History of Suicide Attempt and Clozapine Treatment in Veterans With Schizophrenia or Schizoaffective Disorder

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ABSTRACT

Objective: To evaluate whether a history of suicide attempt increases the odds of receiving clozapine treatment in veterans with schizophrenia or schizoaffective disorder.

Methods: Electronic health record data were obtained for veterans with schizophrenia or schizoaffective disorder treated at any US Veterans Affairs Medical Center between January 1, 2000, and January 31, 2021 (N = 134,692). Logistic regression (adjusted and unadjusted) was applied to estimate odds ratios (ORs) for clozapine treatment in suicide attempters relative to nonattempters.

Results: 3,407 patients had a documented history of suicide attempt, while 6,867 patients had received clozapine treatment. Also, 9.4% (n = 321) of suicide attempters versus 5.0% (n = 6546) of nonattempters had received clozapine treatment. The odds of being treated with clozapine was approximately 2-fold in patients with a history of suicide attempt in unadjusted (OR = 1.98, 95% CI, 1.76–2.22) and adjusted (OR = 1.91, 95% CI, 1.67–2.15) analyses.

Conclusions: Despite the higher odds of clozapine treatment in suicide attempters with schizophrenia or schizoaffective disorder, clozapine was underutilized in the current sample of veterans. Concerted efforts should be made to expand the use of clozapine in patients with schizophrenia or schizoaffective disorder, especially those with a history of suicide attempt.

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Suicide attempts are highly prevalent among veterans with schizophrenia[1] and are correlated with death by suicide. Approximately 5%–13% of patients with schizophrenia or schizoaffective disorder commit suicide[2,3]—a self-inflicted mortality rate 4 to 13 times that of the general population.[4] Currently, clozapine is the only pharmacologic intervention approved for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. However, despite its proven efficacy, only 5% of patients with schizophrenia in the United States are treated with clozapine, compared to 20%–35% in other developed countries.[5] Moreover, estimates for clozapine utilization among veterans are below the national average, ranging from 0% to 3% across regional networks.[6–8] On average, veterans trial 7 antipsychotics before initiating clozapine,[7] resulting in a significant delay in starting the recommended evidence-based intervention for treatment-resistant cases. Intensive monitoring requirements, potential for severe adverse drug reactions, cardiometabolic side effects, and concern for patient adherence are frequently cited as barriers to guideline observance.[9]

To gain a better understanding of the extent of clozapine prescribing, specifically for veterans with schizophrenia or schizoaffective disorder who have a history of a suicide attempt, we sought to determine whether the odds of receiving clozapine is higher in patients with a history of a suicide attempt relative to those without a history of a suicide attempt. Based on the US Food and Drug Administration (FDA) indication of clozapine, we hypothesized that a history of a suicide attempt would be positively associated with clozapine treatment. Knowing the extent to which clozapine is being prescribed in a high-risk population such as suicide attempters with schizophrenia or schizoaffective disorder is the first step prior to designing initiatives to increase utilization of this proven intervention by prescribers.

METHODS

We analyzed cross-sectional data on veterans with a diagnosis of schizophrenia or schizoaffective disorder who received treatment at any US Veterans Affairs Medical Center (VAMC) from January 1, 2000, to January 31, 2021. We performed the analyses on de-identified electronic health records obtained from the Corporate Data Warehouse (CDW) and the Veterans Affairs Informatics and Computing Interface (VINCI). CDW integrates information from several locations (including electronic medical records) throughout the Veteran's Health Administration (VHA) and makes the database available via VINCI. Notably, care received by veterans outside of VHA facilities is not automatically captured by CDW/VINCI. The Institutional Review Board of Baylor College of Medicine and the Michael E. DeBakey VAMC Research and Development Committee provided approval for the study and granted a waiver of consent and HIPAA authorization to use de-identified protected health information from individuals involved in the study.

Clinical Points

- Clozapine, the only medication approved for suicidal behavior in patients with schizophrenia or schizoaffective disorder, is underutilized in the United States.
- Prior suicidal behavior nearly doubles the odds of receiving clozapine among veterans with schizophrenia or schizoaffective disorder, surpassing previous estimates in this population and nationwide averages.
- Perceived barriers and long-term risks with clozapine exist but may be overstated, necessitating a reappraisal by providers.

We identified patients via *ICD-9* and *ICD-10* codes corresponding to diagnoses of schizophrenia and schizoaffective disorder and documentation of suicide attempts. We also extracted the following variables: age (at last visit), sex, race, marital status, body mass index (BMI), and Charlson-Deyo Comorbidity Index (CDCI)[10,11] score. The CDCI assigns an aggregate score (0–6) to patients based on their quantity and severity of comorbid chronic medical conditions. The CDCI is a validated age-independent predictor of various outcomes including mortality, disability, hospital readmissions, and length of stay.

