Association Between Clozapine Exposure and Risk of Hematologic Malignancies in Veterans With Schizophrenia

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Abstract

Objective: The objective of this study was to examine the relationship between clozapine use and hematologic malignancies, using national administrative data from the United States Veterans Health Administration (VHA).

Methods: This case-control study of veterans with schizophrenia matched cases with incident hematologic malignancy to 10 controls without hematologic malignancy by gender, age, and time since first schizophrenia diagnosis from October 1999, the beginning of VHA data archives, to June 2022. Schizophrenia diagnoses were identified using *International Classification of Diseases, Ninth Revision*, code 295.x and *International Statistical Classification of Diseases, Tenth Revision,* codes F20.x and F25.x from inpatient hospitalization and outpatient encounter data. Additional inclusion criteria were age 18–85 years, no prior history of malignancy, and at least 1 year of antipsychotic exposure. Clozapine exposure was assessed using 3 metrics: any exposure, years of exposure, and cumulative defined daily doses (DDD). Conditional multivariable logistic regression was used to adjust for nonmatched confounding variables.

Results: A total of 2,306 veterans with schizophrenia were identified with an incident diagnosis of hematologic malignancy and matched to 23,043 controls. Any prior clozapine exposure was more commonly observed among cases (5.3%) than controls (4.1%) and was significantly different after adjustment (odds ratio [OR], 1.31; 95% CI, 1.08–1.60). Risk was dose-dependent, where cumulative clozapine exposures from 3,000 to 4,999 DDD (OR, 1.78; 95% CI, 1.13–2.79) and ≥5,000 DDD (OR, 1.81; 95% CI, 1.24–2.64) were significantly associated with malignancy risk. Similarly, clozapine exposure of 5 or more years was associated with malignancy risk (OR, 1.88; 95% CI, 1.43–2.47).

Conclusion: Consistent with prior report, this study observed an increased risk of hematologic malignancy associated with clozapine exposure. These findings suggest patients receiving clozapine use, particularly those with long-term use, should be closely monitored for hematologic malignancy.

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Clozapine is widely known as the first, and most effective, atypical antipsychotic approved for the treatment of schizophrenia.[1] Despite demonstrating superior efficacy in reducing overall and positive symptoms of schizophrenia compared to both first-generation and second-generation antipsychotics, the American Psychiatric Association recommends limiting clozapine to treatment-resistant cases.[2,3] This is due to its prominent adverse effect profile, including but not limited to significant weight gain, sedation, dizziness, myocarditis, and agranulocytosis.[4,5]

Three recent reports have further linked clozapine to an increased risk of hematologic malignancies, such as lymphomas, leukemias, and myelomas.[6–8] This relationship is hypothesized to result from clozapine bioactivation in *N*-arylnitrenium ions, a known component of chemical carcinogenesis.[6] The largest study published to date used a prospectively collected national cohort of Finnish patients with schizophrenia linked to national health registry data.[7] In a nested case-control design, 375 cases of hematologic malignancies were identified and matched 1:10 with 3,374 controls. Clozapine was associated with increased odds of hematologic malignancies in a dose-dependent manner compared to other antipsychotics (odds ratio [OR], 2.11; 95% CI, 1.59–2.80). In contrast, clozapine exposure was not significantly associated with other malignancies. Additionally, a disproportionality analysis conducted by the World Health Organization found that clozapine was associated with 9.1-fold higher reporting of lymphomas and 3.5-fold higher reporting of leukemias when compared to other antipsychotics.[6] Lastly, an analysis of

Clinical Points

- Recent studies have linked clozapine with a risk of hematologic malignancy, but replication is needed to inform clinical decision-making.
- Clozapine use for 5 or more years was associated with an increased risk of hematologic malignancy.
- Although the benefits of clozapine on mortality risk outweigh the risks from hematologic malignancy, monthly monitoring of complete blood count may assist with early detection.

spontaneously reported adverse event data from Australia noted an overrepresentation of hematologic cancers compared with other cancer types.[8]

Although these studies have both shown a similar association between clozapine and hematologic malignancies, additional confirmation of this relationship is necessary. Given the potential for differences in population demographics and clozapine prescribing across countries, this study aimed to replicate the case-control analysis conducted by Tiihonen and colleagues[7] and further examine the relationship between clozapine use and hematologic malignancies, using national administrative data from the United States Veterans Health Administration (VHA).

