Schizophrenia & Psychosis Action Alliance

The Clozapine REMS: Eliminating a Barrier to Lifesaving Care

Public Webinar

March 12, 2025
Noon-1:30 pm ET

A Global Impact Organization Moving Individuals, Families, and Policies Forward to Improve and Save Lives

Agenda

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- Introductions
- What exactly did the FDA just announce?
- Lived experience perspective
- Monitoring & pharmacy access
- Prescriber implications
- Optimal treatment approach
- Panel discussion
- Conclusion

Today's expert panel

Schizophrenia & Psychosis Action Alliance

Raymond C. Love, PharmD, BCPP, FASHP
Professor Emeritus
University of Maryland School of Pharmacy

Michael Brisbin
Bachelor's degree in Social Work
Lives with schizophrenia

Angela Brisbin
Assistant producer, *Into the Light: Meaningful Recovery from Psychosis*
Parent of a person living with schizophrenia

Robert O. Cotes, MD
Professor,
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine

Deanna L. Kelly, PharmD, BCPP
Dr. William and Carol Carpenter Professor of Psychiatry for Mental Illness Research
Acting Director, Maryland Psychiatric Research Center,
University of Maryland School of Medicine

Robert Laitman, MD
Private-practice physician, Bronx, NY
President, Doromind Co-founder and Board President, Team Daniel

Disclosures

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Presenters are sharing their own views that may or may not reflect the views of any other organization. Specific medical advice is not being offered. Medication use in an off-label manner may be discussed.

- Dr. Love has no disclosures for the past 36 months.
- In the past 36 months, Dr. Kelly has served on an advisory board for Karuna, Janssen, Alkermes and Teva and served as a one-time consultant for Syneos Health on behalf of the Clozapine Product Manufacturer's Group.
- In the past 36 months, Dr. Cotes has received research funding (to institution) from Otsuka, Bristol Myers Squibb, Roche and Alkermes. He is a consultant to IQVIA, Boehringer Ingelheim and Syneos Health on behalf of the Clozapine Product Manufacturers Group. He is a speaker and consultant to Saladax Biomedical.
- Dr. Laitman has a <1% ownership in Myogenes and Doromind.

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What exactly did the FDA announce?

Raymond C. Love, PharmD, BCPP, FASHP
Professor Emeritus
University of Maryland School of Pharmacy

How did we get here?

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November 2015
FDA institutes first REMS for clozapine; CPNP/APA object to process

8/19/21
FDA begins meetings to review new REMS

11/15/21
New REMS implemented over stakeholder objections

11/19/21
FDA calls emergency meeting with stakeholders and agrees to "enforcement discretion"

12/2/21 to 6/21/23
FDA holds series of meetings with stakeholders and CPMG

October 2023
Congressman Sherman reinforces request for meeting of Advisory Committee to consider Clozapine REMS

11/19/24
FDA Joint Advisory Committee recommends an end to reporting lab values, verification and certification

2/24/25
FDA announces plan to eliminate REMS

Who contributed to the effort?

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- American Association for Community Psychiatry
- American Association of Psychiatric Pharmacists
- American Pharmacists Association
- American Psychiatric Association
- American Psychiatric Nurses Association
- American Society of Health-System Pharmacists
- Black Psychiatrists of America, Inc.
- CURESZ Foundation
- HEALING MINDS NOLA
- National Alliance on Mental Illness
- National Association of State Mental Health Program Directors
- National Council for Mental Wellbeing
- National Shattering Silence Coalition
- Schizophrenia & Psychosis Action Alliance
- Team Daniel Running for Recovery from Mental Illness
- The Angry Moms
- Treatment Advocacy Center

FDA Joint Advisory Committee: 11/19/24

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- 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?
  - ***No!*** *Get rid of Patient Status Form and requirement to submit laboratory results.*
  - ***No!*** *Get rid of REMS Dispensing Authorization.*
- Is the requirement to educate healthcare providers through the REMS about the risk of severe neutropenia and the need for ANC monitoring necessary to ensure safe use?
  - ***No!*** *Get rid of required pharmacy and prescriber education and certification.*

What did the FDA say?

