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PHARMACOLOGICAL TREATMENTS

Risk of neutropenia-related hospitalisation among clozapine initiators

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ABSTRACT

Background Clozapine is highly effective for treatment-resistant schizophrenia but has been associated with an increased risk of agranulocytosis. As a result, until 2025, the Food and Drug Administration required patients receiving clozapine to undergo regular blood testing to monitor for neutropenia as part of a Risk Evaluation and Mitigation Strategy (REMS) programme.

Objective This study sought to compare the risk of neutropenia-related hospitalisations between clozapine and olanzapine initiators.

Methods The study cohort was nested in claims data from Medicaid and two commercial health insurance databases and consisted of adults initiating clozapine or olanzapine who had a recorded diagnosis of schizophrenia or schizoaffective disorder and ≥1 dispensing of a different antipsychotic in the 6 months before initiation. Propensity score matching (1:1) was used to mitigate confounding. The primary outcome was hospitalisation with a neutropenia diagnosis in the primary position. Both as-treated and intention-to-treat analyses were implemented.

Findings After propensity score matching, there were 16 873 initiators in each group. At 6 months postinitiation, there were 12 neutropenia-related hospitalisations among the clozapine cohort (incidence rate: 2.21 per 1000 person-years; 95% CI 1.25 to 3.89) and <11 among the olanzapine cohort (0.18; 95% CI 0.03 to 1.29), corresponding to an incidence rate ratio (IRR) of 12.18 (95% CI 1.58 to 93.71). The IRRs were 5.77 (95% CI 1.29 to 25.76) at 1 year, 5.50 (95% CI 1.23 to 24.55) at 2 years and 5.40 (95% CI 1.21 to 24.13) at 3 years postinitiation. Associations remained but were attenuated in intention-to-treat analyses.

Conclusions Clozapine initiators had an elevated risk of neutropenia-related hospitalisation, especially during the first 6 months of treatment, although the absolute risk was low.

Clinical implications Despite removal of the REMS programme, it is important for prescribers to monitor patients for neutropenia after initiating clozapine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clozapine is highly effective in combatting treatment-resistant schizophrenia but because of its increased risk of agranulocytosis was subject until recently to a Risk Evaluation and Mitigation Strategy (REMS) programme, which required routine blood testing to monitor for neutropenia.

WHAT THIS STUDY ADDS

⇒ We found that the risk of neutropenia-related hospitalisation was increased among clozapine initiators compared with olanzapine initiators. The increased risk was highest within the first 6 months after treatment initiation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite the very low risk of neutropenia from clozapine and the cessation of the REMS programme, our results support the Food and Drug Administration's recommendation that prescribers continue monitoring patients' absolute neutrophil count according to monitoring frequencies described in the prescribing information.

BACKGROUND

Clozapine is highly effective for treatment-resistant schizophrenia. In one key trial, patients with schizophrenia who failed two prior therapies were more likely to respond to clozapine than to chlorpromazine.[1] Similarly, patients with schizophrenia or schizoaffective disorder who had attempted suicide, were hospitalised to prevent suicide or demonstrated moderate-to-severe suicidal ideation had a longer delay in recurrent suicidal behaviour on clozapine than on olanzapine.[2] A 2016 systematic review and meta-analysis reported clozapine had superior effects on symptoms and response rates in treatment-refractory schizophrenia compared with first-generation and other second-generation antipsychotics.[3]

Despite its effectiveness, clozapine remains among the least-used antipsychotics. A 17-country analysis revealed that in 2014, clozapine use ranged from 0.6 per 100 000 persons in Japan to 189.2 per 100 000 persons in Finland, which contrasted with an 'optimal' use benchmark of approximately 200 per 100 000 persons.[4] In the USA, a review of Medicaid claims data from 2002 to 2005 found that only 3% of 629 809 antipsychotic treatment

