

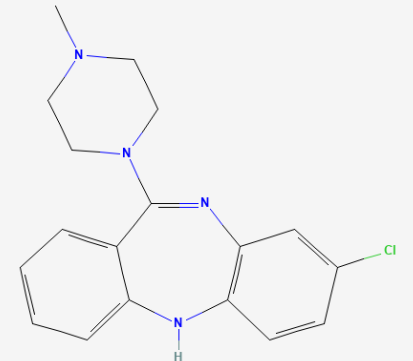
Clozapine Workshop: The nuts and bolts of using clozapine

October 15, 2026

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

- **Karuna** Research grant to institution (PI for MGH site)
- **Medscape** Speaker honorarium (medical peer education)
- **Psychopharmacology Institute** Speaker honorarium (medical peer education)
- **Wolters-Kluwer** Royalties for medical writing (medical peer education)

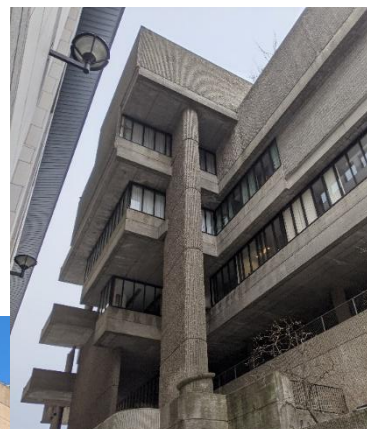


Massachusetts General Hospital
Boston, Massachusetts

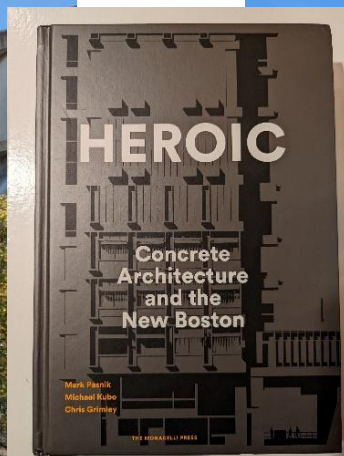
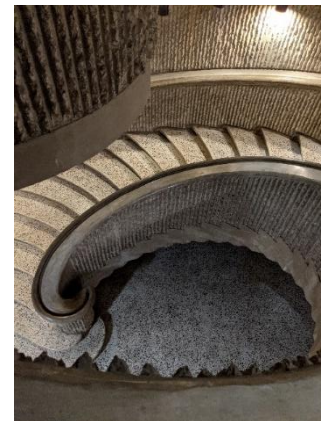
151 Merrimac Street
Boston, Massachusetts



 Massachusetts General Hospital
Founding Member, Mass General Brigham
Psychiatry Academy



Erich Lindemann Mental Health Center
Boston, Massachusetts



Workshop agenda

- 1:00 PM **Clozapine Basics**
- 1:50 PM **Break**
- 2:00 PM **Clinical Vignettes with Q&A**
- 3:00 PM **Adjourn**



What is a good outcome in psychiatry?



Photo courtesy of Oliver Freudenreich

TRS as a biological subtype (?)

- Clinical differences
 - Earlier age of onset
 - Not more common in males
 - Worse outcome (circular reasoning)
- Biological differences
 - More familial and greater genetic loading
 - Possible specific cognitive deficits
 - Response to clozapine but not other antipsychotics
- Pathophysiology
 - Not dopamine-driven
 - Neuromelanin-sensitive MRI as biomarker for TRS in FEP?
 - Inflammation
 - Majority are resistant at presentation; minority develops resistance over time (related to relapse)

“The group of treatment-resistant schizophrenias”*

Prevention of TRS – 2 pathways

80%

First pathway: **early-onset TRS**

- Early diagnosis of TRS to reduce duration of psychosis
- Early use of effective treatment for TRS (clozapine)

20%

Second pathway: **late-onset TRS**

- Prevention of numerous episodes with accrued disability and development of treatment resistance

Psychiatric treatment as prevention.