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- Beginning 2/25/25, FDA does not expect prescribers, pharmacies and patients to participate in the risk evaluation and mitigation strategies (REMS) program for clozapine or to report results of absolute neutrophil count (ANC) blood tests before pharmacies dispense clozapine.
- **FDA still recommends that prescribers monitor patients' ANC** according to the monitoring frequencies described in the prescribing information. Information about severe neutropenia will remain in the prescribing information for all clozapine medicines, including in the existing Boxed Warnings.
- Although the risk of severe neutropenia with clozapine still exists, FDA has determined that the REMS program for clozapine is no longer necessary to ensure the benefits of the medicine outweigh that risk.
- **Eliminating the REMS is expected to decrease the burden on the health care delivery system and improve access to clozapine.** FDA has notified the manufacturers that the clozapine REMS must be eliminated. FDA has instructed the clozapine manufacturers to formally submit a modification to eliminate the clozapine REMS and to update the prescribing information, including removing mandatory reporting of ANC blood tests to the REMS program.
- In the coming months, **FDA will work with the clozapine manufacturers to update the prescribing information** and eliminate the clozapine REMS.

What does it mean?

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- Clozapine still requires blood monitoring, especially at the beginning of treatment.
  - *Eventually, there could be changes through revised labeling or through new standards that develop.*
- Forget about submitting the lab results to the Clozapine REMS.
- Pharmacies shouldn't need an authorization from clozapine REMS or lab data to fill a prescription.
  - *But chain pharmacies and payers may not have changed their procedures.*
  - *It does not mean that a pharmacy will automatically have clozapine in stock.*
  - *No more REMS limits on quantity dispensed, but payers may still limit quantities*
- Pharmacies and prescribers don't have be certified to prescribe or dispense clozapine.
- Old historical data on patients may no longer be available to prescribers.
- This is an administrative change – not a clinical change.

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Stakeholder Perspective: Lived Experience

Michael Brisbin, Bachelor's degree in Social Work; Lives with schizophrenia

Angela Brisbin, Assistant producer, *Into the Light: Meaningful Recovery from Psychosis*
Parent of a person living with schizophrenia

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Michael and Angela Brisbin: Our Perspectives

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Stakeholder Perspective: Monitoring & Pharmacy Access

Deanna L. Kelly, PharmD, BCPP

Dr. William and Carol Carpenter Professor of Psychiatry for Mental Illness Research

Acting Director, Maryland Psychiatric Research Center, University of Maryland School of Medicine

Stakeholder perspective

Schizophrenia & Psychosis Action Alliance

Researcher

Pharmacist

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The Facts

Agranulocytosis (<500 cells/mm^3)

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- Peak incidence = 30-54 days and highest in first 18 weeks.
- Risk is < 0.8% (likely <0.6%).
- 0.38% in US National Registry Data.
- Few cases beyond six months. Declines to negligible levels after 1 year.
- Cases after 18 weeks: 0.39/1000 patient years.
- HLA DQ1B has association (genetic testing becoming available).
- Deaths from agranulocytosis are extremely rare < 0.013- 0.028% .

Myles N, Myles H, Xia S, Large M, Bird R, Galletly C, Kisely S, Siskind D. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. Aust N Z J Psychiatry. 2019 May;53(5):403-412. doi: 10.1177/0004867419833166; Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, Bird R, Siskind D. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatr Scand. 2018 Aug;138(2):101-109. doi: 10.1111/acps.12898; Rubio JM, Kane JM, Tanskanen A, Tiihonen J, Taipale H. Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case-control study in Finland. Lancet Psychiatry. 2024 Jun;11(6):443-450. doi: 10.1016/S2215-0366(24)00097-X.; Kelly DL, et al. Clozapine and neutrophil response in patients of African descent: A six-month, multinational, prospective, open-label clinical trial. Schizophr Res. 2024 Jun;268:312-322. doi: 10.1016/j.schres.2023.08.002.; Honigfeld G, Arellano F, Sethi J et al (1998) Reducing clozapinerelated morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 59(suppl.3):3–7

Neutropenia (< 1500 cells/mm^3)

