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Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request: cder_mpl1r_wp183

Request ID: cder_mpl1r_wp183_nsdp_v03

Request Description: This analysis examined adherence to absolute neutrophil count (ANC) screening recommendations among clozapine users in the Sentinel Distributed Database (SDD).

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis (CIDA) module, version 10.3.2

Data Source: We distributed this request to seven Sentinel Data Partners on June 7, 2021. The study period included data from January 1, 2005 through December 31, 2020. Please see Appendix A for a list of dates of available data for each Data Partner.

Study Design: We identified individuals with incident use of clozapine and assessed for ANC screening events during the clozapine exposure episodes, among a cohort who were at least 12 years of age. We evaluated whether the ANC screening events met various adherence criteria based on the categorical number of ANC screening events per the specified observation window. We assessed the ANC screening adherence among clozapine users in two separate time periods: from January 1, 2010 to August 31, 2015, and from September 1, 2015 to the most recent available data (December 31, 2020). This is a Type 2 analysis with the multiple events add-on in the Query Request Package (QRP) documentation.

Cohort Eligibility Criteria: We required members to be enrolled in health plans with medical and drug coverage in the 30 days prior to their index date and from the index date through the end of each secondary events observation window ("Look", as defined in Secondary Events of Interest below) in order to be included in the cohort; a gap in coverage of up to 30 days was allowed and treated as continuous enrollment. The following age groups were included in the cohort: 12-18, 19-35, 36-50, 51-64, 65-74, and 75+ years.

Primary Exposure of Interest: We defined the primary exposure of interest, clozapine, using outpatient dispensing data and National Drug Codes (NDCs). We defined incident exposure as no prior evidence of clozapine days supplied in the 30 days prior to the first qualifying (index) exposure. Each qualifying dispensing of clozapine (index) was included in the cohort; cohort re-entry was allowed. Please see Appendix B for a list of generic and brand names of medical products used to define exposures in this request.

We created exposure episodes based on the number of days of clozapine supplied per dispensing in the outpatient pharmacy dispensing data. If multiple dispensings were supplied on the same day, we used the maximum days supplied. We bridged together dispensings less than 30 days apart. For adherence assessment, we required clozapine episodes to be different minimum duration lengths. We assessed clozapine episodes that were: 1) at least one day in duration, 2) at least six months in duration (184 days), 3) at least one year in duration (366 days), and 4) at least two years in duration (731 days). Follow-up began on the clozapine initiation day and continued until the first occurrence of any of the following: 1) disenrollment; 2) death; 3) the end of the data provided by each Data Partner; or 4) the end of the query period.

Sensitivity Analysis: We performed a sensitivity analysis where we bridged together dispensings less than seven days apart for clozapine episodes at least one day in duration.

Secondary Events of Interest: We defined the secondary event of interest as ANC screening events using Revenue Codes, Current Procedural Terminology, Fourth Edition (CPT-4), and Healthcare Common Procedure Coding System (HCPCS) procedure codes. For primary clozapine events at least one day in duration, we observed ANC screening events in the 30 days prior to and including clozapine initiation date ("**Look 1**"), and in the first six months of clozapine initiation ("**Look 2**", "**Look 2, 7-Day Gap Allowance**"). For primary clozapine events at least six months in duration, we observed ANC screening events in the first six months of clozapine initiation ("**Look 5**"), and during 6 to 12 months of clozapine use ("**Look 3**"). For clozapine events at least one year in duration, we observed ANC screening events during 6 to 12 months of clozapine use ("**Look 6**"), and during 12 to 24 months of clozapine use ("**Look 4**"). For primary clozapine events at least two years in duration, we observed ANC screenings events during 12 to 24 months of clozapine use ("**Look 7**"). For Looks 2-7, we required additional continuous enrollment after clozapine initiation through the varying end of the observation window, regardless of when clozapine follow-up ended.

Sensitivity Analysis: We performed a sensitivity analysis using a broader definition of ANC screening events. We observed this secondary definition of ANC screenings events during the first six months of clozapine use, among clozapine episodes at least one day in duration ("**Look 2, Relaxed ANC Definition**"). Please see Appendix C for a list of Revenue, CPT-4, and HCPCS codes used to define both ANC screening event definitions.