Demjaha A et al. Psychol Med. 2017;47(11):1981-9. Takeuchi H et al. Neuropsychopharmacology. 2019;44(6):1036-1042.
Emsley R et al. J Clin Psychopharmacol. 2013;33(1):80-83.

Clozapine proficiency

VIEWPOINT

Theodore R. Zarzar, MD
Department of
Psychiatry, University
of North Carolina
School of Medicine,
Chapel Hill.

Clozapine Proficiency as a Milestone in Psychiatric Training

Medical education is shifting from a structure- and process-based focus to one that emphasizes core competencies and outcomes. The former relies on exposure to various content areas for specified periods, while competencies tailor the curriculum to the desired outcome. A competency-based approach requires learners to demonstrate ability to progress through training.

The Accreditation Council for Graduate Medical Education (ACGME) lists 6 competencies that apply across specialties: (1) patient care, (2) medical knowledge, (3) practice-based learning and improvement, (4) professionalism, (5) interpersonal and communication skills, and (6) systems-based practice. In psychiatry, competence

et al,⁵ "prescribers' hesitancy is understandable. However, we would be horrified if oncologists avoided using chemotherapy because the agents had life-threatening side effects and because knowledge and skill are necessary to prescribe them appropriately. ... We have too long valued the comfort of prescribers over the well-being of patients with severe mental illness." Psychiatrists determine which patients meet criteria for treatment resistance, and few medical practitioners other than psychiatrists routinely prescribe clozapine. Thus, only psychiatry can fix the problem of clozapine underuse.

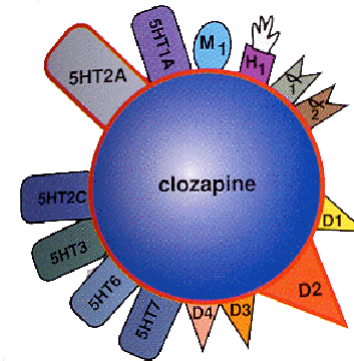
Over the past 30 years, continuing education has been

Zarzar TR. JAMA Psychiatry. 2024;81(7):639-640. [Viewpoint]

Clozapine pharmacology

(Very) basic pharmacology

- Dibenzodiazepine
- “Dirty” receptor profile
 - Weak dopamine binding
 - Multiple other receptors
- Short half life of under 12 hours
- Metabolism
 - 3A4 and 1A2 (smoking!)
 - One active metabolite: nor-clozapine (10%)



Mechanism of action (?)

Partial agonism M4

[See xanomeline!]

Morrison PD et al. J Psychopharmacol. 2025;39(4) 297-300.

Atypicality

- Not causing neuroleptosis in animals
- Triad of clinical features*
 1. Effective for refractory patients
 2. Does not cause extrapyramidal symptoms
 3. Does not increase prolactin
- Clozapine is the only truly “atypical” antipsychotic

*Narrow definition

Clozapine efficacy

Kane trial

- Very rigorous methodology
 - Refractory illness by history
 - Non-response to prospective 6-week haloperidol
- Very large trial (for psychiatry)
 - N=268
- Double-blind design
 - Chlorpromazine (CPZ) vs. clozapine (CLZ)
- **Very clear results**
 - **30% (CLZ) versus 4% (CPZ)**

Kane J et al. Arch Gen Psychiatry. 1988;45(9):789-796.

Numerous RTCs and population studies

- Clozapine usually superior in individual RTCs
- Mixed results in meta-analyses¹
 - Efficacy versus effectiveness²
- Clozapine superior for specific indications
 - Suicidality
 - Violence
 - Mortality reduction
- Excellent for relapse prevention

¹Schneider-Thoma J et al. Lancet Psychiatry. 2025;12(4):254-265.

