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

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Overview

- Clozapine is an atypical antipsychotic indicated for:
  - Treatment-resistant schizophrenia
  - Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder
- Restricted distribution since initial approval due to risk of severe neutropenia
- Shared system REMS since 2015

Treatment-Resistant Schizophrenia

- Schizophrenia is a serious and persistent psychiatric illness
- Prevalence 0.33% to 0.75%
- Affects social, educational, and occupational functioning; physical health; self-care; quality of life
- 12th leading cause of years lost to disability worldwide
- Positive and negative symptoms, cognitive impairment
- Chronic treatment is the norm

Treatment-Resistant Schizophrenia

- Antipsychotic pharmacotherapy is mainstay of treatment
- Significant subset of individuals with schizophrenia continue to experience psychosis despite adequate trials of antipsychotic treatment
  - Subsequent non-clozapine antipsychotic less likely to result in significant improvement
- Approximately 1/3 of individuals with schizophrenia may meet criteria for treatment resistance

Impact of Treatment-Resistant Symptoms

- More severe positive and negative symptoms
- Worse neurocognitive functioning
- Lower quality of life and community functioning
- Higher health care costs
- Greater health care resource utilization
- Decreased family cohesion

Clozapine

- Only medication approved for treatment-resistant schizophrenia
- Approval based on head-to-head comparison with chlorpromazine
  - Inadequate response to at least three different antipsychotics
  - 30% response to clozapine vs 4% response to chlorpromazine

Clozapine

- Only medication approved for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder
- Approval based on 24-month head-to-head comparison with olanzapine
  - History of suicide attempts/hospitalization to prevent attempt + moderate to severe suicidal ideation with either depressive component or command hallucinations
  - Longer delay to recurrent suicidal behavior
  - Probability of attempt or hospitalization was lower with clozapine (24%) vs olanzapine (32%)

Under Utilization

- Drug utilization data indicate that 148,000 people were dispensed an outpatient prescription for clozapine in 2023
  - Versus estimated 814,000 to 1.2 million with treatment-resistant schizophrenia
- Claims data also suggest only a small percentage of those eligible are prescribed clozapine

Risks

- Risk of severe neutropenia is the focus of REMS
- Other risks with clozapine may also impact patient access and prescriber decision making

Severe Neutropenia

- Focus of the Clozapine REMS Program
- Restricted distribution and requirement for monitoring since initial approval in 1989
- Single shared REMS since 2015
- Monitoring requirements have evolved over time
  - Current requirements:
    - Weekly X 6 months
    - Every 2 weeks in months 6 to 12
    - Monthly after 1 year
- REMS program has never been fully implemented

Clozapine REMS Elements

- Healthcare providers who prescribe clozapine must be certified (Prescriber Certification)
- Pharmacies that dispense clozapine must be certified (Pharmacy Certification)
- Clozapine must only be dispensed to patients with documentation of safe use conditions (documentation of patient enrollment, ANC monitoring, or prescriber authorization to continue treatment if the patient misses a lab or the most recent ANC indicates moderate or severe neutropenia for general population patients or severe neutropenia for BEN patients)
- Patients must be monitored (ANC monitoring for neutropenia)
- Patients must be enrolled in the clozapine registry

Considerations for the re-evaluation of the Clozapine REMS

- The Clozapine REMS has never been fully implemented and neither the Agency nor the CPMG have been able to determine the contribution the Clozapine REMS has had on mitigating the risk of severe neutropenia.
- There are concerns about the burden the REMS may have on stakeholders and patient access.
- The re-evaluation is to determine if the Clozapine REMS can be simplified, reduced in scope, or even eliminated without reducing patient safety.

Questions for the Committee

- How reassured or concerned are you that current and potential clozapine healthcare providers have sufficient knowledge and access to resources about the risk of neutropenia and need for ANC monitoring?
- How reassured or concerned are you that current and potential clozapine healthcare providers will perform ANC monitoring without the requirements of the REMS?
- Are the requirements for the prescriber to document ANC results and the pharmacy to verify the ANC results through the REMS necessary to ensure safe use?
- Is the requirement to educate healthcare providers on the risk of severe neutropenia and the need for ANC monitoring through the REMS necessary to ensure safe use?

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Drug Safety and Risk Management Advisory Committee and the Psychiatric Drugs Advisory Committee Meeting November 19, 2024

Clozapine Background and Regulatory History

Leah Hart, PharmD
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Presentation Overview

- Regulatory history of the risk mitigation strategy for clozapine
  - Changes to labeling
  - REMS approval and modifications

Clozapine Drug Products

Currently Marketed Drugs

- NDAs
  - Clozaril (1989)
  - Versacloz (2013)
- ANDAs
  - Clozapine (8 manufacturers)

Risk of Severe Neutropenia in Labeling for Clozaril in 1989

- Boxed Warning
  - Agranulocytosis*
- Monitoring for severe neutropenia
  - Baseline and weekly monitoring of white blood cell count throughout treatment and for 4 weeks after discontinuation
- Managing severe neutropenia
  - WBC <3000/mm^3/ANC <1500/mm^3: Interrupt treatment and monitor
  - WBC<2000/mm^3/ANC <1000 /mm^3: Discontinue treatment and do not rechallenge

*Now referred to as severe neutropenia

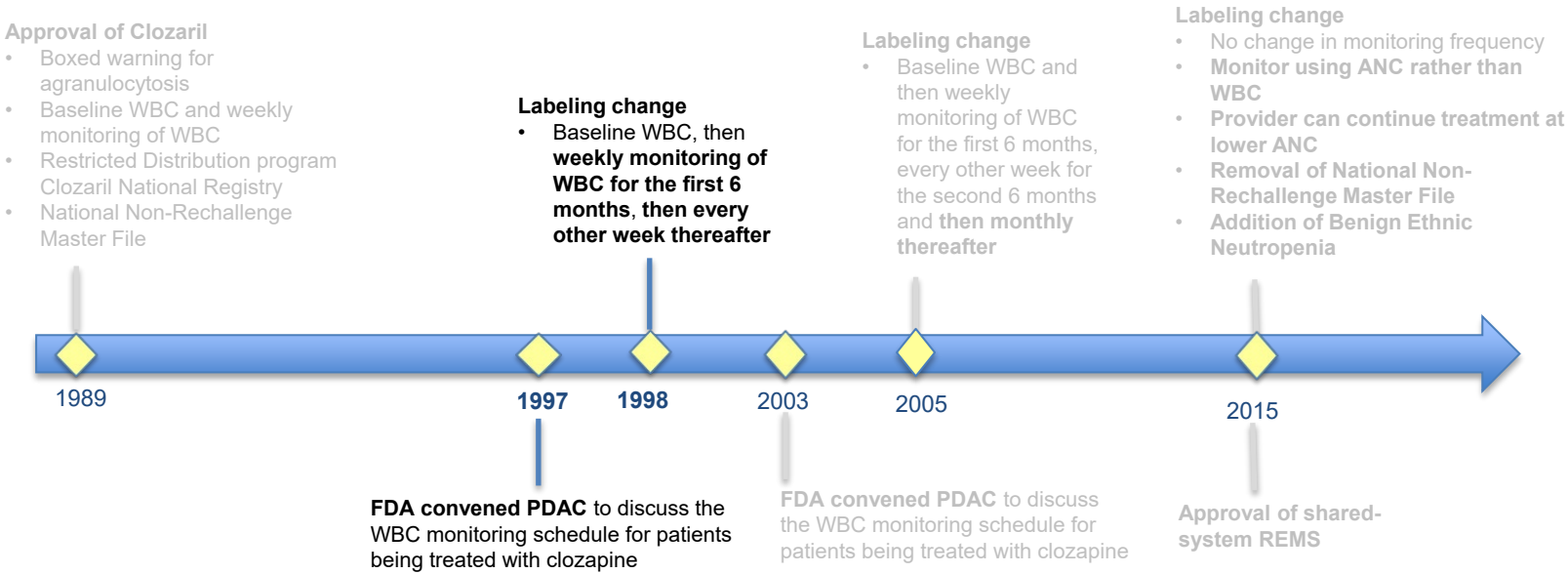
Clozaril Patient Management System – 1989

- Restricted distribution system requiring
  - Documentation of weekly monitoring of white blood cells
  - Enrollment of prescribers, pharmacies, and patients in Clozaril National Registry
  - Prescription day supply limits to support WBC monitoring
- National Non-rechallenge Master File (NNRMF)
  - List of patients who had experienced severe neutropenia while on clozapine and must not be rechallenged
  - Maintained by Novartis
  - Must be checked before dispense

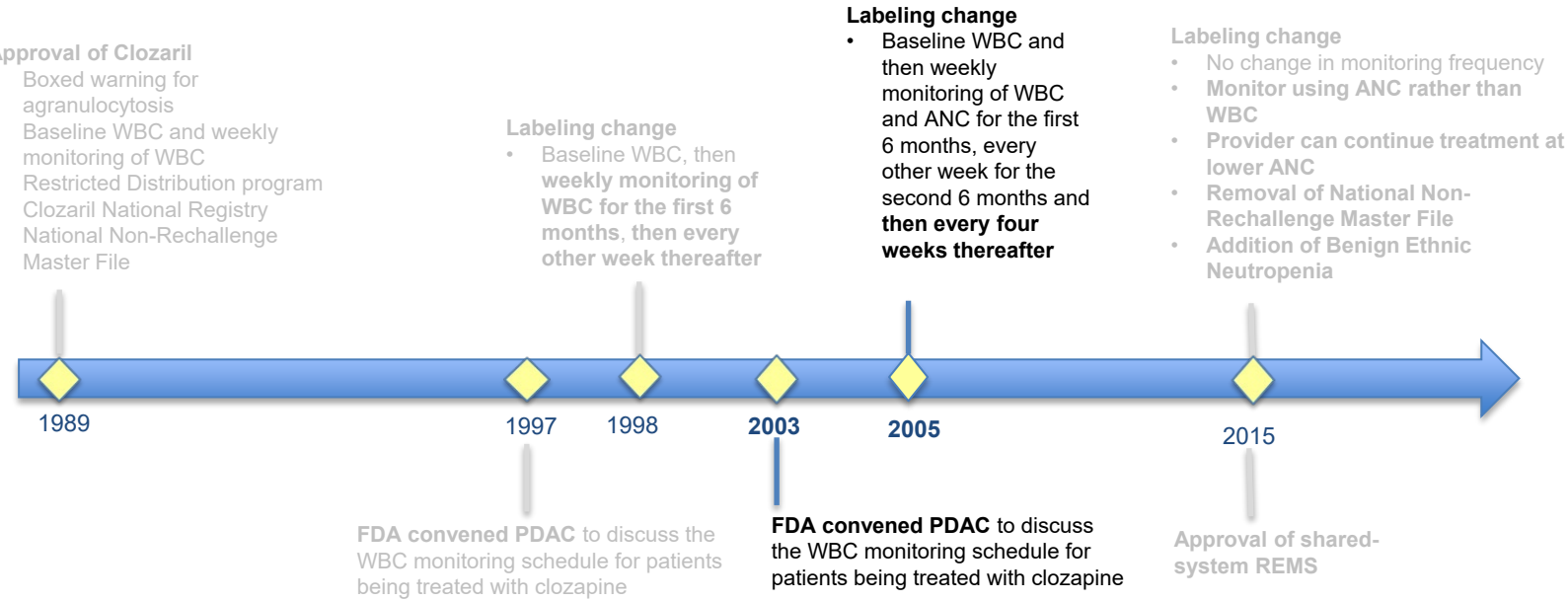
Clozapine Registries Between 1989 – 2015