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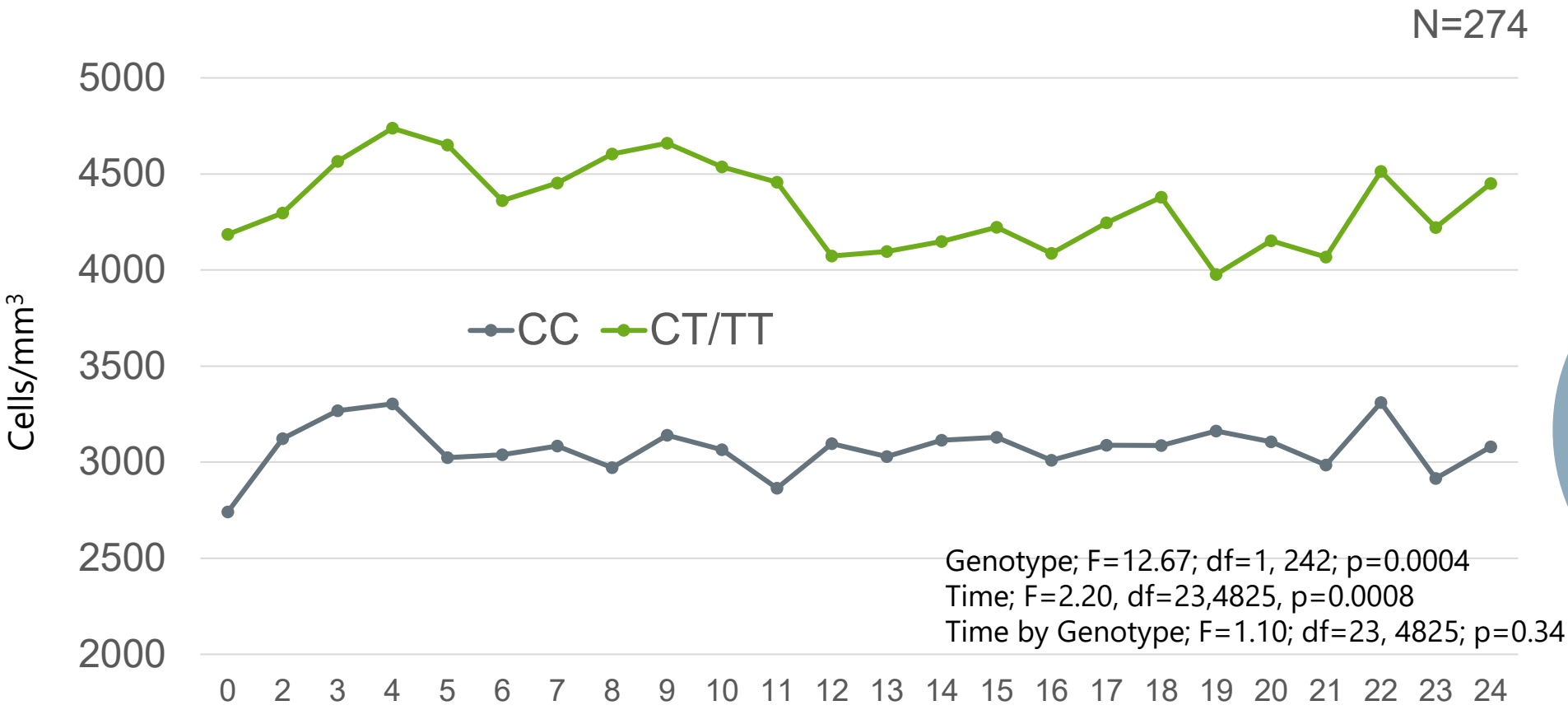
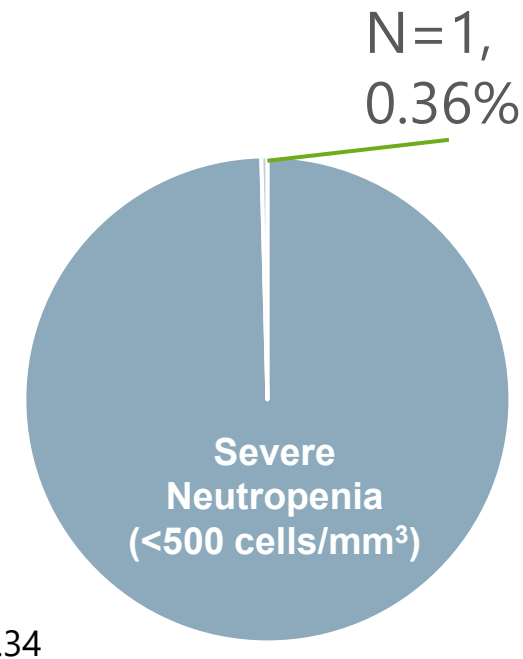
- NOT the same as agranulocytosis.
- About 4% overall (Black and White patients).
- Meta-analysis: Neutropenia risk is same with clozapine as other antipsychotics.
- Black patients naturally have low ANC and “neutropenia” (33% in those with Duffy Null may experience neutropenia during a 6-month period).