Table 1 Characteristics of clozapine and olanzapine initiators

	Unmatched cohort			Matched cohort		
Covariate	**Clozapine**	**Olanzapine**	**Standardised difference**	**Clozapine**	**Olanzapine**	**Standardised difference**
N	21 718	212 083		16 873	16 873	
Age (in years); mean (SD)	38.5 (13.3)	41.6 (15.0)	−0.220	38.0 (13.7)	39.2 (13.6)	−0.090
Female sex; N (%)	9879 (45.5)	101 023 (47.6)	−0.043	7614 (45.1)	7706 (45.7)	−0.011
Region; N (%)						
Midwest (North-Central in MarketScan)	6891 (31.7)	42 708 (20.1)	0.267	5224 (31.0)	5385 (31.9)	−0.020
Northeast	4661 (21.5)	39 603 (18.7)	0.070	3839 (22.8)	3867 (22.9)	−0.004
South	5351 (24.6)	65 177 (30.7)	−0.136	4304 (25.5)	4255 (25.2)	0.007
West	4793 (22.1)	64 399 (30.4)	−0.189	3489 (20.7)	3353 (19.9)	0.020
Unknown/other	22 (0.1)	196 (0.1)	0.003	17 (0.1)	13 (0.1)	0.007
Commercial insurance; N (%)	3406 (15.7)	36 528 (17.2)	−0.042	3012 (17.9)	2975 (17.6)	0.006
Use of antipsychotic therapy; mean (SD)						
Number of different antipsychotic drugs used during baseline	2.0 (1.0)	1.5 (0.7)	0.570	1.9 (0.9)	1.9 (1.0)	0.010
Number of different antipsychotic drugs used on index date	0.2 (0.5)	0.2 (0.5)	−0.020	0.2 (0.5)	0.2 (0.5)	0.020
Neutropenia-related conditions (assessed during 30 days prior to index date); N (%)						
Neutropenia	159 (0.7)	258 (0.1)	0.046	136 (0.8)	85 (0.5)	0.038
Pneumonia	257 (1.2)	3155 (1.5)	−0.013	202 (1.2)	210 (1.2)	−0.004
Hospitalisation with infection	1007 (4.6)	8594 (4.1)	0.054	740 (4.4)	733 (4.3)	0.002
Crohn's disease	18 (0.1)	246 (0.1)	−0.005	13 (0.1)	19 (0.1)	−0.010
Rheumatoid arthritis	51 (0.2)	637 (0.3)	−0.032	38 (0.2)	48 (0.3)	−0.010
Lupus	17 (0.1)	340 (0.2)	−0.034	13 (0.1)	15 (0.1)	−0.003
Aplastic anaemia	<11*	135 (0.1)	0.019	<11*	<11*	−0.003
Neutropenia treatment	<11*	14 (0.01)	−0.014	<11*	<11*	0.014
Neutropenia-causing medications	2384 (10.98)	24 591 (11.59)	0.006	1871 (11.1)	1867 (11.1)	0.001
Other comorbidities (assessed during the 180 days prior to index date); N (%)						
Dementia	875 (4.0)	13 145 (6.2)	−0.099	713 (4.2)	734 (4.4)	−0.006
Parkinson's disease	513 (2.4)	2766 (1.3)	0.079	426 (2.5)	421 (2.5)	0.001
Bipolar and anxiety disorders	11 354 (52.3)	108 972 (51.4)	0.018	8815 (52.3)	8936 (53.0)	−0.014
Drug use disorder	5856 (27.0)	68 158 (32.1)	−0.114	4420 (26.2)	4370 (25.9)	0.007
Ischaemic heart disease	981 (4.5)	11 994 (5.7)	−0.052	723 (4.3)	737 (4.4)	−0.004
Acute kidney injury	384 (1.8)	5319 (2.5)	−0.051	311 (1.8)	301 (1.8)	0.005
Chronic kidney disease	424 (2.0)	5629 (2.7)	−0.047	333 (2.0)	329 (2.0)	0.001
Liver disease	1255 (5.8)	14 353 (6.8)	−0.041	910 (5.4)	899 (5.3)	0.003
Combined comorbidity score; mean (SD)	1.7 (1.4)	1.8 (1.6)	−0.070	1.7 (1.4)	1.7 (1.4)	0.000
Healthcare utilisation (assessed during the 180 days prior to index date); mean (SD)						
Number of ANC tests	2.0 (2.9)	1.2 (2.3)	0.310	N/A†	N/A†	N/A†
Number of WBC tests	2.4 (3.1)	1.5 (2.7)	0.290	N/A†	N/A†	N/A†
Number of hospitalisations	1.5 (2.4)	1.1 (1.8)	0.180	1.4 (2.4)	1.3 (2.3)	0.030
Number of ER visits	2.3 (4.2)	2.4 (4.3)	−0.020	2.2 (4.0)	2.2 (3.5)	−0.010
Number of outpatient visits	2.6 (3.9)	2.9 (3.9)	−0.060	2.7 (3.9)	2.7 (4.0)	0.000
Number of unique drugs dispensed	11.9 (6.5)	10.7 (6.6)	0.170	11.6 (6.4)	11.6 (7.0)	−0.010
Number of hospitalisations with psychiatric diagnosis	1.2 (1.9)	0.7 (1.3)	0.300	1.1 (1.8)	1.0 (2.0)	0.030
Number of outpatient visits with psychiatric diagnosis	1.4 (2.8)	1.4 (2.5)	0.030	1.5 (2.8)	1.5 (3.1)	0.000

*Suppressed as per Centers for Medicare and Medicaid policy regarding cell size.
†The number of ANC tests and WBC tests was not used in the propensity score.
ANC, absolute neutrophil count; ER, emergency room; WBC, white blood count.

episodes involved clozapine compared with an estimated 30% of patients with treatment-resistant schizophrenia.[5] Another US study of 134 692 veterans with schizophrenia or schizoaffective disorder treated between 2000 and 2021 found that 5% received clozapine, including just 9% of 3407 veterans with a history of attempted suicide.[6]

