The Protective Effect of Clozapine on Suicide: A Population Mortality Study of Statewide Autopsy Records in Maryland

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ABSTRACT

Objective: Clozapine is the most efficacious antipsychotic medication, but it is underutilized and its mechanism of action is still poorly understood. One aspect of its unique efficacy that requires further study is its effect on suicidality. A randomized controlled trial, the InterSePT study, yielded evidence that clozapine reduces suicidality more than olanzapine, after which it became the only medication indicated for recurrent suicidal behavior in schizophrenia and schizoaffective disorder. We present here the first study of population mortality data to investigate the effect of clozapine on suicide.

Methods: We reviewed statewide autopsy records of Maryland's Office of the Chief Medical Examiner, which performs uniquely comprehensive death investigations that include full toxicologic panels with postmortem blood levels of antipsychotics. Our study compared clozapine- and olanzapine-positive decedents across demographic, clinical, and manner-of-death outcomes using contingency table analysis and logistic regression.

Results: Of 53,144 decedents from 2003 to 2021, 621 had clozapine or olanzapine detected on autopsy, with the two groups showing no demographic differences. Decedents with clozapine were significantly less likely to have died by suicide than by accident compared to those with olanzapine (odds ratio = 0.47; 95% CI, 0.26–0.84; $P = .011$).

Conclusions: Our study thus adds more naturalistic evidence to the growing literature on the beneficial effect of clozapine on suicidality. Our findings also highlight the utility of statewide autopsy records, an untapped resource for investigating the potential protective effect of psychiatric medications on suicide at a population level.

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Schizophrenia is a devastating illness affecting up to 1% of the general population.[1] The positive symptoms, negative symptoms, and cognitive impairments substantially impact functioning and quality of life and reduce life expectancy by 20% compared to the general population.[2] In particular, the risk of suicide is estimated at 5% in patients with schizophrenia,[3] or 8.5-fold higher than in the general population.[4] Antipsychotic medications are the mainstay of treatment, but up to a third of patients do not respond to trials of at least two antipsychotics and are designated as having treatment-resistant schizophrenia (TRS).[5,6]

Clozapine, the first second-generation (or "atypical") antipsychotic, is the only medication indicated for TRS by the US Food and Drug Administration (FDA). It is reported to elicit a therapeutic response in up to 70% of TRS patients[7] and also is considered to be the most efficacious antipsychotic.[8–10] Unfortunately, clozapine has long been underutilized due to a combination of prescriber hesitancy, common but troublesome side effects, rare but life-threatening side effects such as agranulocytosis and myocarditis, and the burden on patients and prescribers of the safety monitoring program (Risk Evaluation and Mitigation Strategy, or REMS) implemented by the FDA.[11–13]

Clozapine's mechanism of action and the basis for its superior efficacy are still poorly understood but may extend beyond neurotransmitter receptor binding. Of particular importance, clozapine may have an impact on domains other than positive symptoms,[14,15] particularly on suicidality. Meltzer and Okayli[16] published one of the earliest reports of clozapine's potential antisuicidal properties. In a large Finnish study,[17,18] clozapine was found to be associated with significantly lower risk of suicide as well as the lowest mortality among all antipsychotics. Additional evidence supporting the protective effect of clozapine against suicidality has emerged from cohort registries comparing clozapine to no treatment or other antipsychotics,[19–21] studies of patients before and after initiating clozapine,[22,23] and meta-analyses.[24] However, it has been unclear whether the unique antisuicidal properties of clozapine are related to better symptom control with clozapine or to the closer monitoring and follow-up mandated for clozapine use.

These questions were part of the impetus underlying the InterSePT (International Suicide Prevention Trial) study,[25] a 2-year multinational randomized clinical trial that compared clozapine and olanzapine. This trial demonstrated that clozapine was associated with greater reduction in suicidality as measured by suicide attempts, hospitalizations, use of suicide prevention interventions, scores on rating scales of suicidality, and antidepressant prescriptions. These findings led to an FDA indication for clozapine in reducing the risk of recurrent suicidal behavior, the only drug with this indication for schizophrenia and schizoaffective disorder.

