Geographic and Clinical Variation in Clozapine Use in the United States

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Objective: Antipsychotic medications are largely ineffective for approximately 30% of patients with schizophrenia that is considered "treatment resistant." Clozapine is the only antipsychotic approved for treatment-resistant schizophrenia, but it is rarely used. This nationwide study examined predictors of clozapine use to help identify ways to optimize its use. Methods: A retrospective study using U.S. Medicaid claims data from 45 states was conducted among 326,119 individuals with a schizophrenia spectrum disorder (*ICD-9-CM* code 295.X) who initiated one or more antipsychotic treatment episodes between January 2002 and December 2005. Multivariable logistic regression models were used to calculate odds ratios of baseline patient and county factors associated with clozapine initiation. Results: Among 629,809 unique antipsychotic treatment episodes, 79,934 showed service use patterns consistent with treatment resistance. Clozapine accounted for 2.5% of starts of antipsychotic medication among patients in the overall sample and for 5.5% of starts among patients with treatment resistance. Clozapine initiation was significantly associated with male sex, younger age, white race, more frequent outpatient service use for schizophrenia, and greater prior-year hospital use for mental health. Treatment resistance and living in a county with historically high rates of clozapine use were among the strongest predictors of clozapine use. Conclusions: The clozapine initiation rate was low compared with the expected proportion of patients who warrant a clozapine trial and was strongly affected by local treatment practices. Efforts to address irregular access to clozapine are needed to improve recovery opportunities for people with schizophrenia in the United States. (*Psychiatric Services* 65:186–192, 2014; doi: 10.1176/appi.ps.201300180)

Clozapine has a unique role in schizophrenia treatment because of its enhanced benefits and considerable risks. In particular, clozapine is the only antipsychotic approved by the U.S. Food and Drug Administration (FDA) for treatment-resistant schizophrenia and for reducing suicidal behaviors of patients with schizophrenia. Reports have shown that clozapine is rarely used and have suggested that this underuse is a barrier to improved outcomes for people severely affected by schizophrenia (1,2). We conducted this national study to examine clozapine use in the United States and to identify potentially modifiable barriers to its use.

Clozapine was originally introduced in Europe in the 1970s, but its use was curtailed after a series of agranulocytosis-associated deaths. After clozapine was shown to be effective for treatment-resistant schizophrenia, it was reintroduced in 1989 with a strict white blood cell monitoring protocol that requires physicians and patients to enroll in a registry. Although initially clozapine was widely prescribed in the United States because of its superior effectiveness and substantial commercial promotion, clozapine lost market share as new antipsychotics were introduced during the 1990s with the promise of similar benefits but without risk of agranulocytosis (3). While other heavily marketed drugs came to dominate the marketplace, clozapine lost patent protection and was no longer highly promoted. More recently, evidence has emerged that clozapine's efficacy and benefits for treatment resistance are unique (4,5), although there is some evidence that use remains uncommon (2). As a result, there are concerns about access to the only evidence-based treatment for individuals severely ill with schizophrenia who do not respond to standard antipsychotic treatment.

Clozapine's superiority in treatment-resistant schizophrenia was first demonstrated in a randomized controlled trial of patients meeting a rigorous definition of treatment resistance that required, for inclusion, three failed trials

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of antipsychotic medications, persistent psychotic symptoms, and no period of good functioning for five years (6). More recent work has suggested superior efficacy of clozapine in a broader population. One randomized controlled trial found that when an antipsychotic was discontinued because of lack of efficacy, switching to clozapine was more effective than switching to another antipsychotic (5). A meta-analysis found clozapine to be superior to other antipsychotic medications even for non–treatment-resistant patients (7). Treatment algorithms and guidelines now recommend clozapine for schizophrenia after two failed trials of antipsychotic medication (8,9).

Clozapine's usefulness extends beyond treatment of treatment-resistant psychotic symptoms. As a result of a large-scale clinical trial, the FDA approved clozapine to reduce the risk of recurrent suicidal behaviors among people with schizophrenia or schizoaffective disorder even without treatment resistance (10). In addition, there is evidence to support clozapine's use for reducing hostility and violent behaviors (11,12).

