Addendum to FDA Briefing Document

Risk Evaluation and Mitigation Strategy (REMS) for Clozapine Products

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee

November 19, 2024

This addendum contains data from a study conducted in collaboration with Veterans Affairs and included in the FDA's Briefing Document for the November 19, 2024, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee. The committee will discuss the Risk Evaluation and Mitigation Strategy (REMS) for Clozapine.

Neutropenia risks among clozapine users in the Veterans Affairs health system

Objectives: Our primary objectives were to evaluate risks of neutropenia and agranulocytosis following initiation of clozapine use, including periods of discontinuation and rechallenge with the medication, and to further determine conditions under which such risks were modified. A secondary objective included evaluation of adverse outcomes resulting from clozapine-induced severe neutropenia.

Methods: This was a retrospective analysis of data for Veterans Affairs (VA) patients who initiated clozapine treatment from FY2000 – FY2023. The primary data source was the VA Corporate Data Warehouse (CDW), a national repository containing comprehensive patient-level information from medical facilities throughout the VA system. It includes demographics, data from inpatient and outpatient encounters, pharmacy records, laboratory test results, and reports from most medical services. Death records were derived from the VA's vital status database, supplemented by other sources for cause of death, including review of electronic medical records.

Inclusion/exclusion criteria: Patients were eligible for study inclusion if: 1) their Veteran status was confirmed, 2) their age and sex were known, 3) they had at least one year of prior VA service use (outpatient or inpatient) (defined as having at least one visit or hospital stay in the year before clozapine initiation and at least one additional visit or hospital stay in the year prior to that), 4) they had at least one non-clozapine VA-dispensed prescription in the year before clozapine initiation, 5) they had no clozapine possession in the past 365 days.

Outcomes of interest: Mild neutropenia: absolute neutrophil count (ANC) 1000-1499 cells/μL; moderate neutropenia: ANC 500-999 cells/μL; severe neutropenia (agranulocytosis): ANC < 500 cells/μL. Additional events of interest occurring after neutropenia detection included hospitalizations, bacterial infections, administration of granulocyte stimulating factor, and deaths. Outcomes were counted if the ANC was performed while the patient was prescribed clozapine or within 30 days after their most recent dose.

Covariates: From the CDW, we collected patient-level data on demographics, medical and psychiatric comorbidities, prescription medication use, and laboratory test results.

Descriptive analyses: We obtained annual counts of patients with first clozapine prescriptions, number of ANC tests per patient per year, and counts of neutropenia (mild/moderate/severe). We also examined duration and persistence of clozapine use, timing, and frequency of ANC tests relative to clozapine initiation and continued use, and timing of neutropenia over the course of clozapine use.

Neutropenia risk estimation: Patients initiating clozapine were followed forward in time from their first prescription (index date), with monitoring of serial ANC test results. Kaplan-Meier methods were used to estimate the cumulative incidences of mild, moderate, and severe neutropenia. Life table methods were used to estimate interval-specific rates of severe neutropenia. We defined episodes of continuous clozapine use as including all days covered by the days of supply of consecutive clozapine prescriptions, allowing gaps between prescriptions of up to 30 days.

Review of electronic medical records: Electronic medical records were reviewed for patients with neutropenia who died within 180 days of their last clozapine dose. Records were also reviewed for all patients identified with severe neutropenia during VA follow-up.

Results: *Descriptive*: Of 9300 patients treated with clozapine during the study period, 6488 clozapine initiators met the inclusion/exclusion criteria, with approximately 250-300 new patients added each year. The mean age was 50.2 years, 89.3% were male, and 62.9% were white, 18.5% African American, 5.4% Hispanic, and 13.1% "other" or unknown race. In the year prior to clozapine initiation, there was a high prevalence of psychiatric comorbidities (89.3% had a diagnosis of schizophrenia or schizoaffective disorder) and a high prevalence of use of various psychiatric medications (81.8% had been treated with an atypical antipsychotic and 38.4% with a typical antipsychotic) (Table 1).

Table 1. Psychiatric conditions and psychiatric medication use among 6488 new users of clozapine in the year prior to clozapine initiation, Veterans Affairs healthcare system, FY2000-FY2023.