Myles N, Myles H, Xia S, Large M, Bird R, Galletly C, Kisely S, Siskind D. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Aust N Z J Psychiatry*. 2019 May;53(5):403-412. doi: 10.1177/0004867419833166; Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, Bird R, Siskind D. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand*. 2018 Aug;138(2):101-109. doi: 10.1111/acps.12898; Rubio JM, Kane JM, Tanskanen A, Tiihonen J, Taipale H. Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case-control study in Finland. *Lancet Psychiatry*. 2024 Jun;11(6):443-450. doi: 10.1016/S2215-0366(24)00097-X.; Kelly DL, et al. Clozapine and neutrophil response in patients of African descent: A six-month, multinational, prospective, open-label clinical trial. *Schizophr Res*. 2024 Jun;268:312-322. doi: 10.1016/j.schres.2023.08.002.; Honigfeld G, Arellano F, Sethi J et al (1998) Reducing clozapinerelated morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 59(suppl.3):3–7

Weekly mean ANC by genotype





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ANC monitoring

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- Currently we should follow the package label.
  - Weekly blood draw for first 6 months
  - Every other week for 6-12 months
  - Monthly blood draw for >12 months
  - More frequent if low values are observed
- Some other countries moving to less-stringent guidelines.
- New European recommendations released.
- International Delphi Consensus Guidelines in press.
- FDA label likely will NOT change; how to think about off-label use.

Changes occurring elsewhere

- **Chile** changed guidelines in 2022 to as follows:
  - Weekly ANC for first 18 weeks.
  - Every 4 weeks after week 19 to 1 year.
  - Every 8 weeks after 1 year (If no significant hematologic side effects at 1 year (neutropenia, moderate/severe eosinophilia or severe leukocytosis).

GABINETE MINISTRO DE SALUD SUBSEGRETARÍA DE SALUD PÚBLICA DE DIVISIÓN JURÍDICA 2022

European Clozapine Task Force proposal

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	Current Guidelines	Proposed Guidelines
Mandatory routine blood monitoring schedule	WBC and ANC	ANC
	Baseline before initiation Weekly for 18 weeks after initiation Monthly irrespective of treatment duration	Baseline before initiation Weekly for 18 weeks after initiation Then monthly for 34 weeks **After 12 months:** ANC every 12 weeks if no hx of neutropenia **After 24 months:** Yearly ANC if no history of neutropenia during 2 years
Standard thresholds for initiation/continuation	ANC ≥ 2.0 cells/mm^3 WBC ≥ 3.5 cells/mm^3	ANC ≥ 1.5 cells/mm^3
Monitoring twice a week	ANC 1.5-2 cells/mm^3 WBC 3.0-3.5 cells/mm^3	ANC 1.0-1.5 cells/mm^3
Discontinuation	ANC <1.5 cells/mm^3 WBC <3.0 cells/mm^3	ANC <1.0 cells/mm^3

Verdoux H, Bittner RA, Hasan A, et al. The time has come for revising the rules of clozapine blood monitoring in Europe. A joint expert statement from the European Clozapine Task Force. *Eur Psychiatry*. 2025 Jan 10;68(1):e17. doi: 10.1192/j.eurpsy.2024.1816. PMID: 39788917; PMCID: PMC11822956.