- Between 1989 and 2015, multiple generics were approved and with each generic, another registry was developed
- In 2015, there were 6 clozapine registries
- Providers and patients were enrolled in multiple registries depending on the product dispensed to the patient

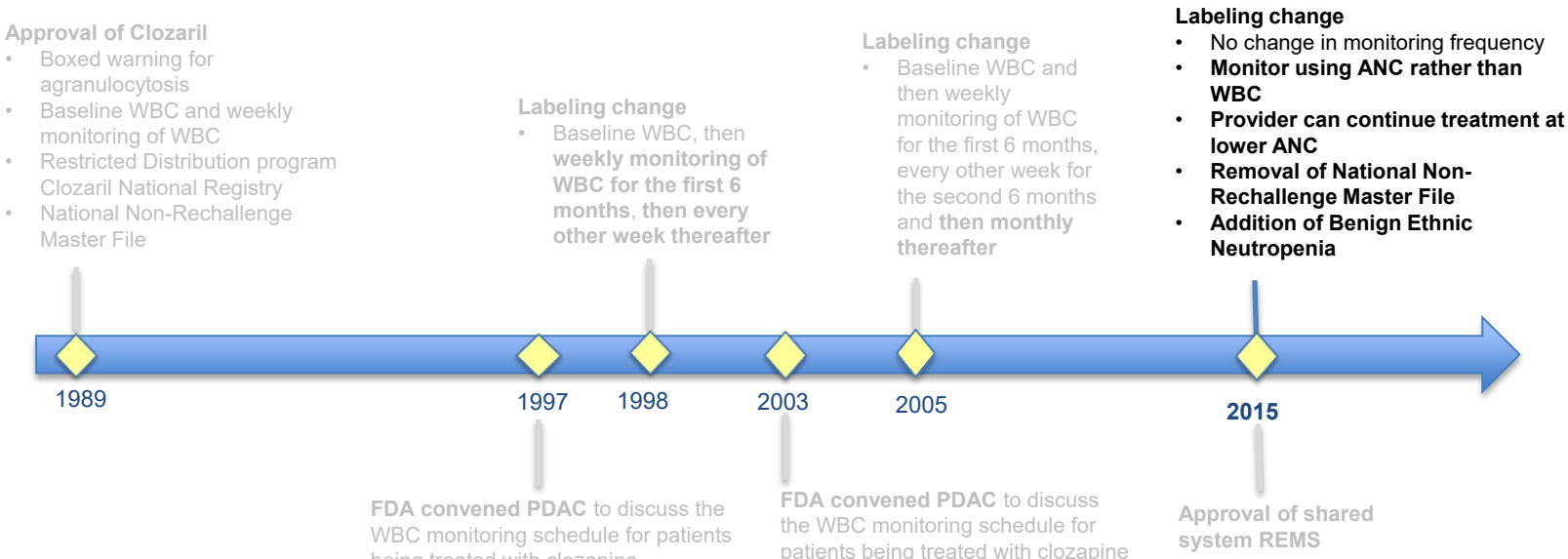
Changes to Labeling 1989 – Present



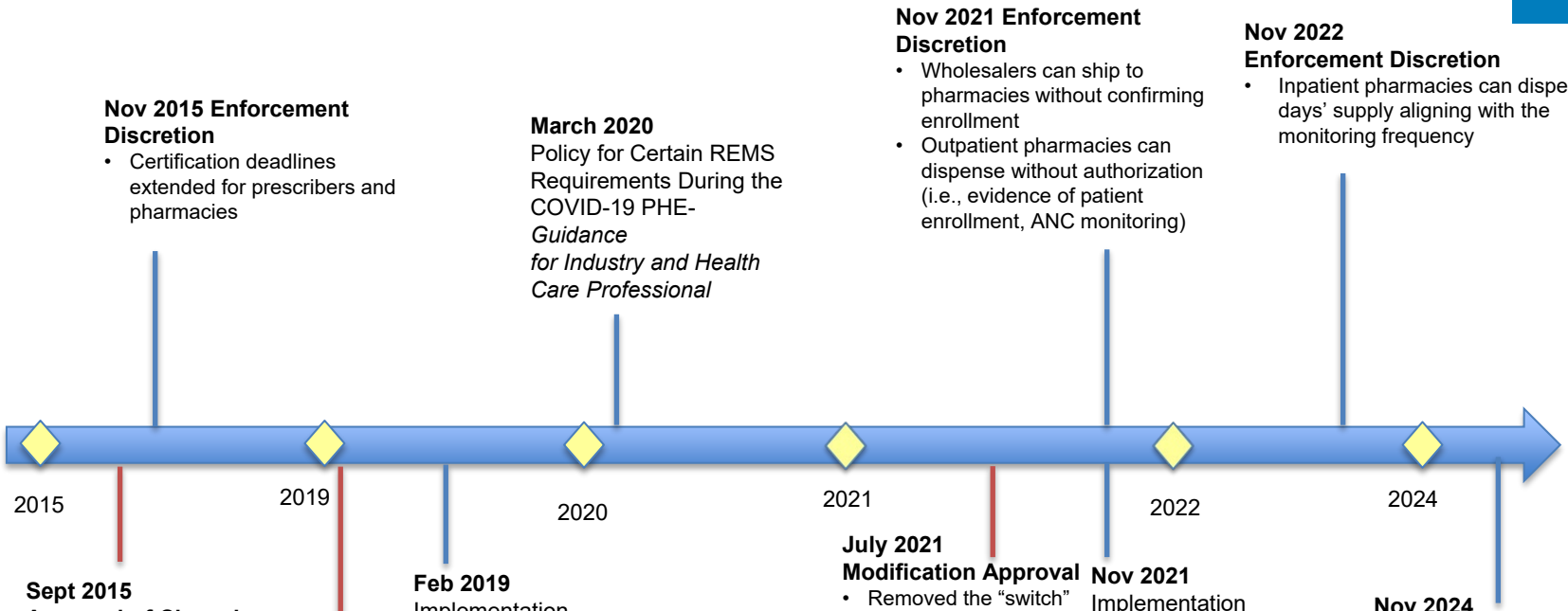
Changes to Labeling 1989 – Present



Changes to Labeling 1989 – Present



Timeline of Clozapine REMS 2015 – Present



Clozapine REMS Approval – 2015

- Shared system REMS for clozapine (NDAs and ANDAs)
- REMS goal: to mitigate the risk of severe neutropenia associated with the use of clozapine by:
  - Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements
  - Informing patients about the risk of severe neutropenia and appropriate monitoring requirements
  - Ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine
  - Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the PI
  - Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry

REMS Requirements as Approved September 2015

Prescriber

- Education/Certification
- Counsel/Enroll patients
- Monitor ANCs
  Submit ANC documentation

Pharmacy

- Education/Certification
- Obtain authorization for every dispense from REMS

Patient

- Counseling
  Baseline ANC
- Get regular ANC tests as directed by prescriber

Clozapine REMS Manufacturers

- Website, Call Center & Registry

Prescriber Requirements – 2015

Approximately 50,000 registered prescribers needed to certify in the Clozapine REMS

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Prescriber Enrollment Form

Prescriber Requirements – 2015

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete knowledge assessment • Complete Prescriber Enrollment Form
Counsel/Enroll patients	• Inform patients of the risks and provide Guide for Patients and Caregivers unless clinical judgement indicates that the patient's adherence to treatment regiment would be negatively impacted • Complete Patient Enrollment Form

Prescriber Requirements – 2015

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Prescriber Enrollment Form
Counsel/Enroll patients	• Inform patients of the risks and provide Guide for Patients and Caregivers unless clinical judgement indicates that the patient's adherence to treatment regiment would be negatively impacted • Complete Patient Enrollment Form
Monitor ANCs Submit ANC documentation	• Report ANC results to the REMS via the ANC Lab Reporting Form according to the monitoring schedule described in the Prescribing Information • Report authorization to continue treatment for patient with an ANC that fell below the acceptable range described in the Prescribing Information, when the prescriber determined the benefits exceed the risks of developing severe neutropenia

Pharmacy Requirements – 2015

Approximately 28,000 registered pharmacies needed to certify in the Clozapine REMS

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Pharmacy Enrollment Form

Pharmacy Requirements – 2015

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Pharmacy Enrollment Form
Obtain authorization for every dispense from REMS	Obtain RDA, which verifies the following: • Prescriber certified and the patient is enrolled • ANC is current (was drawn within the last 7 calendar days) • ANC is within the acceptable range described in the Prescribing Information or the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range