One reason for the underuse of clozapine is its risk profile. In addition to carrying boxed warnings for orthostatic hypotension, bradycardia, syncope, seizure and myocarditis, clozapine can cause agranulocytosis, characterised by severe neutropenia (absolute neutrophil count (ANC) <500/µL).[7] Shortly after clozapine's first launch in Finland in 1979, 18 of 2000 patients taking it developed agranulocytosis, resulting in eight deaths.[8] Owing to this risk, Sandoz, brand-name clozapine's manufacturer, agreed to implement a safety programme for the drug as a condition of marketing in the USA. Starting in 1990, the Clozaril Patient Management System required white blood count (WBC) testing prior to initiation and weekly WBC count monitoring until 4 weeks post-treatment.[9]

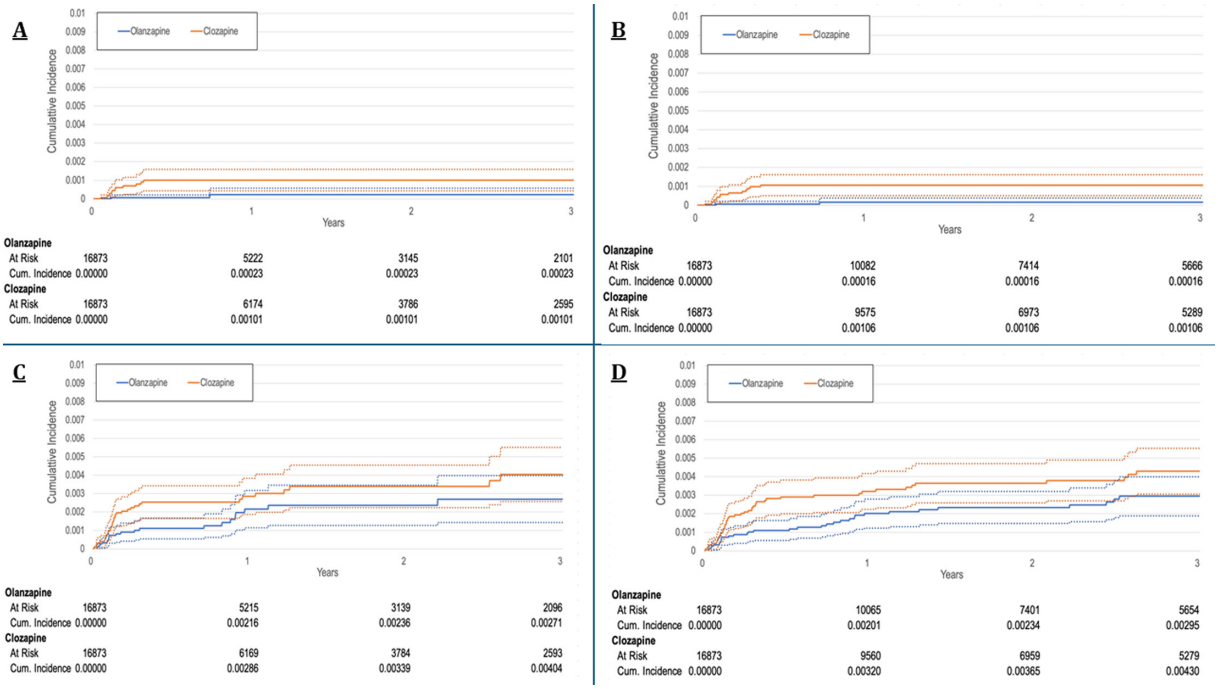

Figure 1 Cumulative incidence of neutropenia-related hospitalisation among the matched cohorts. (A) Primary outcome definition, as treated, (B) primary outcome definition, intent-to-treat, (C) secondary outcome definition, as treated, (D) secondary outcome definition, intent-to-treat. The dotted lines represent the 95% confidence interval for each treatment group.

In 2015, the US Food and Drug Administration (FDA) approved a consolidated Clozapine Risk Evaluation and Mitigation Strategy (REMS) programme to replace separate safety oversight programmes run by Sandoz and the different generic manufacturers that had received FDA marketing approval in the intervening years.[10 11] Under the Clozapine REMS Program, all prescribers and dispensing pharmacies were required to be certified, a process that entailed reviewing educational material, completing a knowledge assessment and attesting to understanding the drug's risk of agranulocytosis and REMS programme requirements.[12] ANC testing had to be done weekly starting on initiation to 6 months on treatment, every 2 weeks from 6 to 12 months, and monthly after 12 months provided ANC levels remain within normal range (≥1500/µL).[13]

Although the risk of neutropenia associated with clozapine has previously been documented—finding the most severe cases occurred within 18 weeks of initiation[14]—the objective of the present study was to directly compare the risk following treatment initiation with clozapine versus olanzapine, an alternative, second-generation antipsychotic often used for treatment-resistant schizophrenia but for which no REMS programme has been in place.[15]