Clinical Points

- Studies indicate that clozapine can reduce suicidality in schizophrenia, but it is unclear if clozapine lowers the risk of actual suicide death at a population level.
- This analysis of statewide autopsy data found significantly lower odds of suicide associated with clozapine.
- Clozapine should be strongly considered for patients at risk of suicide.

However, in the severely ill populations in these studies, it is difficult to be certain about patients' adherence to prescribed clozapine. It is also unclear how much a reduction in suicide-related behaviors such as ideation and attempt translate into the risk of actual suicide death. We sought to address these questions using autopsy toxicology records of known cases of suicide deaths as compared to unintentional accident deaths using a statewide death investigation system.

We extracted data from Maryland's Office of the Chief Medical Examiner (OCME), since Maryland employs a uniquely comprehensive statewide death investigation system with full toxicology testing, including medication levels, on all deaths of unnatural manner including suicide, accident, and deaths of undetermined intent. This has yielded one of the largest datasets for population-level studies of suicide. The Maryland OCME uses a standardized investigation protocol that requires a high degree of certainty to differentiate a suicide death from an accidental one, leaving any uncertain death categorized separately as a death of undetermined cause. However, studies have shown that suicide is often underreported in population mortality datasets, particularly among drug overdose deaths.[26–29] An analysis of overdose deaths in Maryland during the time period of our study found that the majority (75%) of overdose deaths labeled as "undetermined manner" were likely suicides.[30] We therefore grouped deaths by suicide with deaths by poisoning (overdose) whose cause was designated as undetermined, calling this new group "likely suicide." We compared clozapine to olanzapine given that the latter has a chemical structure similar to that of clozapine, has relatively high efficacy among antipsychotics other than clozapine, and was used in the InterSePT study as the comparator for clozapine.[8,25] The OCME also tested for chlorpromazine, thioridazine, and quetiapine, but not for other commonly used antipsychotics such as risperidone and aripiprazole. These other antipsychotics were excluded from the analysis since they are commonly used for indications other than schizophrenia.

METHODS

Study Sample

We obtained data for all deaths by suicide, accident, or undetermined causes in Maryland from January 2003 through December 2021 from the Maryland OCME. Homicide deaths were not available and were not included in this analysis. The Maryland OCME uses a standardized protocol to review all unnatural deaths in the state. Each autopsy recorded a number of demographic, clinical, and toxicology variables and the cause and manner of death. We included decedents of all ages who had undergone autopsy with toxicology.

These data are owned by the state of Maryland and stored on encrypted drives by the OCME. They were accessed through a data use agreement with the OCME. The study was reviewed and exempted from the need for informed consent from the decedents by the institutional review boards of the Maryland Department of Health (Protocol 19–51) and the Johns Hopkins School of Medicine (IRB 00228807).

Antipsychotics

Maryland is relatively unique in that virtually all unnatural deaths receive full toxicology panels as part of autopsy, and these all incorporate a protocolized set of common psychiatric medications as a part of the standard panel, including postmortem blood levels of olanzapine and clozapine. We characterized individuals who tested positive for olanzapine or clozapine based on the autopsy toxicology report. We also reviewed the brief narrative reports made by the police and death investigators for each case to rule out decedents with other reasons for having positive toxicology outside of regularly taking these medicines, such as the use of outside medication in the suicidal act itself.

Outcomes

Our primary outcome was manner of death, comparing likely suicides versus accidents. For the former group, we included deaths categorized as suicide by the OCME as well as overdose deaths categorized as of undetermined cause, as prior studies have shown the majority of such cases to be suicides on further analysis.[26–29]

Analytic Approach

Clozapine- and olanzapine-positive decedent groups were compared with regard to sociodemographic characteristics using contingency table analysis and χ^2 tests. For manner of death comparison, an unadjusted binary logistic regression was performed to calculate the odds ratio, without adjusting for_covariates given the small sample size of the clozapine-positive group.