²Siskind D et al. Lancet Psychiatry. 2025;12(4):240-241. [editorial]

Clozapine timeline

- 1958-74: Discovery and development by Sandoz
- 1975-80: The Finnish agranulocytosis “epidemic” and aftermath
- 1982-89: Recovery and quest for FDA approval
- 1990-99: Marketing and the CPMS
- 2015: Clozapine REMS Program
- 2021: Updated Clozapine REMS Program
- **2025: FDA rescinds Clozapine REMS Program**



Crilly J. History of Psychiatry 2007;18:39.

CPMS = Clozaril Patient Monitoring System
REMS = Risk Evaluation and Mitigation Strategy

Clozapine: 5 black box warnings

1. Severe neutropenia
2. Orthostatic hypotension, bradycardia, and syncope
3. Seizure
4. Myocarditis, pericarditis, cardiomyopathy, and mitral valve incompetence
5. Increased mortality in elderly patients with dementia-related psychosis (class warning for all antipsychotics)

9587 clozapine fatalities based on WHO Global Pharmacovigilance Database¹
- 534 Black box warning (218 neutropenia = 2.3% of all deaths)
- 674 Pneumonia and 596 infection (900 = 9.4% of all deaths)

¹de Leon J et al. J Clin Psychopharmacol. 2025;45(3):197-218.

<https://clozaril.com/wp-content/uploads/2022/12/HLS-Clozaril-PM-US.pdf>

Clozapine and agranulocytosis

- Clozapine can cause agranulocytosis¹
 - Led to complicated path to FDA-approval
 - Led to mandated, registry-based prescribing, with regular ANC
 - Separate pathway for patients with BEN
- Severe neutropenia (ANC < 500/ μ L) is rare
 - 9/1000 people started on clozapine
 - Case fatality rate of 2.1%
- Severe neutropenia has peak incidence in the first several months after starting clozapine
 - Metabolite toxicity or hapten-based immune-mediated mechanism; type B idiosyncratic ADR⁵
 - Negligible incidence (base rate) after 1 year (?) → see Rubio study

POC fingerstick testing
available for ANC⁴

CIA and CIN are not the
same⁵

Critique

1. Large variation in guidelines suggests lack of evidence-based approach²
2. “Benign ethnic neutropenia” reflects structural racism in lab values³

¹Myles N et al. Acta Psychiatr Scand. 2018;138(2):101-109. ²Oloyede E et al. JAMA Psychiatry. 2023;80(6):535-536. [Viewpoint]

³Dotson S et al. Psychiatr Serv. 2021;72(2):232-233. ⁴Leung JG et al. Schizophr Res. 2023;252:127-128. ⁵Silva E et al. BJPsych Bull. 2025;49(3):163-168.

Benign ethnic neutropenia (BEN)

- **Terminology¹**

- Problematic: BEN is not a condition or disease!
- Partially responsible for racial disparities in clozapine prescribing²

- **Pathophysiology³**

- Duffy null [Fy(a-b-)] phenotype
- Duffy antigen receptor for chemokines (DARC) gene (aka ACKR1)
- Protects against malaria
- 100% sub-Saharan African ancestry; <1% European ancestry

- **Diagnosis⁴**

- **History is everything:** Lab history and personal history of infection
- Consider BEN (Duffy-negative) as a cause of neutropenia if the ANC is 500-1000 and the patient has African or Middle Eastern heritage

- **View from hematology:**

- An **ANC >500 is safe**
- Most important is the trajectory of ANC decline
- Adjust testing frequency to practical and common-sense considerations

Use BEN monitoring algorithm

BEN = ANC baseline $\geq 1000/\mu\text{L}$

¹Dotson S et al. Psychiatr Serv. 2021;72(2):232-233. Merz LE and Achebe M. Blood. 2021;137(1):13-15. ²Barry S et al. Psychiatr Serv. 2024;75(8):733-739.

³Rappoport N et al. Brit J Haematol 2019;184:497-507. ⁴Atallah-Yunes SA et al. Blood Rev. 2019;37:100586.

