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Cluster Analysis of Clozapine Consumer Perspectives and Comparison to Consumers on Other Antipsychotics

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Despite its unique efficacy, clozapine remains underutilized in the United States. Perceptions about clozapine and barriers to its use have been examined among prescribers, but insufficiently studied among consumers. We surveyed 211 antipsychotic consumers (86 on clozapine and 125 on other antipsychotics) on their medication-related perspectives in a public hospital system in Atlanta, Georgia, USA. In contrast to their previous regimen, 72% of clozapine consumers reported they were more satisfied with clozapine. When compared with consumers taking other antipsychotics, clozapine consumers reported more side effects but did not differ on other measures of satisfaction or efficacy. We found Caucasians to be overrepresented among clozapine, as compared to other antipsychotic consumers. Side effects most strongly associated with poor safety ratings were sedation, limb jerking, and dizziness when standing. However, clozapine was only rated less safe by consumers who experienced more than one of these side effects. We used an unsupervised clustering approach to identify three major groups of clozapine consumers. Cluster A (19%) had the lowest safety ratings, aversion to blood work, and a high rate of side effects that associate with lower safety ratings. Cluster B (25%) experienced more hospitalizations and reported satisfaction with clozapine that correlated with efficacy ratings, irrespective of safety ratings. Cluster C (56%) experienced fewer hospitalizations, fewer previous drug trials, greater educational attainment, lower rates of smoking, and rated clozapine more highly. This work identifies common side effects that influence the subjective safety of clozapine and suggests that attitudes toward clozapine depend on context-specific factors.

Key words: attitudes/schizophrenia spectrum disorders/shared decision making

Introduction

Decades of research have shown the superior efficacy of clozapine to treat positive symptoms in patients with treatment-resistant schizophrenia.[1–5] Compared to other antipsychotics, clozapine is associated with lower rates of psychiatric hospitalization[6,7] and suicidality.[8,9] However, clozapine is underutilized in the US compared to other developed countries,[10,11] while rates of antipsychotic polypharmacy are high,[12] despite the practice yielding mixed results.[7] In a review of Medicaid data clozapine was only prescribed in 5.5% of antipsychotic starts in patients with treatment patterns consistent with resistant schizophrenia.[13]

Clozapine is underutilized for administrative, prescriber, and consumer-related reasons. Administrative barriers include coordinating inpatient and outpatient settings, developing systems for hematologic monitoring, cost, brief office visits, prescriber turnover, and care coordination with pharmacies. Prescriber concerns include managing side effects such as neutropenia, myocarditis, weight gain, sedation, and sialorrhea. Prescribers often believe their patients will not tolerate the side effects of clozapine[14] or adhere to the frequent hematologic monitoring required,[15] describing blood monitoring in one survey as one of the most "problematic" aspects of clozapine use.[16] Lack of experience can also lead to overestimating clozapine-associated mortality.[16,17]

Consumer perspectives and the disconnect at the consumer–prescriber intersection are critically important to understanding clozapine's underutilization. In a study of outpatient clozapine consumers in the United Kingdom, 88.6% preferred staying on clozapine rather than switching.[18] In another study of largely outpatient

clozapine consumers in Canada with diagnoses of schizophrenia and schizoaffective disorders, 86% of consumers preferred clozapine to other antipsychotics.[19] However, in both studies there was no comparison group, and one might assume that consumers would be relatively satisfied with the antipsychotic medication they were currently taking otherwise it would be changed. Regarding the consumer-prescriber intersection, in Great Britain, 52% of clinicians estimated that consumers would be unhappy about the required blood testing, while only 19% of consumers taking clozapine reported that this was the case.[20] A study of potential clozapine consumers suggested that a requirement of inpatient titration of clozapine was the largest barrier to its initiation, and blood work was less of a concern.[21] With regard to adverse effects, retrospective analyses suggest that clozapine confers a greater burden of side effects than other second-generation antipsychotics.[22]

Given the paucity of data on consumer opinions on clozapine in the US, we conducted a cross-sectional study to examine consumers' preferences and attitudes toward their current antipsychotic regimen, specifically comparing clozapine consumers with consumers of other antipsychotics in a large metropolitan, multi-cultural, community mental health setting. Then, to identify consumer-specific correlates of preference, we applied clustering approaches to identify distinct subgroups of individuals.

