648)
Sex[a]				
Female	542 (49.4%)	2,884 (45.1%)	407 (46.2%)	3,466 (45.3%)
Male	555 (50.6%)	3,509 (54.9%)	473 (53.7%)	4,177 (54.6%)
Other	0	4 (<0.1%)	1 (<0.1%)	5 (<0.1%)
Age, y				
18–29	444 (40.5%)	2,170 (33.9%)	302 (34.3%)	2,605 (34.1%)
30–44	313 (28.5%)	1,863 (29.1%)	240 (27.2%)	2,213 (28.9%)
45–64	267 (24.3%)	1,860 (29.1%)	249 (28.3%)	2,196 (28.7%)
65 or older	73 (6.7%)	503 (7.9%)	90 (10.2%)	634 (8.3%)
Race/ethnicity[b]				
American Indian or Alaskan Native	14 (1.3%)	34 (0.5%)	3 (0.3%)	58 (0.8%)
Asian	49 (4.5%)	317 (5%)	69 (7.8%)	384 (5.0%)
Black	173 (15.8%)	1,401 (21.9%)	113 (12.8%)	1,532 (20.0%)
Hawaiian Native or Pacific Islander	8 (0.7%)	29 (0.5%)	3 (0.3%)	38 (0.5%)
Hispanic	196 (17.9%)	1,229 (19.2%)	191 (21.7%)	1,407 (18.4%)
Non-Hispanic White	555 (50.6%)	2,968 (46.4%)	441 (50.1%)	3,602 (47.1%)
Other	46 (4.2%)	256 (4%)	24 (2.7%)	286 (3.7%)
Unknown	56 (5.1%)	162 (2.5%)	37 (4.2%)	341 (4.5%)

[a]Sex as recorded in health insurance records, typically indicating sex assigned at birth.
[b]Self-reported race and ethnicity, typically reported at the time of visit registration in response to standard categories. All patients reporting Hispanic ethnicity were included in that category regardless of self-reported race.
Abbreviation: ED = emergency department.

Table 2.

Patterns of Clozapine Use Among Patients Experiencing Specific Indication Events

	Self-harm (total n = 1,097)			Suicidal ideation (total n = 6,396)			Hospitalization or ED visit (total n = 881)			Any event (total n = 7,648)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any prior use	32	2.9	2.0–4.1	238	3.7	3.3–4.2	77	8.7	7.0–10.8	288	3.8	3.4–4.2
Dispensed in last 35 days	6	0.5	0.2–1.2	113	1.8	1.5–2.1	18	2.0	1.2–3.2	125	1.6	1.4–1.9
Start in next 12 months	10	0.9	0.4–1.7	70	1.1	0.8–1.4	41	4.7	3.4–6.3	98	1.3	1.0–1.6
No use before or after	1,055	96.2	94.9–97.2	6,088	95.2	94.6–95.7	763	86.6	84.2–88.8	7,262	95.0	94.4–95.4

Abbreviation: ED = emergency department.

low rates of starting clozapine did not reflect prior unsuccessful clozapine treatment.