Clozapine rechallenge CIN

CIN = Clozapine induced neutropenia

- Observational cohort study¹
 - N= 435 rechallenge cohort in UK Central Non-Rechallenge Database (CNRD)
 - 7% recurrence of low WBC/ANC
 - 4% agranulocytosis
 - 74% successful rechallenge
- British case register study²
 - N=96 cases of neutropenia
 - 20% clozapine-induced severe neutropenia
 - 80% unrelated to clozapine
- Clinical recommendations
 - Relative contraindication
 - Risk stratification based on clinical variables
 - High risk: True clozapine-induced severe neutropenia
 - Low risk: threshold-only clozapine cessation (missed BEN)
 - Shared decision making!
 - Support patient and family³

¹Oloyede E et al. Lancet Psych. 2026 May;13(5):387-395. ²Wallman P et al. Br J Psych. 2025; Oct 8:1-7.

³Oloyede E et al. BMC Psychiatry. 2023 Jun 8;23(1):413. mghcme.org

Clozapine and agranulocytosis risk

61 769 schizophrenia (14 037 clozapine; 47 732 non-clozapine antipsychotics)
398 agranulocytosis (231 clozapine; 167 non-clozapine antipsychotics)

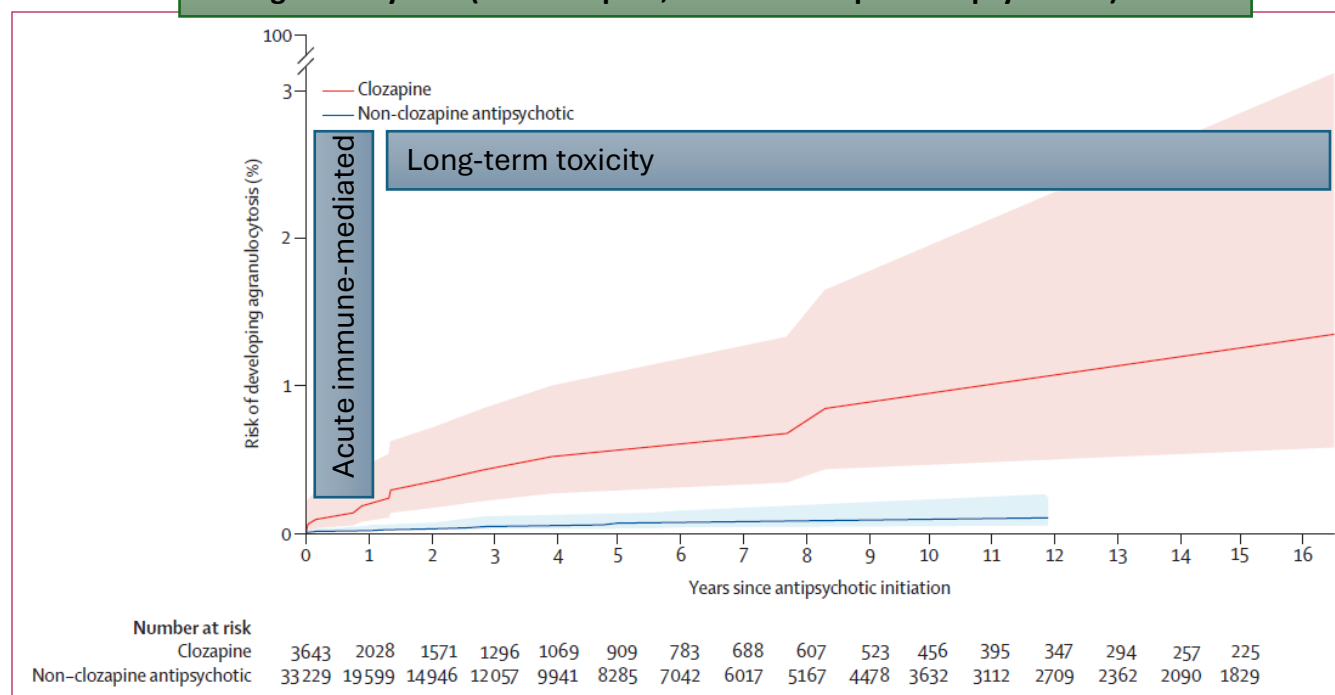


Figure 1: Cumulative risk of agranulocytosis over time on treatment
Shaded areas represent 95% CIs.

