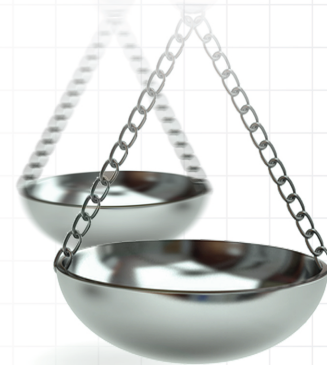




Factors related to the comparative effectiveness of clozapine in patients with schizophrenia

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Aim: To examine the factors related to the comparative effectiveness of clozapine. **Patients & methods:** US insurance claims databases were used to identify schizophrenia patients. To examine the factors modifying the comparative effectiveness of clozapine in relation to other second-generation antipsychotics, a series of variables were interacted with a clozapine indicator in regressions. **Results:** The impacts of clozapine on both persistence and adherence were significantly modified by prior hospitalization, prior epilepsy diagnosis and prior use of antianginal agents. The relative risks of heavy inpatient services use and heavy emergency department services use were also modified by several factors. **Conclusion:** Several factors can be used to identify patients who are more likely to benefit from clozapine than other second-generation antipsychotics.

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Clozapine is the first second-generation antipsychotic (SGA) agent and is the only US FDA-approved antipsychotic for treatment-resistant schizophrenia [1,2]. Its clinical feature of relieving the symptoms of patients whose illness is refractory to other antipsychotics makes it unique in its therapeutic class [3,4]. Moreover, among all antipsychotics, clozapine is associated with the lowest suicide-related and all-cause mortality [5–7] and is approved by the FDA to manage recurrent suicidal behavior among patients with schizophrenia [1,7]. Even more, the superiority of clozapine over other SGAs extends to other outcomes such as persistence to medication and patient satisfaction [6], which may in turn result in better clinical outcomes [8].

Despite its superior efficacy, clozapine is rarely used among patients with schizophrenia [1,5,6]. The underuse largely owes to the risk of fatal agranulocytosis associated with clozapine and the necessity of white blood cells monitoring of clozapine users [1,9]. Obsessive-compulsive disorder has also been documented as a side effect that is more likely to occur among clozapine users than users of other antipsychotics [10], which might have further contributed to the underuse of clozapine. However, previous studies have shown that the underuse is a barrier to optimal care for patients with severe schizophrenia [6,11]. Prominent factors affecting physician's prescription of clozapine include unawareness of clozapine's benefits, apprehension regarding risk of adverse events and lack of experience with the use of clozapine [6,11–13]. Recent work focusing on individual factors related to clozapine use has shown that younger age, more inpatient service utilization, higher mental health expenditure, white race and male sex are positively associated with initiation on clozapine [11]. Researchers have also found that male, older age at onset of illness, shorter duration of illness, bodyweight gain and history of extrapyramidal symptoms while using conventional antipsychotics are positively associated with response to clozapine [14].

Most previous studies have focused on assessing factors predicting response to clozapine. However, given the superiority of clozapine over other SGAs on outcomes such as response and persistence, it is warranted to examine factors related to the comparative effectiveness of clozapine in relation to other SGAs. A better understanding of such factors can provide initiatives to promote the use of clozapine. We know of only one study in which the effect of race-ethnicity on the comparative effectiveness of clozapine and other SGAs was evaluated [5]. However, there

is a paucity of evidence on other individual and clinical factors associated with the comparative effectiveness of clozapine. Therefore, the purpose of the current study was to fill this evidence gap. This study represents a first attempt at examining potential modifiers of clozapine comparative effectiveness.

Methods

Data source & sample selection

This retrospective cohort intent-to-treat analysis used data from Humana medical and pharmacy claims databases (~14 million covered lives) for the period of January 2007 to June 2013. Medical service claims include diagnosis codes in ICD-9-CM format, procedures, service dates and payment amount. Prescription fill information contains the National Drug Codes, days of supply, payment amount, as well as prescription fill dates. The patient file database containing demographic information (age, sex, race-ethnicity, three-digit zip code and geographic areas) and enrollment conditions was also used. The enrollees in the managed care organization consisted of both privately insured individuals and Medicare Advantage beneficiaries. This study was approved by the University of Southern California Institutional Review Board.