Psychiatric conditions	Prevalence (%)	Psychiatric medications	Prevalence (%)
Schizophrenia	71.5	Benzodiazepines	47.1
Schizoaffective disorder	53.3	Typical antipsychotics	38.4
Either condition	89.3	Atypical antipsychotics	81.8
Neither condition	10.7	SSRIs	33.0
Bipolar disorder	49.2	SNRIs	9.6
Depressive disorders	47.0	Lithium	15.8
PTSD	35.7	Anticonvulsants	68.7
Substance use disorder	40.4		
Anxiety	46.9		
Other psychosis	37.5		

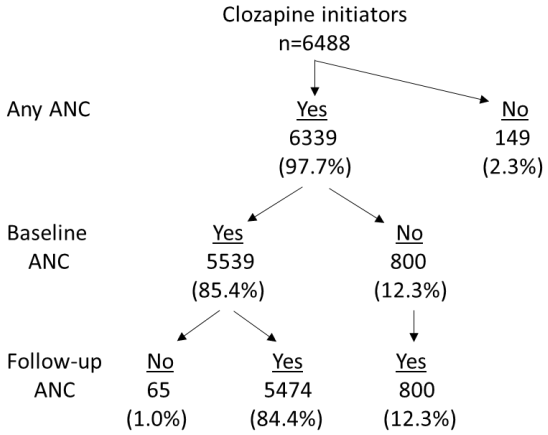
The initial clozapine prescription was for ≤7 days in 6077 (93.7%) patients, with the longest initial prescription covering 30 days of treatment. The median starting daily dose was 100 mg (interquartile range (IQR) 36-300). A small number of patients (n=438 (6.8%)) filled only one clozapine prescription. The median number of treated days during the first episode of clozapine use was 208.5 (IQR 35-1127), with 1500 (23.1%) receiving <30 days and 2102 (32.4%) receiving ≥ 2 years of clozapine supply. Approximately 40% of patients had more than one episode of continuous clozapine use (Table 2). The median time between treatment episodes was 56 days, with a minimum of 31 days and a maximum of 22 years.

Table 2. Distribution of clozapine treatment episodes in the Veterans Affairs health system, FY2000-FY2023.

No. of treatment episodes	Clozapine new user	
	No.	(%)
1	3875	59.7
2	1220	18.8
3	603	9.3
4	290	4.5
5	182	2.8
6	99	1.5
7	73	1.1
8	42	0.6
9	24	0.4
10	19	0.3
11	12	0.2
>=12	49	0.8
Mean (std)	2.0 (1.9)	
Median	1	
Max	30	

ANC monitoring: At least one ANC value was recorded for 6339 (97.7%) clozapine initiators during the study period (Figure 1). Baseline ANC monitoring prior to the first clozapine prescription was recorded in 5539 (85.4%). Regardless of whether baseline monitoring was performed, follow-up ANC monitoring after clozapine initiation was recorded in 6274 (96.7%). No monitoring was recorded in 149 (2.3%) patients. Of the 5539 patients with a recorded baseline ANC, nine had mild neutropenia (ANC 1000-1499/µL), of whom seven (77.8%) were African American.

Figure 1. Distribution of ANC monitoring in patients initiating clozapine in the Veterans Affairs health system, FY2000-FY2023.



ANC monitoring intensity and adherence: Among patients with a clozapine first episode length ≥91 days (13 weeks), 71.8% received ≥11 ANC tests (median=13, IQR 9-13) during their first 91 days of treatment (Table 3). Among patients with a first episode length ≥182 days (26 weeks), 71.6% received ≥21 ANC tests (median=25, IQR 21-28) during their first 182 days.

Table 3. Distribution of number of absolute neutrophil count tests during the first 91 and 182 days of clozapine use during the first episode of use in the Veterans Affairs health system, FY2000-FY2023.