Improvement in competence with education

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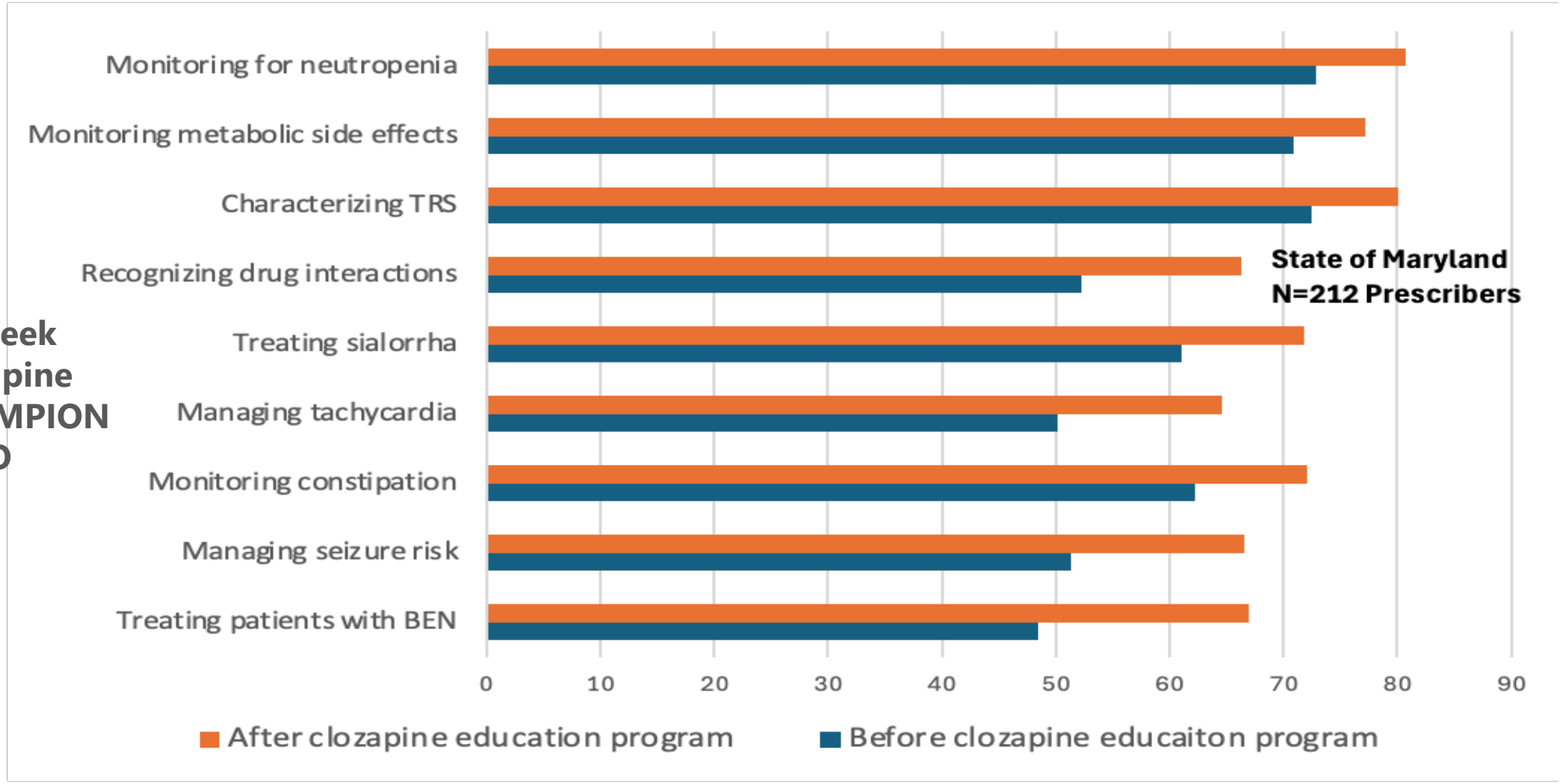
26-week clozapine CHAMPION ECHO



Kelly DL, et al, Schizophrenia Bulletin, in revision 2025

Pharmacist perspective

- American Association of Psychiatric Pharmacists (AAPP)
  - Advanced-practice pharmacists who specialize in treating patients living with psychiatric disorders, including substance use disorders.
- Vision: A world where all individuals living with mental illness receive safe, appropriate and effective treatment.
- Working closely for several years with S&PAA and others to support clozapine REMS changes.
  - Hill briefing
  - Letters
  - FDA meetings
  - Stakeholder conversations

American Association of Psychiatric Pharmacists

aapp

Improving minds. Improving lives.

Chain and front-line dispensing pharmacists

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- CPMG reported approximately 7-day mean time to get clozapine if denied. Goal: NO DELAY.

- NOW:
  - ✓ *Don't need to register.*
  - ✓ *Don't need to have dispensing authorization.*
  - ✓ *Soon to be no clozapine REMS to communicate.*
  - ✓ *Pharmacists remain an important part of the clinical team.*