Patient Requirements – 2015

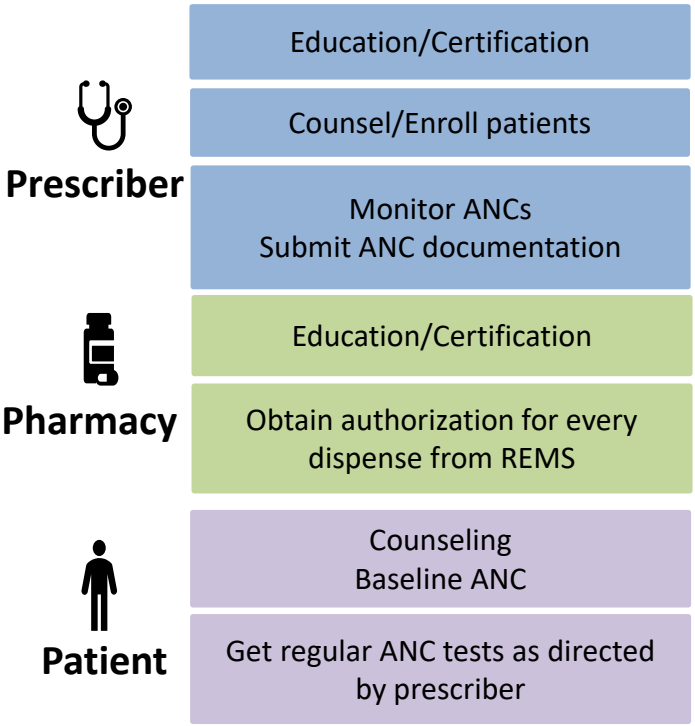
Approximately 90,000 registered pharmacies needed to be enrolled in the Clozapine REMS

Counseling Baseline ANC	• Receive counseling from prescriber • Get baseline ANC

Patient Requirements – 2015 REMS

Counseling Baseline ANC	• Receive counseling from prescriber • Get baseline ANC
Get regular ANC tests as directed by prescriber	Patients who maintain a normal ANC • 0 to 6 months of treatment: weekly • 6 to 12 months of treatment: every 2 weeks • > 12 months of treatment: Every 4 weeks

REMS Approved Sept 2015



Enforcement Discretion November 2015

90 days after implementation the CPMG experienced technical problems with data migration and programming of the website which impacted patient access. To address these challenges:

- Certification deadlines extended for prescribers and pharmacies
- Healthcare providers directed to continue to prescribe and dispense clozapine to patients with an absolute neutrophil count within the acceptable range
- Pharmacies permitted to dispense without verification of safe use conditions

REMS Approved Sept 2015

Prescriber

- Education/Certification
- Counsel/Enroll patients
- Monitor ANCs
  Submit ANC documentation

Pharmacy

- Education/Certification
- Obtain authorization for every dispense from REMS

Patient

- Counseling
  Baseline ANC
- Regular ANC monitoring documented in the REMS

Phased Implementation Began in May 2016

- Pharmacy could verify patient enrollment through a dispense authorization
- Dispense authorization verified only patient enrollment and acceptability of the baseline or most recent ANC or a treatment rationale on file
  - Dispensing permitted without verification of all other safe use conditions
- Certification deadlines were still extended for prescribers and pharmacies

Challenge of Documenting a Current ANC – 2016

Per CPMG, if the REMS system required the prescriber to document a current ANC in the REMS system as part of the dispense authorization, an estimated 52% of clozapine patients would not receive clozapine[1]

[1]Information from CPMG submitted to FDA. August 2016.

REMS Modification – January 2019

- Prescribers and pharmacies had to be certified by February 28, 2019, or they would no longer be able to prescribe/dispense clozapine,
- Inpatient prescribers were not required to be certified if they were prescribing for patients already enrolled in the program,
- If a patient's absolute neutrophil count (ANC) was not current, this would not prevent clozapine from being dispensed,
- If prescriber was not certified, pharmacist could use clinical judgement to dispense and provide prescriber information to the REMS through a Dispense Rationale

	REMS Approved Sept 2015	Implementation of REMS Modification February 2019
Prescriber	Education/Certification Counsel/Enroll patients Monitor ANCs Submit ANC documentation	Pharmacy dispensing permitted without documenting current ANC in REMS Verification of all other safe use conditions required
Pharmacy	Education/Certification Obtain authorization for every dispense from REMS	
Patient	Counseling Baseline ANC Regular ANC monitoring documented in the REMS	

	REMS Approved Sept 2015	COVID-19 Public Health Emergency March 2020
Prescriber	Education/Certification Counsel/Enroll patients Monitor ANCs Submit ANC documentation	Prescribers could consider whether there were compelling reasons not to complete the REMS-required laboratory testing.
Pharmacy	Education/Certification Obtain authorization for every dispense from REMS	
Patient	Counseling Baseline ANC Regular ANC monitoring documented in the REMS	

REMS Modification – July 2021

- Reduced frequency of reporting ANCs to monthly with Patient Status Form regardless of monitoring frequency
- CPMG's use of a new REMS administrator changed how pharmacies verified safe use conditions

REMS Modification – July 2021
REMS goal/objectives

The goal of the Clozapine REMS Program is to mitigate the risk of severe neutropenia associated with the use of clozapine by:

1. Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements
2. Informing patients about the risk of severe neutropenia and appropriate monitoring requirements
3. **Ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia**
4. Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the Prescribing Information
5. Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry

REMS Modification – July 2021
Prescriber Requirements

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Prescriber Enrollment Form
Counsel/Enroll patients	• Inform patients of the risks and provide Guide for Patients and Caregivers unless clinical judgement indicates that the patient's adherence to treatment regiment would be negatively impacted • Complete Patient Enrollment Form
Monitor ANCs Submit ANC documentation	• **Report ANC results to the REMS via the Patient Status Form once monthly** • Report authorization to continue treatment for missing labs or for patient with an ANC that falls below the acceptable range described in the Prescribing Information, when the prescriber determines the benefits exceed the risks of developing severe neutropenia

REMS Modification – July 2021
Pharmacy Requirements

Education/Certification	• Review Prescribing Information and Guide for Healthcare Providers • Successfully complete Knowledge Assessment • Complete Pharmacy Enrollment Form
Obtain authorization for every dispense from REMS	Obtain RDA, which verifies the following: • Prescriber certified and the patient is enrolled • Patient is not interrupted or discontinued in REMS • **Patient Status Form has been completed within the last 37 days (for subsequent dispensing)** • **Prescriber has authorized continuation if one or more labs is missing, or a treatment rationale is required due to ANC below acceptable range (for subsequent dispensing)** If the Patient Status Form is overdue (based on a rejected RDA), pharmacist could dispense if patient had a current ANC (within 30 days of attempted fill). This is a dispense rationale. Maximum of 3 per patient per year for outpatient pharmacies. No limit for inpatient pharmacies.

REMS Approved July 2021

Prescriber

- Education/Certification
- Counsel/Enroll patients
- Monitor ANCs
  Submit ANC documentation

Pharmacy

- Education/Certification
- Obtain authorization for every dispense from REMS

Patient

- Counseling
  Baseline ANC
- Regular ANC monitoring documented in the REMS

Enforcement Discretion November 2021

During implementation of July 2021 modification, CPMG identified issues with duplicate and incomplete data which resulted in all stakeholders having to recertify or re-enroll in the REMS, leading to technical difficulties, long contact center hold times, and disrupted patient access. To address these challenges:

- Wholesalers could ship clozapine to non-certified pharmacies
- Pharmacists could dispense without a REMS dispense authorization
- Dispensing could occur without verification of safe use conditions

REMS Approved
July 2021

Prescriber

Education/Certification

Counsel/Enroll patients

Monitor ANCs
Submit ANC documentation

Pharmacy

Education/Certification

Obtain authorization for every dispense from REMS

Patient

Counseling
Baseline ANC

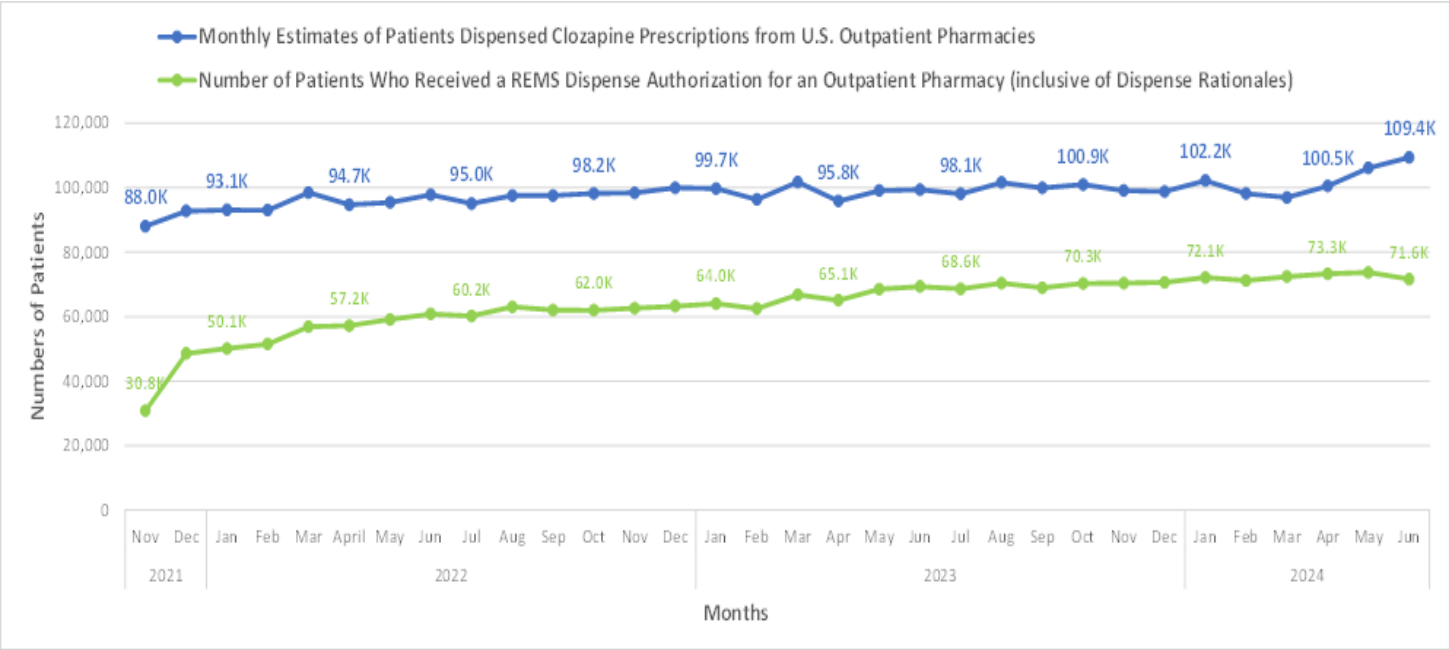
Regular ANC monitoring documented in the REMS

Enforcement Discretion
November 2022

The transition from the inpatient setting to the outpatient setting created difficulties for patients. To ensure continuity of care for patients:

- Inpatient pharmacies could dispense a days' supply of clozapine that aligned with the patient's monitoring frequency.