Patients with clozapine treatment episode ≥91 days (n=4023)		Patients with clozapine treatment episode ≥182 days (n=3381)	
# ANC tests	% patients	# ANC tests	% patients
0	14.0	0	12.8
1-5	5.3	1-10	6.4
6-10	8.8	11-20	9.8
11+	71.8	21+	71.6

Mild, moderate, and severe neutropenia: During follow-up of all patients' first episode of continuous clozapine use, we observed 302 neutropenia events, of which 32 were severe, yielding an incidence rate over all follow-up time of 2.0 severe cases per 1000 person-years of on-treatment follow-up (Table 4). When additional episodes of use were included, the number of severe cases increased to 48 and the incidence rate was 1.7 per 1000 person-years of treatment. When all patient time was followed, including time after clozapine use ended, there were 67 patients with severe neutropenia (incidence rate 1.1 per 1000 person-years).

Table 4. Counts and incidence rates with 95% confidence intervals of neutropenia among patients treated with clozapine in the Veterans Affairs health system, FY2000-FY2023, stratified by level of neutropenia and conditions of follow-up.

	Total neutropenia	Mild 1000-1499/µL	Moderate 500-999/µL	Severe <500/µL
Within 30 days of last clozapine use for 1st episode (n)	302	217	53	32
Incidence per 1000 person-years	19.1 (17.1-21.4)	13.7 (12.0-15.6)	3.3 (2.5-4.3)	2.0 (1.4-2.8)
Within 30 days of last clozapine use for all episodes (n)	445	313	84	48
Incidence per 1000 person-years	16.2 (14.8-17.8)	11.4 (10.2-12.7)	3.0 (2.4-3.7)	1.7 (1.3-2.3)
During entire VA follow-up, on or off clozapine (n)	796	555	174	67
Incidence per 1000 person-years	14.2 (13.3-15.3)	9.7 (8.9-10.5)	2.9 (2.5-3.4)	1.1 (0.9-1.4)

Focusing on the 48 patients with severe neutropenia during or within 30 days after an episode of continuous clozapine use, the mean age was 53.3 years; 87.5% were male; 75% were white, 10.4% were African American, 2.1% were Hispanic, and 12.4% were "other' or unknown race. Nearly 98% had a diagnosis of schizophrenia or schizoaffective disorder, with 89.6% and 41.7% having been treated with an atypical or typical antipsychotic, respectively, in the year before starting clozapine. The initial prescription was for 1-7 days in 97.9 % (47 patients) and 8-14 days in the remaining one patient. Two patients received only one prescription.

Clozapine discontinuation and resumption following neutropenia occurrence: Of 302 patients with documented neutropenia during their first episode of clozapine use, most cases of neutropenia were mild or moderate, and 32 (10.6%) cases were severe. Most cases of neutropenia occurred

following more than 3 months of continuous clozapine use (Table 5). The ANC returned to the normal range (>1500 cells/µL) within 2 weeks of occurrence in 93% with mild and in 81.3% with severe neutropenia. Of note, 27.6% of patients with mild, 52.8% with moderate and 68.7% with severe neutropenia had no additional clozapine prescription fills after the date of their neutropenia and appeared to have permanently discontinued clozapine. Among those filling additional clozapine prescriptions after the date of neutropenia, 80.3% with mild and 60% with severe neutropenia did so within 2 weeks after their neutropenia event.

Table 5. Timing of neutropenia, ANC recovery, and clozapine resumption in patients with neutropenia during their first episode of continuous clozapine use, Veterans Affairs health system, FY2000-FY2023.

	Severity of neutropenia		
	Mild (n=217)	Moderate (n=53)	Severe (n=32)
Neutropenia occurred within:			
4 weeks of clozapine start	16.1%	11.3%	9.4%
3 months of clozapine start	37.3%	32.1%	40.6%
Normal ANC within 2 weeks	93.0%	84.9%	81.3%
Clozapine Rx after neutropenia:			
Ever	72.4%	47.2%	31.3%
Within 2 weeks	58.1%	28.3%	18.8%