¹Rubio JM et al. Lancet Psychiatry. 2024; 11(6):443-450.

²Taipale H et al. World Psychiatry. 2020; 19(1): 61-68.

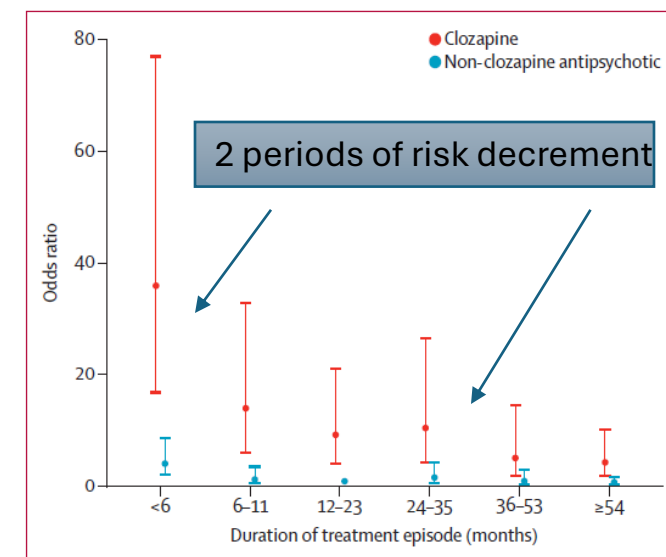


Figure 2: Odds ratio for developing agranulocytosis during various treatment durations

Cumulative agranulocytosis risk: 1.37%
Case fatality: 2.8 of 10,000 clozapine patients
All cause mortality comparisons:²
Clozapine 15.6%
Other antipsychotic 25.7%
No antipsychotic 46.2%

NOW WHAT?

Key points about REMS

- Package insert not modified
 - Monitoring schedule remains unchanged
- Only administrative change

Key points about agranulocytosis

- Clear evidence that granulocytopenia risk is greatly reduced after 6 months
 - Clinically, reduced monitoring makes pragmatic sense and may remove hurdle towards more clozapine utilization
- Competing guidelines/working groups
 - European Working Group
 - International Delphi

The Angry Moms National Clozapine Modernization Initiative: A Roadmap for Modernizing Clozapine Policy, Access, and Clinical Practice in the United States



Response to the U.S. Department of Health and Human Services RFI: Making America
Healthy Again: Chronic Disease Prevention and Treatment

1. Modernize national clozapine treatment guidelines.
2. Recognize clozapine's role in substance use recovery.
3. **Eliminate "Shadow REMS" programs.**
4. Modernize FDA prescribing information.
5. Modernize hematologic monitoring.
6. Expand access to finger-stick and point-of-care ANC testing.
7. Modernize the clozapine workforce and clinical education.
8. Prevent avoidable treatment interruptions.
9. Expand FDA indications.
10. Modernize available tablet strengths.
11. Improve access to GLP-1 therapy.
12. Develop a National Clozapine Action Plan.
13. Launch a National Clozapine Public Awareness Campaign.
14. Establish a National Pediatric Clozapine Initiative.
15. Validate pediatric finger-stick ANC testing.
16. Fund biomarker research for precision clozapine care.
17. Protect continuity through an emergency clozapine supply.
18. Protect the right to access clozapine.
19. Establish a National Clozapine Report Card.
20. Create a National Network of Clozapine Centers of Excellence.

Guideline Comparison ANC



Verdoux H et al. Eur Psychiatry. 2025;68(1):e17.

Siskind D et al. Lancet Psychiatry. 2026;13(1):77-86.