Among adults with schizophrenia, some studies have found patient characteristics to be associated with clozapine use in the United States. Among patients in the Veterans Health Administration, younger age and white race have been associated with clozapine use (13). Younger age, more inpatient service use, higher mental health expenditures, white race, and male sex were associated with clozapine use in a recent analysis of New York State Medicaid claims data (2).

In the United Kingdom, wide geographic variations in clozapine use have been documented. Across National Health Service trusts, variation in clozapine use was reduced from 34-fold in 2002 to fivefold by 2006 (14). The reduction in geographic variation was attributed to a large fall in the price of clozapine after patent expiration and publication of national guidelines recommending clozapine after inadequate response to two antipsychotics (9).

The goal of this retrospective investigation was to answer the question: Can predictors of clozapine use identify modifiable factors to improve clozapine prescribing in the United States?

Methods

Study population

The target population for this study was patients with a schizophrenia spectrum disorder who had initiated treatment with a new antipsychotic medication. Data were from national (45-state) Medicaid Analytic Extracts (2001–2005). These data were supplemented with county-level information from the Area Resource File (ARF), a collection of county-level data that includes information on health professions, socioeconomic characteristics, and other basic county-specific information (15). The ARF permits characterization of treatment episodes by several county characteristics. Study patients included Medicaid-insured adults ages 18–64 years with a schizophrenia spectrum disorder (two or more outpatient or one or more inpatient claims with *ICD-9-CM* code 295.X) who used clozapine or a standard antipsychotic medication in one or more treatment episodes. New clozapine treatment episodes were defined by a clozapine prescription fill after ≥365 days of continuous Medicaid eligibility without a filled clozapine prescription. New treatment episodes of standard antipsychotic medications were defined by a prescription fill after ≥365 days without the index standard antipsychotic or clozapine so that all patients were eligible for both groups. Because of the requirement of ≥365 days of continuous Medicaid eligibility, the study period started on January 1, 2002, and ended on December 31, 2005. Multiple treatment episodes per patient were allowable as long as each episode met the inclusion criteria for the study.

Predictor variables

New treatment episodes of clozapine and standard antipsychotics were compared with respect to geographic, sociodemographic, and clinical characteristics during the 365-day period before the index antipsychotic prescription.

We developed a claims-based definition of treatment resistance to investigate this as a predictor of clozapine use. An episode met treatment-resistance criteria if, during the 365-day preindex period there were prescription fills for two or more different standard antipsychotic agents and a combined medication possession ratio for antipsychotics of >.75 to indicate adequate medication adherence. In addition, the definition required one or more psychiatric hospitalizations in the 180 days preceding the index date to reflect impaired functioning around the start of the new treatment episode. [Additional diagnoses and services were defined by the criteria available online in a data supplement to this article.]

To evaluate how the area where a patient received services might affect clozapine use, we examined geographic variables at the county level. These variables included the rate of psychiatrists per 100,000 residents, annual per capita income, percentage of population in poverty, and population per square mile. To examine whether and to what extent local treatment culture affects geographic variation in clozapine use, we calculated the prevalence of clozapine use in each U.S. county among all patients with a schizophrenia spectrum diagnosis during the year before the study period (2001). To ensure stable estimates of clozapine prevalence, we collapsed counties with low antipsychotic utilization (defined as ≤500 total prescription fills for antipsychotics) in each state (approximately 7% of patients resided in counties with low antipsychotic utilization). We then classified into four categories clozapine utilization of each county: very low (0%−5%), low (>5%−10%), medium (>10%−15%), and high (>15%).