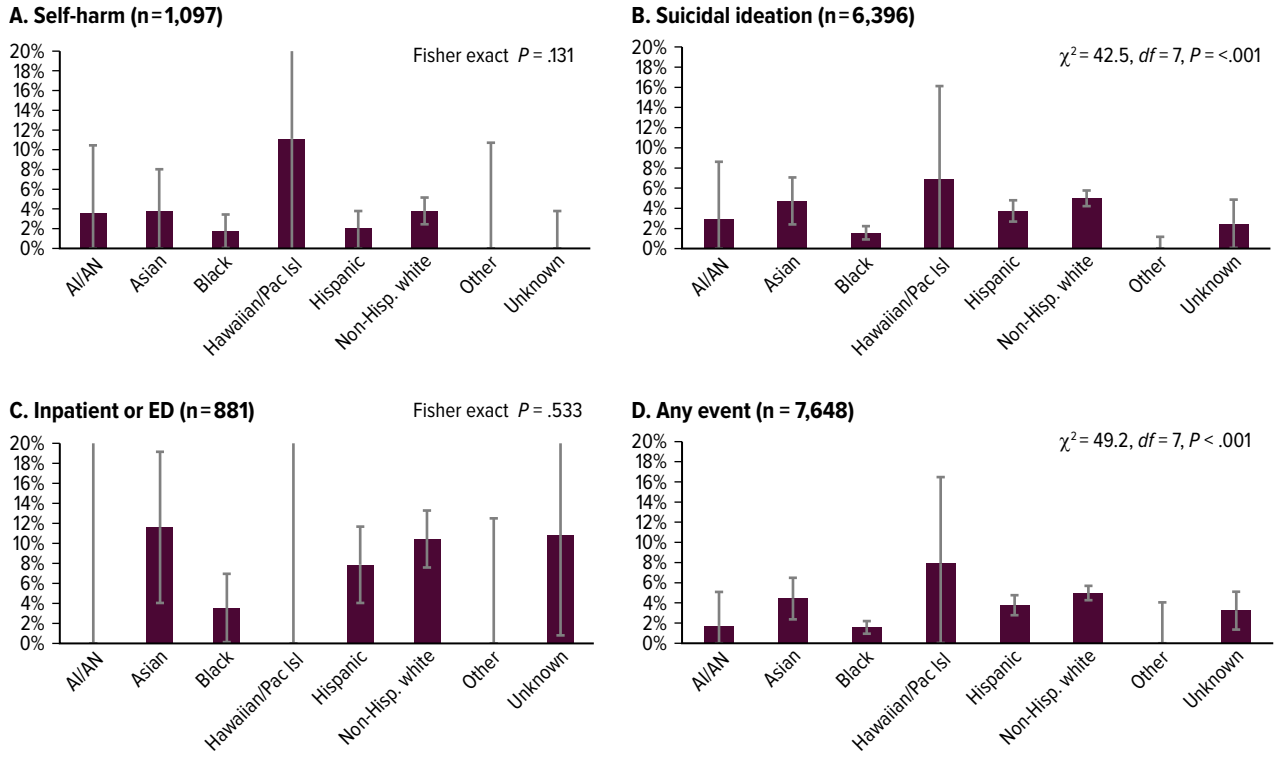
Previous research has estimated that one-third of people with psychotic disorders might meet the criteria for clozapine treatment.[2,12–14] Going beyond previous research, we identified specific indication events and examined both rates of initiating clozapine after a specific indication event and rates of prior clozapine use. We find initiation rates ranging from approximately 1% (following a self-harm event) to approximately 5% (following hospitalization or ED care).

Low rates of clozapine use were seen in these settings despite resources to address some logistical barriers to clozapine use. Mental health care was typically delivered in multispecialty clinics, most including on-site nursing and other support staff to assist with monitoring requirements. Patients all had access to health system laboratory facilities, often colocated with clinics providing mental health care. Clozapine prescriptions and required laboratory testing were fully covered by all health system insurance plans. EHR systems typically included comprehensive data regarding specialty mental health visits, general medical visits, laboratory orders, and laboratory results, reducing barriers to tracking of required laboratory monitoring and identifying potential adverse events.

Racial and ethnic disparities in clozapine treatment were seen in these settings even though patients in different racial and ethnic groups generally received care from the same clinics, had similar insurance coverage for clozapine treatment, and had similar access to laboratory monitoring. Indication events in 2019 all occurred after changes in monitoring requirements allowing for benign ethnic neutropenia, but some clinicians may have been unaware of those recommendations. We cannot determine how often lower rates of clozapine use among

Figure 1.

Rates of Prior Clozapine Use Among Patients Experiencing Specific Indication Events by Race and Ethnicity[a]



[a]All patients reporting Hispanic ethnicity were considered in that category, regardless of self-reported race.
Abbreviations: AI/AN = American Indian or Alaskan Native, ED = emergency department, Pac Isl = Pacific Islander.