METHODS

Data Sources

This retrospective case-control study used national administrative data from the Veterans Affairs (VA) Corporate Data Warehouse accessed via the VA Informatics and Computing Infrastructure. Diagnostic information for schizophrenia, hematologic malignancy, and other medical conditions was identified using *International Classification of Diseases* (*ICD*) codes from inpatient hospitalization and outpatient encounter records. Information concerning dispensed antipsychotic prescriptions was obtained from outpatient pharmacy data. A chart review of the electronic medical record was conducted in a sample of patients to validate the case definition of hematologic malignancy. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

Patients

Cases and controls were selected from patients with schizophrenia, identified using *ICD-9* code 295.x and *ICD-10* codes F20.x and F25.x from inpatient hospitalization and outpatient encounter data from October 1, 1999, the beginning of VHA data archives, through June 30, 2022. Patients were required to have at least 5 encounters coded for schizophrenia and at least 1 year of antipsychotic exposure, to increase the accuracy of the diagnosis and allow adequate longitudinal contact with the VA health care system.

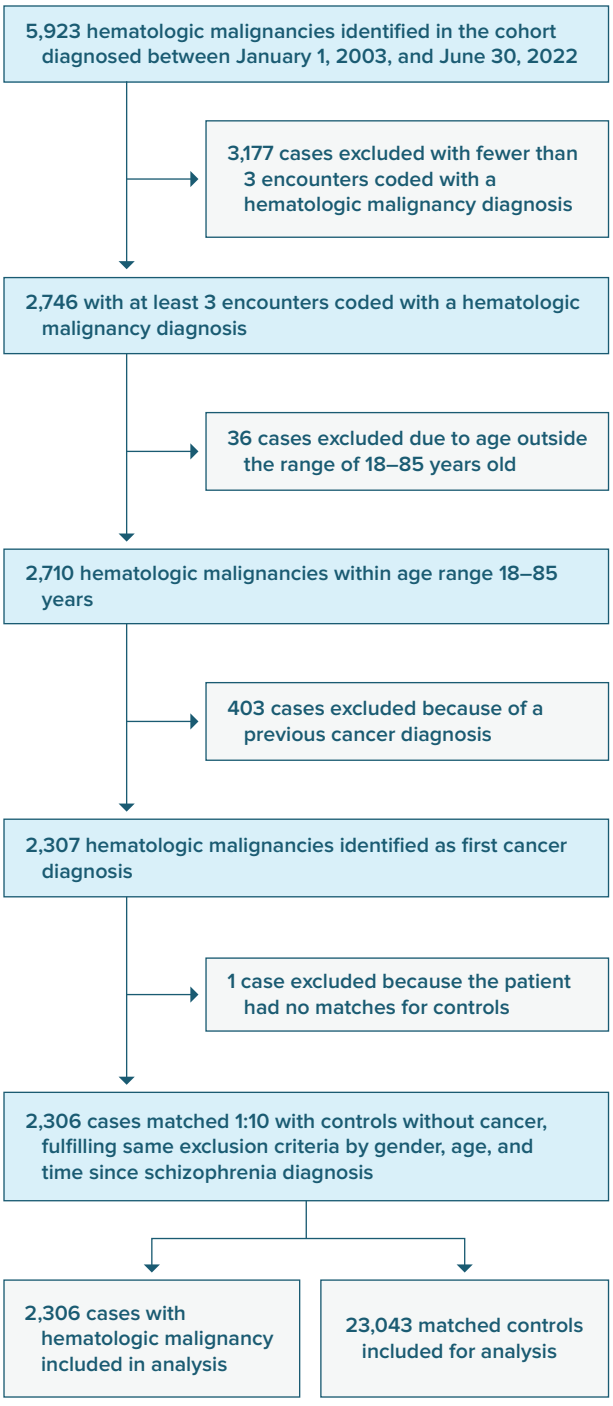
Cases with hematologic malignancy were identified using *ICD-9* codes 200.x–209.x, 238.4, 238.5, 238.6, 238.7x, and 288.4, and *ICD-10* codes C81.x–96.x, D45.x–47.x, and D76.x and required to be observed following the first identified diagnosis of schizophrenia. *ICD* codes for both schizophrenia and hematologic malignancy followed the methods of the prior case-control study by Tiihonen et al.[7] Cases were required to have at least 3 coded encounters of hematologic malignancy. This requirement was based on a manual chart review of medical records, where the reviewer was blinded to the number of coded encounters. At this threshold, 18 of 20 (90%) of patients had confirmed hematologic malignancy by chart review, whereas 30%–50% had confirmed diagnoses with only 1 or 2 encounters. Cases were further restricted to ages of 18–85 years at the time of hematologic malignancy diagnosis and those without any other previous malignancy.[7] Cases were selected from patients diagnosed with a hematologic malignancy on or after January 1, 2003, which allowed 4 years of observable data prior to case ascertainment. For included cases, the date of the first observed encounter coded for hematologic malignancy was set as the index date for assessing covariates and matching to controls.