Patients were initially selected if they were older than 18 years and had an ICD-9-CM diagnosis code of schizophrenia (295.xx). To be eligible for the study, patients were also required to have filled at least one prescription for any of the following oral antipsychotic drugs: clozapine, aripiprazole, quetiapine, risperidone, olanzapine or ziprasidone. The date on which a person first filled one of these medications was used as the index date. The study population were further restricted to those who had at least a 6-month pre-index wash-out period without use of SGAs [15,16] and a 12-month post-index follow-up period in the databases. Thus, each studied patient had an 18-month observation period during which the patient was enrolled. We adopted the initiator approach with which only the first antipsychotic treatment attempt of each patient was included in analysis. The selected patients were finally grouped into clozapine users and other SGA users.

Outcome variables

Studies have shown that adherence and persistence to antipsychotic medication is associated with better clinical outcomes [17,18]. Using adherence or persistence as a measure of antipsychotic effectiveness is supported by prior clinical trials [2] and retrospective comparative effectiveness research studies [5,15]. We evaluated adherence and persistence by two measures. The primary outcome variable in the current study was time to discontinuation for any cause. Time to discontinuation was defined as the number of days since index date until a 15-day or longer gap between two fills (the end of supply of a fill and the fill date of the next fill) for the same drug [5,19,20]. This variable was truncated to be at most as long as the follow-up period. The second measure was the proportion of days covered (PDC). The PDC numerator was the number of days covered by the prescription fills of the index drug during the measurement period [21,22], and the denominator was 360 days. Two other measures of effectiveness were two indicators for heavy use of emergency department (ED) services (≥ 4 ED visits) and heavy use of inpatient services (≥ 3 inpatient admissions), respectively [23].

Baseline characteristics & explanatory variables

Demographic information, pre-index healthcare use and pre-index comorbidity diagnoses were used as baseline characteristics. Demographic information included age, sex, race-ethnicity (categorized as white non-Hispanic, black non-Hispanic, Hispanic/Latino and all other races), and insurance type (private vs medicare advantage). 'All other races' included Asian, North American Native, other races, unknown and missing values. Pre-index healthcare use included total costs, an indicator of inpatient admission, and an indicator of ED visit. Pre-index comorbidity variables included Charlson Comorbidity Index (CCI) [24], major depression, substance abuse and suicide. An additional variable included as a baseline characteristic was an indicator of a diagnosis of bipolar disorder at any time in the databases.

To examine the modification effects of demographic and clinical factors on the comparative effectiveness of clozapine, the following binary variables and their interaction terms with an indicator of clozapine were included in multivariate regressions: demographic variables: age categories (18–34 years, 35–44 years, 45–54 years, 55–64 years, ≥ 65 years) and sex; pre-index health services use: had any inpatient admission and had any ED visit; pre-index diagnoses: asthma, epilepsy, hyperlipidemia, major depression, substance abuse and suicide; pre-index use of drug classes other than SGAs: antidiabetics, diuretics, hypnotics, antihypertensive agents, ophthalmic agents, antihyperlipidemic agents, psychotherapeutic and neurological agents, antimanic agents, antianginal agents and

Table 1. Baseline and pre-index characteristics of unmatched and matched samples.