Methods

Setting and Sample

Consumers were recruited from inpatient and outpatient mental health settings in a metropolitan, public hospital system in Atlanta, GA from January 12, 2015 to January 2, 2018. Most individuals were recruited from a clinic serving individuals with persistent symptoms of psychosis, which specializes in clozapine use. Eligible participants were ≥18 years old, understood English, and were prescribed an antipsychotic medication. No participants were excluded for medical or psychiatric diagnoses, though the clinic primarily serves individuals with schizophrenia-spectrum disorders.

Procedures and Measures

Individuals answered 40 survey questions about their experiences and satisfaction with antipsychotic medications (supplement). Consent was obtained from each participant, and surveys were either self-administered or read aloud by a member of the research team. The Flesch Kincaid grade level of the survey was 7.8. Questions included demographic information, psychiatric history, previous medications, and perceptions of medication safety and efficacy. Participants scored clozapine efficacy, clozapine safety, and satisfaction with their current regimen on a scale of 0–10 (10 being safest or best). Participants completed the survey on paper or electronically through REDCap.[23] Paper surveys were transcribed into REDCap. Evaluations took approximately 20 min and participants were not compensated. The Emory University Institutional Review Board deemed the study exempt, and the Grady Research Oversight Committee approved the study.

Data analyses

Statistical analyses were conducted with R (version 4.0.2). The continuous data in our study were not normally distributed (as determined by Kolmogorov–Smirnov tests) and with unequal group sizes, so the Wilcoxon Rank Sum test was utilized for two sample tests and the Kruskal–Wallis test for multi-sample tests. Post hoc testing was carried out using Dunn's test of multiple comparisons. Categorical data were analyzed using Chi-square contingency table tests and post hoc testing was carried out with Bonferroni correction based analysis of residuals.[24]

Clustering of consumers was carried out using the multiple factor analysis (MFA) approach implemented in the FactoMineR package.[25] MFA implements a principal component-based methodology combined with a multiple correspondence analysis suitable for categorical variable. Three clusters were selected based on total inertia calculations: cluster splitting ended when the total inertia gain, a composite measure of between and within cluster variance, was greatly reduced by further splitting. Clustering was limited to clozapine consumers due to data availability. Questions were excluded if >25% of participants did not answer, and participants were excluded if they did not answer questions with an otherwise high response rate (>95%). Final variables included age, sex, race, site of survey (inpatient/outpatient), education level (did not complete high school, high school or GED, college, master's degree, doctoral degree), cigarette use, marijuana use, previous antipsychotic use, current antipsychotic use, attempted suicide, inpatient hospitalization, number of hospitalizations, current antipsychotic satisfaction, fear of needles, fainting at blood, fear of blood draws, discomfort with clozapine blood work, satisfaction with clozapine compared to the previous regimen, subjective safety of clozapine, subjective efficacy of clozapine, and side effects from clozapine. Other antipsychotics included aripiprazole, ziprasidone, haloperidol, lurasidone, olanzapine, fluphenazine, quetiapine, chlorpromazine, risperidone, and paliperidone. Side effects were adapted from the Glasgow Antipsychotic Side-effects Scale for Clozapine, and included weight gain, diabetes, drooling, dizziness upon standing, limb jerking, dry mouth, nausea or vomiting, bedwetting, constipation, muscle stiffness, sedation, low blood pressure, seizures, sexual problems, and low white blood cell counts.[26]

Cluster integrity analysis was carried out through bootstrapping, or resampling the original dataset with replacement, and implementing MFA to determine both the optimal number of groups and the cluster membership of each consumer. The widely used Jaccard similarity score,[27] the ratio of the intersection and the union of two groups, was used to calculate the similarity between 25 bootstrapped and the original clusters. When greater than 3 clusters were optimal based on the inertia calculation, 3 clusters were forced to calculate Jaccard scores.