In June 2025, after substantial deliberation, the FDA eliminated the Clozapine REMS Program. In announcing its decision that 'the REMS was no longer necessary to ensure the benefits of clozapine outweigh the risk of severe neutropenia', the FDA cited its evaluation of a literature review, data from both the FDA Adverse Event Reporting System and the FDA Sentinel System, and additional studies designed and analysed in collaboration with others.[16] The present analysis, which included the same authors, was among these studies. Some of its findings were presented in an FDA briefing document that was published in November 2024.[17] These and other findings from the analysis will aid clinicians in making monitoring decisions absent a mandate to do so.

METHODS

Data sources and study cohort

We conducted a cohort study nested in longitudinal administrative claims data from three databases: nationwide Medicaid data (Medicaid, 2000–2018), Optum's deidentified Clinformatics Data Mart (Optum CDM, 2004–2022) and the Merative Marketscan Commercial Claims and Encounters Database (Marketscan, 2003–2020). All three databases are national in scope and contain patient-level information from closed insurance claims for inpatient and outpatient encounters, including diagnosis and procedure codes, filled outpatient pharmacy prescriptions and demographic data. Medicaid contains information on publicly insured recipients, totalling about 20% of the US population. Marketscan captures more than 25 million enrolees in private insurance plans annually, and Optum captures approximately 12 million enrolees in UnitedHealth insurance plans at any given time.

The study cohort comprised new users of clozapine and olanzapine (oral formulation only), with new use defined as no dispensing of clozapine or olanzapine (any formulation) in the 6 months prior. Initiators were required to be at least 18 years old and to have continuous insurance plan enrolment, a recorded diagnosis of schizophrenia or schizoaffective disorder, and at least 1 dispensing of a different antipsychotic (not clozapine or olanzapine) between 180 and 31 days prior to the clozapine or olanzapine dispensing.

Enrolees 65 years and older with Medicaid were excluded, as they qualify for Medicare, and claims for these dual eligible patients are incompletely captured in the Medicaid data. Eligible Medicaid beneficiaries were required to be enrolled in fee-for-service plans or managed care plans with evidence of complete claims and dispensing data. Patients with a diagnosis of cancer or evidence of chemotherapy, a diagnosis of HIV or evidence of HIV therapy, or a diagnosis of myelodysplastic syndrome—all

Table 2 Risk of neutropenia comparing clozapine (exposed) to olanzapine (referent) before and after matching, as treated