Control patients with schizophrenia were matched to cases based on sex, age (allowing 1-year differences), and time since first schizophrenia diagnosis (allowing 1-year differences), and controls had no prior encounters coded for hematologic or other malignancies.[7] Controls were eligible for matching to a case based on meeting these criteria at the calendar time of the case's index malignancy diagnosis. Cases and controls were matched 1:10 for all but 6 patients. Five cases had fewer than 10 matches and were included. One case had no eligible matches and was excluded from the analysis.

Antipsychotic Exposure

Clozapine exposure was defined according to 3 metrics. Any clozapine exposure was defined as any outpatient prescription for clozapine dispensed during the observation period and prior to the index date. Among patients with clozapine exposure, the cumulative amount of exposure prior to index was determined by the duration of calendar time of exposure in years and separately by the cumulative dose expressed in defined daily doses (DDD).[9] Established by the World Health Organization, a DDD represents the average maintenance dose per day for a drug used for its main indication in adults, which is 300 mg for clozapine. Cumulative exposure to nonclozapine antipsychotics

Figure 1.
Patient Selection Flowchart



prior to index was also calculated in terms of their respective DDD and used as a covariate in the analysis.

Analysis

Conditional multivariable logistic regression was used to examine the relationship between hematologic malignancy and clozapine exposure, adjusted for unmatched confounding variables. Covariates included race, nonclozapine antipsychotic exposure, somatic comorbidities, psychiatric comorbidities, and other conditions associated with elevated lymphoma risk.[7] Medical comorbidities were identified by the presence of at least 1 inpatient or outpatient encounter coded on or within the 2 years prior to the index date, including cardiovascular disease, type 1 and type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), substance use disorder, human immunodeficiency virus, Epstein-Barr virus, hepatitis A, hepatitis B, hepatitis C, herpes simplex 1, herpes simplex 2, herpes zoster, *Helicobacter pylori* infection, Lyme disease, Sjogren (Sicca) syndrome, systemic lupus erythematosus, and rheumatoid arthritis. A sensitivity analysis was performed on a restricted subset of patients with specific diagnoses of lymphoma, leukemia, and myeloma and their matched controls.

RESULTS

Between January 1, 2003, and June 30, 2022, 5,923 veterans with schizophrenia had at least 1 medical encounter coded for hematologic malignancy. Of these, 3,177 failed to meet the requirement of at least 3 encounters and were excluded (Figure 1). Thirty-six cases were excluded due to age restriction, and an additional 403 cases were excluded due to a previous malignancy. Lastly, 1 case was excluded as the patient had no control matches. This resulted in a total of 2,306 cases that were matched to 23,043 controls without hematologic malignancy based on age, gender, and time since schizophrenia diagnosis. Only 5 case patients matched to fewer than the targeted 10 controls per case: 1 patient with 3 controls, 2 with 7 controls, and 2 with 8 controls.

All matched characteristics, including age, sex, and time since first schizophrenia diagnosis, were balanced between cases and controls (Table 1). The mean age of cases and controls was 61.6 (SD 9.5) and 61.4 (SD 9.5) years, respectively. Both cases and controls had a mean time since first diagnosis of schizophrenia of 9.8 (SD 5.4) years. A majority of cases were male (94.4%). Some unmatched characteristics were fairly balanced, such as white race (57.5% of cases and 58.7% of controls) and those with substance use disorders (15.7% of cases and 13.7% of controls). In contrast, cases and controls were unbalanced on a number of characteristics that were not used in the match process including comorbidities of cardiovascular disease (37.6% of cases and 30.8% of controls) and asthma/COPD (15.2% of cases and 9.7% of controls), and rate of previous infection (16.4% of cases and 10.9% of controls).