Statistical analysis

Demographic and clinical characteristics were compared between the group that initiated clozapine and the group that initiated standard antipsychotic use. Bivariate logistic regression was used to obtain p values. A multivariate logistic regression model was then fit to estimate the odds ratio of each patient characteristic for clozapine use; ratios were adjusted for the other model variables. The multivariate logistic model included state (coded as individual dummy variables)

Table 1

Characteristics of 629,809 treatment episodes of adult Medicaid beneficiaries with schizophrenia, by antipsychotic medication

Characteristic	Clozapine (N=15,524)		Other antipsychotic (N=614,285)		p
	N	%	N	%	
Sex					<.001
Male	8,941	57.6	309,014	50.3	
Female	6,583	42.4	305,262	49.7	
Age					<.001
18–24	1,566	10.1	44,607	7.3	
25–34	3,414	22.0	110,083	17.9	
35–44	4,846	31.2	190,027	30.9	
45–54	4,072	26.2	182,162	29.7	
55–64	1,626	10.5	87,406	14.2	
Race-ethnicity					<.001
White, non-Hispanic	10,025	64.6	325,328	53.0	
African American, non-Hispanic	2,871	18.5	168,201	27.4	
Hispanic	805	5.2	42,977	7.0	
Other	10,025	64.6	325,328	53.0	
Past-year co-occurring disorder or condition					
Substance use disorder	2,003	12.9	90,848	14.8	.03
Depression	5,583	36.0	223,975	36.5	.44
Anxiety	2,426	15.6	96,938	15.8	.74
Deliberate self-harm	202	1.3	6,560	1.1	.06
Diabetes or cardiovascular disease	7,742	49.9	311,178	50.7	.60
HIV	86	.6	11,487	1.9	<.001
Schizophrenia subtype					<.001
Schizophreniform	748	4.8	21,204	3.5	
Schizoaffective	6,792	43.8	256,349	41.7	
Past-year acute services					
Mental health emergency service	2,003	12.9	90,848	14.8	<.001
Outpatient visits for schizophrenia					<.001
0–9	3,970	25.6	236,786	38.6	
10–29	4,122	26.6	176,163	28.7	
30–49	2,254	14.5	66,137	10.8	
≥50	5,178	33.4	135,199	22.0	
Hospital admissions for psychiatric illness					<.001
0	6,902	44.5	353,514	57.6	
1	3,781	24.4	134,811	22.0	
2	2,049	13.2	59,275	9.7	
3	1,069	6.9	26,982	4.4	
≥4	1,723	11.0	39,703	6.5	
Treatment resistance					<.001
Present	4,367	28.1	75,567	12.3	
Absent	11,157	71.9	538,718	87.7	

to account for variation in state Medicaid programs. Generalized estimation equations clustered on county with a logit link and a default independence covariance structure were fit for all logistic regression models to obtain robust standard errors with unbiased parameter estimates.

Results

The study sample included 629,809 treatment episodes from 326,119 patients. A total of 79,934 episodes met the criteria for treatment resistance. Demographic and clinical characteristics are shown in Table 1.

Geographic variation

Figure 1 illustrates variation in clozapine prescribing rates among states during the period from January 2002 to December 2005. [Additional figures, available online in a data supplement to this article, illustrate variation within the counties of two states with disparate rates, New Jersey and Massachusetts.] State-specific clozapine initiation rates varied from .9% to 7.8%, whereas county-specific clozapine initiation rates varied from 0% to more than 15%. Variation in clozapine usage rates might partially reflect Medicaid eligibility and program differences between states. However, variation within states more likely reflects regional practice norms.

Demographic and clinical predictors of clozapine initiations

Compared with treatment episodes with standard antipsychotic medications, clozapine treatment episodes were significantly more likely to occur among males, younger patients, and non-Hispanic patients (Table 2). Treatment episodes of people codiagnosed as having substance use disorders or HIV infection were less likely to

involve clozapine than episodes without these additional diagnoses, whereas patients meeting the treatment-resistance criteria were about twice as likely to initiate clozapine use. Increased numbers of outpatient visits for schizophrenia and psychiatry-related hospital admissions were associated with increased likelihood of initiating clozapine. Diagnosis of schizoaffective disorder, diabetes, or cardiovascular disease or deliberate self-harm was associated marginally or nonsignificantly with clozapine initiation.

Predictors of clozapine use by patient county characteristics

Table 3 shows that after analyses controlled for state, patients residing in counties with historically high clozapine usage were almost twice as likely to start clozapine as patients residing in historically low-use counties. Among county-level characteristics, a high concentration of psychiatrists (≥15 per 100,000 residents) was associated with a greater likelihood of clozapine initiation, but there was no significant effect of population density or measures of poverty or income on clozapine initiation.