Adherence Criteria: The following ANC screening event adherence criteria were evaluated for each "Look":
Look 1:
1) At least 1 ANC screening event
Looks 2, 3, 4, 5, 6, 7 and sensitivity analyses:
1) At Least 1 ANC Screening Event
2) 1-4 ANC Screening Events
3) 5-7 ANC Screening Events
4) 8-11 ANC Screening Events
5) 12-14 ANC Screening Events
6) 15-20 ANC Screening Events
7) 21-24 ANC Screening Events
8) 25-27 ANC Screening Events
9) 28-30 ANC Screening Events
10) 31-35 ANC Screening Events
11) 36+ ANC Screening Events

Please see Appendices D-F for the specifications defining parameters and a visual summary of the cohort "looks" for this request.

Limitations: Algorithms used to define primary events, secondary events, and baseline characteristics are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse).

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[1]Chronic Conditions Data Warehouse. Condition Categories - Chronic Conditions Data Warehouse. https://www.ccwdata.org/web/guest/condition-categories

[2]Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64(7):749-759

Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Module*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

> **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.

> **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.

> **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.

> **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.

> **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Charlson/Elixhauser Combined Comorbidity Score - calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

Code Days - the minimum number of times the diagnosis must be found during the evaluation period in order to fulfill the algorithm to identify the corresponding patient characteristic.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

Computed Start Marketing Date - represents the first observed dispensing date among all valid users within a GROUP (scenario) within each Data Partner site.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions are added after any episode gaps have been bridged.

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Switch Evaluation Step Value - value used to differentiate evaluation step. Each switch pattern can support up to 2 evaluation steps (0 = switch pattern evaluation start; 1 = first evaluation; 2 = second evaluation).

Switch Gap Inclusion Indicator - indicator for whether gaps in treatment episodes that are included in a switch episode will be counted as part of the switch episode duration.

Switch Pattern Cohort Inclusion Date - indicates which date to use for inclusion into the switch pattern cohort of interest as well as optionally as the index date of the treatment episode initiating the switch pattern. Valid options are the product approval date, product marketing date, other requester defined date, or computed start marketing date.

Switch Pattern Cohort Inclusion Strategy - indicates how the switch pattern cohort inclusion date will be used: 01: used only as a switch cohort entry date. First treatment episode dispensing date is used as index for computing time to first switch; 02: used as switch cohort entry date and as initial switch step index date for computing time to first switch.

Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

Table 1. Summary of Absolute Neutrophil Count (ANC) Screening Event Adherence during Clozapine Use in the Sentinel Distributed Database (SDD) between January 1, 2005 and December 31, 2020

| | Overall | | 1+ ANC Screening Event | | Number of ANC Screening Events (1-14) | | | | | | | |
| | | | | | 1-4 | | 5-7 | | 8-11 | | 12-14 | |
Look	N	%	N	%	N	%	N	%	N	%	N	%
January 1, 2010 to August 31, 2015												
1	77,028	100.0%	52,228	67.8%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	72,384	100.0%	66,714	92.2%	14,433	19.9%	16,051	22.2%	8,570	11.8%	4,675	6.5%
5	39,869	100.0%	37,474	94.0%	3,667	9.2%	9,499	23.8%	4,308	10.8%	2,479	6.2%
3	38,055	100.0%	35,716	93.9%	5,048	13.3%	10,033	26.4%	5,789	15.2%	5,306	13.9%
6	28,711	100.0%	27,220	94.8%	2,318	8.1%	7,893	27.5%	4,247	14.8%	4,548	15.8%
4	26,241	100.0%	25,181	96.0%	2,293	8.7%	1,676	6.4%	3,460	13.2%	6,528	24.9%
7	17,134	100.0%	16,591	96.8%	756	4.4%	409	2.4%	1,642	9.6%	5,264	30.7%
2, Relaxed ANC Definition	72,384	100.0%	67,429	93.2%	13,513	18.7%	16,305	22.5%	8,870	12.3%	4,768	6.6%
2, 7-Day Gap Allowance	74,023	100.0%	68,205	92.1%	14,839	20.0%	16,646	22.5%	8,794	11.9%	4,739	6.4%
September 1, 2015 to Most Recent Available Data												
1	59,786	100.0%	40,312	67.4%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	49,738	100.0%	46,203	92.9%	10,097	20.3%	11,350	22.8%	5,642	11.3%	2,808	5.6%
5	29,240	100.0%	27,445	93.9%	2,992	10.2%	6,773	23.2%	2,981	10.2%	1,446	4.9%
3	24,572	100.0%	23,248	94.6%	3,165	12.9%	6,664	27.1%	3,863	15.7%	4,118	16.8%
6	20,133	100.0%	19,117	95.0%	1,866	9.3%	5,499	27.3%	3,111	15.5%	3,731	18.5%
4	13,747	100.0%	13,362	97.2%	741	5.4%	689	5.0%	1,864	13.6%	4,282	31.1%
7	10,959	100.0%	10,673	97.4%	430	3.9%	367	3.3%	1,275	11.6%	3,778	34.5%
2, Relaxed ANC Definition	49,738	100.0%	46,588	93.7%	9,569	19.2%	11,486	23.1%	5,868	11.8%	2,851	5.7%
2, 7-Day Gap Allowance	50,863	100.0%	47,254	92.9%	10,382	20.4%	11,807	23.2%	5,790	11.4%	2,857	5.6%