MGH PCRP Clozapine Guideline

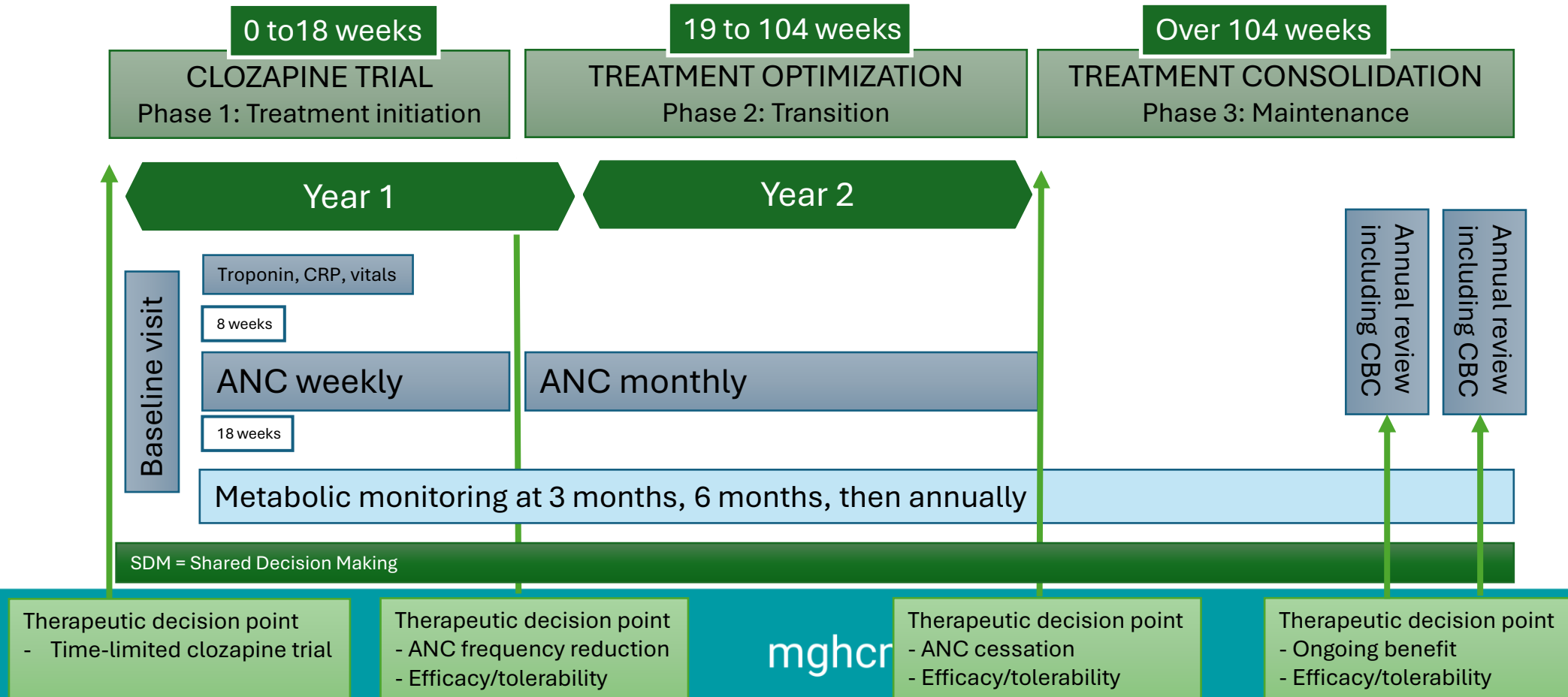
PRINCIPLES

- Evidence-based recommendations
- As simple as possible, as any complexity introduces room for error
- Flexibility with regards to limited resource settings
- Three clozapine treatment phases
- Shared decision making



