A Retrospective Review of the Use of Clozapine in Restoration of Competency to Stand Trial

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Most defendants found incompetent to stand trial have psychotic illnesses. Clozapine has been shown to be superior to other antipsychotic medications in treatment-resistant schizophrenia. It is vastly underutilized, however, including in forensic settings. To our knowledge, there have been no studies exploring the risks and benefits of clozapine for incompetent to stand trial defendants with severe mental illness. We sought to explore the characteristics of patients who were prescribed clozapine in a retrospective sample of defendants deemed incompetent to stand trial with diagnoses of psychotic and bipolar disorders. We found that 25 of 240 defendants (10%) were prescribed clozapine, with 15 (60%) eventually being discharged on it. Of those 15, 8 defendants were successfully restored to competency to stand trial. The restoration rate in the clozapine group was much lower than in the non-clozapine group (32% versus 87%). Our results emphasize the need for prospective comparative studies assessing the efficacy and tolerability of clozapine and other antipsychotic medications related to restoration of competency to stand trial.

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Clozapine is an atypical antipsychotic medication typically used in individuals diagnosed with psychosis who have not responded to adequate treatment with at least two other antipsychotic medications.[1] It has been commercially available for use in the general population in the United States since 1990.[1] Clozapine is superior to numerous typical and atypical antipsychotic medications in the treatment of schizophrenia.[2] Despite its documented superiority, clozapine remains underutilized in the United States, primarily due to its side-effect profile (particularly agranulocytosis) and mandatory hematological monitoring.[1,3] Clozapine is being prescribed more frequently for off-label purposes, including management of self-harm and other-directed aggression.[4] Currently, clozapine is the only FDA-approved medication for the treatment of suicidal behavior in patients with a diagnosis of schizophrenia or schizoaffective disorder. In addition to addressing suicidal behavior, clozapine's potential benefits of addressing self-injurious behavior, as well as hostility and aggression, make it an effective treatment option in forensic populations.[4,5]

Although clozapine has been shown to be effective in the forensic population in a small number of studies, the use of clozapine in correctional facilities and forensic populations in the United States remains limited.[5] Correctional systems in the United States are often independent of mental health systems, and routine psychiatric care may be challenging. The challenges of using clozapine (including frequent blood draws, necessary provider training, and lack of provider familiarity with this medication) lead to it's

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being overlooked and underutilized in forensic settings.[5,6] Research on clozapine in forensic settings has been limited given that prisoners are considered a vulnerable population and are thus afforded special protections in accordance with federal regulations.[7] Studies focusing on clozapine in forensic populations have been conducted in England, Wales, Australia, and Scotland.[5] In England, one study reported that 30 percent of men with schizophrenia (with or without personality disorders) who had a history of serious violence were prescribed clozapine.[8] Another study noted that among 56 men in a British forensic hospital who had been treated with clozapine for a minimum of 90 days, 89 percent reported greater satisfaction with clozapine than with previously prescribed antipsychotic medication.[9]

Research on clozapine's use in prisons and jails has focused on the management of behaviors and symptoms of prisoners with a diagnosis of schizophrenia. Another potential use of clozapine for forensic purposes involves restoration of competency to stand trial. Our previous study explored the association between competency restoration and type of antipsychotic medication in a retrospective sample of defendants with psychotic disorders admitted to a state hospital after being deemed incompetent to stand trial.[10] That study examined the class (i.e., typical versus atypical) and the formulation (i.e., oral versus long-acting injectable) of antipsychotics regarding successful restoration to competency. We reported that the use of long-acting injectable antipsychotics did not seem to significantly increase the odds of being restored to trial competency.[10] The current study examined the potential benefits of clozapine in achieving restoration of competency to stand trial. To our knowledge, there have been no published studies examining the association between clozapine and successful restoration of trial competency among defendants with a diagnosed psychotic disorder.

Methods

Data Source

This study consisted of a retrospective chart review of defendants aged 18 or older who were hospitalized between July 2011 and June 2017 at the Metropolitan Saint Louis Psychiatric Center (MSLPC) for restoration of competency to stand trial.[10] We only included the first admission record of individuals who had been deemed incompetent to stand trial and were ordered by a court to transfer to MSLPC for restoration of competency. From a record review, we recoded the main psychiatric discharge diagnosis. We classified the diagnoses into categories based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. We also retrieved a variety of demographic variables and pharmacological treatment information.[11] This study was approved by the Saint Louis University Institutional Review Board and the Protocol Review Committee of Missouri's Department of Mental Health. All data were de-identified.