Results

Comparison of Clozapine and Other Antipsychotic Consumers

Demographic and Clinical Characteristics. We surveyed 211 participants and analyzed those who responded, "I am currently taking clozapine" (n = 70), "I recently started clozapine titration" (n = 16), or "I have currently been prescribed an antipsychotic but have never taken clozapine in the past and am not considering taking it in the future" (n = 108). Respondents were divided into those currently taking clozapine ("clozapine consumers", n = 86, 44.3%) and those currently taking a different antipsychotic ("other consumers", n = 108, 55.7%). The ages of clozapine consumers ranged from 20 to 72, mean 42 (SD 13.6), while the ages of other consumers ranged from 18 to 75, mean 43 (SD 12.3).

Demographically, the two groups differed by clinical site and race (table 1). While most participants completed the survey in the outpatient clinic, clozapine consumers were more likely to take the survey on the inpatient unit than those in the other antipsychotic group. Most respondents identified as Black or African American (n = 150, 77.7%), followed by White/Caucasian (n = 25, 12.9%), other race (n = 9, 4.7%), Asian (n = 6, 3.1%), or Hispanic/Latino (n = 3, 1.6%). Other race, Asian, and Hispanic/Latino were combined for statistical analyses (table 1). Clozapine use differed significantly among racial groups (χ^2 = 6.48, P = 0.039), with White/Caucasian consumers overrepresented in the clozapine group compared to chance. This overrepresentation approached significance in post hoc multiple correction testing (residual = 2.53, Bonferroni corrected P-value = 0.069).

Clozapine is often reserved for treatment-resistant psychosis, so we examined whether metrics of illness course in clozapine consumers differed from other consumers. Clozapine consumers had trialed more antipsychotics before their current regimen (median = 4, IQR = 3) than other consumers (median = 2, IQR = 2). Clozapine consumers also reported significantly more hospitalizations than other consumers, but the number of individuals who had attempted suicide in each group did not significantly differ (χ^2 = 0.043845, P = 0.8341).

Perceptions of Side Effects, Satisfaction, Safety, and Efficacy. Previous studies suggest that clozapine confers more adverse effects than other second-generation antipsychotics,[22] so we compared side effects reported by clozapine consumers and other consumers. Clozapine consumers reported a median of 4 side effects (IQR = 4) while other consumers reported a median of 3 side effects (IQR = 4; Wilcox test = 4642, P = 0.0098). Ratings of current antipsychotic satisfaction, quality of

Table 1. The chi-square test for homogeneity was employed to test for imbalances between clozapine and other consumers. Under the Race category, Other includes participants who responded as Asian (n = 6, 3.1%), Hispanic (n = 3, 1.6%), and Other (n = 9, 4.7%).

		All		Clozapine		Other		Chi-square	
		n	%	n	%	n	%	χ^2	P-value
Sex	Female	65	33.5	30	34.9	35	32.4	0.04	0.83
	Male	129	66.5	56	65.1	73	67.6		
Race	African American	150	77.7	61	70.9	89	83.2	6.48	0.039
	Causasian	25	13	17	19.8	8	7.5		
	Other	18	9.3	8	9.3	10	9.3		
Site	Inpatient Unit	11	5.7	10	11.6	1	0.9	8.35	0.004
	Outpatient Clinic	183	94.3	76	88.4	107	99.1		
Education	Did not Complete High School	57	29.5	23	27.1	34	31.5	3.09	0.54
	High School/GED	98	50.8	44	51.8	54	50		
	College	28	14.5	13	15.3	15	13.9		
	Masters	8	4.1	5	5.9	3	2.8		
	Doctoral	2	1	0	0	2	1.9		
Cigarettes	Yes	89	46.1	37	43.5	52	48.1	0.24	0.62
	No	104	53.9	48	56.5	56	51.9		
Marijuana	Yes	118	62.8	47	58	71	66.4	1.03	0.31
	No	70	37.2	34	42	36	33.6		
Suicide Attempt	Yes	75	51.7	32	37.6	43	40.2	0.04	0.83
	No	117	60.9	53	62.4	64	59.8		