Form follows function

TREATMENT PHASES



Medico-legal medical record documentation

3 Key Decision Points

- Clinical decision support for treatment initiation
- Script for ANC monitoring intensity reduction after 18 months
- Script for ANC monitoring cessation and move to maintenance phase

MGH Clozapine Guideline [DRAFT]

"I discussed with the patient and caregivers the risks, benefits and alternatives of changing clozapine ANC monitoring from weekly to monthly starting at week 18. Risks included the rare possibility of missing severe neutropenia and potential associated mortality; benefits included fewer blood draws, more convenience, and ease with continued clozapine adherence. Alternatives include making no change in the monitoring schedule. Although monthly monitoring after 18 weeks differs from the current FDA label, it aligns with the 2025 International Delphi guideline, which notes that most neutropenia cases occur within the initial 18 weeks, after which the risk becomes similar to other antipsychotics. The patient and caregivers understood, had all their questions answered, and chose to proceed with monthly monitoring. They agreed to immediately contact us for urgent evaluation if signs of neutropenia (fever, sore throat, flu-like symptoms) occur. We will resume more frequent monitoring if clinically indicated or ANC falls below FDA thresholds."

Clozapine and blood cancer risk

- Pharmacovigilance study¹
 - Increased risk for malignant lymphoma and leukemia
 - Earlier onset
- Prospective case-control study in Finland^{2,3}
 - Mean 12-year follow-up
 - 375 cases of hematological malignancies
 - 37 deaths
 - 3 deaths from agranulocytosis
 - 2.7-fold increased risk of hematological malignancies
 - Dose-dependent
 - Mostly lymphomas
 - No relationship to other cancers
- Surveillance bias
- Very small absolute risk
 - NNH > 5000
- Generalizability to other populations

MOST IMPORTANTLY
Clozapine lowers mortality

Perhaps annual full blood count beyond two years?

¹Chrétien B et al. Psychol Med. 2021;51(9):1459-1466. ²Tiihonen J et al. Lancet Psychiatry. 2022;9(5):353-362. ³Siskind D et al. Lancet Psychiatry. 2022;9(5):338-339. [Editorial]

Clozapine-associated myocarditis (CAM)

Myocarditis risk 5.3%³

- Clinical features
 - Non-specific! Need high index of suspicion
- Highest risk period is four weeks¹
- Management
 - Increased case detection with monitoring²
 - Consensus monitoring³
 - Weekly troponin is key for detection⁴
 - Other inflammatory markers are insensitive and non-specific
 - Minimum 4 weeks, better 8 weeks (30% of experts)
 - Consultation with cardiology
- Rechallenge discouraged in clear cases^{5,6}
 - Slow titration may be protective
 - Avoiding valproate may be protective

Pre-exposure minimum: hs-troponin, CRP, FBC, vital parameters, ECG

Pre-exposure enhanced: + TTE, +NT-proBNP^f

Starting dose of clozapine: 12.5mg/day

Monitoring in weeks 1–4 (minimal and enhanced requirements):

Parameter	Minimum	Enhanced
CRP	Weekly	Weekly
FBC ^g	Weekly	Weekly
hs troponin	Weekly	Weekly
NT-proBNP ^f	–	Weekly
ECG	Every 2 weeks	Weekly
Heart rate	Twice weekly	Daily
Oxygen saturation	Weekly	Twice weekly
Postural blood pressure	Weekly	Twice weekly
Temperature	Twice weekly	Daily

Dose range at day 7: 50 mg

Dose range at day 14: 100–25 mg

¹Ronaldson KJ et al. Aust N Z J Psychiatry. 2011;45:458-465. ²Neufeld NH and Remington G. Schizophr Res. 2019;206:462-463.

³Wagner E et al. Br J Psychiatry. 2026;228(4):348-356. ⁴Sandarsh S et al. Acta Psychiatr Scand. 2021;144(2):194-200.

⁵Noël MC. J Clin Psychopharmacol. 2019;39(4):380-385. ⁶McMahon L et al. CNS Spectr. 2024;29(6):585-592.