Black and Hispanic patients reflect biases in individual clinicians' treatment decisions, broader structural biases in access to or quality of mental health care,[39] or Black and Hispanic patients' lower likelihood of accepting an offer of clozapine. Lower rates of clozapine use among Black patients may also reflect broader preferences for nonpharmacologic treatments over medication.[40] In these health systems, Black patients with diagnoses of schizophrenia were less likely to be prescribed any psychiatric medication and more likely to receive formal psychotherapy.[27] As illustrated by confidence limits in Figures 1 and 2, the numbers of patients identifying as American Indian/Alaskan Native or Native Hawaiian/Pacific Islander were too small for reliable estimates of clozapine use.

We might observe low rates of recent clozapine dispensing prior to hospitalization or ED care if clozapine treatment were completely effective in preventing crises or clinical deterioration. Such a phenomenon, however, would not explain low rates of clozapine initiation among patients experiencing an event suggesting that clozapine should be considered. We might observe low rates of clozapine initiation among people with prior unsuccessful treatment, but rates of prior treatment were uniformly low. Rates of clozapine initiation reported in Figure 2 only consider patients with no record of prior clozapine use.

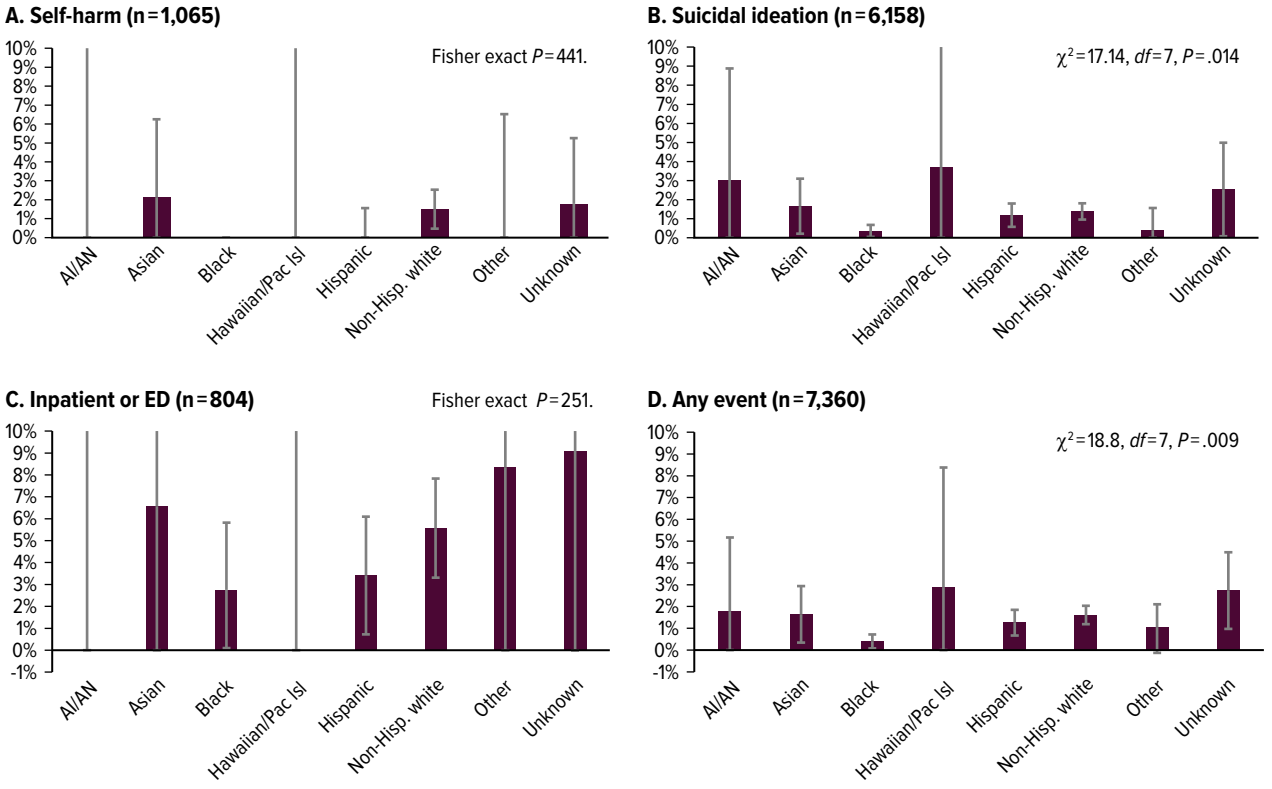
Low rates of clozapine initiation after self-harm events, ED visits, or hospitalizations suggest that clinicians may not recognize these events as prompts to consider clozapine. Quality improvement programs to increase clozapine uptake could focus on these and similar sentinel events as triggers for intervention.[41] Increasing rates of clozapine initiation will likely require both clinician-focused and patient-focused interventions to increase awareness, address concerns regarding adverse effects, and reduce the burden of monitoring.[16–19,41,42]