Top-down + bottom-up education & communication

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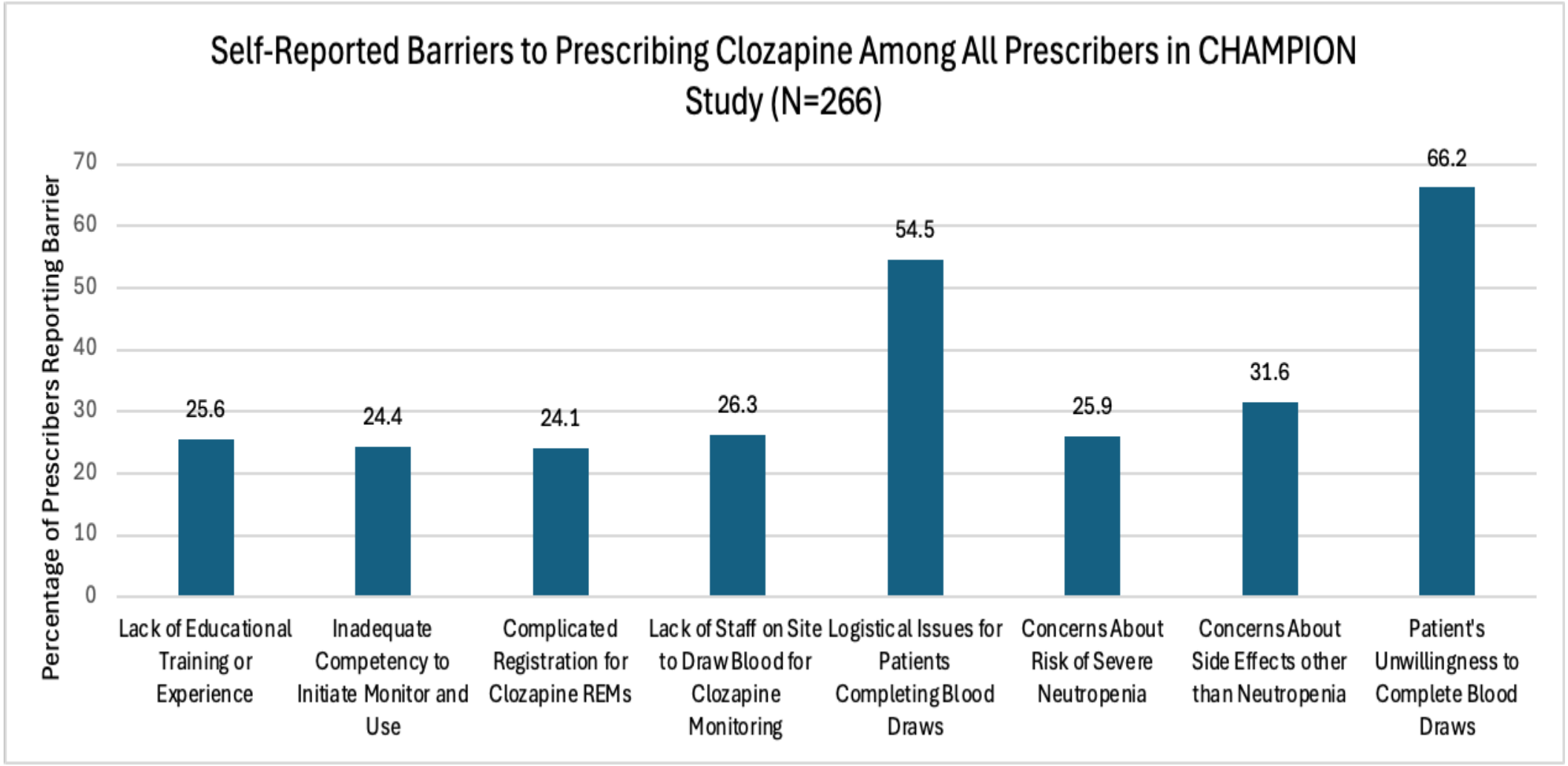
- Professional organizations and advocacy groups collectively interact with:
  - Pharmacy organizations
  - PBMs
  - Pharmacy chains
  - Pharmacist education

Reminder: REMS not the only barrier to clozapine use



Kelly, et al. Schizophrenia Bulletin, in revision, 2025

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Stakeholder Perspective: Prescriber Implications