Measures

Our main sample included all patients whose main discharge diagnosis was classified as either "schizophrenia spectrum and other psychotic disorders" or "bipolar and related disorders." We designed our independent variable based on whether the patient was prescribed clozapine during hospitalization.

Our dependent variable was dichotomous, indicating whether a patient was found competent to stand trial or permanently incompetent to stand trial based on the opinion of MSLPC's forensic examiners and the court ruling. We extracted information about the maximum prescribed dose of clozapine as well as documented blood levels of clozapine and norclozapine prior to the opinion for each patient. For subjects who had their clozapine discontinued, we surveyed their charts to identify reasons for discontinuation. We also retrieved the following information: age at admission; sex; race/ethnicity; time to competency opinion; length of stay; type of charges (i.e., felony, misdemeanor, or both); number of antipsychotic medications used; formulation and class of antipsychotic medications used; whether the patient was discharged on antipsychotic, mood-stabilizing or antidepressant medications; and whether the patient had a prior history of psychiatric treatment.

Statistical Analysis

Given the small sample size of patients on clozapine, our statistical analysis was mainly descriptive and exploratory. We first compared the sociodemographic, legal, and clinical variables between the clozapine (CLZ) group and the non-clozapine (NoCLZ) group in the total sample. We then compared these variables within the CLZ group between those who were deemed competent to stand trial and those who were

Table 1. Sociodemographic, Clinical, and Legal Characteristics by Clozapine Use

Characteristic	Clozapine Group	No Clozapine Group	*P*
Age, years[a]	32.4 (10.0)	37.5 (18.0)	**.044**
Time to opinion, days[a]	202.0 (129)	147.0 (89.0)	**<. 001**
Length of stay, days[a]	343.0 (333.0)	178.0 (137.0)	**< .001**
Male	22 (88.0)	170 (79.1)	.429
Race			.686
Non-Hispanic white	12 (48.0)	121 (56.3)	
Non-Hispanic black	13 (52.1)	84 (39.1)	
Main psychiatric discharge diagnosis			.748
Schizophrenia spectrum and other psychotic disorders	23 (92.0)	188 (87.4)	
Bipolar and related disorders	2 (8.0)	27 (12.6)	
Competency			**< .001**
Competent to stand trial	8 (32.0)	187 (87.0)	
Permanently incompetent to stand trial	17 (68.0)	28 (13.0)	
Charges type			.651
Felony	17 (70.8)	128 (59.5)	
Misdemeanor	3 (12.5)	35 (16.3)	
Both	4 (16.7)	52 (24.2)	
Prior psychiatric treatment	22 (88.0)	199 (92.6)	.429
Antipsychotic use through stay			
Formulation			.913
Oral	15 (60.0)	130 (60.5)	
Long-acting injectable ± oral	10 (40.0)	79 (36.7)	
Class			.223
Atypical only	10 (40.0)	100 (46.5)	
Typical and atypical	15 (60.0)	89 (41.4)	
Number of antipsychotics through stay			**.009**
One	1 (4.0)	61 (28.4)	
Two or more	24 (96.0)	147 (68.4)	
Psychiatric medications upon discharge			
Antipsychotics	24 (96.0)	172 (80.0)	.056
Mood stabilizers	9 (36.0)	55 (25.6)	.338
Antidepressants	5 (20.0)	60 (27.9)	.483

[a] Data presented as median (interquartile range).
All other data are presented as *n* (%). *P* values in bold indicate statistical significance: $p < 0.05$. Clozapine Group: $n = 25$; No Clozapine Group: $n = 215$.

determined to be permanently incompetent to stand trial. We measured the bivariate associations using the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. For both sets of bivariate analyses, we determined statistical significance using two-sided tests at the alpha level cutoff of five percent. We used SPSS 21 (IBM Corp., Armonk, NY) to conduct the data analysis.

Results

Between-Group Comparison

Our main sample consisted of the records of 240 defendants, of whom 25 (10.4%) were treated with clozapine during their stay. The CLZ group was significantly younger (32.4 versus 37.5 years, $P = .044$). The time to opinion and length of stay were significantly shorter for the NoCLZ group (68% versus 13%; $P < .001$) (Table 1). There were no significant differences in sex, race/ethnicity, main psychiatric discharge diagnoses, and charges between the two groups.