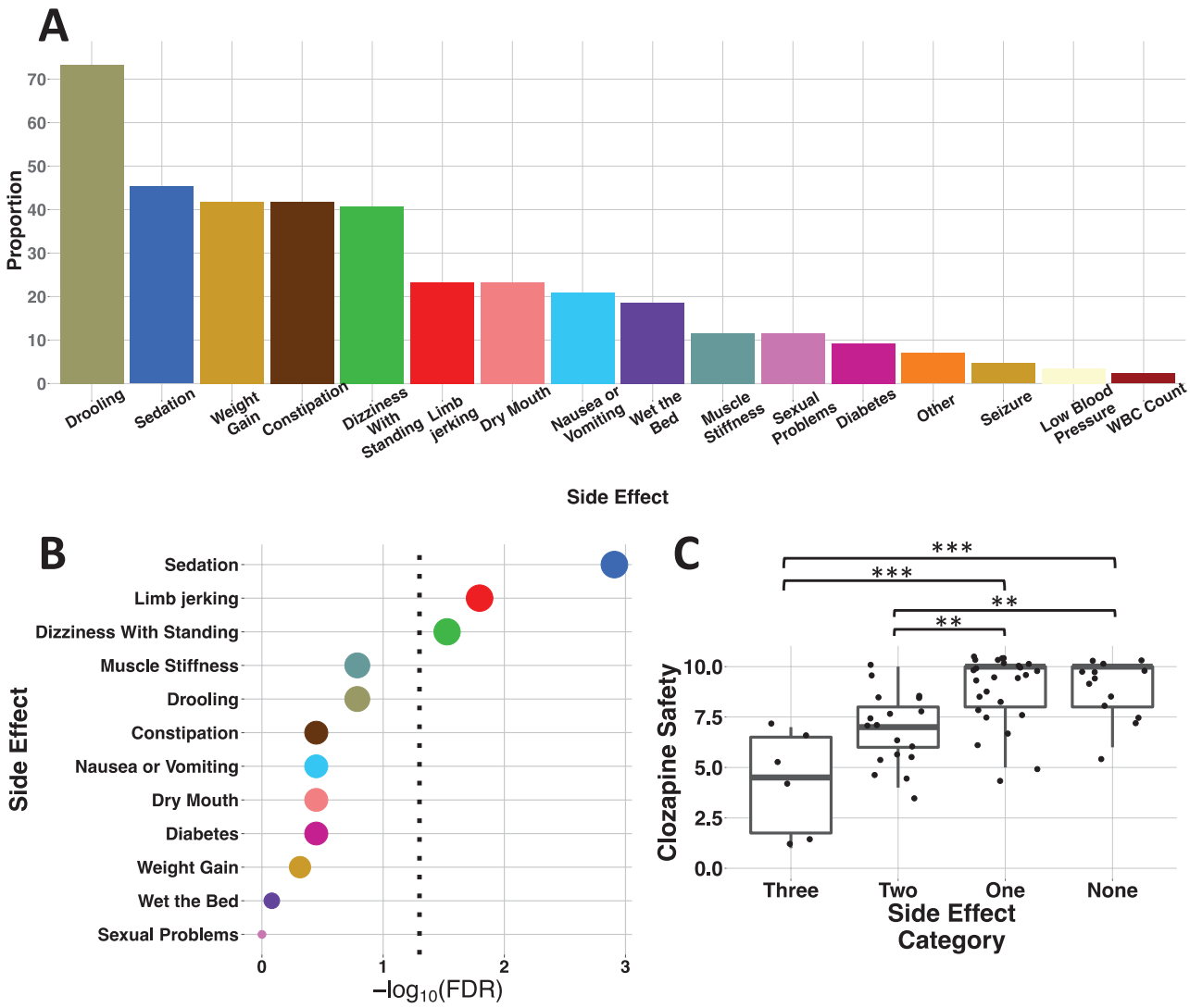

Fig. 1. (A) Proportion of clozapine consumers reporting each side effect. (B) Statistical difference in clozapine safety scores among consumers with/without each side effect. Dotted line is the false discover rate (FDR) adjusted *P*-value of 0.05. (C) Clozapine safety scores according to number of these significant side effects, Kruskal–Wallis $\chi^2 = 26.067$, df = 3, $P = 9.236 \times 10^{-6}$. Symbols represent statistics from post hoc tests: ** 0.01–0.001; *** 0.001–1×10^{-4}.

life improvements, and change in social ability did not differ between groups.

Analysis of Clozapine Consumers

Current Regimen Satisfaction. Most (72%) clozapine consumers said they were "more satisfied with clozapine" than with their previous regimen, while 20.5% reported the "same degree of satisfaction" and 1.5% said they were "less satisfied with clozapine." When asked how clozapine helped them, consumers described fewer positive symptoms (e.g., hallucinations, paranoia), as well as better sleep and less anxiety.

Significant Side Effects. The clozapine side effects most frequently reported were drooling ($n = 63$; 73%), sedation ($n = 39$; 45%), constipation ($n = 36$; 42%) and weight gain ($n = 36$; 42%; figure 1A). We compared safety ratings from individuals who did or did not experience each side effect to determine which side effects were associated with lower consumer safety ratings. Dizziness upon standing ($n = 35$, 40.6%), limb jerking ($n = 20$, 23.2%), and sedation ($n = 39$, 45.3%) were all significantly associated with lower clozapine safety ratings, with FDR corrected *P*-values < 0.05 (figure 1B).

Clozapine consumers reported an average of 4 different side effects, so we examined whether multiple of these significant side effects (dizziness upon standing, limb jerking, or sedation) cumulatively influenced safety ratings. We stratified clozapine consumers into those with all three of these significant side effects, any two, any one, or none. Individuals with either two or three significant