	Primary outcome definition: inpatient diagnosis of neutropenia in primary position				*Secondary outcome definition: inpatient diagnosis of neutropenia in any position*			
	Before matching		After matching		Before matching		After matching	
	Clozapine (N=21 718)	Olanzapine (N=212 083)	Clozapine (N=16 873)	Olanzapine (N=16 873)	Clozapine (N=21 718)	Olanzapine (N=212 083)	Clozapine (N=16 873)	Olanzapine (N=16 873)
Follow-up; median (IQR) in days	155 (37–611)	148 (60–505)	175 (43–640)	146 (60–498)	155 (37–611)	148 (60–504)	175 (43–640)	146 (60–497)
Full follow-up								
Events; N	15	23	14	<11*	46	244	43	28
IR per 1000 person-years (95% CI)	0.48 (0.29 to 0.8)	0.08 (0.05 to 0.12)	0.56 (0.33 to 0.94)	0.13 (0.04 to 0.42)	1.48 (1.11 to 1.98)	0.87 (0.76 to 0.98)	1.71 (1.27 to 2.30)	1.26 (0.87 to 1.82)
IRR (95% CI)	5.94 (3.10–11.38)		4.13 (1.19–14.36)		1.72 (1.25–2.35)		1.36 (0.84–2.18)	
6 months								
Events; N	13	<11*	12	<11*	34	104	32	15
Cumulative incidence; %	0.09 (0.05–0.15)	0.003 (0.001–0.007)	0.10 (0.06–0.17)	0.007 (0.0008–0.04)	0.22 (0.15–0.30)	0.07 (0.05–0.08)	0.25 (0.18–0.36)	0.11 (0.06–0.18)
IR per 1000 person-years (95% CI)	1.92 (1.11 to 3.30)	0.07 (0.03 to 0.17)	2.21 (1.25 to 3.89)	0.18 (0.03 to 1.29)	5.01 (3.58 to 7.02)	1.48 (1.22 to 1.80)	5.89 (4.17 to 8.33)	2.72 (1.64 to 4.51)
IRR (95% CI)	26.90 (9.59–75.47)		12.18 (1.58–93.71)		3.38 (2.30–4.98)		2.17 (1.17–4.00)	
1 year								
Events; N	13	<11*	12	<11*	36	139	34	21
Cumulative incidence; %	0.09 (0.05–0.15)	0.009 (0.005–0.02)	0.10 (0.06–0.17)	0.02 (0.005–0.09)	0.24 (0.17–0.34)	0.11 (0.09–0.13)	0.29 (0.20–0.40)	0.22 (0.13–0.34)
IR per 1000 person-years (95% CI)	1.15 (0.67 to 1.99)	0.09 (0.05 to 0.17)	1.32 (0.75 to 2.33)	0.23 (0.06 to 0.92)	3.20 (2.31 to 4.43)	1.26 (1.07 to 1.49)	3.75 (2.68 to 5.25)	2.41 (1.57 to 3.70)
IRR (95% CI)	12.73 (5.58–29.03)		5.77 (1.29–25.76)		2.54 (1.76–3.66)		1.56 (0.90–2.68)	
2 years								
Events; N	13	13	12	<11*	39	184	37	22
Cumulative incidence; %	0.09 (0.05–0.15)	0.02 (0.008–0.03)	0.10 (0.06–0.17)	0.02 (0.005–0.09)	0.29 (0.20–0.39)	0.20 (0.17–0.24)	0.34 (0.24–0.47)	0.24 (0.15–0.37)
IR per 1000 person-years (95% CI)	0.75 (0.44 to 1.30)	0.08 (0.05 to 0.14)	0.86 (0.49 to 1.52)	0.16 (0.04 to 0.63)	2.26 (1.65 to 3.10)	1.14 (0.99 to 1.32)	2.66 (1.93 to 3.68)	1.73 (1.14 to 2.63)
IRR (95% CI)	9.34 (4.33 to 20.16)		5.50 (1.23 to 24.55)		1.98 (1.40 to 2.80)		1.54 (0.91 to 2.61)	
3 years								
Events; N	13	14	12	<11*	42	207	39	23
Cumulative incidence; %	0.09 (0.05–0.15)	0.02 (0.01–0.03)	0.10 (0.06–0.17)	0.02 (0.005–0.09)	0.36 (0.25–0.51)	0.27 (0.23–0.32)	0.40 (0.28–0.58)	0.27 (0.17–0.43)
IR per 1000 person-years (95% CI)	0.61 (0.36 to 1.06)	0.07 (0.04 to 0.12)	0.70 (0.40 to 1.24)	0.13 (0.03 to 0.52)	1.99 (1.47 to 2.69)	1.07 (0.93 to 1.23)	2.29 (1.67 to 3.13)	1.50 (1.00 to 2.26)
IRR (95% CI)	8.49 (3.99 to 18.07)		5.40 (1.21 to 24.13)		1.86 (1.33 to 2.59)		1.53 (0.91 to 2.55)	

*Suppressed as per Centers for Medicare and Medicaid policy regarding cell size.
IR, incidence rate; IRR, incidence rate ratio.

Table 3 Risk of neutropenia comparing clozapine (exposed) to olanzapine (referent) before and after matching, intent to treat

