



Improving minds. Improving lives

The Clozapine REMS: Eliminating a Barrier to Lifesaving Care

Deanna L. Kelly, PharmD, BCPP

MPower Professor of Psychiatry, MPowering the State Acting Director, Maryland Psychiatric Research Center Chief, Treatment Research Program, University of Maryland School of Medicine Director of the clozapine CHAMPION project & Statewide Consultation Line American Psychiatric Association SMI Advisor Expert American Association of Psychiatric Pharmacists (AAPP) Past President

Dr. Deanna Kelly – Credentials & Expertise

- 25 years of research and clinical experience with schizophrenia and clozapine
- Director of an inpatient schizophrenia research unit
- APA SMI Advisor, clozapine expertise and tip developer
- SAMHSA Clozapine Advisory Committee
- FDA Advisory committees
- International clozapine publications and guidelines
- Led statewide educational intervention program on clozapine
- Director of the State of Maryland clozapine consultation line
- Published over 230 publications (over 25% on clozapine)
- Published books and book chapters on schizophrenia and clozapine
- 30+ grants in schizophrenia, including 10 NIH grants





Schizophrenia

- Today is <u>World Schizophrenia Day</u>
- Schizophrenia* is a chronic **brain disorder** that affects about 1.6% of the U.S. population
 - ~5.6 million individuals
- Delusions, hallucinations, disorganized speech, thought and movement disorders
- Important: Schizophrenia is treatable with medications





*<u>Schizophrenia spectrum and other psychotic disorders</u>: Schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, psychotic disorders from a medical condition; Mojtabai R. Schizophr Res. 2021 Apr;230:48-49. doi: 10.1016/

Challenges of schizophrenia care

- Top 15 leading causes of disability worldwide
- Schizophrenia lifespan is cut short by more than 25 years
- 5% die by suicide
- 50% attempt suicide
- Very high financial burden of <u>undertreated</u> schizophrenia:
 \$281.6 billion annually (direct and indirect costs)





Treatment pitfalls

 Up to 50% of a people with schizophrenia have Treatment-Resistant Schizophrenia (TRS)

CLOZAPINE:

- The ONLY FDA-approved medication for TRS
- The ONLY FDA-approved medication to reduce suicide
- Up to 2.8 million people in U.S. with TRS

In US used in <u>less than 5%</u> of all patients





A major problem

Clozapine saves lives and lowers costs

Clozapine is **severely underused!**

WHY?





Sources: Fayak et al. Psychiatric Services 2003; Carruthers et al. Psychiatric Services 2016

A major barrier: Frequent Blood Tests

Mandatory laboratory blood tests for ALL clozapine patients:

- WEEKLY draw for "neutrophil counts" (ANC) for 6 months
- Biweekly ANC for months 6 through 12
- Monthly ANC after 1 year INDEFINITE

 History: In 1975, 8 patients in same area of Finland died from "severe neutropenia"

- Clozapine was pulled from the US drug market
- The FDA allowed clozapine to be returned in 1990 with conditions:
 - Frequent blood testing of "ANC" to detect severe neutropenia
 - A surveillance program to monitor the testing







American Association of Psychiatric Pharmacists



Overview of Risk Evaluation and Mitigation Strategies (REMS)

Frequent Blood Tests: How?

- Risk Evaluation and Mitigation Strategy (REMS)
 - Intended as safety program
 - FDA establishes need for program
 - This particular REMS is referred to as "The clozapine REMS"
 - A surveillance platform to monitor the blood test results (ANC)
 - A cumbersome system that requires certification of prescriber and pharmacy, submit blood results, pharmacy authorization, etc.
 - Patients must participate to receive clozapine
 - Errors, missing data, and missed bloodwork prevent clozapine dispensing
 - Prescribers have some discretionary ability but often pharmacies don't
- The current clozapine REMS compounds the underuse problem...
 - It does not improve clozapine prescribing!