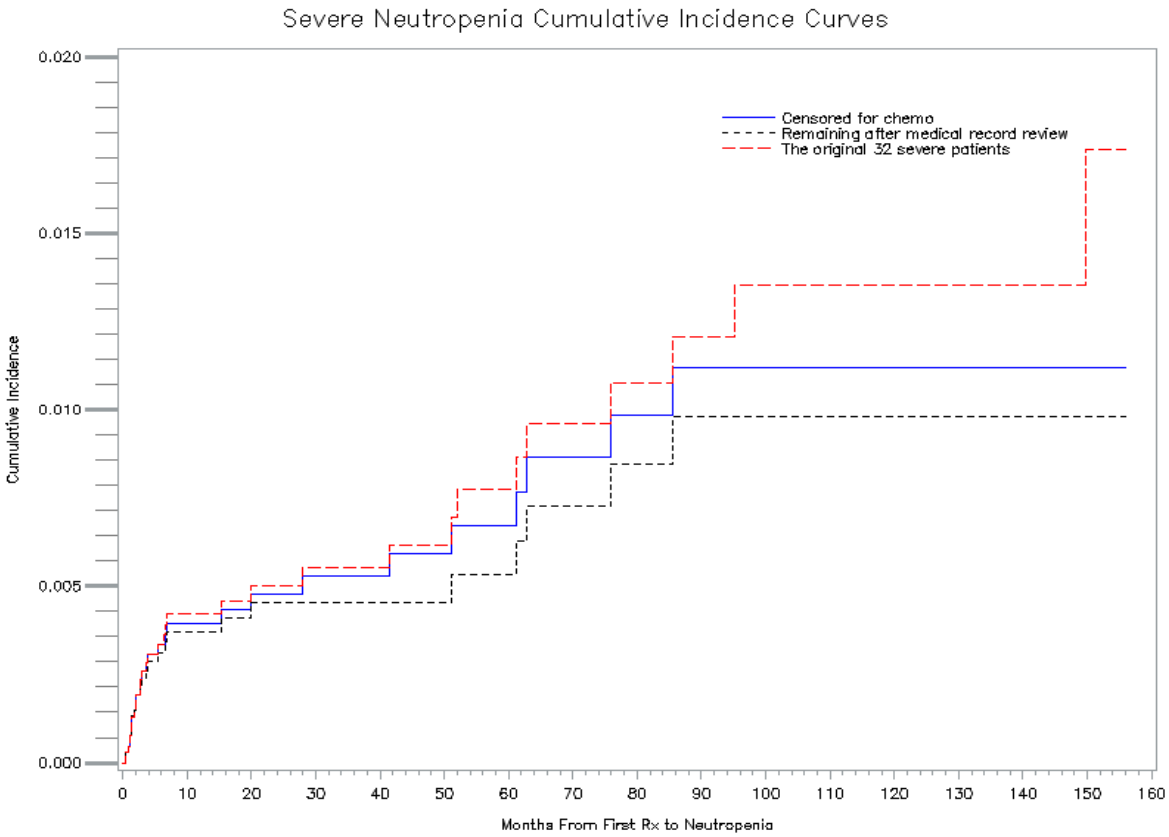
Kaplan-Meier and life table analyses: Based on 32 severe neutropenia events, the incidence of severe neutropenia during the first episode of clozapine use was highest during the first 9 months, with a somewhat lower risk through 8 years of use, after which the number of patients on treatment was small (<10% of original cohort) and the incidence of severe neutropenia was consequently also low (Figure 2, original severe patients). For the first episode of use, the cumulative incidence of severe neutropenia with clozapine per 1000 treated patients was 4.2 (95% CI 2.6-6.5) at 12 months, 7.8 (95% CI 4.8-11.9) at 5 years, 13.5 (95% CI 8.4-20.9) at 8 years, and 17.4 (95% CI 9.5-29.3) at 13 years and beyond.

Because treatment with myelosuppressive chemotherapy for cancer is not uncommon and could be a cause of severe neutropenia, we performed another analysis where clozapine patients were censored from follow-up if they initiated chemotherapy. This resulted in slightly smaller sample sizes during follow-up and in the censoring of four cases of severe neutropenia from the original total. Three of these cases occurred beyond 5 years of clozapine use. For the first episode of use, based on 28 cases, the cumulative incidence of severe neutropenia per 1000 treated patients was 3.9 (95% CI 2.4-6.1) at 12 months, 6.7 (95% CI 4.2-10.5) at 5 years, 11.2 (95% CI 6.7-17.6) at 8 years and beyond.