RESULTS

There were 53,144 decedents fully investigated by the Maryland OCME over the study period (2003–2021). Of these, 621 individuals had olanzapine or clozapine detected in their blood (Table 1). One individual had died by suicide and had clozapine detected in her blood, but the medico-legal investigator had determined that she had taken her husband's clozapine, so she was excluded from the analysis. We compared the 571 decedents positive for olanzapine to the 50 positive for clozapine and found no significant differences in age, sex, race, or urban residence, but clozapine-positive decedents were significantly less likely to have opioids or cocaine detected on autopsy.

Table 1. Sociodemographic Characteristics of Decedents With Olanzapine and Clozapine Detected on Autopsy[a]

Characteristic	Olanzapine (n = 571)	Clozapine (n = 50)	Total (n = 621)	*P* Value
Sex, female	190 (33)	12 (24)	202 (33)	.18
Age, y				.50
≤ 30	101 (18)	7 (14)	108 (17)	
31–45	192 (34)	13 (26)	205 (33)	
46–60	211 (37)	23 (46)	234 (38)	
> 60	67 (12)	7 (14)	74 (12)	
Race				.46
White	410 (72)	36 (72)	446 (72)	
Black	139 (24)	11 (22)	150 (24)	
Hispanic	5 (1)	0 (0)	5 (1)	
Asian	11 (2)	1 (2)	12 (2)	
Other	6 (1)	2 (4)	8 (1)	
Urbanicity				.77
Large Central Metro	116 (20)	11 (22)	127 (20)	
Large Fringe Metro	329 (58)	31 (62)	360 (58)	
Medium Metro	23 (4)	2 (4)	25 (4)	
Small Metro	17 (3)	0 (0)	17 (3)	
Micropolitan	9 (2)	1 (2)	10 (2)	
Non-Core	10 (2)	0 (0)	10 (2)	
Missing	67 (12)	5 (10)	72 (12)	
Antidepressants	286 (50)	21 (42)	307 (49)	.27
Alcohol	152 (27)	11 (22)	163 (26)	.48
Opioids	308 (54)	13 (26)	321 (52)	< .001
Benzodiazepines	97 (17)	7 (14)	104 (17)	.59
Cocaine	120 (21)	3 (6)	123 (20)	.011

[a]Values are shown as n (%) unless otherwise noted.

Table 2. Manner of Death of Decedents With Olanzapine and Clozapine Detected on Autopsy[a]

Manner of Death	Olanzapine (n = 571)	Clozapine (n = 50)	Total (n = 621)
Accident	163 (29)	23 (46)	186 (30)
Likely suicide	408 (71)	27 (54)	435 (70)

[a]Values are shown as n (%). Decedents with clozapine were significantly less likely to have died by suicide than by accident compared to those with olanzapine: odds ratio = 0.47; 95% CI, 0.26–0.84; *P* = .011.

Table 3. Manner of Death of Decedents With Clozapine vs All Other Antipsychotics[a]

Manner of Death	Non-Clozapine[b] (n = 1,647)	Clozapine (n = 50)	Total (n = 1,697)
Accident	431 (26)	23 (46)	454 (27)
Likely suicide	1,216 (74)	27 (54)	1,243 (73)

[a]Values are shown as n (%). The odds of suicide compared to accident in decedents with clozapine were much lower than in those with any other tested antipsychotic individually or in combination: odds ratio = 0.42; 95% CI, 0.24–0.73; *P* = .002.
[b]Chlorpromazine, thioridazine, quetiapine, olanzapine.

The odds of death by suicide in decedents with clozapine were less than half the odds in decedents with olanzapine (odds ratio [OR] = 0.47, 95% CI, 0.26–0.84; *P* = .011) (Table 2).