Patient characteristics	Unmatched			Matched	
	Clozapine (n = 373)	other SGAs (n = 16808)	p-value	other SGAs (n = 1510)	p-value
Age	48.8 (12.5)	53.5 (15.1)	<0.001	49.1 (13.6)	0.682
Male (n, [%])	220 (58.98)	7975 (47.45)	<0.001	865 (57.28)	0.553
Race/ethnicity (n, [%])					
White	237 (63.54)	9278 (55.20)	0.001	843 (55.83)	0.007
Black	27 (7.24)	2443 (14.53)	<0.001	143 (9.47)	0.178
Hispanic	13 (3.49)	571 (3.40)	0.926	64 (4.24)	0.511
Other races	96 (25.74)	4516 (26.87)	0.626	460 (30.46)	0.073
Medicare (n, [%])	353 (94.64)	15191 (90.38)	0.006	1394 (92.32)	0.121
Total costs (US\$)	2680 (12716)	6776 (20964)	<0.001	2995 (13774)	0.689
Hospitalization (n, [%])	79 (21.18)	6271 (37.31)	<0.001	342 (22.65)	0.542
ED attendance (n, [%])	29 (7.77)	5163 (30.72)	<0.001	137 (9.07)	0.428
CCI	0.09 (0.57)	0.38 (1.11)	<0.001	0.12 (0.66)	0.496
Bipolar disorder at any time (n, [%])	147 (39.41)	8598 (51.15)	<0.001	650 (43.05)	0.203
Pre-index diagnoses (n, [%])					
Major depression	12 (3.22)	2435 (14.49)	<0.001	83 (5.50)	0.072
Substance abuse	24 (6.43)	2486 (14.79)	<0.001	108 (7.15)	0.627
Suicide	1 (0.27)	105 (0.62)	0.384	2 (0.13)	0.556

Values are presented as mean (standard deviation) unless otherwise specified.

CCI: Charlson Comorbidity Index; ED: Emergency department; n: Number of sample; SGA: Second-generation antipsychotic.

anxiety medications. Additional covariates which were included to control for potential bias in regressions were the clozapine indicator, race/ethnicity groups, insurance type, pre-index total costs, pre-index number of outpatient visits, pre-index number of psychiatric facility (place of service codes 51–57) visits/admissions [25], pre-index CCI and indicators of pre-index somnia, pre-index dizziness, pre-index headache and bipolar disorder.

Statistical analyses

To address potential selection bias in medications received, we carried out a propensity score matching (PSM) process [26]. A logistic model was used to predict clozapine use with all the explanatory variables described in the previous section except the interaction terms and the clozapine indicator. We then performed a nearest neighbor matching [26,27] process with a caliper of 0.2. For each clozapine user (treated unit), six patients in the other SGAs group (controls) were identified. Baseline characteristics of clozapine users and other SGA users were compared for both the full cohort and the matched cohort. T-tests and χ^2 square tests were used to compare continuous and categorical variables, respectively. OLS regressions were then used to model time to discontinuation using the matched samples, and logistic regressions were used to model heavy use of ED services and heavy use of inpatient services. The analyses were conducted using SAS (version 9.3) and Stata (version 13).

Results

A total of 17,181 patients who met the inclusion criteria were identified. 373 (2.17%) of them were clozapine users and 16,808 (97.83%) of them were other SGA users. The matching process selected 1510 patients in the other SGAs group. The actual ratio of the controls to the treated units was 4.05 instead of 6. This is because some controls were matched to more than one treated unit.

The descriptive statistics of the full cohort and the matched cohort are listed in Table 1. Three baseline characteristics were not significantly different between the clozapine group and the control group in the full cohort, while all of the other baseline characteristics were significantly different. Namely, the proportions of Hispanic patients, the proportions of patients in all other race groups, and the proportions of patients who had suicidal behavior in the pre-index period were not significantly different between the two groups. However, when the matched cohort was examined, all the baseline characteristics except the proportions of white patients were not significantly different between the two groups.

Table 2 presents the results from the unadjusted analyses of outcomes. The mean time to discontinuation of

Table 2. Unadjusted comparison of outcomes between clozapine users and other second-generation antipsychotics users.

Outcome	Clozapine	Other SGAs	p-value
Time to discontinuation (days)	316.4 (104.5)	258.4 (141.5)	<0.001
PDC	0.82 (0.27)	0.68 (0.37)	<0.001
Heavy inpatient services use (n, [%])	195 (52.28)	794 (52.58)	0.916
Heavy ED services use (n, [%])	118 (31.64)	592 (39.21)	0.007

Values are presented as mean (standard deviation) unless otherwise specified.

ED: Emergency department; n: Number of sample; PDC: Proportion of days covered; SGA: Second-generation antipsychotic.