Individuals in the CLZ group were more likely to be determined permanently incompetent to stand trial than those in the NoCLZ group ($P < .001$). A large majority of patients in both groups (92% of the total sample) had a history of psychiatric treatment prior to their admission to the hospital. Nearly all patients in the CLZ group (96%) were tried on two or more antipsychotics during their hospitalization, compared with 68 percent of the NoCLZ group ($P = .009$).

CLZ Group Characteristics

Our CLZ sample included the records of 25 defendants, of whom 8 (32%) were deemed competent to stand trial (Table 2). All defendants except one were treated with clozapine prior to their competency reevaluation, with a median maximum dose of

Table 2. Sociodemographic, Clinical, and Legal Characteristics of the Clozapine Group by Outcome of Competency Restoration

Characteristic	Competent to Stand Trial	Permanently Incompetent to Stand Trial	*P*
Age, years[a]	36.2 (7.3)	28.9 (10.3)	.315
Time to opinion, days[a]	183.0 (83.0)	225.0 (166.0)	**< .001**
Length of stay, days[a]	214.0 (77.5)	415.0 (324.0)	.063
Maximum clozapine dose prior to opinion[a]	475.0 (275.0)	400.0 (462.5)	.892
Clozapine dose at blood draw[a]	375.0 (250.0)	450.0 (300.0)	.314
Last clozapine level prior to opinion[a]	397.0 (141.0)	473.0 (431.0)	.209
Last norclozapine level prior to opinion[a]	158.0 (43.0)	293.0 (105.0)	**.010**
Clozapine dose upon discharge[a]	425.0 (206.3)	500.0 (250.0)	.593
Male	7 (87.5)	15 (88.2)	1.000
Race			1.000
Non-Hispanic white	4 (50.0)	8 (47.1)	
Non-Hispanic black	4 (50.0)	9 (52.9)	
Main psychiatric discharge diagnosis			1.000
Schizophrenia spectrum and other psychotic disorders	7 (87.5)	16 (94.1)	
Bipolar and related disorders	1 (12.5)	1 (5.9)	
Charges type			.339
Felony	7 (87.5)	10 (62.5)	
Misdemeanor	1 (12.5)	2 (12.5)	
Both	0 (0.0)	4 (25.0)	
Prior psychiatric treatment	5 (62.5)	17 (100.0)	**.024**
Antipsychotic use through stay			
Formulation			1.000
Oral	5 (62.5)	10 (58.8)	
Long-acting injectable ± oral	3 (37.5)	7 (41.2)	
Class			.667
Atypical	4 (50.0)	6 (35.3)	
Typical and atypical	4 (50.0)	11 (64.7)	
Number of antipsychotics through stay			.320
One	1 (12.5)	0 (0.0)	
Two or more	7 (87.5)	17 (100.0)	
Psychiatric medications upon discharge			
Clozapine	8 (100.0)	7 (41.2)	**.008**
Antipsychotics	8 (100.0)	16 (94.1)	1.000
Mood stabilizers	3 (37.5)	6 (35.3)	1.000
Antidepressants	1 (12.5)	4 (23.5)	1.000

[a] Data presented as median (interquartile range).
All other data are presented as *n* (%). Competent to Stand Trial Group: *n* = 8; Permanently Incompetent to Stand Trial Group: *n* = 17.

450.0 mg (interquartile range (IQR) = 337.5). Only 15 defendants (60%) were discharged on clozapine, with a median discharge dose of 450.0 mg (IQR = 200.0). Clozapine side effects led to the discontinuation of clozapine for 5 defendants (i.e., one for agranulocytosis, one for orthostatic hypotension, one for elevation of liver enzymes, one for chest pain and sinus tachycardia, and one unspecified), and a lack of effectiveness or nonadherence to blood draws led to the discontinuation for the remaining five.

Clozapine blood levels were drawn for only 14 defendants prior to their competency reevaluation. Data were retrieved for the last blood draws before the competency opinions, with a corresponding median dose of clozapine of 450 mg (IQR = 225.0). The median clozapine level was 446.5 mg (IQR = 243.5) and the median norclozapine level was 209.0 mg (IQR = 151.0).

