

Changes in Neutropenia Outcomes Following Implementation of the Clozapine Risk Evaluation and Mitigation Strategy Update

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Introduction

- The Clozapine Risk Evaluation and Mitigation Strategy (REMS) was originally introduced by the US Food and Drug Administration as a drug safety program to mitigate clozapine-induced neutropenia risk in October 2015.
- In February 2019, the Clozapine REMS was updated to require prescriber and pharmacy certifications before prescribing or dispensing clozapine.

Objective

- This study examined the impact of the Clozapine REMS update on neutropenia outcomes among clozapine users.

Methods

Data Source

- Komodo Research Dataset linked to the Komodo Lab Results via de-identified, precertified member identification tokens

Komodo Research Dataset (KRD): Composed of administrative data and claims, KRD captures routinely collected health services utilization records and expenditures for over 330 million de-identified unique individuals in the US. Native to HIPAA-compliant, privacy-preserving tokens, KRD offers extended patient-level observations of medical encounters and outpatient pharmacy dispensings via linkage across health and pharmacy insurance plans. Data availability is as early as 2016. Specialty datasets such as genomics, laboratory test results, and electronic medical records are readily accessible via additional linkage. KRD is the optimized schema of the underlying Healthcare Map™ from Komodo Health for RWE generation and HEOR.

Komodo Lab Results (KLR): Unit-standardized laboratory results of routine and specialized tests generated by over 73 million unique individuals across care settings of hospitals, nursing facilities, and ambulatory offices in the US.

Cohort Eligibility

- Inclusion criteria: Adults (18 years or older) with ≥1 observable absolute neutrophil count (ANC) value between January 2017 and July 2023, and outpatient clozapine dispensation in the prior 30 days
- Exclusion criteria: Patients with severe neutropenia ineligible for contributing to future months until subsequent ANC >1000/μL

Analysis

- Personal lowest ANC was assigned to individual clozapine users in any given month and categorized as the following neutropenia outcomes:

Mild (1000-1499/μL), *Moderate* (500-999/μL), *Severe* (<500/μL)

- Interrupted time series analyses for each neutropenia outcome:

- Quasi-poisson regression with monthly population offset
- 3-month anticipatory period excluded
- Independent variables:
 - Post-2019 REMS update (binary)
 - Pre-update period: January 2017–November 2018
 - Post-update period: March 2019–July 2023
 - Month (continuous, recentered on March 2019)
 - Interaction term

Results

Figure 1. Monthly Neutropenia Rate Among Clozapine Users With an Absolute Neutrophil Count (ANC) Test Result, January 2017 Through July 2023