Table 3. Results from multivariate ordinary least squares regressions and logistic regressions.

Baseline and pre-index characteristics	Time to discontinuation (days)	PDC	Heavy inpatient services use (presented as OR)	Heavy ED services use (presented as OR)
Main effect of clozapine	37.2 [‡] (8.9 to 65.5)	0.10 [‡] (0.03 to 0.18)	2.047 [†] (1.37 to 4.030)	0.570 (0.182 to 1.787)
Hospitalization	35.2 [†] (0.3 to 70.1)	0.10 [†] (0.01 to 0.19)	5.150 [§] (2.100 to 12.632)	
ED attendance			0.095 [§] (0.022 to 0.415)	
Asthma				0.002 [†] (0.000 to 0.271)
Epilepsy	-343.9 [§] (-468.0 to -219.7)	-0.89 [§] (-1.22 to -0.56)		
Major depression			15.266 [†] (1.516 to 153.745)	61.736 [‡] (3.470 to 1098.208)
Use of antianginal agents	-205.2 [§] (-308.6 to -76.1)	-0.56 [§] (-0.86 to -0.26)		
Anxiety medications				0.054 [†] (0.003 to 0.894)

[†]p < 0.05

[‡]p < 0.01

[§]p < 0.001.

Values are presented as estimate (95% CI).

ED: Emergency department; OR: Odds ratio; PDC: Proportion of days covered.

the clozapine group and the other SGAs group were 316.4 and 258.4 days, respectively ($p < 0.001$). Similarly, the mean PDC of the clozapine group was significantly greater than that of the other SGAs group (0.82 vs 0.68; $p < 0.001$). The proportion of patients who had heavy post-index inpatient services use in the clozapine group was similar to that in the other SGAs group (52.28 vs 52.58%; $p = 0.916$). However, a significantly smaller proportion of patients in the clozapine group incurred heavy ED services use compared with the other SGAs group (31.64 vs 39.21%; $p = 0.007$).

The regression results of the interactive effects are summarized in Table 3. For simplicity, only the results of the main effects of clozapine and statistically significant interactive effects ($p \leq 0.05$) are presented. Clozapine was significantly associated with longer time to discontinuation (37.2 days) and greater PDC (0.10) compared with other SGAs. Prior hospitalization significantly positively moderated the effects of clozapine on time to discontinuation and PDC (35.2 days and 0.10). In contrast, prior epilepsy (-343.9 days and -0.89) and prior use of antianginal agents (-205.2 days and -0.56) significantly inhibited the effects of clozapine on time to discontinuation and PDC. Clozapine was associated with a higher risk of heavy inpatient services use (Odds ratio [OR]: 2.047) compared with other SGAs. However, the main effect of clozapine on the risk of heavy ED services use was not significant. Prior hospitalization (OR: 5.150) and prior major depression (OR: 15.266) negatively moderated the risk of heavy inpatient services use associated with clozapine, whereas prior ED attendance (OR: 0.095) positively moderated this risk. Moreover, prior major depression (OR: 61.736) negatively moderated the risk of heavy ED services use associated with clozapine, yet prior asthma (OR: 0.002) and prior use of anxiety medications (OR: 0.054) positively moderated this risk.

Discussion

In this retrospective cohort study, we examined demographic and clinical factors which could affect the comparative effectiveness of clozapine in relation to five other SGAs among patients with schizophrenia. To our knowledge, this is the first study which screened a long list of individual and clinical factors potentially affecting the comparative effectiveness of clozapine. Only a small portion of patients initiated clozapine therapy in the current study. Given the superior efficacy [1,6,7,11] and severe underuse of clozapine [1,6,11], the findings of the current study provide

important evidence for the identification of patients who could benefit from clozapine. It is useful to identify individual factors that can be potentially used in clinical practice to promote the use of clozapine.