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Table 1. Summary of Absolute Neutrophil Count (ANC) Screening Event Adherence during Clozapine Use in the Sentinel Distributed Database (SDD) between January 1, 2005 and December 31, 2020

	Number of ANC Screening Events (15-36+)											
	15-20		21-24		25-27		28-30		31-35		36+	
Look	N	%	N	%	N	%	N	%	N	%	N	%
January 1, 2010 to August 31, 2015												
1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	6,598	9.1%	5,817	8.0%	7,659	10.6%	1,839	2.5%	664	0.9%	408	0.6%
5	3,530	8.9%	4,507	11.3%	7,058	17.7%	1,618	4.1%	531	1.3%	277	0.7%
3	4,700	12.4%	1,882	4.9%	2,108	5.5%	476	1.3%	193	0.5%	181	0.5%
6	3,892	13.6%	1,614	5.6%	1,966	6.8%	442	1.5%	152	0.5%	148	0.5%
4	5,075	19.3%	1,466	5.6%	1,186	4.5%	740	2.8%	702	2.7%	2,055	7.8%
7	3,964	23.1%	1,025	6.0%	922	5.4%	573	3.3%	458	2.7%	1,578	9.2%
2, Relaxed ANC Definition	6,749	9.3%	5,933	8.2%	8,095	11.2%	2,030	2.8%	719	1.0%	447	0.6%
2, 7-Day Gap Allowance	6,685	9.0%	5,870	7.9%	7,698	10.4%	1,851	2.5%	*****	0.9%	*****	0.6%
September 1, 2015 to Most Recent Available Data												
1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	4,671	9.4%	4,508	9.1%	5,801	11.7%	944	1.9%	253	0.5%	129	0.3%
5	2,837	9.7%	3,780	12.9%	5,490	18.8%	861	2.9%	203	0.7%	82	0.3%
3	3,041	12.4%	1,052	4.3%	1,068	4.3%	195	0.8%	*****	0.2%	*****	0.1%
6	2,711	13.5%	929	4.6%	1,015	5.0%	183	0.9%	43	0.2%	29	0.1%
4	3,165	23.0%	715	5.2%	458	3.3%	261	1.9%	299	2.2%	888	6.5%
7	2,731	24.9%	587	5.4%	362	3.3%	193	1.8%	214	2.0%	736	6.7%
2, Relaxed ANC Definition	4,704	9.5%	4,589	9.2%	6,021	12.1%	1,079	2.2%	278	0.6%	143	0.3%
2, 7-Day Gap Allowance	4,724	9.3%	4,537	8.9%	5,825	11.5%	*****	1.9%	*****	0.5%	129	0.3%

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (June 7, 2021)

DP ID	DP Start Date[1]	DP End Date[1]
DP01	01/01/2007	10/31/2020
DP02	01/01/2000	07/31/2019
DP03	01/01/2000	12/31/2018
DP04	01/01/2008	12/31/2020
DP05	01/01/2010	09/30/2020
DP06	01/01/2008	03/31/2020
DP07	01/01/2006	08/31/2020

[1]The start and end dates are based on the minimum and maximum dates within each DP. The month with the maximum date must have at least 80% of the number of records in the previous month.