There were no statistical differences in maximum dose of clozapine and clozapine level prior to the opinion for defendants found competent to stand trial and those deemed permanently incompetent to stand trial; however, norclozapine level prior to the opinion was significantly higher in the permanently incompetent to stand trial group ($P = .010$). All patients for whom clozapine was discontinued were deemed permanently incompetent to stand trial.

Patients in both the competent to stand trial group and the permanently incompetent to stand trial group were overwhelmingly male and charged with felonies. The groups did not differ in rates of prescription of long-acting injectable and typical

antipsychotic medications, as 24 of 25 patients were prescribed two or more antipsychotic medications throughout their stay. Patients who were competent to stand trial were more likely to have had no psychiatric treatment prior to their admission to the hospital ($P < .024$).

Discussion

To our knowledge, this is the first study exploring the use of clozapine among defendants deemed incompetent to stand trial. We found that half of the defendants discharged on clozapine were successfully restored to competency to stand trial. Conversely, all patients who had their treatment with clozapine discontinued were deemed non-restorable. The restoration rate in the CLZ group was much lower than in the NoCLZ group (32% versus 87%). Most defendants on clozapine had a history of prior psychiatric treatment and were treated with multiple antipsychotic medications during their hospitalization.

An estimated one out of three individuals with a diagnosis of schizophrenia are considered treatment-resistant.[1] Ex-convicts with serious mental illness are two times more likely to be re-arrested within one year than their non-mentally ill counterparts.[12] These numbers emphasize the beneficial role that clozapine may play in forensic mental health systems. Clozapine is superior to other drugs in managing treatment-resistant schizophrenia and aggression and is recommended in forensic populations, potentially leading to lower recidivism rates.[5,13] Moreover, clozapine use has been associated with increased treatment adherence compared with the use of all other antipsychotic medications.[14] A recent study reported that a majority of individuals with treatment-resistant psychosis did not adequately respond to first-line treatment at the time of their first-episode psychosis; predictors of treatment resistance were a diagnosis of schizophrenia, younger age at onset, negative symptoms, and a longer duration of untreated psychosis.[15] The authors argued that clinicians should initiate clozapine treatment early in the course of the illness when treating patients who fit the profile of treatment resistance.[15] Furthermore, there is evidence that suggests clozapine can be used off-label in individuals with bipolar disorder and psychotic depression,[16] diagnoses that are prevalent in the incompetent to stand trial population.[10]

In this retrospective study, only a small minority of patients were prescribed clozapine, mostly after several failed trials of other antipsychotic medications. Indeed, "clozaphobia" (the fear of prescribing clozapine) is a worldwide phenomenon, with clozapine accounting for less than 5 percent of prescribed antipsychotics.[17] Although 68 percent of the clozapine group were eventually deemed permanently incompetent to stand trial, it is likely that this finding was affected by multiple factors. Patients prescribed clozapine were more likely to be treatment-resistant and possibly to have a more severe illness. Furthermore, there was a high number of clozapine discontinuations in this population. In only one case was clozapine discontinued for a severe side effect, namely agranulocytosis. Among those who were discharged on clozapine, half were found competent to stand trial. Most of our incompetent to stand trial population had a history of psychiatric treatment prior to their arrest.[10] Research has shown that patients with a first-episode psychosis and a history of prior incarceration had a longer duration of untreated psychosis and had poorer prognosis.[18] It is therefore possible that a substantial proportion of our population fit the profile of treatment resistance and might have benefited from early initiation of clozapine. This may improve the odds of restoration of competency to stand trial and reduce the duration and costs of hospitalization in cases of successful restoration.

Median clozapine levels prior to the competency opinion were > 350 ng/mL for both the competent to stand trial group and the permanently incompetent to stand trial group; 350 ng/mL is the consensus lower threshold for therapeutic efficacy.[19] Interquartile ranges were large, however, and only a portion of the total sample had a clozapine level checked. Clozapine and norclozapine level monitoring can be helpful to evaluate medication adherence and verify that the medication trial was adequate in case of nonresponse.[20]