	Primary outcome definition: inpatient diagnosis of neutropenia in primary position				*Secondary outcome definition: inpatient diagnosis of neutropenia in any position*			
	Before matching		After matching		Before matching		After matching	
	Clozapine (N=21 718)	Olanzapine (N=2 12 083)	Clozapine (N=16 873)	Olanzapine (N=16 873)	Clozapine (N=21 718)	Olanzapine (N=2 12 083)	Clozapine (N=16 873)	Olanzapine (N=16 873)
Follow-up; median (IQR) in days	482 (71–1393)	566 (160–1430)	507 (90–1414)	566 (147–1525)	480 (70–1390)	564 (159–1427)	506 (90–1410)	563 (146–1523)
Full follow-up								
Events; N	20	65	19	<11*	76	525	66	47
IR per 1000 person-years (95% CI)	0.35 (0.23 to 0.54)	0.11 (0.08 to 0.13)	0.42 (0.27 to 0.65)	0.08 (0.03 to 0.22)	1.34 (1.07 to 1.67)	0.85 (0.78 to 0.93)	1.45 (1.14 to 1.84)	0.97 (0.73 to 1.29)
IRR (95% CI)	3.33 (2.01 to 5.49)		5.03 (1.71 to 14.78)		1.56 (1.23 to 1.99)		1.49 (1.02 to 2.16)	
6 months								
Events; N	15	<11*	14	<11*	43	138	39	16
Cumulative incidence; %	0.09 (0.05–0.15)	0.005 (0.003–0.01)	0.11 (0.06–0.18)	0.007 (0.0008–0.04)	0.25 (0.19–0.34)	0.08 (0.07–0.09)	0.29 (0.21–0.40)	0.11 (0.07–0.18)
IR per 1000 person-years (95% CI)	1.87 (1.13 to 3.10)	0.10 (0.05 to 0.20)	2.19 (1.30 to 3.69)	0.15 (0.02 to 1.04)	5.35 (3.97 to 7.22)	1.59 (1.35 to 1.88)	6.10 (4.46 to 8.35)	2.36 (1.44 to 3.85)
IRR (95% CI)	17.99 (7.87 to 41.10)		14.86 (1.95 to 113.03)		3.36 (2.39 to 4.74)		2.59 (1.45 to 4.63)	
1 year								
Events; N	15	20	14	<11*	47	215	42	26
Cumulative incidence; %	0.09 (0.05–0.15)	0.01 (0.008–0.02)	0.11 (0.06–0.18)	0.02 (0.004–0.06)	0.29 (0.21–0.38)	0.13 (0.12–0.15)	0.32 (0.24–0.43)	0.20 (0.14–0.29)
IR per 1000 person-years (95% CI)	1.02 (0.62 to 1.69)	0.13 (0.08 to 0.20)	1.20 (0.71 to 2.02)	0.16 (0.04 to 0.64)	3.20 (2.41 to 4.26)	1.36 (1.19 to 1.56)	3.59 (2.66 to 4.86)	2.10 (1.43 to 3.08)
IRR (95% CI)	5.71 (3.05 to 10.70)		7.42 (1.69 to 32.67)		2.35 (1.72 to 3.23)		1.71 (1.05 to 2.79)	
2 years								
Events; N	15	28	14	<11*	51	316	46	29
Cumulative incidence; %	0.09 (0.05–0.15)	0.02 (0.01–0.03)	0.11 (0.06–0.18)	0.02 (0.004–0.06)	0.32 (0.24–0.42)	0.23 (0.20–0.25)	0.37 (0.27–0.49)	0.23 (0.16–0.34)
IR per 1000 person-years (95% CI)	0.60 (0.36 to 1.00)	0.11 (0.07 to 0.15)	0.70 (0.42 to 1.19)	0.10 (0.02 to 0.38)	2.04 (1.55 to 2.69)	1.19 (1.06 to 1.32)	2.32 (1.74 to 3.09)	1.38 (0.96 to 1.99)
IRR (95% CI)	5.71 (3.05 to 10.70)		7.41 (1.68 to 32.58)		1.72 (1.28 to 2.31)		1.68 (1.05 to 2.67)	
3 years								
Events; N	15	35	14	<11*	58	391	50	33
Cumulative incidence; %	0.09 (0.05–0.15)	0.03 (0.02–0.04)	0.11 (0.06–0.18)	0.02 (0.004–0.06)	0.41 (0.31–0.53)	0.32 (0.29–0.35)	0.43 (0.32–0.57)	0.30 (0.20–0.42)
IR per 1000 person-years (95% CI)	0.46 (0.28 to 0.76)	0.10 (0.07 to 0.14)	0.54 (0.32 to 0.91)	0.07 (0.02 to 0.29)	1.78 (1.37 to 2.30)	1.13 (1.02 to 1.25)	1.93 (1.46 to 2.54)	1.20 (0.85 to 1.69)
IRR (95% CI)	4.54 (2.48 to 8.31)		7.42 (1.69 to 32.63)		1.57 (1.19 to 2.07)		1.61 (1.03 to 2.49)	

*Suppressed as per Centers for Medicaid and Medicare policy regarding cell size.
IR, incidence rate; IRR, incidence rate ratio.;

conditions that increase the risk of neutropenia—during the 6-month baseline period were excluded, as were patients with missing age or sex information (online supplemental eFigure1, eTable 1).

Patient characteristics

Patient demographics assessed on the date of initiation (index date) included age, sex, race/ethnicity (Medicaid and Optum only) and region. Other patient characteristics were assessed during the 6 months prior to cohort entry (baseline period), including the use of other antipsychotics, neutropenia-related conditions and treatments, and comorbid burden.[18 19] We further assessed healthcare use measures such as the number of hospitalisations, emergency room visits and distinct prescriptions filled during the baseline period (see online supplemental eTable 2 for a list of assessed variables and online supplemental eTable 3 for their definitions).

Study outcomes and follow-up

We used two different outcome definitions of neutropenia, a broader category than agranulocytosis. In the first more specific definition, all inpatient hospitalisations with an International Classification of Diseases (ICD)−9-CM or ICD-10-CM discharge diagnosis code for neutropenia (online supplemental eTable 4) recorded in the primary position were considered. In the second more sensitive definition, the neutropenia diagnosis could be in any position on inpatient claims.

For the as-treated analyses, patients were followed from the day after the index date until the occurrence of the outcome, death, end of insurance enrolment, end of data, admission to a nursing facility or hospice, filling a prescription for the other exposure group or drug discontinuation (defined as a gap greater than 30 days following the end of days' supply without a refill), whichever occurred first. In intention-to-treat analyses, follow-up continued for patients irrespective of drug discontinuation or switching.

Statistical analysis

Patient characteristics were compared between clozapine and olanzapine initiators. An absolute standardised mean difference of less than 0.1 was considered to indicate covariate balance.