Robert O. Cotes, MD

Professor, Department of Psychiatry and Behavioral Sciences

Emory University School of Medicine

Opportunities

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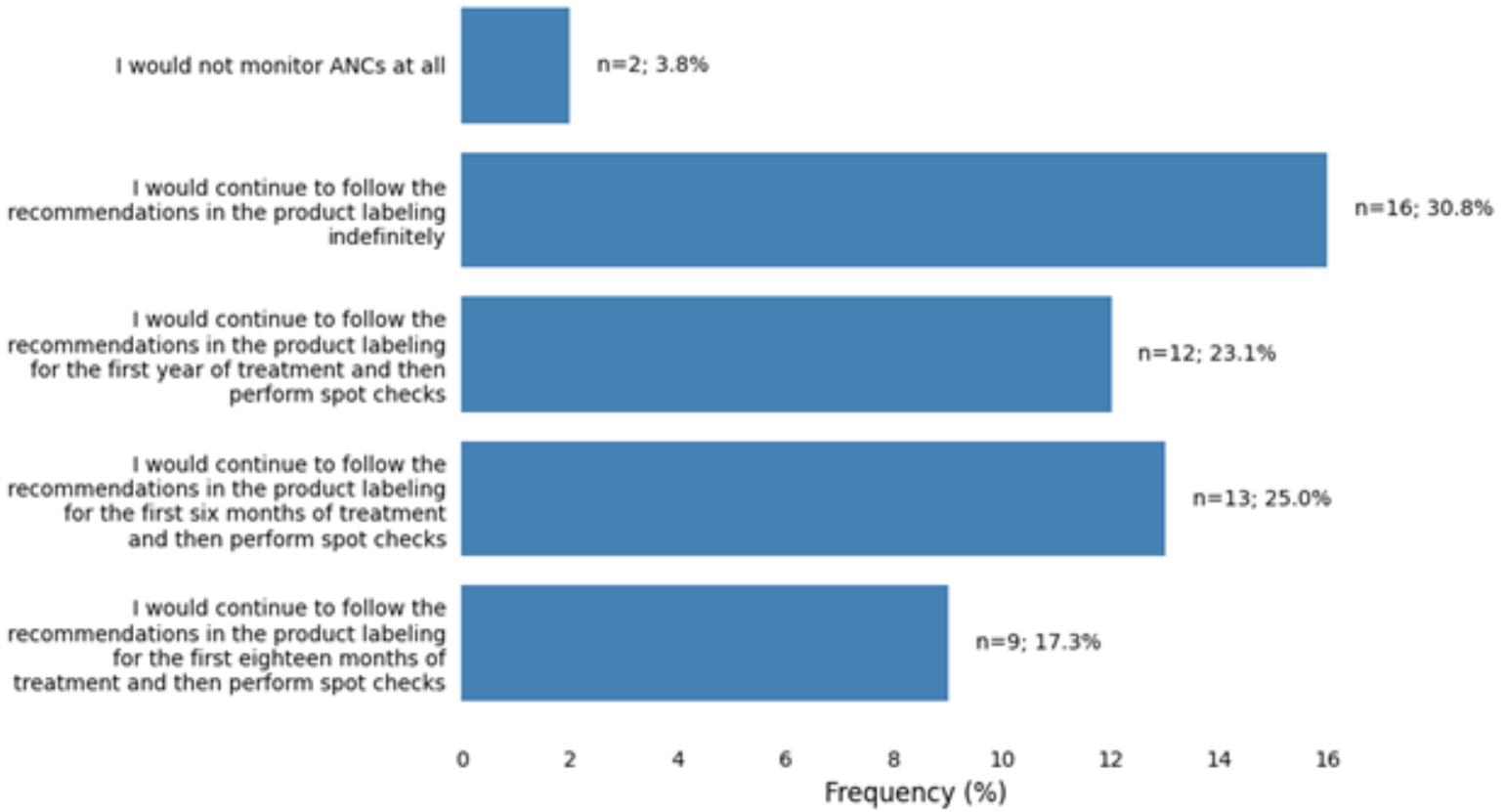
- Potential for fewer interruptions in clozapine access, reducing devastating treatment interruptions.
- Greater flexibility in certain prescribing and monitoring situations.
  - Greater discretion in dispensing clozapine despite missing ANC (this flexibility did exist before).
  - New clozapine starts may be possible with extensive risk/benefit discussions when initial monitoring is challenging.

FDA 2/24 announcement: Still recommends ANC monitoring per prescribing information.

Strategies for ANC monitoring without REMS



96% of prescribers surveyed said they would continue monitoring per the USPI for the first 6 months after clozapine initiation.

Cotes et al., in preparation (2025)

Opportunities

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- No quantity limits tied to monitoring frequency:
  - Inpatients may receive 30-day supplies, easing discharge transitions.
  - 3-month supplies could be dispensed, pending insurance approval.
  - Increased flexibility for extended travel, particularly internationally.
- Easier access to having a few extra doses for emergencies.
- Potential for broader pharmacy stocking without certification barriers.
- Opportunities to revisit a more holistic monitoring approach.
- Fewer barriers, less prescriber hesitation?

Potential challenges

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- Lack of standardization across systems.
  - Potential for fragmented "quasi-REMS" approaches.
  - Variability could cause confusion for prescribers and pharmacists.
- Potential for increased neutropenia adverse effects, but monitoring wasn't perfect before.
- If monitoring for neutropenia decreases, will monitoring for other risks also decline? Levels?
- Existing clozapine patients may not be found in the registry, which was helpful for transitions in care and transient individuals.
- Perceived risk shifting to prescribers and lack of structure, potentially increasing hesitancy?

Next steps for prescribers

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- Clarify REMS timeline and download historical ANC records before access ends.
- Revise protocols:
  - System to keep track of monitoring cadence.
  - How outreach was occurring if the pharmacy was doing it.
  - Clear language around risk-benefit of off-label monitoring.
- No more potential for the REMS to serve as a prescriber locator tool.
- Emphasize symptom-based monitoring and educate patients to report infections promptly:
  - "If you have a fever, call me."
- Standardize monitoring protocol to advocate for in a package insert revision.
- Research on clozapine utilization – will use change after the 2/2025 FDA decision?
- Loss of REMS-provided education will require alternative high-quality training and resources.

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Stakeholder Perspective: Optimal Treatment Approach for Clozapine

Robert Laitman, MD

Private-practice physician, Bronx, NY

Co-founder and Board President, Team Daniel

EASE method

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A set of general principles that constitute the correct approach:

- **E**arly intervention with clozapine.
- **A**ssertive monitoring (TDM) & managing predictable side effects.
- **S**low titration.
- **E**ngage the patient and the family to provide support.