Since February 2023, the Estimated Patient Participation in the REMS Ranges Between 65- 75%



Source: [a]Symphony Health Metys™, November 2021 through June 2024. Data extracted July 2024. [b]CPMG response to the Agency's October 17, 2023, Information Request that was received on October 19, 2023, and the CPMG response to the Agency's September 10, 2024, Information Request that was received on September 20, 2024.
* Unique patient counts may not be added across time periods, as this could lead to overestimates due to the possibility of double counting patients receiving treatment over multiple periods in the study.
Abbreviation: REMS, Risk Evaluation and Mitigation Strategy

Status of Enforcement of REMS Requirements 2015 – Present

REMS Requirement	Nov 2015	May 2016	Feb 2019	Nov 2021	Oct 2024
Patient must be enrolled	Not enforced	**Enforced**	**Enforced**	Not enforced	Not enforced
At least one ANC on file (baseline ANC)	Not enforced	**Enforced***	**Enforced***	Not enforced	Not enforced
Most recent ANC within normal range or treatment rationale	Not enforced	**Enforced***	**Enforced***	Not enforced	Not enforced
Prescriber certified	Not enforced	Not enforced	**Enforced**	Not enforced	Not enforced
Pharmacy certified	Not enforced	Not enforced	**Enforced**	Not enforced	Not enforced
Most recent ANC is current (Patient Status Form current)	Not enforced	Not enforced	Not enforced	Not enforced	Not enforced

* Either baseline ANC, most recent ANC within normal range, or treatment rationale from prescriber

Summary

- Approved REMS has evolved since 2015, and dispensing of clozapine continues without verification of safe use conditions
- Today, prescribers, pharmacies and patients do not have to participate in the REMS in order for patients to obtain clozapine.

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Drug Safety and Risk Management Advisory Committee and the Psychiatric Drugs Advisory Committee Meeting November 19, 2024

Summary of the studies conducted for FDA's re-evaluation of the Clozapine REMS

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Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Presentation Overview

Rationale for conducting additional studies

Risk of severe neutropenia

- Literature review
- Brigham and Women's Hospital (BWH)
- Sentinel Distributed Database (Sentinel)
- Veterans Affairs

Adherence to ANC monitoring

- Sentinel
- BWH

Prescribers experience with the Clozapine REMS

- BWH

Rationale for conducting additional studies

- The Sponsors' assessment reports have been insufficient to inform us of the risk of severe neutropenia, the outcomes associated with the risk of severe neutropenia, and adherence to monitoring
  - REMS never fully implemented
  - In the 6th and 7th reports, the CPMG acknowledged issues with data entry and processing
  - Since the 2021 REMS modification the CPMG has been unable to confirm reports of severe neutropenia
- Additional studies were conducted to better understand:
  - if the risk of clozapine-induced severe neutropenia has changed since 1989
  - the types and incidence of serious outcomes, including death, associated with severe neutropenia
  - If patients are being monitored as described in labeling

Studies conducted to assess the risk of severe neutropenia

Literature Review	• Studies of risk of neutropenia ***without*** hematologic monitoring • Studies of risk of neutropenia ***with*** hematologic monitoring
BWH	• Neutropenia-related hospitalization among clozapine initiators compared to olanzapine Initiators
Sentinel	• Descriptive query to compare clozapine users with and without ANC tests results, Jan 2010-July 2024 • Patient episode profile retrieval • Medical chart review to describe ANC monitoring, neutropenia-related outcomes, and clozapine discontinuation
VA	• To evaluate risks of neutropenia and agranulocytosis following initiation of clozapine use and over time • Retrospective cohort study performed in the VA healthcare database 1999-2023

Literature Review

Literature review

Risk of severe neutropenia in patients treated with clozapine

Severe neutropenia risk ***without*** hematologic monitoring

- Only one study, 1977 Finnish study (de la Chapelle, A., et al., Hum Genet, 1977)
  - 16 cases of agranulocytosis attributed to clozapine, 7 (44%) of which were fatal
  - Agranulocytosis risk estimated at ~2.6 cases per 100 patient-years of clozapine treatment

Severe neutropenia risk ***with*** hematologic monitoring

- 13 studies published through July 25, 2024, provided data on incidence of severe neutropenia among clozapine users undergoing regular hematologic monitoring
  - Most cases occur in first ~18 weeks of treatment
  - ~1% of patients developed agranulocytosis over the course of treatment
  - Fatality rates with severe neutropenia ranged from 0 to 6% across studies
  - Data on risk beyond one year of use are sparse

Cumulative incidence of agranulocytosis based on patients treated with clozapine between Feb 1990 – Apr 1991*

Data source: manufacturer's surveillance database

Weekly hematologic monitoring

Agranulocytosis

Cumulative incidence at 1 year

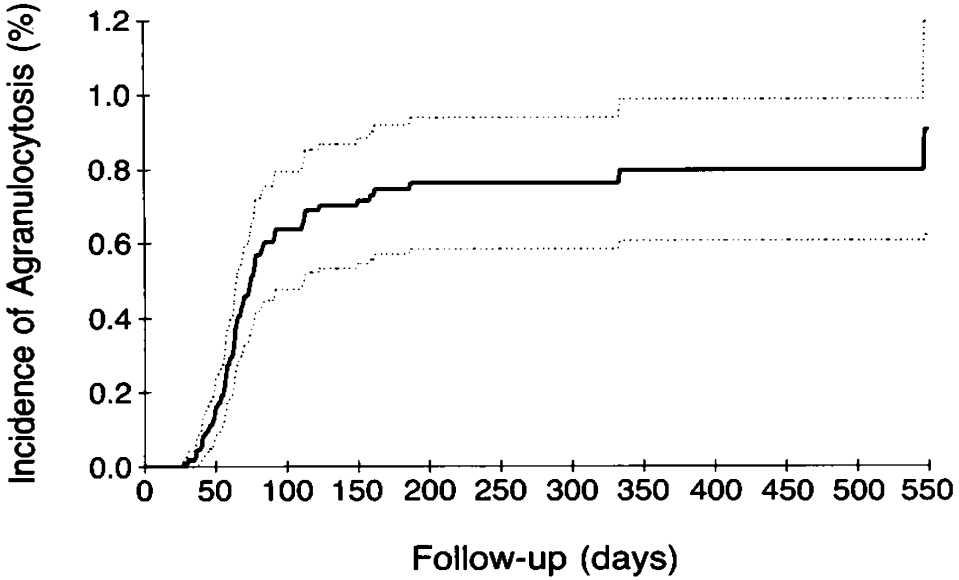
0.80% (95% CI: 0.61-0.99)

Cumulative incidence at 1.5 years

0.91% (95% CI: 0.62-1.20)

73 cases of agranulocytosis, 2 fatal

*Alvir et al. NEJM 1993



. Cumulative Incidence of Agranulocytosis among 11,555 Patients Taking Clozapine.
The dotted lines denote the 95 percent confidence limits.

Brigham and Women's Hospital (BWH)

Neutropenia-related hospitalization among clozapine initiators compared to olanzapine Initiators

BWH

Neutropenia-related hospitalization among clozapine initiators compared to olanzapine Initiators (1 of 2)

Study Design	• New users of clozapine and olanzapine, defined as no dispensing of the two drugs, but ≥1 dispensing of a different antipsychotic in the prior 6 months • Excluded patients with cancer or HIV
Outcomes	• All inpatient hospitalizations with a discharge diagnosis code for neutropenia occurring in ANY position (less stringent) or in the PRIMARY position (more stringent)
Study Cohort	• Consisted of 16,873 patients each in clozapine and olanzapine group that were well matched

BWH

Neutropenia-related hospitalization among clozapine initiators compared to olanzapine Initiators (2 of 2)

Results	**First 6 months** • The incidence rates of neutropenia-associated hospitalization per 1,000 person-years were 2.2 (1.3-3.9) and 0.2 (0.03 – 1.3) for clozapine and olanzapine, respectively • The incidence rate ratio was 12.2 (1.6-93.7) at 6 months **1-year, 2-year and 3-year** • The incidence rates of neutropenia-associated hospitalization per 1,000 person-years were 1.3 (0.8-3.9), 0.9 (0.5-1.5) and 0.7 (0.4-1.2), respectively for clozapine • Incidence rate for olanzapine did not change
Limitations	• ANC test results were not available to confirm the diagnosis code of neutropenia • The median follow up time was 6 months

Sentinel

Risk of severe neutropenia

Sentinel Study 1: Design and Results

Descriptive query to compare clozapine users with and without ANC tests results, Jan 2010 – Jul 2024

All data partners

- There were 164,971 episodes of new clozapine use among 105,067 unique patients

Subset with ANC tests results

- Primarily privately insured patients
- 10,473 episodes of new clozapine use among 6,698 unique patients
- **2,223 clozapine episodes had complete ANC test information**

This subset of clozapine users with complete ANC test results had

- fewer schizophrenia diagnoses recorded in claims [77.9 versus 85.2%]
- fewer ambulatory visits [mean (SD)=13.8(13.9) versus 19.3(23.3)]
- fewer dispensed prescriptions [mean(SD)=25.2 (21.8) versus 31.1 (27.3)]

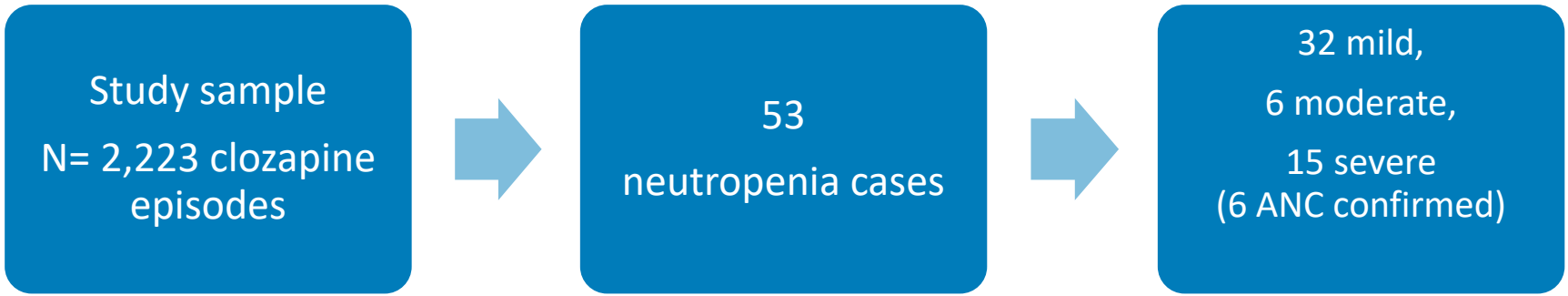
Sentinel Study 2

Patient episode profile retrieval (1 of 2)