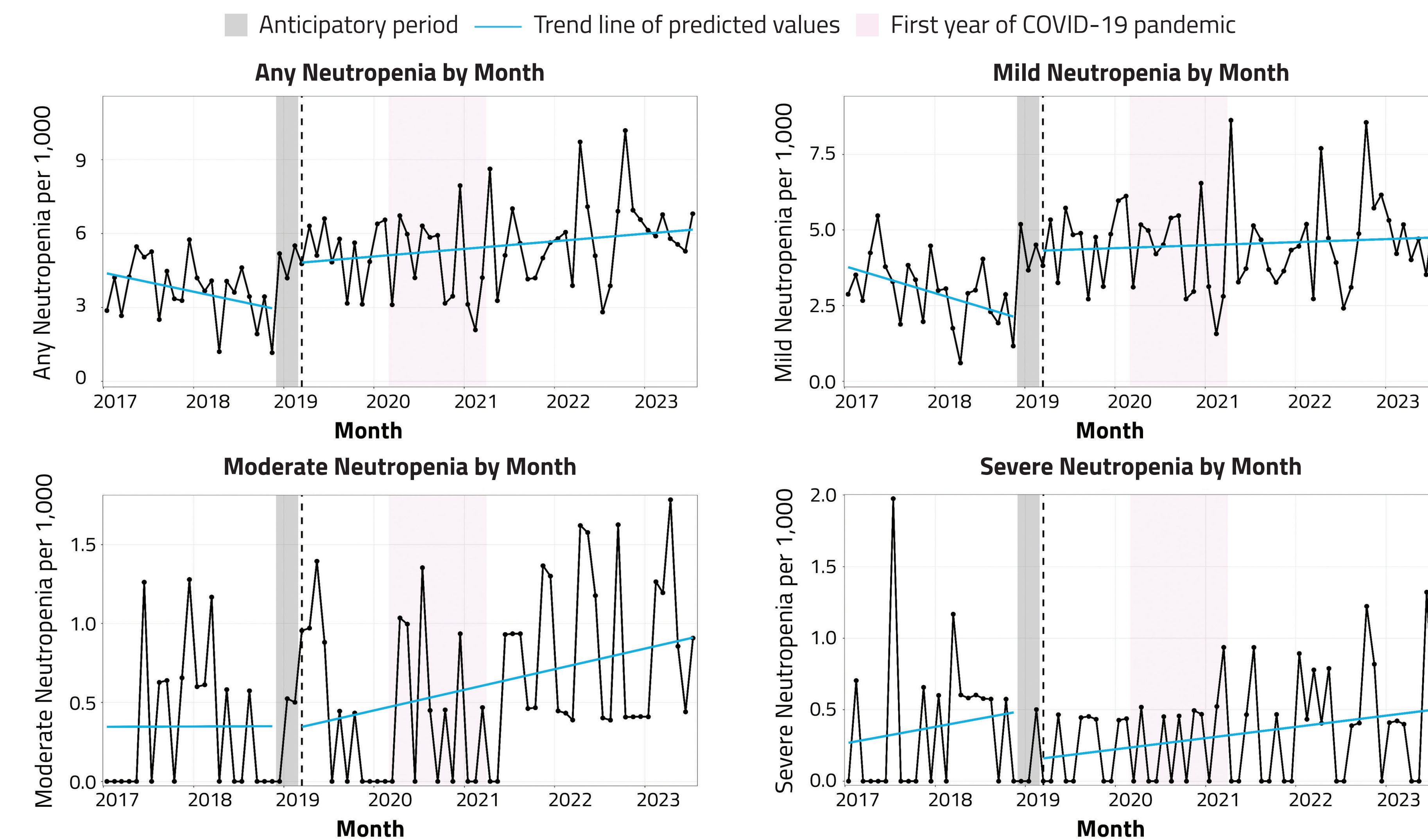


Table 1. Changes in Monthly Neutropenia Rate Following the 2019 Clozapine Risk Evaluation and Mitigation Strategy Update

Characteristic	Any Neutropenia			Mild Neutropenia			Moderate Neutropenia			Severe Neutropenia		
	IRR ^a	95% CI ^a	p-value	IRR ^a	95% CI ^a	p-value	IRR ^a	95% CI ^a	p-value	IRR ^a	95% CI ^a	p-value
Month	0.982	0.958, 1.007	0.166	0.975	0.948, 1.002	0.077	0.994	0.916, 1.080	0.894	1.026	0.953, 1.108	0.499
Post-2019 REMS Update	1.609	1.123, 2.347	0.013	1.960	1.321, 2.977	0.002	1.109	0.375, 3.908	0.862	0.371	0.127, 1.155	0.080
Month * Post-2019 REMS Update	1.023	0.997, 1.050	0.087	1.027	0.999, 1.057	0.062	1.024	0.941, 1.113	0.576	0.994	0.919, 1.073	0.884

^aIRR = incidence rate ratio, CI = confidence interval.

Table 2. Characteristics of Individuals With an ANC Value and a Clozapine Outpatient Pharmacy Dispensing in the Prior 30 Days

Characteristic	Age ^a	Sex ^b	Race ^b		Region ^b				Insurance Type ^b		
	Years	Male	Black	White	Northeast	Midwest	South	West	Commercial	Medicaid	Medicare
Clozapine Users, 1+ ANC Value (N = 15,781) ^c	47.9 (15.2)	9,364 (59.3)	2,345 (14.9)	10,927 (69.2)	5,595 (35.5)	≥2,390 (15.2)	3,720 (23.6)	4,057 (25.7)	1,434 (9.1)	4,415 (28.0)	9,733 (61.7)
Clozapine Users, Overall (N = 163,485) ^d	47.9 (15.6)	96,976 (59.3)	22,362 (13.7)	94,030 (57.5)	44,949 (27.5)	43,628 (26.7)	39,099 (23.9)	34,757 (21.3)	14,784 (9.1)	47,264 (29.0)	97,550 (59.7)

^aMean (SD). ^bn (%). ^cAs of first qualifying testing date. ^dAs of first dispensing date.

Conclusion

- Observed increase in *mild* neutropenia among clozapine users after the 2019 Clozapine REMS update may reflect earlier detection of neutropenia as intended by the program.
- Study limitations:
 - Neutropenia trends analyzed for only clozapine users with ANC result availability and summarized at population level
 - Clozapine exposure identified via outpatient pharmacy dispensing claims only and possibly not reflective of utilization via professional administration or during an inpatient or facility stay
 - Adherence to ANC monitoring frequency recommended by the Clozapine REMS not assessed
- Future research should consider long-term follow-up and ANC monitoring adherence to complete evaluation of the REMS update's impact on neutropenia outcome among clozapine users.

References

- Center for Drug Evaluation and Research. FDA is temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine. FDA, 2 Nov. 2022, <https://www.fda.gov/drugs/drug-safety-and-availability/fda-temporarily-exercising-enforcement-discretion-respect-certain-clozapine-rems-program>. Accessed 27 Mar. 2024.
- Clozapine REMS. Patient Information. <https://www.newclozapinerems.com/Public/home/Patient>. Accessed 27 Mar. 2024.

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