After medical record review of severe neutropenia cases, three additional cases were removed from analysis (two were probably laboratory errors[1] and one was possibly due to previously undiagnosed lymphoma). Based on 25 cases, the cumulative incidence of severe neutropenia per 1000 treated patients was 3.7 (95% CI 2.3-5.9) at 12 months, 5.3 (95% CI 3.2-8.5) at 5 years, and 9.8 (95% CI 5.6-16.0) at 8 years and beyond.

[1] One patient had an ANC<500 cells/µL with a repeat ANC later the same day being normal. Clozapine was not stopped. In a second patient, ANC<500 cells/µL was rechecked the next day and ANC was normal. Clozapine was not stopped.

Figure 2. Kaplan-Meier plot showing cumulative incidence of severe neutropenia during the first episode of continuous clozapine use, without censoring, with censoring for chemotherapy, and after medical record review, from the Veterans Affairs health system, FY2000-FY2023.



Using life table methods, we estimated the treatment-interval-specific incidence rates of severe neutropenia during the first episode of continuous clozapine use, for each use-case scenario (all cases without censoring for chemotherapy, with censoring for initiation of cancer chemotherapy, and after medical record review to confirm each case) (Table 6). In all analyses, the rate of severe neutropenia was highest during the first 3 months of use with somewhat lower risk through 9 months, after which the rate appeared to level off at approximately one case per 1000 person-years from 1 through 5 years and slightly higher from 5 through 8 years of use. The one case occurring during years 8 through 13 in the initial analysis was in a patient treated with chemotherapy. The sample size of patients at risk was low beyond 8 years and especially low beyond 13 years.

Table 6. Life table estimates of interval-specific incidence of severe neutropenia per 1000 person-years during the first episode of continuous clozapine use, without and with censoring for cancer chemotherapy, and after medical record review, Veterans Affairs health system, FY2000-FY2023.

		Based on outpatient prescription data only (n=32 events)		Censoring for chemotherapy (n=28 events)		Including medical record review (n=25 events)	
Treatment Interval (months)	No. entering interval	No. of events	Rate per 1000 person-years	No. of events	Rate per 1000 person-years	No. of events	Rate per 1000 person-years
0-3	6488	13	9.6	13	9.6	12	8.9
3-6	4324	4	4.1	4	4.1	4	4.1
6-9	3510	3	3.6	2	2.4	2	2.4
9-12	3051	0	0.0	0	0.0	0	0.0
12-18	2777	1	0.8	1	0.8	1	0.8
18-24	2406	1	0.9	1	0.9	1	0.9
24-36	2100	1	0.5	1	0.5	0	0.0
36-60	1661	3	1.1	2	0.7	1	0.4
60-96	1058	5	1.9	4	1.6	4	1.6
96-156	639	1	0.4	0	0.0	0	0.0
156-216	227	0	0.0	0	0.0	0	0.0
216-290	65	0	0.0	0	0.0	0	0.0
290+	2	---	---	---	---	---	---

Review of potential clozapine-related fatalities: Within the cohort of 6488 clozapine initiators, all deaths occurring within 180 days after the last recorded use of clozapine were identified and their electronic medical records were reviewed for patients with either severe or moderate neutropenia.

Among five patients with severe neutropenia who died within 180 days after their last clozapine dose, one definite clozapine-associated severe neutropenia case was found. This patient had an ANC=0 on day 23 of clozapine use. Clozapine was stopped and the patient was treated with filgrastim, but developed fever, infection, and respiratory failure, with death occurring 31 days after clozapine was stopped. One other patient with chronic respiratory failure and pre-existing neck cellulitis, who had been on clozapine for 5.3 years, was admitted to hospital for acute on chronic respiratory failure. Two weeks into the hospitalization, the ANC fell to 400, and clozapine was stopped. The patient's ANC recovered but the patient died from septic shock 38 days later. Death seemed unlikely due directly to clozapine-related neutropenia, but we could not exclude the possibility that neck cellulitis developed or worsened while the patient was severely neutropenic, possibly contributing to this death. In the remaining three patients, death was related to medical comorbidities. We also identified two patients with moderate neutropenia who died within 180 days after their last clozapine dose. In both cases, death occurred 5 to 6 months after clozapine was stopped and appeared to be unrelated to clozapine use.