Any prior history of clozapine exposure was more commonly observed among cases (5.3%) than controls

Table 1.

Patient Characteristics of Cases With Hematologic Malignancy and Controls, Among Veterans With Schizophrenia

	Cases, N = 2,306	Controls, N = 23,043
Age in years, mean (SD)	61.6 (9.5)	61.4 (9.5)
Years since schizophrenia diagnosis, mean (SD)	9.8 (5.4)	9.8 (5.4)
Sex		
Male, n (%)	2,176 (94.4)	21,754 (94.4)
Female, n (%)	130 (5.6)	1,289 (5.6)
Race, n (%)		
White/Caucasian	1,327 (57.5)	13,524 (58.7)
Black/African American	786 (34.1)	7,198 (31.2)
Other/missing	193 (8.4)	2,321 (10.1)
Type of hematologic malignancy, n (%)		
Lymphoma	595 (25.8)	NS
Leukemia	461 (20.0)	NS
Myeloma	242 (10.5)	NS
Other	1,008 (43.7)	NS
Comorbidities, n (%)		
Cardiovascular disease	866 (37.6)	7,099 (30.8)
Diabetes	502 (21.8)	4,054 (17.6)
Asthma or COPD	350 (15.2)	2,232 (9.7)
Substance use disorder	361 (15.7)	3,157 (13.7)
Any of the following infections (HIV, Epstein-Barr, hepatitis, herpes, *Helicobacter pylori*, Lyme disease), n (%)	379 (16.4)	2,518 (10.9)
Conditions associated with increased lymphoma risk (organ transplant, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis), n (%)	13 (0.6)	32 (0.1)

Abbreviations: COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, NS = not significant.

Table 2.

Risk of Hematologic Malignancy Associated With Clozapine Exposure Among Veterans With Schizophrenia

	Cases, N = 2,306, n (%)	Controls, N = 23,043, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Ever used clozapine				
No	2,183 (94.7)	22,099 (95.9)	1.00 [reference]	1.00 [reference]
Yes	123 (5.3)	944 (4.1)	1.33 (1.09–1.61)	1.31 (1.08–1.60)
Clozapine duration, y				
< 1	26 (1.1)	267 (1.2)	0.99 (0.66–1.49)	0.94 (0.62–1.40)
1–4	31 (1.3)	302 (1.3)	1.04 (0.72–1.52)	0.99 (0.68–1.44)
≥5	66 (2.9)	375 (1.6)	1.81 (1.38–2.37)	1.88 (1.43–2.47)
Cumulative dose				
<999 DDD	44 (1.9)	398 (1.7)	1.13 (0.82–1.54)	1.07 (0.78–1.48)
1,000–2,999 DDD	22 (1.0)	209 (0.9)	1.07 (0.69–1.67)	1.01 (0.65–1.59)
3,000–4,999 DDD	23 (1.0)	131 (0.6)	1.79 (1.15–2.80)	1.78 (1.13–2.79)
≥5,000 DDD	34 (1.5)	206 (0.9)	1.70 (1.18–2.47)	1.81 (1.24–2.64)

Abbreviations: DDD = defined daily doses, OR = odds ratio.

(4.1%) and was significantly different after adjustment using multivariable conditional logistic regression (OR, 1.31; 95% CI, 1.08–1.60) (Table 2). Risk was dose-dependent, where cumulative clozapine exposures from 3,000 to 4,999 DDD (OR, 1.78; 95% CI, 1.13–2.79) and ≥5,000 DDD (OR, 1.81; 95% CI, 1.24–2.64) were significantly associated with malignancy risk, but exposures <3,000 DDD were not. Similarly, clozapine exposure of 5 or more years was associated with malignancy risk (OR, 1.88; 95% CI, 1.43–2.47), but shorter durations were not.