(Subset of clozapine users with complete ANC test results)

Objective	• To estimate neutropenia risk during the first 6 months of treatment and describe frequency and timing of ANC monitoring
Study Design 2010 – 2020	• Retrospective, cohort study • New clozapine episodes, defined as a clozapine dispensing with no dispensing of clozapine in the 30 days prior
Outcomes	• ANC monitoring: weekly, biweekly, and monthly • Neutropenia: mild, moderate, and severe

Sentinel Study 2: Sample Size and Results
Patient episode profile retrieval (2 of 2)



Results:

- Severe neutropenia (based on ANC test results) event rate: 8 per 1,000 person-years at risk (95% CI=4 to 18 per 1,000 person-years)
- Mild neutropenic clozapine episodes were about twice as likely as severe neutropenic clozapine episodes to have an ANC screening in the 30 days prior to the day of the neutropenic event

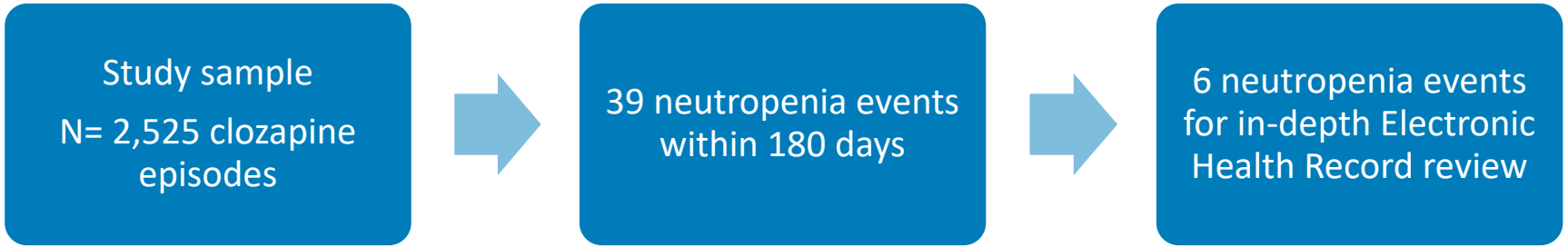
Sentinel Study 3

Medical chart review to describe ANC monitoring, neutropenia-related outcomes, and clozapine discontinuation (1 of 2)

Objective	• To describe ANC monitoring, neutropenia-related outcomes, and clozapine discontinuation in the 1st 6-months of clozapine treatment among individuals with Medicare or Medicaid insurance
Study Design (2000 – 2020)	• Specific and non-specific diagnosis codes for neutropenia identified neutropenia cases and dates for medical record extraction • Medical records and inpatient ANC test results from Massachusetts General Brigham affiliated facilities 7 days prior and after neutropenic events were reviewed • New clozapine episodes, defined as a clozapine dispensing with no dispensing of clozapine in the 30 days prior
Outcomes	• Captured concepts: Information about neutropenia cause and treatment, ANC monitoring, indications, and additional information about clozapine use

Sentinel Study 3: Sample Size and Results

Medical chart review (2 of 2)



Results:

- Management strategies included prophylactic antibiotics and/or filgrastim
- Neutropenia led to a serious infection requiring inpatient management in one case
- No deaths were identified
- Electronic health records included no information on ANC monitoring/adherence to monitoring

Veterans Affairs (VA)

Risk of neutropenia

VA Study

Risk of neutropenia among clozapine users in VA (1 of 6)

Objective	• To evaluate risks of neutropenia and agranulocytosis following initiation of clozapine use and over time
Study Design	• Retrospective cohort study performed in the VA healthcare database 1999 – 2023 • New users of clozapine, with no clozapine prescription in the prior 12 months, aged 18 year and older
Outcomes	• Mild, moderate, and severe neutropenia defined by ANC values • Deaths attributed to neutropenia

Statistical Methods	• Descriptive analysis
	• Cumulative incidence of neutropenia by duration of clozapine
	  • Life table analysis of the data
	  • Kaplan-Meier plot

VA Study

Risk of neutropenia among clozapine users in VA (2 of 6)

Study Sample	• 6,488 clozapine users met the inclusion/exclusion criteria • Mean age 50 years, 89% male • High psychiatric comorbidity burden • About 200-300 new users each year • Up to 23 years of follow up
Results	• ~70% of patients had at least 21 tests performed in the 1st 6 month of treatment • 32 events of severe neutropenia during first episode of treatment • Cumulative 12-month incidence of severe neutropenia 0.4 % (95% CI 0.3 - 0.7) • ~1/5 of severe neutropenia cases occurred after more than 2 years on treatment; a few cases involved recent dose increases • Two deaths involving severe neutropenia: 1 related to severe neutropenia (23 days on treatment), and 1 possibly related (5 years on treatment)

VA Study: Life table analysis for severe neutropenia (3 of 6)

		Based on outpatient prescription data only (n=32 events)		Data censored at the time of chemotherapy (n=28 events)		Events with medical record review (n=25 events)	
Treatment Interval (months)	No. of patients 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	---	---	---	---	---	---

VA Study: Life table analysis for severe neutropenia (3 of 6)

		Based on outpatient prescription data only (n=32 events)		Data censored at the time of chemotherapy (n=28 events)		Events with medical record review (n=25 events)	
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216-290	65	0	0.0	0	0.0	0	0.0
290+	2	---	---	---	---	---	---

VA Study: Life table analysis for severe neutropenia (4 of 6)

		Based on outpatient prescription data only (n=32 events)		Data censored at the time of chemotherapy (n=28 events)		Events with medical record review (n=25 events)	
Treatment Interval (months)	No. of patients 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
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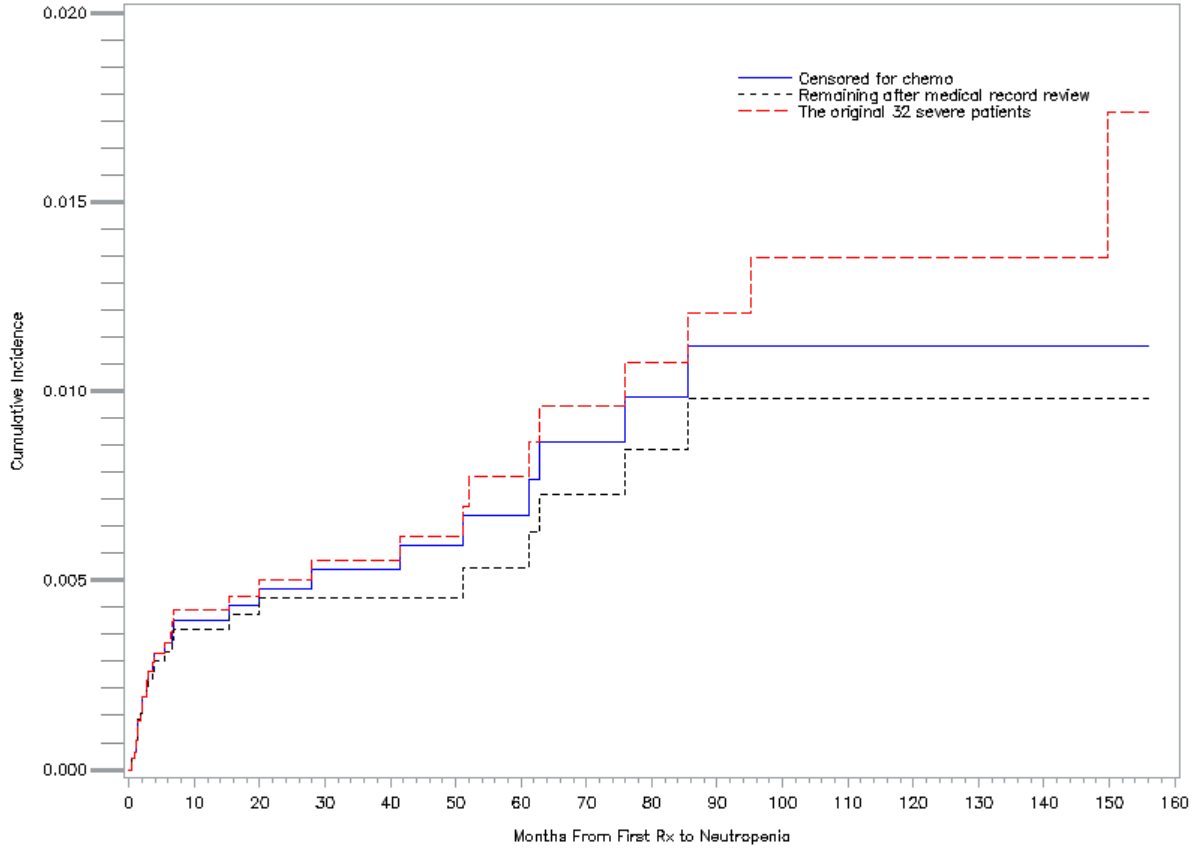
156-216	227	0	0.0	0	0.0	0	0.0
216-290	65	0	0.0	0	0.0	0	0.0
290+	2	---	---	---	---	---	---

VA Study: Cumulative incidence of severe neutropenia (5 of 6)



VA Study
(6 of 6)

Strengths	• Completeness of ANC test results • Comprehensive data (clinical, pharmacy and laboratory) • Long-term follow up • Chart review of the neutropenic cases
Limitations	• Data on inpatient clozapine use not included - ongoing analysis • Pharmacy records do not show brief interruptions in clozapine therapy • May not generalize to other, less structured healthcare delivery settings • Population that had reasonably good adherence to monitoring • Sparse data on longer treatment durations • Older male population