According to the results from the current study, patients who have prior hospitalizations are likely to have greater gain on persistence and adherence from choosing clozapine over other SGAs than patients without prior hospitalization. On the other hand, patients who have prior epilepsy diagnosis and patients who have prior use of antianginal agents are less likely to have the relatively good persistence with and adherence to medication associated with clozapine. Clozapine is associated with a higher risk of heavy inpatient services use. Also, the higher relative risk could be aggravated by prior hospitalization and prior diagnosis of major depression but attenuated by prior ED attendance. Clozapine has no impact on the risk of heavy ED services use in relation to other SGAs. However, the risk of heavy ED services use associated with clozapine relative to that of other SGAs increases if the patient has prior diagnosis of major depression, yet decreases if the patient has prior diagnosis of asthma or prior exposure to anxiety medications. Future research on whether patients who are more likely to benefit from clozapine compared with other drugs can actually have greater gains in outcomes from clozapine treatment than other patients is warranted. If future evidence converges, prescribers should consider taking account of these individual factors that affect the comparative effectiveness of clozapine and target the patients who are more likely to gain from clozapine use.

Using recent administrative claims databases (2007–2013) of a big managed care organization, we identified a large group of patients with schizophrenia who initiated SGA therapy with one of the study medications. To reduce potential treatment selection bias, we carried a PSM process to identify clozapine users and other SGA users who were comparable at baseline. The initiator approach was used in this study. Thus, the overlapping episodes issues which are often encountered in multi-episode approaches was avoided [28]. Also, clinicians and patients normally use prior treatment history information to make current treatment decisions. Hence, using the multi-episode approach may incur stronger treatment selection bias than the initiator approach because there may be more factors affecting subsequent treatment decisions than initial treatment decisions.

The results of this study should be interpreted in light of several limitations. Although a PSM procedure was used and a long list of variables were included as control variables in regressions, confounding bias could not be ruled out due to the nature of the administrative claims databases. Some important information such as disease severity and clinical symptoms is typically not included in claims databases. Another limitation is that although the initiator approach allowed a clean comparison [28], it also excluded treatment-resistant patients from analysis. As a result, the clozapine users in this study may not be representative of all clozapine users. Also, this study excluded Medicaid patients. This may further undermine the external validity. A fourth limitation is that the sample size of clozapine users in this study is modest. As such, the statistical power of this study may not be optimal. Furthermore, some of the statistically significant findings had small effect sizes. For these results, gaps may exist between statistical significance and clinical significance. Last but not least, the 6-month wash-out period could not enable us to capture truly treatment-naïve subjects. It also restricts our understanding of additional patient characteristics such as the time gap between first diagnosis and the index treatment. However, this problem is unlikely to be solved with retrospective administrative claim data resources in the USA because data of lifetime history are normally not available.

Conclusion

We found several factors which modified the comparative effectiveness of clozapine in relation to other SGAs. The findings of this study suggest that patients who have prior ED attendance, patients who have prior diagnosis of asthma, and patients who have prior use of anxiety medications are associated with better comparative effectiveness of clozapine in relation to other SGAs. In addition, patients who have prior diagnosis of epilepsy, patients who have prior diagnosis of major depression and patients who have prior use of antianginal agents are associated with worse comparative effectiveness of clozapine in relation to other SGAs. Patients who have prior hospitalization can expect better persistence and adherence to clozapine than other patients but also higher relative risk of heavy inpatient services use.

Summary points

- Clozapine is the only US FDA-approved antipsychotic for treatment-resistant schizophrenia.
- Despite its superior efficacy, clozapine is rarely used among patients with schizophrenia due to its unique safety profile.
- The prudential prescription of clozapine may have led to its underuse and might be a barrier to those who can benefit from it.
- Previous studies have examined several factors that were related to the responsiveness to clozapine but seldomly its comparative effectiveness.
- We confirmed that clozapine was associated with better persistence and adherence than other second-generation antipsychotics (SGA) in the real-world setting.
- Patients who had any prior hospitalization were more likely to respond to clozapine in relation to other SGAs.
- Patients who had prior epilepsy diagnosis and prior use of antianginal agents were less likely to respond to clozapine in relation to other SGAs.
- If these modifiers of comparative effectiveness can be confirmed in future research, they should be taken into consideration of identifying appropriate candidates of clozapine use.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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