Review of later-occurring severe neutropenia events: From our medical record review of the 25 cases included in the Kaplan-Meier analysis, we noted that among the four cases of severe neutropenia that occurred during the interval from 5 to 8 years (60-96 months) of continuous clozapine use, the clozapine dose had been increased recently in two patients. In the other two, another medication had been recently initiated, azithromycin in one and topiramate in the other. Neither of these drugs was listed as increasing the risk of neutropenia with clozapine at the website DrugBank.com, but the combination of clozapine and azithromycin was listed as increasing the risk of QTc prolongation, which increases the risk of ventricular arrhythmias, and the combination of clozapine and topiramate was listed as increasing the risk of hyperthermia.

Study limitations: The VA population was predominantly male, skewing towards older age and higher comorbidity burden compared with the general population. This could affect generalizability.

The data used in this study were based on outpatient clozapine prescriptions and inpatient or outpatient ANCs, both of which are collected by the VA's clozapine registry and the Department of Veterans Affairs prescription database. If clozapine use occurred during an inpatient hospitalization or within a long-term care facility, we did not capture it because inpatient prescriptions were not included as part of the initial analysis. This limitation could lead to misclassification bias whereby a patient is classified as no longer using clozapine because of an intercurrent hospitalization. A case of severe neutropenia occurring after that hospitalization could also be misclassified as unrelated to active clozapine use.

Also, we counted severe neutropenia events that occurred while patients were actively using outpatient clozapine or within 30 days of their last clozapine dose. For a patient who developed mild or moderate neutropenia within this timeframe but who progressed to severe neutropenia beyond 30 days, the severe neutropenia would not be counted.

To explore the extent of misclassification bias arising from not having the data on inpatient clozapine use available for inclusion in our analysis at the time of the upcoming clozapine REMS advisory committee meeting, we reviewed the medical records of all 67 patients with documented severe neutropenia. We identified all intercurrent hospitalizations and inpatient clozapine use and determined whether this changed each patient's exposure classification status at the time when severe neutropenia was detected. From this exercise, we identified five additional patients with severe neutropenia that could be included in the final analysis of these data. In one case, the patient's clozapine was continued during a prolonged hospitalization and severe neutropenia developed while in hospital on clozapine. In three other cases, we had classified severe neutropenia as occurring during a second episode of continuous clozapine use, but our review showed that it occurred during the first episode of use. In these, an intercurrent hospitalization during which clozapine use was continued, served as a bridge linking two periods of outpatient clozapine use together into the same episode of use. A fifth case was identified in which mild neutropenia developed while a patient was on clozapine, at which time clozapine was stopped. Over the next 98 days, this patient progressed to severe neutropenia.

Ongoing analyses and future steps: It was not possible to revise our analysis by merging inpatient and outpatient clozapine prescription data in time for the advisory committee meeting. That updated analysis will include the 25 case-patients included in the Kaplan-Meier analysis shown above plus the five additional case-patients described in the *Limitations* section. However, we were able to estimate the impact that inclusion of these cases will probably have on our results. These five cases occurred after 3.6 months, 4.6 months, 6.9 months, 4.8 years, and 9.3 years of clozapine use. Based on this information, we estimated that the cumulative incidence of severe neutropenia would be approximately 0.7% at 5 years, 1.2% at 8 years, and 1.4% at 13 years, somewhat higher than the analysis based on 25 case-patients.

In our original analysis, we classified 16 patients as having severe neutropenia during a subsequent episode of clozapine use beyond the first episode. Review of medical records with cross-checking against inpatient and outpatient prescription data led to this number being revised downwards to nine patients. Reasons for the revision include cancer chemotherapy (n=4) and inpatient clozapine use shifting cases from the second to the first episode of use (n=3).

Review of the medical records for these nine case-patients uncovered potentially important clinical details. Five of these cases occurred during a second episode of use, with four occurring during

the first 3 months after resuming clozapine. Among three patients with severe neutropenia during a third episode of use, two occurred after 9 years of clozapine.