Appendix B. Generic and Brand Names of Medical Products Used to Define Primary Events (Exposures) in this Request

Generic Name	Brand Name
Clozapine	
clozapine	Clozaril
clozapine	FazaClo
clozapine	Versacloz
clozapine	clozapine

Appendix C. List of Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology, Fourth Edition (CPT-4), and Revenue Procedure Codes Used to Define Secondary Events in this Request

Code	Description	Code Category	Code Type
Absolute Neutrophil Count (ANC) Screening			
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	Procedure	CPT-4
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)	Procedure	CPT-4
85004	Blood count; automated differential WBC count	Procedure	CPT-4
85007	Blood count; blood smear, microscopic examination with manual differential WBC count	Procedure	CPT-4
85009	Blood count; manual differential WBC count, buffy coat	Procedure	CPT-4
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	Procedure	CPT-4
G0306	Complete CBC, automated (HgB, HCT, RBC, WBC, without platelet count) and automated WBC differential count	Procedure	HCPCS
0305	Laboratory-Hematology	Procedure	Revenue
ANC Screening Sensitivity Analysis Definition			
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	Procedure	CPT-4
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)	Procedure	CPT-4
85004	Blood count; automated differential WBC count	Procedure	CPT-4
85007	Blood count; blood smear, microscopic examination with manual differential WBC count	Procedure	CPT-4
85008	Blood count; blood smear, microscopic examination without manual differential WBC count	Procedure	CPT-4
85009	Blood count; manual differential WBC count, buffy coat	Procedure	CPT-4

Appendix C. List of Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology, Fourth Edition (CPT-4), and Revenue Procedure Codes Used to Define Secondary Events in this Request

Code	Description	Code Category	Code Type
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	Procedure	CPT-4
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)	Procedure	CPT-4
85032	Blood count; manual cell count (erythrocyte, leukocyte, or platelet) each	Procedure	CPT-4
85048	Blood count; leukocyte (WBC), automated	Procedure	CPT-4
G0306	Complete CBC, automated (HgB, HCT, RBC, WBC, without platelet count) and automated WBC differential count	Procedure	HCPCS
G0307	Complete CBC, automated (HgB, HCT, RBC, WBC; without platelet count)	Procedure	HCPCS
0305	Laboratory-Hematology	Procedure	Revenue

Appendix D. Specifications Defining Parameters in this Analysis

This request utilized the Cohort Identification and Descriptive Analysis (CIDA) module, version 10.3.2 to estimate rates of ANC screening adherence among clozapine users in the Sentinel Distributed Database (SDD).

Query period:	Multiple Query Periods, specified per scenario. See below.
Coverage requirement:	Medical & Drug Coverage
Pre-index enrollment requirement:	30 days
Post-index enrollment requirement:	0 days
Post-episode enrollment requirement for Type 2 analyses:	0 days
Enrollment gap:	30 days
Age groups:	12-18, 19-35, 36-50, 51-64, 65-74, 75+ years
Restrictions:	No
Envelope macro:	Reclassify encounters during inpatient stay as inpatient
Distribution of index-defining codes:	No
Never-exposed cohort:	No
Freeze data:	No

Exposure

Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
1	Look 1	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
2	Look 2	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date

Appendix D. Specifications Defining Parameters in this Analysis

								Exposure								
Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
3	Look 5	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	6 months (184 days)	n/a	n/a	Death; DP end date; Query end date
4	Look 3	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	6 months (184 days)	n/a	n/a	Death; DP end date; Query end date
5	Look 6	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 year (366 days)	n/a	n/a	Death; DP end date; Query end date
6	Look 4	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 year (366 days)	n/a	n/a	Death; DP end date; Query end date

Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
								Exposure								
7	Look 7	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	2 years (731 days)	n/a	n/a	Death; DP end date; Query end date
8	Look 2	01/01/2010 - 08/31/2015	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
9	Look 2	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	7 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
10		01/01/2010 - 08/31/2015	Secondary Episode	ANC Screening (primary definition)	All valid exposure episodes during query period	n/a	n/a	n/a	Yes	1	n/a	n/a	n/a	Any	n/a	Death; DP end date; Query end date

Appendix D. Specifications Defining Parameters in this Analysis

Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
								Exposure								
11		01/01/2010 - 08/31/2015	Secondary Episode	ANC Screening (secondary definition)	All valid exposure episodes during query period	n/a	n/a	n/a	Yes	1	n/a	n/a	n/a	Any	n/a	Death; DP end date; Query end date
12	Look 1	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
13	Look 2	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
14	Look 5	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	6 months (184 days)	n/a	n/a	Death; DP end date; Query end date

Appendix D. Specifications Defining Parameters in this Analysis

																Exposure	

Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
15	Look 3	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	6 months (184 days)	n/a	n/a	Death; DP end date; Query end date
16	Look 6	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 year (366 days)	n/a	n/a	Death; DP end date; Query end date
17	Look 4	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 year (366 days)	n/a	n/a	Death; DP end date; Query end date
18	Look 7	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	2 years (731 days)	n/a	n/a	Death; DP end date; Query end date

Appendix D. Specifications Defining Parameters in this Analysis

								Exposure								
Scenario	Corresponding Look in Diagram	Query Period	Multiple Events Episode	Index Exposure	Cohort definition	Incident exposure washout period	Incident with respect to	Exclude evidence of days supply if exposure washout includes dispensings	Point Exposure?	Max Episode Duration	Treatment episode gap	Exposure episode extension	Minimum exposure episode duration	Care setting	Principal diagnosis position	Censor treatment episode at evidence of
19	Look 2	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	30 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
20	Look 2	09/01/2015 - Most Recent Available Data	Primary Episode	Clozapine	All valid exposure episodes during query period	30 days	Clozapine	Washout lookback period should search for evidence of days supply (N)	No	n/a	7 days	0 days	1 day	n/a	n/a	Death; DP end date; Query end date
21		09/01/2015 - Most Recent Available Data	Secondary Episode	ANC Screening (primary definition)	All valid exposure episodes during query period	n/a	n/a	n/a	Yes	1	n/a	n/a	n/a	Any	n/a	Death; DP end date; Query end date
22		09/01/2015 - Most Recent Available Data	Secondary Episode	ANC Screening (secondary definition)	All valid exposure episodes during query period	n/a	n/a	n/a	Yes	1	n/a	n/a	n/a	Any	n/a	Death; DP end date; Query end date

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes are provided by Optum360.

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Scenario	Secondary Episode	Multiple Events Assessment						Adherence Criteria 1			Adherence Criteria 2		
		Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Minimum Adherence	Minimum Adherence Scale	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
1	ANC Screening (ANC_def1)	Primary Episode Index Date	-30	Primary Episode Index Date	0	1	Count	EpiCount	1	--	-	-	-
2	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
3	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
4	ANC Screening (ANC_def1)	Primary Episode Index Date	183	Primary Episode Index Date	364	1	Count	EpiCount	1	--	EpiCount	1	4
5	ANC Screening (ANC_def1)	Primary Episode Index Date	183	Primary Episode Index Date	364	1	Count	EpiCount	1	--	EpiCount	1	4
6	ANC Screening (ANC_def1)	Primary Episode Index Date	365	Primary Episode Index Date	729	1	Count	EpiCount	1	--	EpiCount	1	4
7	ANC Screening (ANC_def1)	Primary Episode Index Date	365	Primary Episode Index Date	729	1	Count	EpiCount	1	--	EpiCount	1	4
8	ANC Screening Sensitivity Definition (ANC_def2)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4