side effects rated clozapine significantly less safe than those with one or none of the significant side effects (figure 1C).

We asked a subset of other consumers who had discontinued clozapine (n = 16) why they made this choice. Most cited side effects (n = 12), many endorsed multiple side effects (n = 10), and the most prevalent of which was drooling (n = 6).

Clustering of Clozapine Consumers. To better understand the factors driving consumer preferences, we used the FactoMineR[25] package to identify sub-groups of clozapine consumers based on the variables we collected. We identified three subgroups of consumers, referred to as Clusters A, B, and C. Stability assessment of clusters was assessed using bootstrapping and revealed Jaccard similarity coefficients of 0.77 for cluster A, 0.33 for cluster B, and 0.52 for cluster C (methods). When fewer clusters were identified as optimal in bootstrapping, clusters B and C became mixed.

The main variables delineating each cluster were clozapine safety, number of hospitalizations, attitudes toward clozapine blood work (including fear of needles and fainting at blood), and previous use of risperidone and quetiapine. Racial differences between clusters were not statistically significant (χ^2 = 8.0991, P-value = 0.09).

Cluster A. Individuals in Cluster A (n = 13, 18.8%) rated clozapine less safe and were the same or less satisfied than with their previous regimen. These individuals gave strong negative responses to all questions about blood work, including fear of having blood drawn and fainting at the sight of blood. These consumers were more likely to experience the side effect of dizziness upon standing. Consumers who experienced all three of the side effects linked to lower safety ratings (dizziness, limb jerking, and sedation) were more likely to be in Cluster A, whereas consumers with just one of these side effects were less likely to be in cluster A (overall model statistics: χ^2 = 27.833, df = 6, P = 1.01 x 10^{-4}). 38% (n = 5) of Cluster A individuals reported all three significant side effects and 46% (n = 6) reported two significant side effects.