Predictors of clozapine use among treatment-resistant patients

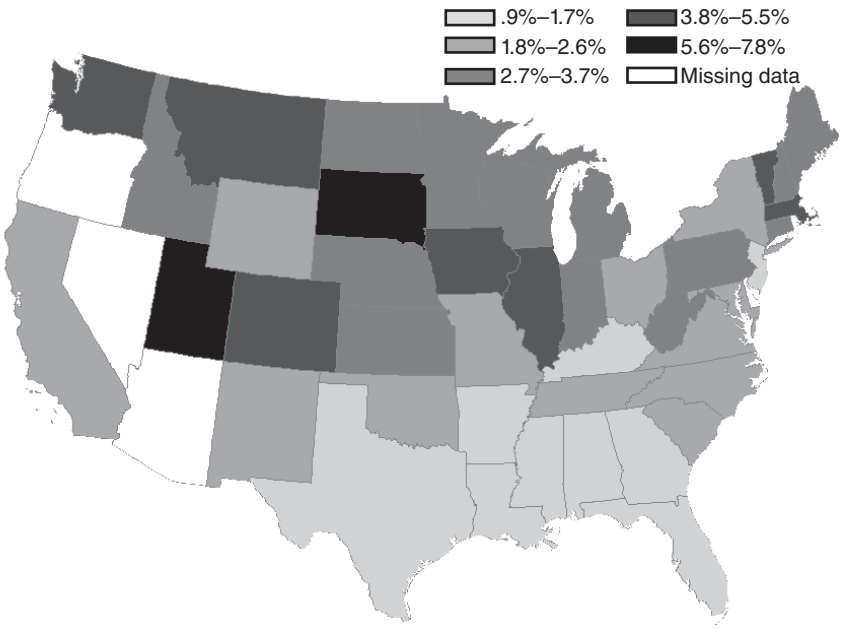
In a similar analysis of episodes where service use was consistent with treatment resistance (N=79,934 episodes), predictors of clozapine use were quite similar to those for the whole population who started a different antipsychotic, although the magnitude of effects was somewhat attenuated. In particular, the effects of age and race-ethnicity persisted but were slightly attenuated among the patients who met criteria for treatment resistance.

Discussion

Clozapine treatment of Medicaid-eligible adults with schizophrenia fell far below the expected proportion of patients likely to benefit from a trial of clozapine. This observation is in line with previous reports from smaller, less generalizable populations. Although the precise proportion of people with schizophrenia disorders who warrant a trial of clozapine is unknown, most estimates suggest a figure ranging from 20% to 30% (16), which is approximately ten times the rate observed in our study. Although treatment resistance was associated with twice the odds of starting clozapine, only one in 18 patients with service use patterns consistent with treatment resistance started a trial of clozapine, the only FDA-approved antipsychotic agent for treatment-resistant schizophrenia.

Figure 1

Clozapine prescribing rates among Medicaid-insured adults with schizophrenia, January 2002–December 2005



Substantial variation occurred in clozapine prescribing rates across U.S. counties. In 1,240 counties of 2,885 examined, there were no new starts of clozapine in the Medicaid program during the study period. Even after controlling for patient demographic and clinical characteristics and other county-level factors, we found that historic usage rates of clozapine were only slightly less important than evidence of treatment resistance in predicting clozapine initiation. One possible explanation is that patient characteristics vary between counties. If this were true, then among patients identified as having treatment resistance, the geographic variability would be expected to be attenuated. However, the magnitude of geographic variation remained largely unchanged in the subgroup of patients with treatment resistance, suggesting that variation in clozapine initiation reflected underlying geographic variation in access to clozapine rather than variation in case mix.