As a sensitivity analysis, we reanalyzed the data to compare clozapine with all other antipsychotics (chlorpromazine, thioridazine, quetiapine, and olanzapine), which yielded a similar result that the odds of suicide compared to accident in decedents with clozapine were much lower than in those with any other tested antipsychotic individually or in combination (OR = 0.42; 95% CI, 0.24–0.73; *P* = .002) (Table 3). As a further sensitivity analysis, we attempted the comparison using a smaller sample of deaths in which the OCME had characterized intent with utmost certainty, removing decedents with any level of undetermined intent from the analysis. In this reduced sample of 166 accidental deaths to 120 suicide deaths, there were no statistical differences between decedents taking clozapine compared to olanzapine (OR = 0.74, 95% CI, 0.34–1.60; *P* = .440).

DISCUSSION

In this study, we evaluated autopsy data from the Maryland Office of the Medical Examiner, which detected postmortem blood levels of olanzapine and clozapine in 53,144 postmortem examinations of decedents over 19 years. We found that clozapine-positive individuals had significantly lower odds of suicide compared to olanzapine-positive individuals. We are not aware of any prior studies that have used statewide medical examiner records to examine the antisuicidal effect of clozapine or other psychiatric medications. As such, this study highlights the utility of this untapped resource for investigating the potential protective effect of psychiatric medications on suicide deaths at a population level.

The conclusions of this study must be tempered by several assumptions and limitations. In examining alternative explanations for the lower relative odds of suicide among individuals taking clozapine than among those taking olanzapine, we could not exclude the possibility that individuals on clozapine had received closer clinical care or supervision, which might be protective. Of note, however, the individuals on clozapine and olanzapine had equal contact with clinicians during the InterSePT study, indicating that the relative protective effect of clozapine was not from more clinical attention.[25] Second, records of diagnoses or other clinical data for the antipsychotic-positive individuals are not available. Our analysis is therefore unable to integrate important factors such as history of suicide attempts or the dose and duration of clozapine use. The indications for which each medicine was prescribed are also not known. However, clozapine prescriptions generally are limited to individuals with severe schizophrenia or schizoaffective disorder, and occasionally bipolar disorder, while olanzapine is used primarily for these disorders but occasionally for other psychiatric conditions and for more off-label uses.[31,32] It is possible that olanzapine was prescribed for individuals more vulnerable to suicide, but this seems unlikely. Given the current literature already supporting clozapine's antisuicidal effect, it may even be the case that clozapine was given to higher-risk patients.

Third, we grouped deaths by suicide with deaths of undetermined cause by overdose, given the underreporting of suicide among undetermined overdoses shown in prior studies, as the Maryland OCME's conservative method of categorizing manner of death left many possible suicides in the undetermined group. However, our analysis is thus more conservative, and the reduction in odds of suicide that we found with clozapine is likely to be an underestimate if we

captured accidents from the undetermined group. When decedents with any level of questionable manner of death were excluded in a sensitivity analysis, reducing the sample size by 64%, no significant difference could be found. We expect this to be due to low power. Fourth, our data do not capture the general prevalence of olanzapine or clozapine use in Maryland, and thus we are unable to calculate the relative risk for suicide for either antipsychotic.

Fifth, we limited our comparison of clozapine to olanzapine, based on the findings of the InterSePT study and consistent with findings that olanzapine is among the most efficacious antipsychotics after clozapine,[8] as well as the structural similarities of the two drugs. Moreover, the other antipsychotics tested by the OCME do not include many commonly used antipsychotics (such as risperidone and aripiprazole), and those that were tested (most commonly quetiapine) are commonly used for indications other than schizophrenia (such as augmentation of antidepressants or for insomnia), so they were not included in this study.

Despite these limitations, to our knowledge, our analysis is the first study of clozapine's effect on suicide based on epidemiologic data on population mortality. Our data, from a large sample of statewide autopsy records, add more naturalistic evidence for the protective effect of clozapine on suicide, for which there is growing support without its being clearly established yet. Whether this effect is due to the greater efficacy of clozapine in symptom control, or if clozapine has an independent effect on suicidality, remains to be determined. Regardless, our findings provide further support for the use of clozapine in protecting against suicide.

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