To address potential confounding, 1:1 propensity score matching was used.[20] Propensity scores were calculated as the predicted probability of initiating clozapine versus olanzapine conditional on 101 baseline covariates. Matching was conducted using a nearest-neighbour algorithm, with a calliper of 0.05 on the natural scale of the propensity score (see online supplemental eTable 5 for a list of variables included in the propensity score analysis). We evaluated propensity score distributional overlap before and after matching and assessed baseline covariate balance in the matched cohort.[21]

The primary analyses used an as-treated approach. Kaplan-Meier survival analyses were used to assess cumulative incidence over time. The incidence rates (IRs) of neutropenia per 1000 person-years with 95% confidence intervals (CIs) and corresponding incidence rate ratios (IRRs) were calculated at 6 months, 1 year, 2 years and 3 years postinitiation as well as over the entire follow-up.

Two sensitivity analyses were conducted to test the robustness of the findings. First, intent-to-treat analyses were conducted in place of as-treated analyses. Second, analyses were conducted on cohorts in which a neutropenia diagnosis recorded in the 180 days prior to the index date was an exclusion criterion.

When interpreting the results, we focused on the consistency of estimates across different analyses, the magnitude of the IRR and the precision of the estimate as reflected in the width of the 95% CI, instead of dichotomising the results as statistically significant ($p<0.05$) or not. Analyses for the study were performed using SAS, V.9.4 (SAS Institute) and R.

RESULTS

Cohort characteristics

The unmatched cohort included 21 718 clozapine initiators and 212 083 olanzapine initiators (table 1, online supplemental eTable 2, eFigure 2). The clozapine initiators were on average slightly younger (38.5 vs 41.6 years) and more commonly from the Midwest (31.7% vs 20.1%) and the Northeast (21.5% vs 18.7%). Clozapine initiators also used a greater number of distinct antipsychotic drugs during the baseline period (2.0 vs 1.5 drugs) and had more healthcare use, including a greater number of hospitalisations with a psychiatric diagnosis (1.2 vs 0.7). As expected, owing to REMS requirements in place during these years, clozapine initiators received more ANC tests (2.0 vs 1.2) and WBC tests (2.4 vs 1.5) during the baseline period compared with olanzapine initiators.

Propensity score matching yielded 16 873 clozapine and 16 873 olanzapine initiators (table 1, online supplemental eTable 5). All covariates used in propensity scoring were adequately balanced in the matched cohort, judged by an absolute standardised difference <0.1. The average age of the matched population was just under 40 years. The vast majority, approximately 80%, had public insurance. Initiators in the matched population used on average approximately two antipsychotics in the baseline period.

Rates of neutropenia-related hospitalisation

Follow-up time

Cumulative incidence plots for the matched cohorts are presented in figure 1. Median follow-up times for the as-treated analysis were 175 days (IQR 43–640) for the clozapine cohort and 146 days (IQR: 60–498) for the olanzapine cohort (table 2). These follow-up times increased to 507 days (IQR: 90–1414) and 566 days (IQR: 147–1525) in intent-to-treat analyses (table 3). Given that neutropenia is so rare, the follow-up times were virtually identical when using the primary versus secondary outcome definition.

Primary outcome definition: inpatient diagnosis of neutropenia in the primary position

In the matched as-treated analysis, 12 events were observed in the clozapine cohort during the first 6 months postinitiation versus <11 (actual number suppressed in accordance with data use agreement to protect patient confidentiality) in the olanzapine cohort, corresponding to IRs of 2.21 (95% CI 1.25 to 3.89) and 0.18 (95% CI 0.03 to 1.29) per 1000 person-years, and an IRR of 12.18 (95% CI 1.58 to 93.71). Fewer than 11 additional events subsequently transpired among olanzapine initiators up to year 3 of follow-up, while no additional events occurred among clozapine initiators, resulting in IRRs of 5.77 (95% CI 1.29 to 25.76) at 1 year, 5.50 (95% CI 1.23 to 24.55) at 2 years and 5.40 (95% CI 1.21 to 24.13) at 3 years postinitiation (table 2).

The results were similar in intent-to-treat analyses: IRRs of 14.86 (95% CI 1.95 to 113.03) at 6 months, 7.42 (95% CI 1.69 to 32.67) at 1 year, 7.41 (95% CI 1.68 to 32.58) at 2 years and 7.42 (95% CI 1.69 to 32.63) at 3 years postinitiation (table 3).

Results were consistent when excluding patients with a history of neutropenia (online supplemental eTables 6 and 7).