Potential drug–drug interactions must also be considered when prescribing clozapine. Adding fluvoxamine increases the level of clozapine and decreases the level of norclozapine in plasma by inhibiting CYP1A2; some studies have suggested that this strategy can optimize clozapine efficacy and minimize its metabolic side effects.[21] Additionally, prescribing lithium with clozapine can increase both white blood cell and absolute neutrophil count values.[22,23] Patients prescribed lithium have demonstrated increased circulating neutrophils via enhancement of granulocyte

colony-stimulating factor.[24,25] There are published case studies in which clozapine treatment could be continued after neutropenia with concurrent use of lithium.[22,26]

Common reasons for clinicians' reluctance to use clozapine include discomfort with its extensive side-effect profile.[1,3] Studies have reported, however, that a majority of patients who were stabilized on clozapine were more satisfied with their treatment than their psychiatrists assumed they would be.[27] Clozapine education in the form of practice-based learning should be an integral part of psychiatry residency and forensic psychiatry fellowship training.[6]

Another important barrier to treatment is patient adherence to regular blood draws, which are essential to monitor the neutrophil count and to have the medication dispensed within the Clozapine Risk Evaluation and Mitigation system.[6] One potential solution might be the use of point-of-care testing devices, which rely on the finger-prick method to run a complete blood count and differential count; patients have consistently favored this form of monitoring over the classic venous blood draw.[28] Several devices have been approved by the FDA, and integrating these devices within health care systems, particularly forensic health care systems, can increase patient comfort and adherence to treatment.[28]

One potential obstacle might arise related to the prescription and administration of clozapine to defendants deemed incompetent to stand trial who refuse treatment. U.S. Supreme Court decisions in *Washington v. Harper*[29] and *Sell v. U.S.*[30] allowed the government to involuntarily treat mentally ill defendants with antipsychotic medications in limited circumstances, including if the defendant is dangerous to self or others. It is unclear whether these decisions also cover monitoring requirements, including blood tests and electrocardiograms. We are not aware of any legal precedent whereby courts specifically addressed the question of involuntary blood draws for defendants maintained on clozapine.

A recent study of nondangerous defendants deemed incompetent to stand trial who were involuntarily treated with antipsychotic medications through a "*Sell* order"[30] reported that only one of 132 defendants was treated with clozapine; the authors did not provide additional information as to how they ensured the patient's adherence to the monitoring requirements.[31] Cochrane *et al.*[31] did specify that, in most cases, they were able to persuade the patients to take the antipsychotic medications without the use of force. This demonstrates the importance of establishing a strong therapeutic alliance with patients, a key determinant in ensuring treatment adherence. In *McDougald v. Stone*,[32] the District Court for the Southern District of Ohio, Western Division, ruled that forcing a defendant to have his blood drawn for a medically valid purpose was not a violation of the Fourth or Eighth Amendments.[32]

Additional barriers include administrative factors and lack of knowledge about the unique benefits and risks of clozapine within forensic mental health systems.[6] Thirteen of 20 U.S. states surveyed reported that clozapine was available on the prison formulary; a median of only eight inmates per state were reported to be on it.[33] This shows that clozapine is underutilized in correctional settings, despite schizophrenia being up to six times more prevalent in U.S. prisons than in the general population.[34] It is thus recommended that clozapine be readily available in forensic mental health systems. An expanded availability of clozapine in competency restoration and correctional settings implies a greater need for community case management staff to optimize uninterrupted clozapine treatment following release to the community. Policies emphasizing continuity of care can provide a supportive environment to individuals released on clozapine that will help reduce their recidivism risk.

Our study had several limitations. First, our sample size was small and was gathered from one state hospital. This limited our ability to conduct a quantitative statistical analysis comparing clozapine users and non-clozapine users. Second, we did not have consistent information regarding medication and substance use history prior to arrest, nor did we have data pertaining to baseline cognitive level. Our results might have been affected by these parameters.[10] Third, only a portion of our sample had their clozapine levels checked, and it is possible that some of our patients did not have an adequate medication trial. We were also unable to verify whether augmentation strategies were considered or used for patients who failed the trial. Medications such as aripiprazole, fluoxetine, and lithium have been shown to be effective augmentation agents.[35] Fourth, our study is a retrospective record review and thus cannot assess for causality between exposure and outcome.

In conclusion, our study suggests that clozapine is underused for restoration of trial competency,

despite having a sizable therapeutic potential in forensic populations with serious mental illness. Future studies with prospective, longitudinal designs should focus on the risk–benefit ratio of clozapine use for restoration of trial competency and reduction of criminal recidivism.

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