LIMITATIONS

We cannot independently confirm clinicians' encounter diagnoses of schizophrenia, schizoaffective disorder, or other psychotic disorder. While some patients may not have met formal criteria for those

Figure 2.

Rates of Starting Clozapine During 12 Months After Specific Indication Events by Race and Ethnicity (Limited to Patients With No Prior Use)[a]



[a]All patients reporting Hispanic ethnicity were considered in that category, regardless of self-reported race.
Abbreviations: AI/AN = American Indian or Alaskan Native, ED = emergency department, Pac Isl = Pacific Islander.

diagnoses, we believe it is reasonable to examine clinicians' prescribing decisions on the basis of those clinicians' recorded diagnoses.

Prescribing data cannot determine how often clinicians considered or suggested clozapine. Clinicians may have chosen not to recommend clozapine because of specific contraindications (such as low white blood cell count) or other clinical considerations. Patients may have declined clozapine because of concern regarding adverse effects, need for frequent laboratory monitoring, or a preference for nonpharmacologic therapies. In the prescription data available for these analyses, those choices would all appear as failure to initiate clozapine.

Pharmacy dispensing records might not capture clozapine treatment prior to enrollment in these health systems, clozapine prescriptions that were written but never filled, or clozapine treatment received solely during inpatient treatment or other institutional care. Consequently, our methods would not capture brief trials of clozapine during inpatient care, either prior to or after an indication event.

These analyses examined only 3 specific events that would appear to indicate a trial of clozapine. This method almost certainly underestimates the number of patients with treatment-resistant psychotic symptoms or significant risk of suicidal behavior. Records available for these analyses do not include structured assessment of psychotic symptoms. Receipt of hospital or ED care despite adequate pharmacotherapy likely identifies only a small proportion of patients with treatment-resistant psychotic symptoms. Diagnostic data regarding self-harm or suicidal behavior would not capture suicidal behavior that did not prompt care-seeking or that was not recognized or recorded by treating clinicians. Suicidal ideation might not be detected when standardized assessments were not offered by clinicians or completed by patients.

Patients with suicidal ideation were the largest group identified by our criteria. Self-report measures such as the PHQ-9 and the CSSRS do identify increased risk of suicidal behavior,[30,32] including among people with psychotic disorders.[43] But FDA-approved indications and treatment guidelines do not specify a specific risk level at which clozapine is indicated.

Specific procedures for inquiring about and recording self-reported race and ethnicity may vary among health

systems, especially regarding classification of patients who report identifying with more than 1 racial group.

Some criteria for indication events, such as hospitalization despite ongoing pharmacotherapy or completion of questionnaires, may select patients more engaged in care. Consequently, our findings may give an optimistic picture of clozapine use among all health system members with psychotic disorders.