A sensitivity analysis was performed in a restricted subset of patients with diagnoses of lymphoma, leukemia, and myeloma (n = 1,298) and their matched controls, which excluded patients with hematologic malignancies classified as other (n = 1,008). Findings were similar to the primary analysis, where the association between any clozapine exposure and hematologic malignancy was

statistically significant (OR, 1.43; 95% CI, 1.10–1.86), as was clozapine duration of 5 or more years (OR, 2.08; 95% CI, 1.46–2.95) and cumulative clozapine exposures of 3,000–4,999 DDD (OR, 2.23; 95% CI, 1.32–3.76) and ≥5,000 DDD (OR, 1.92; 95% CI, 1.15–3.20).

DISCUSSION

This case-control study of US veterans with schizophrenia replicated the prior study of Tiihonen and colleagues,[7] finding an increased risk of hematologic malignancies associated with clozapine exposure, relative to other antipsychotics. Both the current study and Tiihonen et al[7] displayed a statistically significant association for the primary analysis based on any clozapine exposure with OR = 1.31 (95% CI, 1.08–1.60) and 2.11 (95% CI, 1.59–2.80), respectively. In additional analyses, clozapine use for 5 or more years was significantly associated with hematologic malignancy in both studies, OR = 1.88 for the current study and OR = 2.94 for Tiihonen et al[7] whereas shorter durations were not. Similarly, the current and Tiihonen[7] studies both showed significant associations with cumulative clozapine exposure from 3,000 to 4,999 DDD (OR = 1.78 and OR = 2.42, respectively) and ≥5,000 DDD (OR = 1.81 and OR = 3.35, respectively), whereas lower cumulative exposures were not associated with hematologic malignancy. This detailed contrast demonstrates parallel findings between studies in terms of which analyses demonstrated significant associations between clozapine exposure and hematologic malignancy, and which did not.

One important difference between studies was that the magnitude of risk estimates was consistently lower in the current study, which may be in part due to a substantially lower rate of overall clozapine exposure in our study population of US veterans (5.3% cases and 4.1% controls) compared to the national Finland data registry (27.2% cases and 16.7% controls).[7] Clozapine prescribing varies internationally, where 1 prior study noted that clozapine prescribing prevalence in Finland was 2.84-fold greater than that of a publicly insured US cohort.[10] This difference is likely because clozapine prescribing in the United States is generally limited to patients with treatment-refractory schizophrenia. It is possible that risk of hematologic malignancy is different in this subgroup of patients, relative to nonrefractory patients, due to differences in competitive mortality from other causes prior to the development of hematologic cancer or the prevalence of other cancer-related risk factors, such as smoking.

Several other factors could contribute to the difference in risk estimates for hematologic malignancy between studies. First, the proportion of males was 94.4% in our study of US veterans, compared to a more balanced distribution of males and females in Tiihonen et al.[7] It is possible that sex-related differences in the effect of clozapine on hematologic malignancy could explain differences in risk estimates between studies. As both studies matched on sex between cases and controls, and as the effect of matched variables cannot be assessed in case-control studies, neither study was able to determine whether risk of hematologic malignancy associated with clozapine differs between men and women. Also, the duration of historical data available to assess the time since schizophrenia diagnosis and prior antipsychotic exposure was much longer in the Tiihonen et al[7] study. Lastly, the proportion of hematologic malignancies other than the main categories of lymphoma, leukemia, and myeloma was markedly higher in this study (43.7%) compared to Tiihonen et al[7] (1.6%) despite using the same *ICD* codes. This may reflect differences in coding practices, or true differences in the prevalence of certain cancer types attributable to differences in the underlying populations, such as country of origin or the potential for hazardous exposures during military service. Importantly, our findings were identical in a sensitivity analysis restricted to patients with diagnoses of lymphoma, leukemia, and myeloma, which excluded patients with diagnoses in this other category. Both studies showed similarities in mean age and proportion of somatic and psychiatric comorbidities in the population. Despite these similarities and differences, the pattern of significant findings across clozapine exposure metrics was identical between studies, strengthening the evidence for a potential association between hematologic malignancies and clozapine exposure.