Because of the clozapine REMS:

- Many prescribers will not enroll in the system
- Patients have not been able to find doctors willing to prescribe clozapine
- Patients cannot find pharmacies willing to dispense clozapine
- Healthcare providers experience a high burden & little benefit from the REMS
- Treatment has been disrupted
- Some patients have relapsed, some hospitalized, some injured... even deaths
- Some patients have not returned to previous levels of functioning
- Utilization of clozapine has not improved it may be even lower

Lack of studies showing benefit after 30 years of blood tests and 8 years of the clozapineREMS





Mental Health Community Consensus

No available evidence the REMS prevents more harm than it causes

Reduce Scope of Clozapine REMS

- Eliminate mandatory reported blood tests
 - Eliminate pharmacy authorizations
 - Improve provider education

The Clozapine REMS Should Be Eliminated







American Association of Psychiatric Pharmacists



Pressure from All Fronts

Professional associations speak out

FDA Listening Session, Feb. 1, 2023:

Proposed elimination of REMS or change to education-based program





NATIONAL COUNCIL for Mental Wellbeing

Leading provider associations represented 54,000 members

Largest U.S. mental health advocacy organizations also participated





Patients and families speak out

Families complain to NAMI:



- Can't find doctors willing to prescribe clozapine
- Pharmacy & lab errors, miscommunication
- Lifelong requirements for blood testing
- Years of unnecessary suffering, suicide, near-death events due ineffective treatment instead of clozapine
- Families have to "stockpile" clozapine to avoid interruptions





Patients and families speak out

S&PAA's Patient-Focused Drug-Development meeting on schizophrenia (Nov 2022).

"Please, stop making it so hard to get a lifesaving medication. My daughter has had a meaningful recovery because of clozapine!"

"REMS has now robbed us of our wonderful psychiatrist." "One family resorted to buying clozapine from Mexico."





Sources: NAMI report presented to FDA, Feb 2023; S&PAA Voice of the Patient Report, submitted to FDA Jan 2023.

Media speak out

Improving minds. Improving lives.

1

Action Alliance

American Pharmacists Association For Every Pharmacist. For All of Pharmacy. Membership V Educatio Pharmacy News TAGS: Risk Management Drug Review Neurology ASK THE ANALYST R FIRST OPINION **Clozapine REMS Program Paused After Problems** Flawed FDA safety requirements are 🍐 Dr Marie Sartain / Monday, December 13, 2021 / Categories: Psychiatry, Medication Safety, REMS, APhA News, Drug The With Re-Certification FDA puts clozapine REMS requirements on temporary hold hamstringing a highly effective treatmen 22 Nov 2021 NEWS id it is tomporarily balting its risk evaluation and mitigation strategy (REMS) program for clozapine, a for severe schizophrenia n's original Novem By Brian Barnett May 5, 2022 by Brenda Sandburg **Issues With Patient Access to Clozapine** brenda.sandburg@informa.com **Prompt REMS Update Executive Summary** Brian Park, PharmD | November 3, 2022 US FDA says pharmacists may dispense the antipsychotic without wholesalers may continue to ship it during temporary suspens. long wait times have impacted patient access since the modifie You may also be interested in. More adult patients ape **PSYCHIATRIC NEWS** NEWS & PERSPECTIVE DRUGS & DISEASES CME & EDUCATION H 🛱 🗖 💽 💽 💽 🖛 🛜 🕫 DEPARTMENTS V PN in ADVANCE Clinical & Research Professional Government & Legal Community Education & Trainin LYBALVI Back to table of contents PROFESSIONAL News > Medscape Medical News APA Joins in Negotiations Over New Problematic Clozapine REMS FDA Puts Clozapine REMS on Hold MARK MORAN Published Online: 23 Dec 2021 | https://doi.org/10.1176/appl.pn.2022.2.21 Start Using Clozapine and Stop Interrupting It #endtheclozapinerems #EndtheClozapineREMS **The Angry Moms** American Association of Psychiatric Pharmacists Schizophrenia & Psychosis

oin the Army of Angry Moms

Media Inquiries / Request Info

Report a Problem Obtaining Clozapine

Original architect speaks out

Dr. Gilbert Honigfeld

- 50 years of experience
- Oldest surviving member of U.S. medical team that helped shepherd clozapine through regulatory review

The Clozapine REMS should be eliminated ASAP!