We separated the entire sample into 2 groups based on whether patients had a documented history of suicide attempt. Demographic and clinical variables were compared between the 2 groups using *t* test or χ^2 test as appropriate. All variables are reported as mean ± SD and n (%). Logistic regression was applied to estimate the odds of having a history of clozapine treatment based on existence of a prior suicide attempt (or lack thereof), with additional analysis adjusting for age, sex, race, BMI, marital status, and CDCI score. *P* values < .05 were considered statistically significant. All statistical analyses were performed with IBM SPSS, version 27.

RESULTS

The sample (N = 134,692) was predominantly male (92%) and white (55%), with a mean age of 59 years. Approximately one-third (37%) were obese but with mild severity of medical comorbidities (CDCI = 0.85). Suicide attempters were almost 5 years younger on average, had a slight female and White predominance, and were more likely to have been divorced (Table 1).

The results showed that 9.4% (n = 321) of patients with a history of suicide attempt versus 5.0% (n = 6,546) of patients without a documented history of suicide attempt had received clozapine treatment. The odds of being treated with clozapine was approximately 2-fold higher in patients with a history of suicide attempt (OR = 1.98, 95% CI, 1.76–2.22), and this value remained relatively unchanged after controlling for age, sex, race, BMI, marital status, and comorbid medical burden (OR = 1.91, 95% CI, 1.67–2.15).

DISCUSSION

As hypothesized, among veterans with schizophrenia or schizoaffective disorder, prior suicide attempt (relative to no prior suicide attempt) was associated with almost twice the odds of being prescribed clozapine. Therefore, our results suggest adherence to treatment guidelines by prescribers in the VHA. In addition, the reported frequency of clozapine administration in this large cohort exceeds that of prior VA studies (0%–3%), but still falls short of expectations based on official recommendations and worldwide prescribing patterns.[5,9]

Several studies[2,12–16] that employed different research designs have consistently demonstrated the efficacy of clozapine in reducing the risk of suicide in patients with schizophrenia or schizoaffective disorder. Indeed, in the United States, it has been estimated that one-third of suicides among patients with schizophrenia or schizoaffective disorder may be prevented if treated with clozapine.[17] Although further validation is needed, evidence also suggests that recent suicidal ideation in veterans may confer a superior response to clozapine.[18] In that regard, leveraging psychopharmacology (ie, clozapine) can work synergistically with other targeted approaches (eg, multidisciplinary interventions for select patients based on suicide risk stratification) to reduce suicidality. Moreover, clozapine's antisuicidal effect remains consistent provided there is adherence to the medication and appears to be independent of its increased clinical monitoring requirements.[2]

Although risk of increasing side effects exists with expanding the use of clozapine, net benefits in suicide reduction and secondary enhancements (eg, potential for improved cognition, adherence, and quality of life) must be considered as well, particularly given that these are some of the most important predictors of functional outcomes in this population.[19] Likewise, clozapine appears to have some advantages in patients with comorbid substance use disorder or affective components (ie, schizoaffective disorder and bipolar with psychotic features)—attributes that are likewise associated with increased risk of suicide.[20,21]

Contrary to the general population in which suicide risk increases into middle age, among veterans and patients with schizophrenia, young adults are at highest risk for completing suicide.[22,23] Despite having greater tolerability for the medication, younger patients are much less likely to be started on clozapine compared to their middle-aged counterparts.[24] Older patients in turn experience higher rates of postural hypotension, confusion, leukopenia, and agranulocytosis.[24–26] In addition to these side effects, clozapine also carries black box warnings for myocarditis, cardiomyopathy, seizures (dose dependent), and increased mortality in elderly patients with dementia-related psychosis.[27] While myocarditis risk is highest among patients aged 15–44 years, 90% of cases have been found to occur within the first 2 months following initiation.[28] Likewise, rates of agranulocytosis decrease significantly after 18 weeks of treatment.[29] Thus, increasing clozapine

Table 1. Characteristics of the Total Sample of Veterans With Schizophrenia or Schizoaffective Disorder and Those With and Without a History of Suicide Attempt