Consistent with prior research, we found that African Americans with schizophrenia diagnoses were less likely than their white counterparts to initiate clozapine treatment (2,13,17). Low clozapine initiation rates among African-American patients may be due in part to "benign ethnic neutropenia," a phenomenon that is an artifact of using white populations to define the normative neutrophil counts required for clozapine use (18). Because members of certain racial and ethnic groups are more likely than whites to have neutrophil counts below the threshold levels required to initiate clozapine, these groups, including African Americans, may have lower eligibility rates for clozapine use (19). It is possible that racial-ethnic differences in attitudes toward psychotropic medications, which have been demonstrated in other clinical contexts (20,21), may contribute to racial-ethnic differences in clozapine initiation. The persistence of racial-ethnic differences in clozapine usage suggest that this disparity is not simply a matter of slower diffusion to minority

Table 2

Adjusted odds of clozapine initiation among 629,809 antipsychotic episodes of adult Medicaid beneficiaries with schizophrenia, stratified by demographic and clinical characteristics[a]

Patient group	AOR	95% CI
Male (reference: female)	1.26	1.22–1.30
Age (reference: 55–64)		
18–24	1.81	1.62–2.02
25–34	1.53	1.40–1.67
35–44	1.29	1.19–1.41
45–54	1.15	1.09–1.22
Race-ethnicity (reference: white, non-Hispanic)		
African American, non-Hispanic	.663	.61–.72
Hispanic	.788	.71–.87
Other	.889	.84–.94
Diagnosis (reference: schizophrenia)		
Schizophreniform	.93	.83–1.05
Schizoaffective	.91	.86–.97
Substance use disorder diagnosis, past year (reference: absent)	.71	.65–.76
Deliberate self-harm, past year (reference: absent)	.98	.85–1.13
Diabetes diagnosis, past year (reference: absent)	.90	.86–.95
Cardiovascular diagnosis, past year (reference: absent)	1.03	1.00–1.07
HIV diagnosis, past year (reference: absent)	.42	.35–.50
Mood stabilizers, past year (reference: absent)	1.55	1.47–1.62
Long-acting injectable antipsychotic, past year (reference: absent)	1.16	1.06–1.27
Mental health emergency service use, past year (reference: none)	.96	.90–1.04
Outpatient visits for schizophrenia, past year (reference: 0–9 visits)		
10–29	1.32	1.23–1.42
30–49	1.77	1.57–1.98
≥50	2.06	1.82–2.33
Mental health hospital admissions, past year (reference: 0)		
1	1.19	1.11–1.27
2	1.36	1.25–1.48
3	1.51	1.35–1.68
≥4	1.62	1.41–1.87
Treatment resistance (reference: absent)	1.92	1.83–2.03

[a] Adjusted odds ratio (AOR) from a single logistic regression, with all variables entered as independent variables and antipsychotic medication (clozapine versus other) entered as the dependent variable. The analysis controlled for state, coded as individual dummy variables (state coefficients not shown).

groups, as has been described for other antipsychotics (22).

Greater clozapine use among male and younger patients is consistent with prior research (2,13). The sex difference may be clinically appropriate given that men are known to have a more severe course of schizophrenia than women (23,24). An association of clozapine initiation with younger age may reflect efforts to prevent long-term disability, although it may also reflect poorer clozapine access among older patients. The strong association of higher levels of recent mental health service use with clozapine initiation reflects sound clinical decision making.

Among people with schizophrenia who also have substance use disorders, some data suggest that clozapine is associated with higher rates of abstinence from addictive substances (25). However, the finding of lower rather than higher rates of clozapine use among persons with substance use disorders is consistent with prior research (13). Low rates of clozapine initiation among people with substance use disorders may reflect concerns about the reliability of these patients to follow blood-monitoring requirements and concerns that medication nonadherence will require clozapine retitration. Another factor affecting clozapine prescribing in this population may be concerns about interactions between clozapine and substances of abuse (26).

The use of clozapine by people with HIV is complex. On one hand, because HIV primarily affects T4 helper cells and clozapine affects neutrophils, there is no absolute contraindication to using clozapine for people living with HIV. On the other hand, some antiretroviral medications and some antivirals and antibiotics (such as trimethoprim-sulfamethoxazole) that are used for opportunistic infections are also associated with bone marrow toxicity (27). Further, HIV-related infections themselves may affect granulocytes. Thus the low rate of clozapine use by people living with HIV is not surprising but underscores that clozapine treatment is possible for those with HIV infection and can and should be considered for the treatment of refractory symptoms of schizophrenia (27).