Cluster B. Cluster B (n = 17, 24.6%) individuals had experienced more hospitalizations than other individuals and had almost all trialed both risperidone and quetiapine. Cluster B individuals were more tolerant of blood work and less afraid of needles. Across all clozapine consumers, antipsychotic satisfaction was positively correlated with both clozapine safety and efficacy ratings. However, antipsychotic satisfaction in Cluster B was strongly correlated with clozapine efficacy, but not related to clozapine safety.

Cluster C. Cluster C (n = 39, 56.6%) encompassed most clozapine consumers. These individuals preferred clozapine to their previous regimen and gave high safety and efficacy ratings. They had experienced fewer hospitalizations and fewer previous drug trials than individuals in other clusters. They were less likely to use tobacco or marijuana and more likely to have a college degree than those in other clusters.

Discussion

Our work presents an analysis of key consumer perspectives in a cohort of outpatient clozapine consumers in a multicultural, urban setting. Our analyses revealed that (1) clozapine consumers are equally satisfied with their regimen when compared head-to-head with other antipsychotic consumers, despite endorsing a higher median number of side effects; (2) sedation, dizziness with standing, and limb jerking in combination negatively influence consumer perceptions of clozapine safety; and (3) distinct clusters of clozapine consumers can be identified with clozapine safety ratings, bloodwork related discomfort, and measures of disease severity segmenting consumers.

Previous work has demonstrated that consumers stable on clozapine are, in general, highly satisfied with their treatment, and prefer clozapine to their previous regimen.[18,19,28] One previous study directly compared clozapine and risperidone consumers, and found that while clozapine consumers had higher positive responses to the drug, there was no difference in negative drug opinions.[28] We extend this work finding that clozapine and consumers of a wide array of other antipsychotics do not differ in measures of drug satisfaction and efficacy, but we include a wider array of consumers on other antipsychotics as a comparison group.

Similar to previous work, we have found that clozapine confers a greater side effect burden compared to other antipsychotic medications.[22] Existing investigations of clozapine-related side effects have largely focused on those that associate with discontinuation. One retrospective analysis of 316 patients found that of the 45% of patients who discontinued, half were due to side effects, with consumer-driven discontinuation due to sedation, followed by nausea and salivation.[29] In another large study (n = 183) utilizing a combination of machine learning based analysis of medical records and manual review, 28% of discontinuation events were due to side effects. Within that set, hematologic side effects were most common (45%), followed by central nervous system-related side effects of which somnolence was the most commonly cited reason.[30] In both of these large studies, the authors also state that multiple side effects were endorsed, and all were included, however, no combination analysis was carried out to determine whether specific sets of side effects are influential. Our work supports the result that sedation is one of the more disconcerting side effects, even amongst clozapine consumers still using

the drug. However, we also find that greater than 40% of our consumers endorse sedation as a side effect. It may be that the degree of sedation differs widely, or as we found that sedation may need to co-occur with other side effects (dizziness with standing and limb jerking) to drive consumer dissatisfaction. Whether this relationship holds with regards to discontinuation is unknown. Future efforts may seek to determine the functional impact of specific side effects and whether specific combinations of side effects associated with medication discontinuation.

In this work, we characterize consumer heterogeneity using an unbiased clustering approach and identify clinical characteristics that delineate groups. Bootstrapped analyses revealed good stability of the clusters, with cluster A having the highest Jaccard score, followed by cluster C. Previous work has indicated that, as a whole, clozapine consumers tend to not be distressed by bloodwork.[20,21] We observe a subset of patients (Cluster A) who are bothered by blood work and have lower scores of medication safety and satisfaction. We find these consumers also endorse a greater number of side effects associated with reduced safety scores. Discomfort around bloodwork may share common biological substrates with these side effects. Alternatively, individuals with aversions to blood work may be more likely to generalize dissatisfaction with these interventions to their perceptions of the medication or more adverse effects from clozapine may produce a general aversion to encounters with the health care system. Practically, providers may wish to spend more time educating clients who raise concerns about hematologic monitoring and develop plans for monitoring and responding to side effects. Blood and injection fears are common and treatable[31] through cognitive behavioral therapies such as exposure and applied tension when starting clozapine or before.