Characteristic	Total Sample (N = 134,692)	Suicide Attempt (n = 3,407)	No Suicide Attempt (n = 131,285)	*P* Value
Clozapine status, n (%)				
Clozapine	6,867 (5.1)	321 (9.4)	6,546 (5.0)	<.001
No clozapine	127,825 (94.9)	3,086 (90.6)	124,739 (95.0)	
Sex, n (%)				
Male	124,006 (92.1)	3,014 (88.5)	120,992 (92.2)	<.001
Female	10,686 (7.9)	393 (11.5)	10,293 (7.8)	
Age, mean ± SD, y	59.07 ± 13.5	54.52 ± 12.3	59.19 ± 13.5	<.001
Marital status, n (%)				
Never married	51,159 (38.0)	1,133 (33.3)	50,026 (38.1)	<.001
Divorced	39,875 (29.6)	1,314 (38.6)	38,561 (29.4)	
Married	29,884 (22.2)	590 (17.3)	29,294 (22.3)	
Separated	7,160 (5.3)	204 (6.0)	6,956 (5.3)	
Widowed	5,724 (4.2)	154 (4.5)	5,570 (4.2)	
Single	304 (0.2)	10 (0.3)	294 (0.2)	
Unknown	586 (0.4)	2 (0.1)	584 (0.4)	
Race, n (%)				
White	74,914 (55.6)	4,890 (71.2)	70,024 (54.8)	<.001
Black or African American	43,946 (32.6)	909 (26.7)	43,037 (32.8)	
Native Hawaiian or other Pacific Islander	1,449 (1.1)	27 (0.8)	1,422 (1.1)	
Asian	1,253 (0.9)	24 (0.7)	1,229 (0.9)	
American Indian or Alaska native	1,188 (0.9)	40 (1.2)	1,148 (0.9)	
Unknown	11,942 (8.9)	163 (4.8)	11,779 (9.0)	
Body mass index, n (%)				
Obese	49,649 (36.9)	1,277 (37.5)	48,372 (36.8)	.447
Not obese	85,043 (63.1)	2,130 (62.5)	82,913 (63.2)	
Total CDCI score, mean ± SD[a]	0.85 ± 1.6	0.91 ± 1.6	0.85 ± 1.6	.029

[a]CDCI score quantifies severity of medical comorbidities. *P* values for between-group differences (all by suicide attempt status) based on χ^2 or *t* test.
Abbreviation: CDCI = Charlson-Deyo Comorbidity Index.

utilization to target suicidality in younger patients should also entail closer cardiac monitoring and gradual titrations to optimize tolerability.

Severe agranulocytosis has been observed to occur in 0.05%–0.86% of patients, which has necessitated frequent monitoring of neutrophil counts as part of the FDA's Risk Evaluation and Mitigation Strategy for clozapine.[30] Despite recent attempts to streamline surveillance, practitioners often cite this paradigm as a major barrier to initiation.[9] However, evidence suggests that clinicians vastly overestimate the burden of routine monitoring, assuming that 52% of patients will be inconvenienced by testing compared to only 19% of patients themselves.[31] Despite increased need for monitoring, it has been estimated that clozapine initiation would save approximately $22,444 per veteran per year, mostly in reduced hospitalizations.[32] Furthermore, the risk of self-inflicted mortality in this population is over 10 times that of fatal agranulocytosis.[33]

While suicide is the leading cause of premature death in schizophrenia, cardiovascular disease represents the greatest proportion of overall mortality.[4] Compared to other antipsychotics, clozapine is associated with the highest risk of cardiometabolic side effects.[34] However conflicting results exist as to whether clozapine itself is associated with higher cardiovascular disease mortality compared to other antipsychotics.[35,36] Some studies[37,38] have suggested that the benefits from suicide prevention with clozapine may be mostly offset by increases in cardiometabolic mortality. However, a more recent systematic review[39] does not support this hypothesis. Meta-analyses[36,39–41] have consistently demonstrated lower disease-specific and all-cause mortality risk with long-term clozapine use compared to other antipsychotics or nontreatment. Moreover, viable yet underutilized strategies exist to mitigate metabolic side effects from these medications.[42]

Strengths and Limitations

This study collected data from a larger nationwide cohort of patients than has previously been assessed in this subject area. It also combines data from both inpatient and outpatient centers, more accurately reflecting real-world conditions. However, given the scope of sites included in this sample, it was not possible to stratify prescribing odds across individual centers. Future studies designed to uncover any possible regional barriers to prescription are highly warranted.

Further limitations of this study include the strong male predominance of our sample (which limits the generalizability of our findings) and the lack of information on duration of treatment, mean dosage, and adjunctive therapy. Concurrent use of lithium may be a significant confounder. It should be noted, however, that a recent randomized placebo-controlled trial using adjunctive lithium to prevent suicide-related events in veterans with mood disorders was halted for futility[43]—a finding that underscores the need to consider multimodal strategies for suicide prevention in the veteran population.

A final limitation inherent in electronic medical records is that suicide attempts could have been underreported, as some patients might not have reported their suicide

attempt(s) either because they were not asked directly or due to feeling embarrassed. Finally, we do not have data on deaths from suicide.

CONCLUSION

Rather than interpreting cause and effect from our data, we hope to give a snapshot of the current situation. Increased likelihood of clozapine usage in suicidal patients in our study reflects the notion that many clinicians are attempting to combat this public health crisis through pharmacologic means, as we have also recommended. Though the higher rates of clozapine usage reported in our study are encouraging, they are still inadequate by evidence-based standards. Clozapine's promise to ameliorate a substantial portion of the tragedy of suicide is belied by perceived risks and burdens from clinicians—often inappropriately so. Expanding the use of clozapine, particularly to younger patients, and initiating treatment earlier in the disease course represent viable strategic additions to multimodal suicide prevention. Special focus should be placed on enhancing strategies to reduce cardiometabolic burden, particularly given the ancillary benefits associated with prolonged use.

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