Adherence to monitoring

- Sentinel
- BWH

Sentinel

Adherence to ANC monitoring

Objective	• To assess adherence to ANC monitoring requirements in the Sentinel Distributed Database
Data Sources	• 4 national commercial health insurers, Medicare fee-for-service, Medicaid
Clozapine Episodes	• Clozapine episodes of use were identified based on dispensed prescriptions' dates and days' supply • New clozapine episodes had 30 days with no prior clozapine use • Secondary analysis: new clozapine episodes had 180 days with no prior clozapine use
Study Design	• ANC testing was assessed during individual episodes of clozapine use for three different episode periods: months 0-6, months 7-12, and months 13-24 • Two different ways to assess adherence: 1) number of ANC tests per month and 2) time (days) between ANC tests

Sentinel

Adherence to ANC monitoring | Number of tests per month

		January 1, 2010 – September 30, 2015	October 1, 2015 – December 31, 2019	January 1, 2020 – October 31, 2021
Total number of clozapine episodes		**81,656**	**83,877**	**41,487**
Episodes with ≥1 ANC laboratory test in the 30 days prior to clozapine initiation (%)		69.1%	65.2%	63.4%
Months 0-6	Episodes with no ANC laboratory tests (%)	15.8%	20.1%	21.9%
	ANC tests per month (median (IQR))*	2.3 (1 – 4)	2.1 (1 – 4)	1.6 (1 – 4)
	ANC tests per month (secondary cohort) (median (IQR))*	3.8 (2 – 4)	3.5 (2 – 4)	3.1 (1 – 4)
Months 7-12	Episodes with no ANC laboratory tests (%)	8.0%	12.1%	14.0%
	ANC tests per month (median (IQR))*	1.8 (1 – 3)	1.6 (1 – 2)	1.3 (1 – 2)
Months 13-24	Episodes with no ANC laboratory tests (%)	5.7%	9.0%	10.1%
	ANC tests per month (median (IQR))*	1.3 (1 – 2)	1.2 (1 – 2)	1.1 (1 – 2)

*Monthly ANC testing was calculated among episodes with at least one ANC test

IQR: interquartile range

Sentinel

Adherence to ANC monitoring | Time between ANC tests results

		January 1, 2010 – September 30, 2015	October 1, 2015 – December 31, 2019	January 1, 2020 – October 31, 2021
Total number of clozapine episodes		**81,656**	**83,877**	**41,487**
Months 0-6	Episodes with all gaps ≤10 days (%)	10.1%	8.6%	7.2%
	Episodes with all gaps ≤10 days (secondary cohort) (%)	16.7%	13.4%	12.4%
	Episodes with all gaps ≤33 days (%)	41.1%	37.9%	35.7%
	Episodes with all gaps ≤33 days (secondary cohort) (%)	46.1%	42.8%	41.4%
Months 7-12	Episodes with all gaps ≤17 days (%)	17.8%	14.6%	12.6%
Months 13-24	Episodes with all gaps ≤33 days (%)	34.9%	29.0%	28.7%

Sentinel

Adherence to ANC monitoring | Time between ANC tests results

		January 1, 2010 – September 30, 2015	October 1, 2015 – December 31, 2019	January 1, 2020 – October 31, 2021
Total number of clozapine episodes		**81,656**	**83,877**	**41,487**
Months 0-6	Episodes with all gaps ≤10 days (%)	10.1%	8.6%	7.2%
	Episodes with all gaps ≤10 days (secondary cohort) (%)	16.7%	13.4%	12.4%
	Episodes with all gaps ≤33 days (%)	41.1%	37.9%	35.7%
	Episodes with all gaps ≤33 days (secondary cohort) (%)	46.1%	42.8%	41.4%
Months 7-12	Episodes with all gaps ≤17 days (%)	17.8%	14.6%	12.6%
Months 13-24	Episodes with all gaps ≤33 days (%)	34.9%	29.0%	28.7%

BWH

Adherence to ANC monitoring

Objective	• Assess the prevalence and frequency of ANC monitoring in patients starting clozapine
Data source	• Claims data • Medicaid (2000 to 2018); and Optum's de-identified Clinformatics® Data Mart (2004 to March 31, 2022); Marketscan (2003 to 2020)
Clozapine initiations	• Clozapine initiators with at least 6 months of enrollment and no prior clozapine use were included
Results	Among 62,003 clozapine initiations • 63% were preceded by ANC testing within 31 days • During the first 6 months of treatment the median testing rate was 2.1 tests per 30 days • During months 7-12 the median testing rate was 1.6 tests per 30 days • During year 2 of treatment the median testing rate was 1.1 tests per 30 day

BWH

Prescriber experience survey

BWH

Physician experience survey

Objective	• To understand how the Clozapine REMS Program has impacted clinical practice
Study Design	• The survey had 57 closed-field questions • 750 randomly selected physicians (targeted 200) using IQVIA • 196 physicians returned the survey (26% response rate)
Demographics of respondents	• 86% were psychiatrists • 84% were in practice for more than 15 years • 80% spent >80% of their time in direct patient care • 53% prescribed clozapine to 11 or more patients in the past 3 years

BWH

Physician experience survey

REMS Activities	• 66% of survey respondents agreed it is reasonable that clozapine has prescriber certification • 75% of survey respondents agreed the certification provided useful information • 77% of survey respondents agreed testing is clinically necessary • 53% of survey respondents agreed the paperwork facilitates discussion • 88% of respondents indicated that they always or almost always discussed the risk of severe neutropenia with patients starting clozapine
Burden with the safe use requirements	• 71% of survey respondents agreed - safe use requirements are burdensome for most patients • 44% of survey respondents reported it's hard to complete the ANC testing • 60% of survey respondents agreed - safe use requirements have often caused a delay in patients receiving clozapine • 31% of survey respondents reported that insurance is more burdensome than safe use requirements

Summary of key study findings

- Risk of neutropenia
  - The risk of severe neutropenia with clozapine is greatest in the first several months of treatment
  - BWH: Risk of neutropenia-associated hospitalization was higher with clozapine compared to olanzapine
  - Sentinel Study 2: Severe neutropenia (based on ANC test results) event rate: 8 per 1,000 person-years at risk
  - Sentinel Study 3: The small number of cases identified interventions included stopping treatment of clozapine, the use of prophylactic antibiotics and G-CSF
  - VA: Cumulative 12-month incidence of severe neutropenia 0.4 %, in a populations with reasonably good adherence to monitoring. ~1/5 of severe neutropenia cases occurred after more than 2 years on treatment and the risk persists through at least 8 years of treatment
- Adherence to monitoring
  - Sentinel and BWH: For the 1st 6-months, patients are monitored but less frequently that what is described in labeling
  - Adherence to monitoring improves as the monitoring frequency decreases
  - VA: ~70% of patients had at least 21 tests performed in the 1st 6 month of treatment, this may not be generalizable
- Physician experience
  - BWH survey: Most thought that certain aspects of the REMS were useful, but also noted there was burden with the safe use requirements and they that delayed treatment

U.S. FOOD & DRUG ADMINISTRATION

Drug Safety and Risk Management Advisory Committee and the Psychiatric Drugs Advisory Committee Meeting November 19, 2024

FDA's Updated Assessment of Risk of Severe Neutropenia and Gaps In Healthcare

Carolyn Tieu, PharmD, MPH
Team Leader, Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Presentation Overview

- Introduction
- FDA's updated assessment of risk of severe neutropenia
- FDA's updated assessment of the healthcare gaps addressed by the Clozapine REMS
- REMS Considerations

Risk Mitigation for Severe Neutropenia Associated With Clozapine

- When clozapine was first approved in US in 1989, there were two care gaps[1]:
  1. There were minimal guidelines and resources and general lack of knowledge about severe neutropenia risk with clozapine and the need for frequent ANC monitoring[2]
  2. Monitoring for neutropenia and its management wouldn't have been typically performed by psychiatrists practicing at the time
- Risk mitigation focused on two strategies: educating healthcare providers and ensuring that ANC monitoring was performed

These care gaps and strategies continue to be the basis for the Clozapine REMS today

[1] A care gap is the discrepancy between best practices and the care that is provided or anticipated to be provided in clinical practice. For REMS, the discrepancy between the necessary care a patient needs for the benefits of the drug to outweigh its risks and the care that is actually (or anticipated to be) provided

[2] Weekly monitoring of white blood cells was required at the time of approval

FDA's Approach to Re-Evaluate the Clozapine REMS

1. Assess the risk of severe neutropenia today

2. Assess whether two gaps that are addressed in the Clozapine REMS still exist by analyzing the extent to which:

1. Practitioners understand the risk of severe neutropenia and the appropriate actions that need to occur if neutropenia is detected (**knowledge**)
2. ANC monitoring per approved labeling is being performed **(behavior)**

1 UPDATED ASSESSMENT OF RISK OF SEVERE NEUTROPENIA

Severe Neutropenia Is a Serious Risk of Clozapine

- What we know about the risk of severe neutropenia today is consistent with what we've known since 1989
  - Risk of severe neutropenia is greater for clozapine than it is for other antipsychotic drugs.
  - From the VA study, the risk of severe neutropenia was highest during the first 3 months of clozapine use, subsequently declined but was still seen beyond 8 years.
  - Fatal outcomes are still associated with clozapine.