Secondary outcome definition: inpatient diagnosis of neutropenia in any position

Using the second, more sensitive definition of neutropenia, there were 32 events in the clozapine cohort and 15 events in the olanzapine cohort for the matched as-treated analysis at 6 months, corresponding to IRs of 5.89 (95% CI 4.17 to 8.33) and 2.72 (95% CI 1.64 to 4.51) per 1000 person-years, and an IRR of 2.17 (95% CI 1.17 to 4.00). The IRR attenuated to 1.56 (95% CI 0.90 to 2.68) at 1 year of follow-up and remained stable thereafter: 1.54 (95% CI 0.91 to 2.61) at 2 years, and 1.53 (95% CI 0.91 to 2.55) at 3 years (table 2).

Intent-to-treat analyses resulted in IRRs of 2.59 (95% CI 1.45 to 4.63) at 6 months, 1.71 (95% CI 1.05 to 2.79) at 1 year, 1.68 (95% CI 1.05 to 2.67) at 2 years and 1.61 (95% CI 1.03 to 2.49) at 3 years (table 3).

As for the primary definition, excluding patients with a history of neutropenia in the baseline period did not appreciably alter the findings (online supplemental eTables 6 and 7).

DISCUSSION

In a large cohort of commercially and publicly insured patients, we observed a very low absolute risk of neutropenia-related hospitalisation with an increased risk after clozapine initiation compared with olanzapine initiation in the first 6 months postinitiation. The strength of the association diminished with longer follow-up time but remained in sensitivity analyses excluding patients with an existing neutropenia diagnosis.

These results show that despite the requirement of regular ANC tests in the Clozaril Patient Management System and the Clozapine REMS Program, clozapine initiators were more susceptible to neutropenia-related hospitalisation, particularly in the first 6 months of treatment.[22] One possible explanation of this finding is suboptimal adherence to the REMS requirements, which has been observed for other similarly-situated drugs.[23 24] It may be that some patients were still able to access clozapine without having undergone ANC testing, preventing early intervention that could avert neutropenia-related complications. The Clozapine REMS Program and its precursor safety programmes may still have meaningfully mitigated the occurrence of neutropenia, with the prevalence reduced from the level that might have been observed without training, counselling or testing requirements.

In September 2023, the FDA announced that it was reevaluating the Clozapine REMS Program to determine whether it could be modified 'to minimise the burden on patients, pharmacies and prescribers while maintaining the safe use of clozapine'.[25] Patient advocates and healthcare providers called for the FDA to remove barriers to prescribing that they ascribed to the Clozapine REMS Program and improve patient access to clozapine.[26 27] In February 2025, following an advisory committee vote overwhelmingly in favour of removing the restrictions on clozapine based on a large set of data, including the prepublication results from this study, the FDA decided to eliminate the Clozapine REMS Program.[28]

An important limitation of this study was its reliance on claims-based diagnostic codes of neutropenia as a proxy for agranulocytosis given the lack of information on ANC in claims data. Although the identified events may have represented mild or moderate neutropenia or laboratory error rather than severe neutropenia, this likely affected both the clozapine and olanzapine cohorts equally, attenuating results towards the null. This is supported by the stronger associations observed when using the more specific primary definition. Nevertheless, some differential misclassification due to the greater frequency of blood tests in the clozapine group cannot be ruled out. Events that resulted in death before hospital admission are likely to be underascertained; this could have resulted in an underestimate of the relative risks if more common among clozapine initiators. Our study did not assess adherence with REMS requirements; thus, we do not know whether the increased risk of neutropenia-related hospitalisation in the first 6 months was due to events occurring despite adherence to the REMS or occurring owing to non-adherence. Finally, given the low absolute rate of neutropenia-related hospitalisation, our estimates of risk were imprecise despite the large cohorts. However, the low absolute risk is important from a public health perspective.

CONCLUSIONS

This large-scale investigation found that among patients who initiated clozapine while it was under the Clozapine REMS Program or its precursor programmes, neutropenia-associated hospitalisations were extremely rare, but the risk was elevated during the first 6 months of treatment compared with patients who take olanzapine. Although the Clozapine REMS Program has now been eliminated, the recommendation that prescribers regularly check ANC levels remains in the drug labelling, and, according to our results, remains most salient in the first 6 months after treatment initiation.

Over time, it will be important to assess the extent to which ANC testing remains a part of routine care, and to evaluate whether removal of the formal REMS requirements effectively increases patient access to clozapine while maintaining low risks of agranulocytosis and neutropenia-related adverse events.

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Competing interests AS reports serving as an expert witness in litigation challenging the implementation of the Mifepristone REMS programme. ASK reports serving as an expert witness on behalf of a class of individual plaintiffs in a case against Gilead relating to its tenofovir-containing products, on behalf of a payor in a case against Johnson & Johnson regarding patents and biosimilar Stelara entry, and on behalf of a group of state attorneys general and payors in a case against multiple generic manufacturers related to alleged price fixing. KFH reports being an investigator on grants to Brigham and Women's Hospital from Takeda, GSK, and UCB, unrelated to this work.

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Ethics approval This study involves human participants and was approved by Mass General Brigham IRB (2020P002183), which waived the need for informed consent.

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