Multiple studies have shown clozapine to be systemically underutilized among racial and ethnic minorities compared to Caucasians.[32] In a 2011 study investigating VA patients initiated on clozapine, the only baseline factor found to be associated with future discontinuation was African-American race.[33] Furthermore, Black and Latino consumers tend to discontinue clozapine at higher rates, but the medicine is equally effective for these groups.[34] Our participants were predominantly Black, male outpatients with a high school education. We observed an imbalance in the racial distribution between clozapine and other consumers, with Caucasians approaching statistically significant overrepresentation in the clozapine group. One of the potential contributors to this may be the lack of awareness of benign ethnic neutropenia—leading to increased discontinuation or reduced initiation of treatment.[35] Future work should aim to increase our understanding of the source of the disparity in clozapine utilization between Caucasians and African Americans. Another solution may be identification of clozapine candidates from electronic medical databases in hospital systems.

Limitations

This work focuses on a cohort of largely outpatient consumers of clozapine and other antipsychotics. These consumers are largely stable on clozapine, so their subjective ratings and experiences are likely to be more positive than those who have discontinued clozapine. We did not audit clinical records so we could not validate participants' self-reported psychiatric histories, side effect profiles, and other clinical variables. We also did not assess whether reported side effects were directly attributable to the antipsychotic medication(s) the participants were taking, nor did we assess adherence or plasma antipsychotic concentrations. Although the clozapine and other antipsychotic groups were similar, the clozapine group reported more extensive psychiatric histories and may have been more likely to meet the criteria for medication-resistant schizophrenia. The other antipsychotic group included 10 different antipsychotics drugs, each with different pharmacodynamic properties and side effect profiles. Furthermore, we did not have data around acute illness severity, time on drug, or time since last exacerbation. We are further limited by our small sample size in comparison to clozapine consumer datasets in the literature thus far.[19,20,28,36,37]

Conclusions and future directions

Our work suggests that consumers of clozapine are equally satisfied with their medication regimen as compared to consumers of other antipsychotics. The novel clustering approach reveals distinct factors in antipsychotic satisfaction among subgroups of clozapine consumers. Future research should explore (1) the durability of these clusters in other samples; (2) correlation of perceived satisfaction, safety, and/or efficacy with clozapine discontinuation; (3) the potential for targeted interventions to maximize resources by focusing on those at highest risk of discontinuation; and (4) whether the dynamic characteristics associated with clozapine satisfaction can serve as a pre- or peri-clozapine initiation treatment target.

Because of their low clozapine safety ratings, the co-occurrence of detrimental side effects, and aversion to bloodwork, Cluster A consumers may be particularly amenable to intervention. These consumers may be considered for augmentation with a psychotherapeutic intervention that can target somatic concerns and/or blood draw-related concerns. Perhaps a limited set of high yield questions could be used to identify individuals who fall into this category and allow future investigators to assess whether side effect support, mitigation of blood work-related fears, or regimen alteration are appropriate for consumers with these characteristics.

The identification of these clusters poses the question of whether the cluster-characteristics persist across psychiatric treatment regimens beyond clozapine. For instance, is there a population of Cluster A individuals with more discomfort around medical procedures who tend to experience more negative side effects no matter which antipsychotic medication they are taking? Do Cluster B individuals consistently overlook side effects and safety concerns in the interest of symptom relief? Do the protective factors of Cluster C individuals predispose them toward better health outcomes across psychiatric contexts?

As medicine shifts toward more personalized treatment, approaches integrating large datasets can generate hypotheses to advance care for specific subsets of individuals. This work provides a consumer-focused roadmap for this approach in psychiatry.

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