ANC Monitoring Remains Necessary

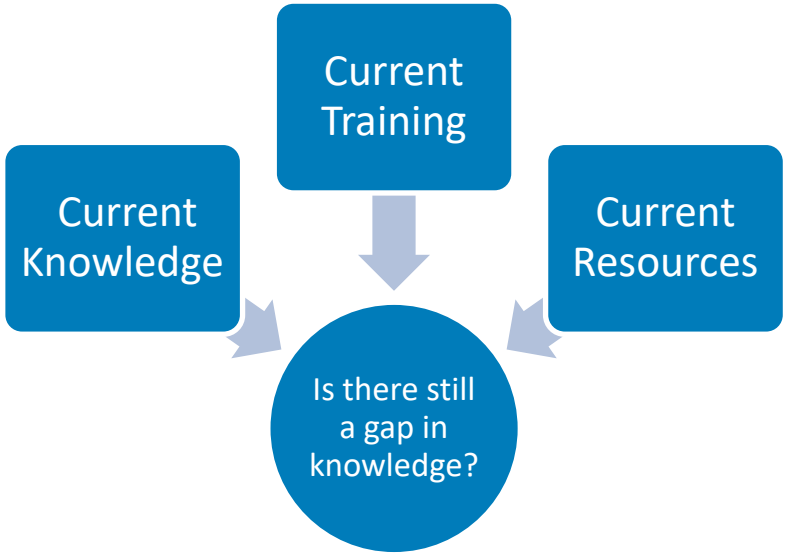
- Frequent ANC monitoring can mitigate severe neutropenia and neutropenia-related deaths
  - Prior to our updated assessment:
    - Without monitoring, agranulocytosis risk estimated at ~2.6 cases per 100 patient-years of clozapine treatment for the first 6 months.[1] The proportion of fatal cases ranged from 35% to 44% of those with severe neutropenia.
  - In our updated assessment:
    - With monitoring, the cumulative incidence at 1 year ranged from 0.4% to 1.3%. The proportion of fatal cases decreased significantly to 6% or less among those with severe neutropenia

[1] de la Chapelle, A., Kari, C., Nurminen, M., & Hernberg, S. (1977). Clozapine-induced agranulocytosis. A genetic and epidemiologic study. Human genetics, 37(2), 183–194.

2 UPDATED ASSESSMENT OF THE HEALTHCARE GAPS ADDRESSED BY THE CLOZAPINE REMS

Is Knowledge of Risk Still Lacking in the Prescribing Population?

- In 1989, our initial assessment was that knowledge of risk and need for ANC monitoring was lacking in the prescribing population



Current Knowledge of Risk in the Prescribing Population

Knowledge among prescribers in the REMS

- Four surveys from REMS assessment evaluating certified prescriber and pharmacist knowledge between 2017 – 2024 have been conducted
- In total, 1,116 prescribers and 1,109 pharmacists have been surveyed. Results indicated sustained knowledge of the risk and the need for monitoring
- Respondents across all surveys reported that they use other resources outside of the REMS, such as UpToDate, Micromedex, ePocrates

Current Knowledge of the Risk in the Prescribing Population

Knowledge among prescribers who may or may not participate in the REMS

- BWH survey conducted among physicians who prescribed clozapine found
  - ~75% of respondents indicated that the REMS certification provided useful information
  - ~88% of respondents indicated that they always or almost always discussed the risk of severe neutropenia with patients starting clozapine
- Data from the VA and Sentinel studies suggest that prescribers understanding of the risks and management is supported by the actions that they are taking in a patient who has developed neutropenia

Available Training Outside of REMS

- Assessed clozapine incorporation into psychiatric medical training and examinations, we outreached to:
  - The American Board of Psychiatry and Neurology (ABPN)
  - The American College of Psychiatry (ACP)
  - Accreditation Council for Graduate Medical Education (ACGME)
- Questions related to clozapine are part of the question bank for the physician-in-training and board certification exams. Psychiatrists may prepare for clozapine-related exam questions
- Generally, residents may be trained or exposed to clozapine during the didactic session of the residency training
- Literature review on training identified mixed findings

Available Guidelines and Resources

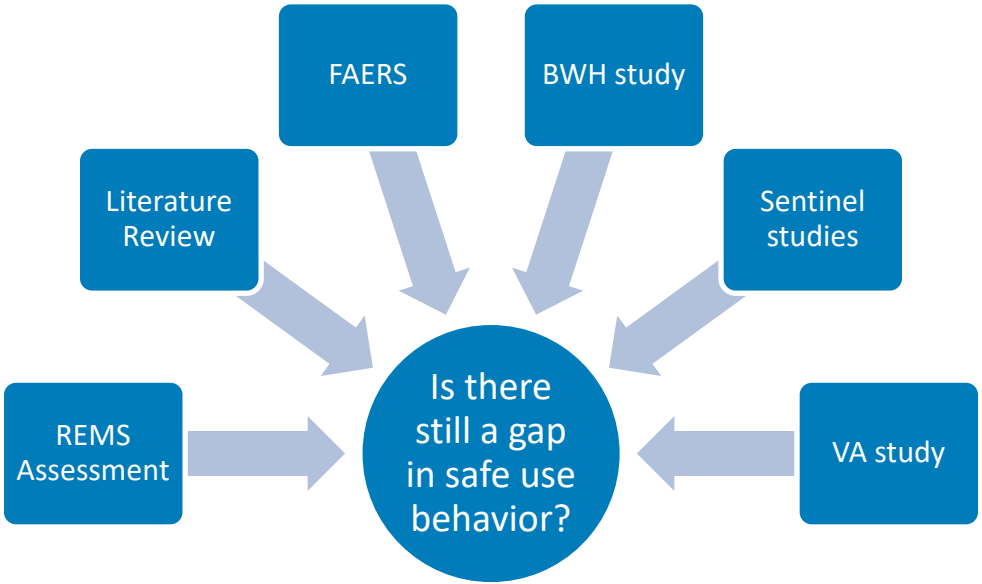
- 8 of the 9 guidelines we reviewed included recommendations for using clozapine and varying amounts of information regarding monitoring for neutropenia
  - Notable guidelines include “Practice Guideline for the Treatment of Schizophrenia” from American Psychiatric Association (APA) 3rd edition last updated in 2020 and “Practice parameter for the assessment and treatment of children and adolescent with schizophrenia” from the American Academy of Child and Adolescent Psychiatry last updated in 2013
- Books, such as Clozapine Handbook (2020), Maudsley’s Prescribing Guidelines in Psychiatry (2022), cover extensive information about the management of patients on clozapine
- Information on clozapine and its safe use is also incorporated in several common electronic resources such as Uptodate, Micromedex, Medscape, and Dynamed

Conclusion – Knowledge Gap Has Likely Narrowed for the Prescribers

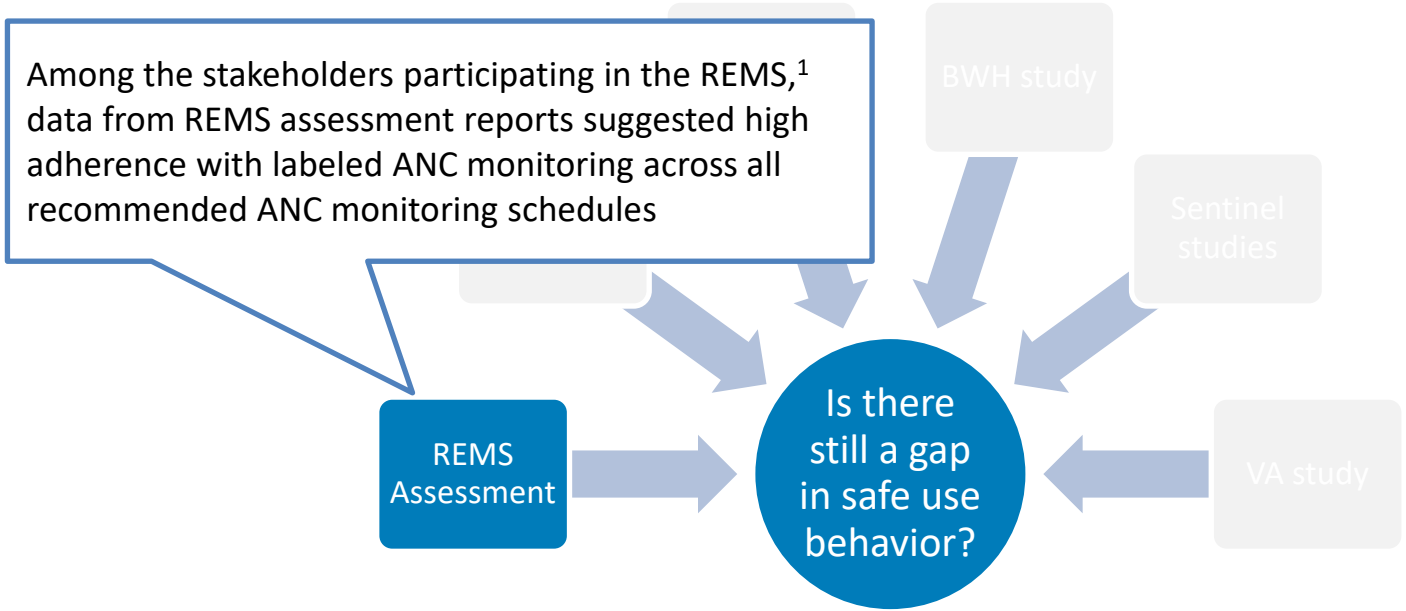
- Our assessment suggests that the knowledge gap has likely narrowed due to the availability of resources beyond the educational materials in the Clozapine REMS
- Generally, prescribers have greater knowledge about the risk of clozapine-induced severe neutropenia and the need to monitor ANC compared to prescribers in 1989
- Information and training on clozapine and its safe use is more widely incorporated into medical training and healthcare systems since 1989.

To What Extent Is ANC Monitoring Routinely Performed?