The criteria used to identify likely indications for clozapine might not identify the same levels of clinical need across racial and ethnic groups. For example, some groups of patients might be less likely to seek ED care or more likely to be hospitalized. Clinicians' likelihood of assessing or recording suicidal ideation might differ by race or ethnicity. Lower rates of clozapine use in Black patients could be misleading if Black patients with less severe symptoms were more likely to be hospitalized or receive emergency care. Conversely, our method could underestimate disparities if Hispanic and Black patients were less likely to receive diagnoses or care at the same level of need.

CONCLUSIONS

Among people with chronic psychotic disorders who experience an event suggesting that clozapine could be indicated, fewer than 2% initiate clozapine treatment during the following year, and only 5%–10% have any record of previous clozapine use. Rates of clozapine use remain approximately half as high in Black patients for whom clozapine could be indicated as for non-Hispanic White patients. Systematic, multicomponent interventions[16,41] are needed to increase the use of clozapine where indicated and address persistent racial disparities in care.

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Data Sharing Statement: Analyses were conducted using standard queries of research data warehouses in each participating health system. Only aggregate results were returned, and no individual-level data were shared or retained. Tables of aggregate data (eg, counts of people in a specific racial/ethnic group experiencing a specific indication event who did and did not start clozapine treatment) can be shared with interested researchers on request.

Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Clozapine Use Among People With Psychotic Disorders Who Experience Specific Indications for Clozapine

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1 – Characteristics of patients experiencing specific indication events, limited to those enrolled for at least 2 years prior to and 1 year after the indication event

	Self-Harm (total n=590)	Suicidal Ideation (total n=3285)	Hospitalization or ED Visit (total n=721)	Any Event (total n=4111)
Sex[a]				
Female	329 (55.8%)	1692 (51.5%)	344 (47.7%)	2107 (51.3%)
Male	261 (44.2%)	1591 (48.4%)	376 (52.1%)	2001 (48.7%)
Other	0	2 (0.1%)	1 (0.1%)	3 (0.1%)
Age				
18 to 29	260 (44.1%)	1207 (36.7%)	245 (34.0%)	1506 (36.6%)
30 to 44	134 (22.7%)	789 (24.0%)	184 (25.5%)	987 (24.0%)
45 to 64	143 (24.2%)	944 (28.7%)	213 (29.5%)	1178 (28.7%)
65 or older	53 (9.0%)	345 (10.5%)	79 (11%)	440 (10.7%)
Race/Ethnicity[b]				
American Indian or Alaskan Native	6 (1.0%)	20 (0.6%)	2 (0.3%)	28 (0.7%)
Asian	36 (6.1%)	201 (6.1%)	55 (7.6%)	249 (6.1%)
Black	72 (12.2%)	496 (15.1%)	92 (12.8%)	576 (14.0%)
Hawaiian Native or Pacific Islander	4 (0.7%)	13 (0.4%)	2 (0.4%)	19 (0.5%)
Hispanic	116 (19.7%)	736 (22.4%)	160 (22.2%)	866 (21.1%)
Non-Hispanic White	303 (51.4%)	1611 (49.0%)	365 (50.6%)	2029 (49.4%)
Other	0	3 (0.1%)	1 (0.1%)	4 (0.1%)
Unknown	32 (5.4%)	78 (2.4%)	25 (3.5%)	197 (4.8%)

a - Sex as recorded in health insurance records, typically indicating sex assigned at birth

b - Self-reported race and ethnicity, typically reported at time of visit registration in response to standard categories

Supplementary Table 2 – Patterns of clozapine use among patients experiencing specific indication events (limited to patients continuously enrolled in participating health systems for at least 2 years prior to and 1 year after the indication event).