Even the original architect speaks out!

Dr. Honigfeld's Letter to the FDA:

- The clozapine REMS was intended to be short-lived
- Many other medications linked to severe neutropenia:
 - Yet, it's the ONLY medication with a REMS requiring blood tests!
- U.S. clozapine use is lower than any other country!
 - Finland's use is 10x higher

"After 30 years of post-market experience, psychiatrists are well informed on hematologic risk"





Clinicians speak out

Clozapine CHAMPION program:

- Clozapine education program and consultation hotline in the State of Maryland
- Created to improve access to clozapine and help providers improve use

Most common call: Requesting help with the clozapine REMS

- 40% more calls come in seeking help with REMS than for all other issues of severe side effects, adjunct treatment or off-label use
- Many prescribers continue to avoid clozapine REMS registration
- Challenges finding outpatient prescribers once out of hospital

More people have confusion, issues and misunderstandings about the clozapine REMS than with using the medication itself





Researchers speak out

- Growing body of published literature suggesting that clozapine REMS is problematic
- Presentation today in San Francisco at APA meeting showing focus groups identified numerous barriers and issues
- Collective CALL to ACTION in research community





Oloyede O, Taylor D, MacCabe J. International variation in clozapine hematologic monitoring-a call for action. JAMA Psychiatry 2023; JLeung, JG, Ehret, Megan, Love RC, Cotes RO Improving clozapine utilization will require continued advocacy, drug sponsor interest, and FDA support to address REMS issues, Expert Review of Clinical Pharmacology, 202316:3, 177-179, DOI: 10.1080/17512433.2023.2183192.

Angry parents speak out

Kevin Keith Langemeier, 49, died in March 2023 in an officer-involved shooting in Texas while he was experiencing severe delusions

His relapse occurred soon after his clozapine prescription was interrupted

"His mother desperately tried to get his Clozapine restocked... However, despite Kevin running out of Clozapine on Wednesday, it wasn't filled until Monday. This was the day before his death. By that point, his mental disorder had taken control and his mother didn't have resources to calm him down and stabilize him."





Three decades of science should speak the <u>final</u> word

- Little known published data available supports the safety of the clozapine REMS
- We now know:
 - Neutropenia is not as dangerous as previously thought (risk of death 0.05%)
 - The original concerns from the 1970s have not repeated
 - Blood draw logistics (i.e., REMS) is the No. 1 reason for underuse
 - Patients of African descent face worse discrimination
 - Suicide risk associated with not using clozapine is MUCH HIGHER than the 0.4% that develop severe neutropenia from clozapine
- Other countries have fewer clozapine restrictions:
 - They have higher clozapine use
 - Their rates of severe neutropenia are NOT higher
- Clozapine saves lives and prevents suicide

No known FDA data available suggests the clozapine REMS saves lives, reduces interruptions, or that patients benefit from testing





Correll CU, et al. World Psychiatry. 2022 Jun;21(2):248-271. doi: 10.1002; Meltzer HY, et al. Arch Gen Psychiatry. 2003 Jan;60(1):82-91. doi: 10.1001: Li XH, Zhong XM, et. al. Psychol Med. 2020 Mar;50(4):583-594. doi: 10.1017/S0033291719000369.

Conclusions

- Patients who need clozapine often can't access this vital treatment
- The risk of clozapine nonuse and consequences outweigh the low risk of death from severe neutropenia
- **ALL** key U.S. stakeholders are calling for ACTION:
 - Providers, parents, advocacy groups, experts, healthcare workers, mental health associations, researchers, pharmacy groups and the media
- After 30 years, it's time to revisit the rationale for stringent blood test oversight

Patients with schizophrenia deserve access to the ONLY medication FDA-approved for TRS and suicidal behavior: opportunity for life saving care







American Association of Psychiatric Pharmacists



Thank You