- In 1989, our initial assessment was that monitoring for and managing neutropenia typically would not have been routinely performed by psychiatrists practicing prior to US approval of clozapine

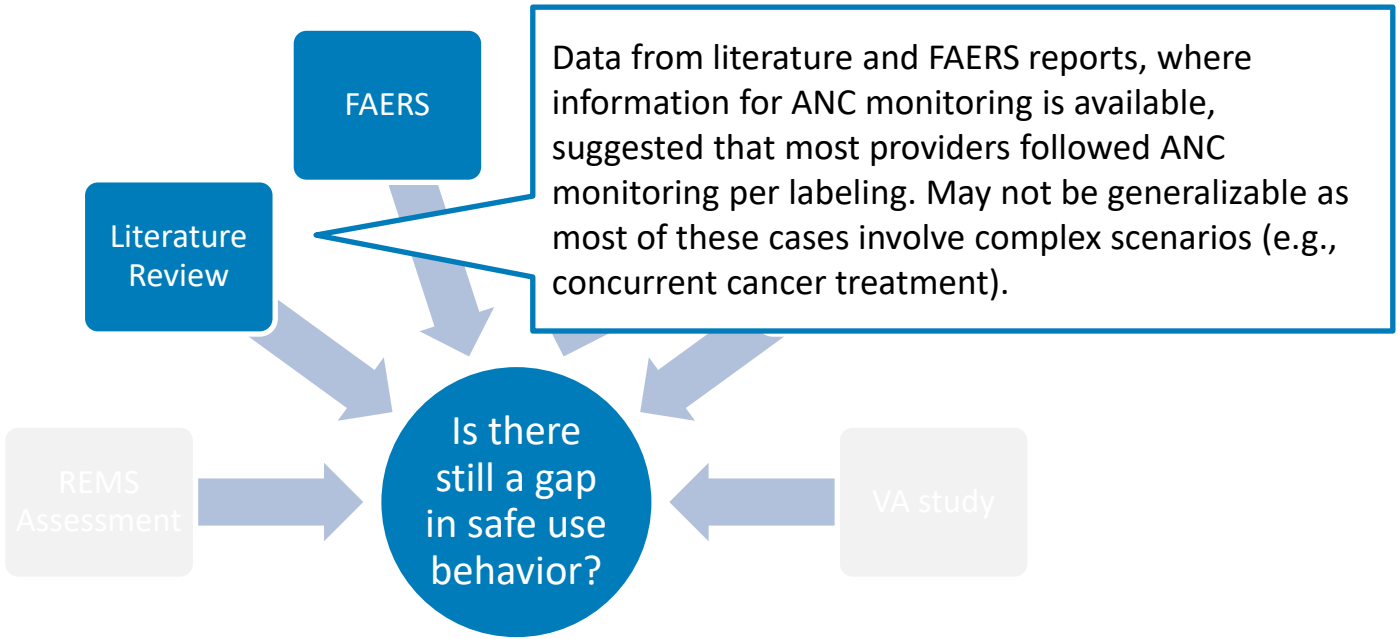


To What Extent Is ANC Monitoring Routinely Performed?



[1] We estimate that there are approximately 65-70% of outpatients who are treated with clozapine have some participation in the REMS per month

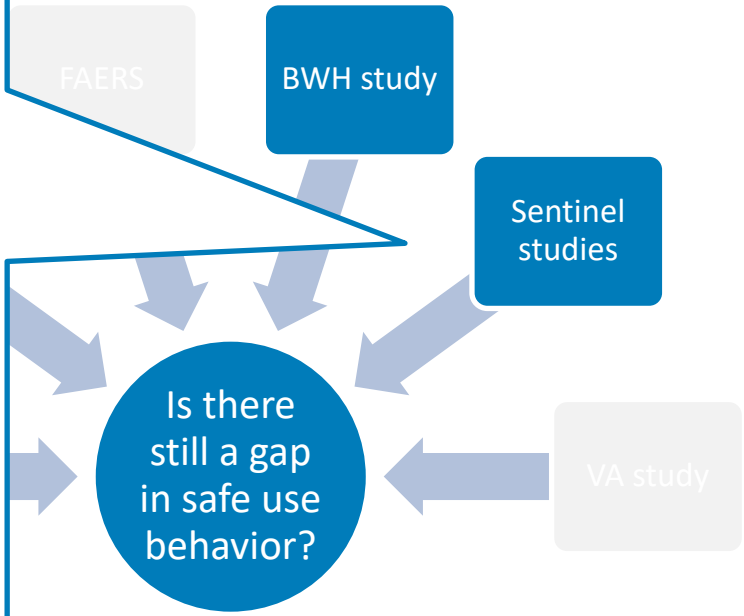
To What Extent Is ANC Monitoring Routinely Performed?



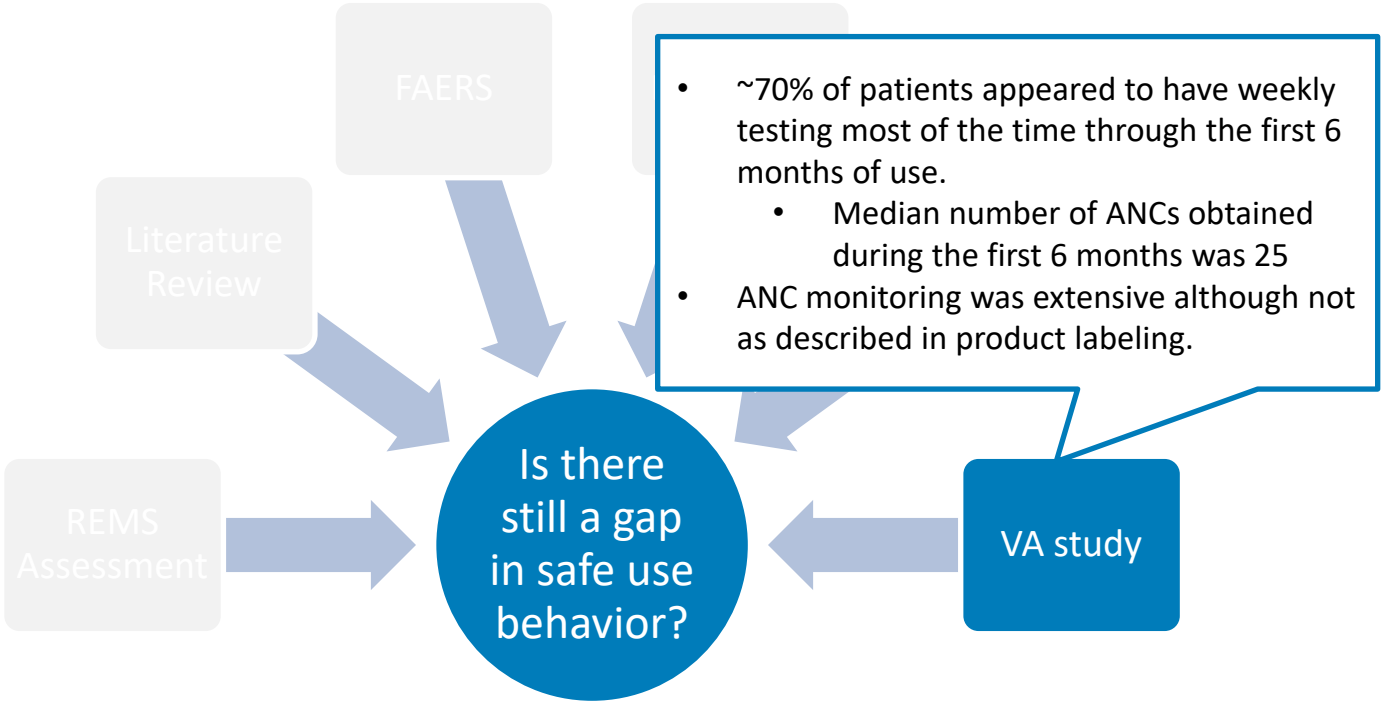
To What Extent Is ANC Monitoring Routinely Performed?

- Similar proportions in both studies (~20%) had no ANC monitoring during the first six months
- Median number of ANC tests per month during first 6 months of treatment, when frequency should be 4 per month:
  - BWH: 2.1 (all treatment episodes)
  - Sentinel: 3.1 (episodes with ≥1 ANC)
- In Sentinel, 12% of clozapine episodes had nearly perfect adherence (≤10 day gaps between all ANC tests) during the first 6 months of treatment
- After 6 months, adherence to ANC monitoring is improved

➢ **ANC monitoring is being performed but not as described in labeling, particularly for the first six months when the risk is greatest.**



To What Extent Is ANC Monitoring Routinely Performed?



Conclusions – ANC Monitoring Is Occurring But Not As Described in Labeling

- The data are consistent across studies which support that monitoring is occurring; however, adherence to monitoring is worse when the recommended monitoring frequency is weekly.
- It is unclear how much the REMS contributes to appropriate ANC monitoring or mitigating the risk of severe neutropenia because the REMS has not been fully implemented.
- Despite the REMS not being fully implemented, we know that some ANC monitoring is occurring.
- In population-based studies where monitoring was high, the incidence of severe neutropenia and clozapine-related mortality was substantially lower than in the pre-monitoring era

Summary of FDA's Re-Evaluation of the REMS

1. Assessment of the risk of severe neutropenia

- What we know about the risk of severe neutropenia today is consistent with what we've known since 1989
- Severe neutropenia is a serious risk of clozapine, it is greatest in the first several months of clozapine treatment; however, the risk never goes to zero
- ANC monitoring is an effective intervention to identify neutropenia early so appropriate action can occur

2. Assessment of healthcare gaps that are addressed in the Clozapine REMS

- Knowledge of the risk and the need for ANC monitoring appears to be more broadly understood today
- There are training, guidelines, and resources for clozapine outside of the REMS
- There is evidence of ANC monitoring, but it is less than what is recommended in the labeling for the first 6 months
- After the first 6 months, adherence is more consistent with labeling as monitoring frequency is reduced

REMS CONSIDERATIONS

Considerations for REMS Modifications

Burden/Access	• Fully implementing the REMS as designed may result in more burden than what we are seeing today
Time Since Approval	• Clozapine has been approved for 35 years. • New research evidence takes an average of 17 years to be adopted into clinical practice.[1]
Other Healthcare Gaps	• Changing the REMS to reduce burden or eliminating the REMS will not resolve all healthcare gaps.

[1] Morris ZS, Wooding S, Grant J. (2011). The answer is 17 years, what is the question: understanding time lags in translational research. Journal of the Royal Society of Medicine, 104(12):510-520.

Considerations for REMS Modifications

Interconnectedness of REMS Requirements

- REMS requirements are connected to each other, not exclusive of one another, and in combination can form a closed system.

Clozapine REMS – Requirements

Prescriber Certification

Pharmacy Certification

Patient Enrollment

Documentation of ANC Monitoring

Patient Registry

If the REMS Is Modified To Remove Documentation of ANC…

Prescriber Certification

Pharmacy Certification

Patient Enrollment

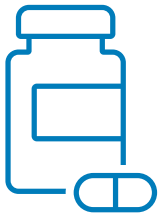
Documentation of ANC Monitoring

Patient Registry

- No ANC test results would be collected in the REMS
- Patient enrollment, documentation of ANC monitoring, and patient registry would be removed

If the REMS Is Modified To Retain Prescriber Education…

Prescriber Certification



Pharmacy Certification

- A closed system for restricted distribution is still needed
- Pharmacy certification must also be maintained to link prescriber certification to the dispense of the drug

Considerations for REMS Modifications

Prescribing Information

- Regardless if the REMS is modified or removed, the boxed warning for severe neutropenia and ANC monitoring will still be a part of the Prescribing Information

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