Discussion: From October 1999 through September 2023, 9300 patients were treated with clozapine within the VA health system, of whom 6488 were new initiators who met all cohort inclusion criteria. Most were diagnosed with schizophrenia or schizoaffective disorder and had been treated previously with other antipsychotic agents. Nearly 60% of patients had a single episode of clozapine use, with the remainder having multiple episodes of use separated by periods of non-use. Absolute neutrophil count monitoring within this cohort was extensive although not perfectly compliant with product labeling, with approximately 70% of patients appearing to have weekly testing most of the time through the first 6 months of use.

During the first episode of continuous clozapine use, 302 patients had documented neutropenia, with 32 having severe neutropenia. The cumulative incidence of severe neutropenia was 4.2 per 1000 at 1 year, increasing to 17.4 per 1000 at 13 years and beyond of on-drug follow-up. In an analysis that censored for treatment with cancer chemotherapy, there were 28 patients with severe neutropenia, resulting in a cumulative incidence of 3.9 per 1000 at 1 year, increasing to 11.2 per 1000 at 8 years of follow-up and beyond. After medical record review of these cases, three were removed from the analysis because the severe neutropenia was probably due to laboratory error in two cases and to underlying previously undiagnosed lymphoma in one case. Based on the remaining 25 cases, the cumulative incidence of severe neutropenia was 3.7 per 1000 at 1 year, 5.3 per 1000 at 5 years, and 9.8 per 1000 at 8 years. For all analyses, the period of greatest risk was during the first 3 months following initiation of clozapine, with somewhat lower risk through 9 months, after which risk appeared to level off at approximately one to two cases per 1000 person-years through 8 years of use. Updating the analysis to include in-hospital clozapine use will lead to the inclusion of five additional cases of severe neutropenia in the analysis of risk during the first episode of continuous clozapine use, and somewhat higher estimates of cumulative risk during follow-up than in the analysis based on 25 case-patients. Also, from our preliminary updated analyses of first and later episodes of use, risk of severe neutropenia persists beyond 9 years of clozapine use, despite falling sample size.

The cumulative incidence of severe neutropenia experienced by this VA cohort at 1 year of follow-up was somewhat lower than that reported with other large, longitudinal cohorts (Table 7).

Table 7. Longitudinal studies of severe neutropenia risk in patients treated with clozapine.

Author (year)	Country	No. new clozapine users	No. severe neutropenia	Cumulative incidence
Alvir (1993)	USA	11,555	55	0.8% @ 1yr 0.9% @ 18 mos
Atkin (1996)	UK and Ireland	6,316	48	1.0% @ 1 yr 1.1% @ 3 yrs
Kang (2006)	Korea	6,782	54	0.7% @ 1 yr 1.6% @ 6 yrs
Rubio[a] (2024)	Finland	3,643	?	0.2% @ 1 yr 1.4% @ 22 yrs
Northwood[b] (2024)	Australia	15,973	232	1.4% @ 2 yrs

[a] Cases of severe neutropenia were defined by a diagnosis code, not ANC

[b] Moderate and severe neutropenia were combined as “serious neutropenia leading to cessation”

The study by Alvir et al.[1] was limited by a relatively short duration of follow-up while that by Atkin et al.[2] did not estimate cumulative incidence using Kaplan-Meier methods but presented sufficient data to allow cumulative incidence estimation by the FDA review team using life table methods. The study by Kang et al.[3] followed patients through 6 years, with a cumulative incidence estimate of 1.6% (16 per 1000). Rubio et al.[4] did not have access to ANC data and identified cases of severe neutropenia based on diagnoses from electronic health records. This could account for the relatively low cumulative incidence at 1 year, which was estimated from inspection of their Kaplan-Meier plot. The study by Northwood et al.[5] is not comparable to the other studies discussed here because these investigators pooled moderate and severe neutropenia together rather than focusing on severe neutropenia alone.

Conclusion: Over the years from October 1999 through September 2023, risk of severe neutropenia was highest during the first 9 months of clozapine use but persisted at a somewhat lower level through at least 8 years of continuous use. Sample size beyond 8 years was low, falling to <10% of the starting cohort size.

References

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