Early intervention with clozapine

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- APA Guidelines: 2 antipsychotic trials of 2-4 weeks given in an adequate dose with minimal or no response, or persistent risk of suicide, or persistent risk of aggressive behavior.
- TRRIP Working Group Consensus Guidelines: 2 antipsychotic trials of 6-week duration with doses equivalent to 600 mg chlorpromazine, with documented 80% adherence, documented by pill count and therapeutic drug monitoring.
- Clozapine is the only effective antipsychotic for treatment-resistant schizophrenia.
  - Response rate for other U.S.-available antipsychotics is <5%, except for olanzapine, which is 7%.
- Delay in starting clozapine has sequelae: Delay of more than 2.8 years is a predictor of failure to adequately respond.
- First year of psychotic illness associated with up to 5% mortality from suicide and 50-fold mortality risk. Clozapine use here could reduce risk by 90%.
- 2025 Finnish study in *Lancet Psychiatry:* In patients with FEP, overall 71% relapse within 2 years.
  - Switching to clozapine after first relapse lowered relapse risk 34%.
  - Patients not on antipsychotics (45%) after the first episode had a 48% lower risk.
  - Switching to non-clozapine antipsychotic had no benefit.
  - Switching off clozapine doubled the risk.

Assertive monitoring & management

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- Assertive monitoring allows you to confirm medication compliance.
- Assertive monitoring with therapeutic drug monitoring (TDM) optimizes treatment effect, as there is a clear dose response for both efficacy and side effects.
- Threshold TDM 350 ng/ml. This is not optimal dose; increased response seen with levels up to 1000 ng/ml, but side-effect management often more problematic over 700 ng/ml.
- Rational polypharmacy – "Doing the Medicine" – can manage the side effects, so that constipation, weight gain, excessive sialorrhea, tachycardia and other cardiac issues, seizure risk and nocturnal enuresis can be dramatically mitigated.
  - Wraparound services, including psychosis-informed CBT, CET, socialization and befriending, diet and exercise are offered.

Slow, careful titration of clozapine

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- Clozapine rarely first antipsychotic used, so current antipsychotic must be slowly cross-tapered off as clozapine is slowly initiated to avoid a rebound psychosis.
- Slow titration:
  - Dramatically improves side effects and overall tolerability, leading to a decrease in discontinuation from over 50% to less than 10% secondary to aforementioned side effects.
  - Minimizes risk of myocarditis and neutropenia.
  - Allows you to find the optimal dose for any individual and minimizes the risk of dramatic overshoot.
- For this reason, we start our stable outpatients at 12.5 mg at bedtime and only increase by 12.5 mg every 3 days. Standard to maintain current antipsychotic until clozapine is at 100 mg, then start cross-taper.

Engagement of the treated individual & family

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- Voluntary: Patients not experiencing anosognosia (less than 40%) may be receptive, especially since the typical journey to clozapine involves multiple failed antipsychotics and years of inadequate care.
  - For patients with less-pervasive anosognosia, use LEAP method (reflective listening, followed by empathy and ultimately, agreement and partnering toward a common goal).
- Involuntary: Use the courts: Medication over objection (inpatient) and Assisted Outpatient Treatment (AOT) to compel use.
  - NY AOT criteria (Kendra's Law): 2 or more admissions with documented non-adherence in a 3-year period and/or violence in the setting of non-adherence.
- Family must be involved, as it is difficult to impossible to sustain a clozapine regimen without caregiver support.
  - Train caregivers to observe patient symptoms and adherence.
  - Never let Health Information Portability and Accountability act (HIPAA) interfere with this. Zero prosecution for "violating HIPAA" when best judgment is used.
- Community: We have Team Daniel in-person gatherings in a non-medical setting, and weekly Zoom sessions for both patients and family. We encourage involvement in NAMI.

How is Team Daniel different?

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- We use **clozapine first**… NOT as a last resort! Clozapine is the gold standard!
- We believe patients have a **right to be well;** we encourage the use of LEAP and if needed, court-ordered Assisted Outpatient Treatment (AOT).
- We do not tolerate side effects, including weight gain, and we aggressively use **adjunctive medications, ultra-slow titrations, diet and exercise** to treat and prevent them.
- Our goal is **meaningful recovery** and returning patients to their pre-illness baseline level of functioning and wellbeing.
- We promote a sense of **community** and engage and communicate with the patient's **family**. After learned helplessness and hopelessness, we restore optimism.

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Panel Discussion

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Thank you for joining us!