		Multiple Events Assessment						Adherence Criteria 1			Adherence Criteria 2		
Scenario	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Minimum Adherence	Minimum Adherence Scale	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
9	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
10	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-
12	ANC Screening (ANC_def1)	Primary Episode Index Date	-30	Primary Episode Index Date	0	1	Count	EpiCount	1	--	-	-	-
13	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
14	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
15	ANC Screening (ANC_def1)	Primary Episode Index Date	183	Primary Episode Index Date	364	1	Count	EpiCount	1	--	EpiCount	1	4
16	ANC Screening (ANC_def1)	Primary Episode Index Date	183	Primary Episode Index Date	364	1	Count	EpiCount	1	--	EpiCount	1	4

Appendix D. Specifications Defining Parameters in this Analysis (Continued)

Scenario	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Minimum Adherence	Minimum Adherence Scale	Adherence Criteria 1			Adherence Criteria 2		
								Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
17	ANC Screening (ANC_def1)	Primary Episode Index Date	365	Primary Episode Index Date	729	1	Count	EpiCount	1	--	EpiCount	1	4
18	ANC Screening (ANC_def1)	Primary Episode Index Date	365	Primary Episode Index Date	729	1	Count	EpiCount	1	--	EpiCount	1	4
19	ANC Screening Sensitivity Definition (ANC_def2)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
20	ANC Screening (ANC_def1)	Primary Episode Index Date	1	Primary Episode Index Date	182	1	Count	EpiCount	1	--	EpiCount	1	4
21	-	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-	-	-

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes are provided by Optum360.

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 3-7)

Scenario	Adherence Criteria 3			Adherence Criteria 4			Adherence Criteria 5			Adherence Criteria 6			Adherence Criteria 7		
	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
3	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
4	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
5	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
6	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
7	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
8	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 3-7)

Scenario	Adherence Criteria 3			Adherence Criteria 4			Adherence Criteria 5			Adherence Criteria 6			Adherence Criteria 7		
	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
9	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
14	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
15	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
16	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 3-7)

Scenario	Adherence Criteria 3			Adherence Criteria 4			Adherence Criteria 5			Adherence Criteria 6			Adherence Criteria 7		
	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
17	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
18	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
19	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
20	EpiCount	5	7	EpiCount	8	11	EpiCount	12	14	EpiCount	15	20	EpiCount	21	24
21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes are provided by Optum360.

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 8-11)

Scenario	Adherence Criteria 8			Adherence Criteria 9			Adherence Criteria 10			Adherence Criteria 11		
	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
1	-	-	-	-	-	-	-	-	-	-	-	-
2	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
3	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
4	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
5	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
6	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
7	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
8	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 8-11)											
	Adherence Criteria 8			Adherence Criteria 9			Adherence Criteria 10			Adherence Criteria 11		
Scenario	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
9	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
10	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-
13	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
14	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
15	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
16	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--

	Adherence Criteria 8			Adherence Criteria 9			Adherence Criteria 10			Adherence Criteria 11		
Scenario	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End	Adherence Type	Adherence Start	Adherence End
17	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
18	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
19	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
20	EpiCount	25	27	EpiCount	28	30	EpiCount	31	35	EpiCount	36	--
21	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-	-

Appendix D. Specifications Defining Parameters in this Analysis (Continued, Adherence Criteria 8-11)

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes are provided by Optum360.

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Appendix E. Specifications Defining Stockpiling Parameters Used in this Analysis

		Stockpiling			
Stockpiling group	Same day dispensing processing for days supplied	Same day dispensing processing for amount supplied	Range of allowable days supplied values	Range of allowable amount supplied values	Overlap percentage
clozapine	Uses maximum	Uses maximum	n/a	n/a	n/a

		Observation window (Day*)			
		-30 to 0	1 to 182	183 to 364	365 to 729
Total episode duration (number of days)	1 to 183	Look 1	Look 2		
	184 to 365			Look 3	
	366 to 730				Look 4
	>730				

*Day 0 refers to the date of clozapine dispensing preceded by no evidence of clozapine days supply in the prior 30 days

		Observation window (Day*)			
		-30 to 0	1 to 182	183 to 364	365 to 729
Total episode duration (number of days)	1 to 183				
	184 to 365		Look 5		
	366 to 730			Look 6	
	>730				Look 7

*Day 0 refers to the date of clozapine dispensing preceded by no evidence of clozapine days supply in the prior 30 days