Diabetes, cardiovascular disease, and self-harm had little or no relationship to clozapine initiation, although such a relationship could be reasonably expected. Individuals who have not responded to other antipsychotic treatments may prioritize improvement of schizophrenia symptoms over weight and metabolic risks that might exacerbate preexisting cardiovascular disease. In this context, close clinical monitoring and appropriate management of cardiovascular disease are necessary. It is surprising that a recent history of self-harm was not associated with starting clozapine in this population because clozapine earned FDA approval for this indication on the basis of a large-scale clinical trial (10). This clozapine indication may not be well known.

The study had some limitations. First, the definition of treatment resistance is based on service use and does not capture symptoms or functional status. However, the claims-based definition of treatment resistance, which required at least two antipsychotic medication trials and a psychiatric hospitalization in the past year, has face validity and identified a group with heavy mental health service use. Second, because some patients are

prescribed clozapine but do not fill their prescription (28) and others decline efforts to initiate clozapine (29), the results may not reflect the therapeutic intent of the prescribing physicians. Third, the results may not extend to patients who are not covered by the Medicaid program. However, in the United States, Medicaid is the largest source of payment for the treatment of schizophrenia. Approximately two-thirds of adults with schizophrenia in the United States are Medicaid beneficiaries (30). In addition, some of the most severely ill people with schizophrenia do not use services and therefore are not included in this analysis. Finally, data in this study were from the period 2001–2005, but there is evidence suggesting that clozapine use has remained low (2).

Table 3

Likelihood of clozapine initiation among 629,809 antipsychotic episodes of adult Medicaid beneficiaries with schizophrenia, stratified by county characteristics[a]

Patient group	AOR	95% CI
Clozapine-treated patients in county, % (reference: 0%–5%)		
Low (5%–10%)	1.26	1.12–1.42
Medium (10%–15%)	1.71	1.52–1.94
High (>15%)	2.03	1.75–2.30
Psychiatrists per 100,000 residents (reference: 0)		
Medium (.01–14.90)	.97	.88–1.07
High (≥15)	1.17	1.03–1.33
Annual income per capita, county (reference <$25,000)		
Medium ($25,000–49,999)	.99	.87–1.12
High (≥$50,000)	.84	.69–1.02
County population in poverty, % (reference: 0%–14.9%)		
Medium (15.0%–19.9%)	.96	.87–1.06
High (≥20%)	1.01	.86–1.19
County population per square mile (reference: ≤399)		
Medium (400–1,000)	1.08	.98–1.20
High (>1,000)	1.005	.90–1.12

[a] Adjusted odds ratio (AOR) from a single logistic regression, with all variables in Tables 2 and 3 entered as independent variables and antipsychotic medication (clozapine versus other) entered as the dependent variable. The analysis controlled for state, coded as individual dummy variables (state coefficients not shown).

Conclusions

The rate of clozapine initiation among patients with schizophrenia in the Medicaid population was much lower than what would be expected given the prevalence of treatment-resistant schizophrenia. Several groups, including women, members of racial-ethnic minority groups, and older patients, were less likely to start clozapine than those without these characteristics. The geographic variation found in these analyses suggests that local practice patterns greatly influenced clozapine use. To optimize opportunities for recovery from schizophrenia, efforts to make clozapine reliably available in all geographic areas and to all patients for whom it is indicated are needed. Because didactic approaches alone are known to have little impact on prescriber behavior (31), multilevel interventions based on implementation science may be needed (32). Consideration should be given to expanding targets of intervention beyond psychiatrists to include mental health care teams, mental health clinics and systems, policy makers, and patients. In this context, some potentially promising components of vigorous efforts to promote evidence-based clozapine prescribing include academic detailing of psychiatrists, clinical and administrative support to facilitate initiation and monitoring of clozapine trials, regular audit and feedback of clinic performance, payment policies that support clozapine usage, and impartial educational initiatives for patients and family members.

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