	Self-Harm (total n=590)			Suicidal Ideation (total n=3285)			Hospitalization or ED Visit (total n=721)			Any Event (total n=4111)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Prior Use	23	3.9%	2.5% - 5.8%	145	4.4%	3.7% - 5.2%	63	8.7%	6.8% - 11.0%	198	4.7%	4.1% - 5.4%
Dispensed in Last 35 Days	5	0.9%	0.3% - 2.0%	73	2.2%	1.8% – 2.8%	14	1.9%	1.1% - 3.2%	87	2.1%	1.7% - 2.5%
Start in Next 12 Months	6	1.0%	0.4% - 2.2%	41	1.3%	0.9% - 1.7%	31	4.3%	2.9% - 6.0%	61	1.5%	1.1% - 1.9%
No Use Before or After	560	94.9%	92.8% - 96.5%	3072	93.5%	92.7% - 94.4%	622	86.4%	83.9% - 88.9%	3820	90.7%	89.8% - 91.6%

Supplementary Table 3 – Patterns of clozapine use after indication events using alternative definitions

	Hospitalization for Psychosis (total n=643)			Suicidal Ideation Diagnosis (total n=5510)			Self-Reported Suicidal Ideation (total n=3771)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Prior Use	60	9.3%	7.2% - 11.9%	176	3.2%	2.8% - 3.7%	140	3.7%	3.1% - 4.4%
Dispensed in Last 35 Days	16	2.5%	1.4% - 4.0%	71	1.3%	1.0% - 1.6%	79	2.1%	1.7% - 2.6%
Start in Next 12 Months	35	5.4%	3.8% - 7.5%	63	1.1%	0.9% - 1.5%	37	1.0%	0.7% - 1.4%
No Use Before or After	548	85.2%	82.2% - 87.9%	5271	95.7%	95.1% - 96.2%	3594	95.3%	94.6 – 96.0%

Supplementary Table 4 – Counts and rates of prior clozapine treatment among patients experiencing different indication events, stratified by race and ethnicity

	American Indian Alaskan Native	Asian	Black	Native Hawaiian Pacific Islander	Hispanic	Non-Hispanic White	Other	Unknown
Self-Harm Event								
Total number	14	49	173	8	196	555	46	56
Number with prior use	0	2	3	1	4	21	0	0
% with prior use	0.0%	4.1%	1.7%	12.5%	2.0%	3.8%	0.0%	0.0%
Suicidal Ideation								
Total number	34	317	1401	29	1229	2968	256	162
Number with prior use	1	15	22	2	46	148	0	4
% with prior use	2.9%	4.7%	1.6%	6.9%	3.7%	5.0%	0.0%	2.5%
Hospitalization or ED Care								
Total number	3	69	113	3	191	441	24	37
Number with prior use	0	8	4	0	15	46	0	4
% with prior use	0.0%	11.6%	3.5%	0.0%	7.9%	10.4%	0.0%	10.8%
Any Indication Event								
Total number	58	384	1532	38	1407	3602	286	341
Number with prior use	1	17	24	3	51	181	0	11
% with prior use	1.7%	4.4%	1.6%	7.9%	3.6%	5.0%	0.0%	3.2%

Supplementary Table 5 – Counts and rates of starting clozapine treatment among patients experiencing different indication events, stratified by race and ethnicity (limited to patients with no use of clozapine prior to indication event)

	American Indian Alaskan Native	Asian	Black	Native Hawaiian Pacific Islander	Hispanic	Non-Hispanic White	Other	Unknown
Self-Harm Event								
Total number	14	47	170	6	192	534	46	56
Number starting	0	1	0	0	0	8	0	1
% starting	0.0%	2.1%	0.0%	0.0%	0.0%	1.5%	0.0%	1.8%
Suicidal Ideation								
Total number	33	302	1379	27	1181	2822	256	158
Number starting	1	5	5	1	14	39	1	4
% starting	3.0%	1.7%	0.4%	3.7%	1.2%	1.4%	0.4%	2.5%
Hospitalization or ED Care								
Total number	3	61	109	3	176	395	24	33
Number starting	0	2	3	0	6	22	2	5
% starting	0.0%	3.3%	2.8%	0.0%	3.4%	5.6%	8.3%	15.2%
Any Indication Event								
Total number	57	367	1508	35	1354	3423	286	330
Number starting	1	6	6	1	17	55	3	9
% starting	1.8%	1.6%	0.4%	2.9%	1.3%	1.6%	1.0%	2.7%