Additional support for this relationship is provided by a disproportionality analysis conducted by the World Health Organization in 2021.[6] This study examined literature via VigiBase, the World Health Organization global individual case safety report database, to identify an association between clozapine and hematologic malignancies. Among the 913,780 reports of hematologic malignancy and at least 1 antipsychotic exposure, clozapine was reported in 15.4% of the cases and found to be associated with a higher reporting of lymphoma (OR, 9.13; 95% CI, 7.75–10.77) and leukemia (OR, 3.54; 95% CI, 2.97–4.22) compared to other antipsychotics. No significant associations between lymphoma or leukemia were observed for quetiapine, olanzapine, or loxapine. This study, however, had some major limitations including overall underreporting of hematologic malignancies to the database and inability to determine a causal relationship between malignancy and clozapine exposure.

This relationship is further supported by an observational study using spontaneous adverse event reporting in Australian public case reports to examine the representation of different types of cancers.[8] Of the

384 spontaneous reports of cancer associated with clozapine, hematologic cancers were the most frequent, accounting for 27% of the cancers reported. The mean daily dose of clozapine at the time of hematologic cancer report was 400 mg with a median duration of clozapine use before hematologic cancer diagnosis of 7 years. Like the World Health Organization's study, this study shares limitations associated with the examination of spontaneously reported adverse events, including underreporting, inability to assess causality, and inability to account for confounding risk factors.

While our study mirrors the findings of Tiihonen and colleagues,[7] it is important to stress the context of these findings. The absolute risk difference of hematologic malignancy in clozapine users is small compared to the previously observed absolute risk reduction in all-cause mortality.[7] General antipsychotic use is associated with a 21% lower risk of cumulative mortality in patients with schizophrenia, where clozapine is associated with a further 10% reduction when compared to other antipsychotics.[11] Meta-analyses have also shown that clozapine treatment is associated with substantially decreased overall risk of death when compared to use of other antipsychotics in the treatment of schizophrenia.[12,13]

Absolute risk of hematologic malignancy among clozapine users must also be interpreted in relation to risk of other known adverse events. For example, the risk of sudden cardiac death with use of atypical antipsychotics is estimated to be 90 per 1,000 person-years,[14] which is more than 1,000 times higher than the estimated risk of 61 cases per 100,000 person-years for hematologic malignancy with clozapine.[7] While it is important to identify novel adverse effects associated with clozapine to facilitate appropriate monitoring, the risk of hematologic malignancy in the context of overall mortality risk and accepted risks for other known adverse effects does not support the avoidance of clozapine prescribing in populations that may greatly benefit from its use.

There were some potential limitations inherent to this research. First, monthly hematologic monitoring is required throughout the entirety of clozapine use in the United States but not for most other antipsychotics, creating the potential for surveillance bias in identifying malignancy among patients receiving clozapine. Second, other potential risk factors, such as Agent Orange exposure in the Vietnam War or cigarette smoking status, may have played a role in the occurrence of hematologic malignancies in veterans independent from, or perhaps in conjunction with, clozapine use.[15,16] These factors limit our ability to fully determine causation attributable to clozapine exposure. Additionally, archiving of national VA administrative data began on October 1, 1999, whereas clozapine was FDA approved in the United States for the treatment of schizophrenia in 1989. Thus, there was a 10-year period where information regarding prior clozapine exposure was unavailable in our veteran population. Finally, we were only able to access information about health care received in the VHA. Information regarding antipsychotic exposure or cancer diagnoses outside this system could have led to the exclusion of cases or misclassification of exposure status and outcomes. However, we do not anticipate that this type of misclassification would be differential between antipsychotic exposure groups, and it is thus unlikely to account for the observed relationship between clozapine exposure and hematologic malignancy.

In conclusion, the risk of hematologic malignancy was found in the current study to be most significant after 5 or more years of clozapine use or in cumulative DDD exceeding 3,000. This finding was consistent with the significant associations observed by Tiihonen et al[7] strengthening the evidence for a potential association. Overall, this risk is small compared to the risk of all-cause mortality in untreated schizophrenia, or even schizophrenia treated with other antipsychotics. It is also smaller than other serious adverse events associated with antipsychotic use. While providers should be mindful when performing routine physical and laboratory examinations to assess for signs and symptoms of hematologic malignancy, particularly among long-term recipients, this should not be a reason to avoid clozapine prescribing and use.[17,18]

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