Seizures

- Clozapine had highest seizure rate in drug safety program¹
 - 0.18% versus others (0.03% – 0.05%)
- Dose-related seizure risk²
 - High cumulative seizure risk: 10% over 3.8 years (!)
- Most are tonic-clonic
- Prevention
 - Titration!
 - Therapeutic drug monitoring!
 - Pay attention to clinical comorbidities that increase seizure risk
 - Note red flag: myoclonus
- Treatment
 - Depakote is good choice
 - Carbamazepine is poor choice

¹Druschky K et al. World J Biol Psychiatry. 2018;1-29. ²Devinsky O et al. Neurology 1991;41:369.

Clinical review: Varma S et al. Ther Adv Psychopharmacol. 2011;1(2):47-66.

Orthostatic hypotension

- Clozapine needs to be titrated
 - New patient
 - Establish sensitivity with 12.5 mg
 - No one titration scheme set in stone
 - Inpatient: increase 25 to 50 mg/d until you reach target dose of 300 to 450 mg per day (divided doses)
 - Take into account the patient when choosing a titration schedule
 - Consider TDM after reaching 100 mg/d
 - Established patient (!) after two missed doses
 - Start with 12.5 mg bid, then adjust more quickly
- Persistent tachycardia in 44%¹

Review need for benzodiazepines
[They can be necessary and safe]

Clozapine and sialorrhea

- Common and vexing problem
- Not just a cosmetic problem
 - Stigmatizing
 - Aspiration pneumonia^{1,2}
 - Parotid swelling and parotitis
- Pathophysiology
 - Seemingly paradoxical
 - Not just hypersalivation but peristalsis (swallowing problem) too
 - Muscarinic receptors but also alpha-adrenergic receptors
 - Circadian aspect
- Management
 - TDM may play some role
 - Pharmacology
 - Topical approaches better³
 - If glycopyrrolate necessary, use sufficient dose (2 mg target dose)⁴

Clozapine-induced sialorrhea = CIS

Wet pillow sign

NB Pneumonia risk⁵

The Thomas-Stonell and Greenberg
Drooling Severity and Frequency Scale (DSFS)

Sublingual atropine 2 drops three times daily
Sublingual ipratropium spray; start with two SL sprays at night

¹De Leon H et al. World Psychiatry. 2020;19(1):120-1. ²Luykx JJ et al. JAMA Psychiatry. 2024; 81(10):967-975.

³Van der Poorten T and de Hert M. Clin Case Rep. 2019;7(11):2108-2113. Freudenreich et al. J Clin Psychopharmacol. 2004;24(1):98-100.

⁴Man WH et al. J Clin Psychopharmacol. 2017;37(2):155-161. ⁵de Leon J et al. J Clin Psychopharmacol. 2025;45(3):197-218.

Clozapine-associated constipation

CIGH = Clozapine-induced gastric hypomotility

- FDA strengthened warning
- Constipation can progress to serious bowel problems (bowel obstruction)
 - Risk is underappreciated! [Partanen JJ et al. Am J Psychiatry. 2024;181(10):879-892.]
- Risk increases with higher doses and with concomitant anticholinergics
- Clinician guidance
 - Evaluate bowel habits prior to clozapine
 - Monitor bowel function throughout treatment
 - Asking about constipation not sensitive!²
 - Educate patients about constipation prevention
 - Exercise
 - No bulking agents (Metamucil) or fiber supplements!
 - Consider prophylactic bowel treatment
 - “Porirua protocol” reduced colonic transit time by 48 hours³
 - Step-up with linaclotide or lubiprostone

**1 mg benztropine
=
50 to 100 mg clozapine¹**

Table

Bowel regimen for chronic constipation

Stool softener (daily)
Docusate sodium 100 mg twice daily
Stimulant laxative (weekly and as needed)
Bisacodyl, 5 to 15 mg/d, as needed
Senna glycoside, 15 mg/d, as needed

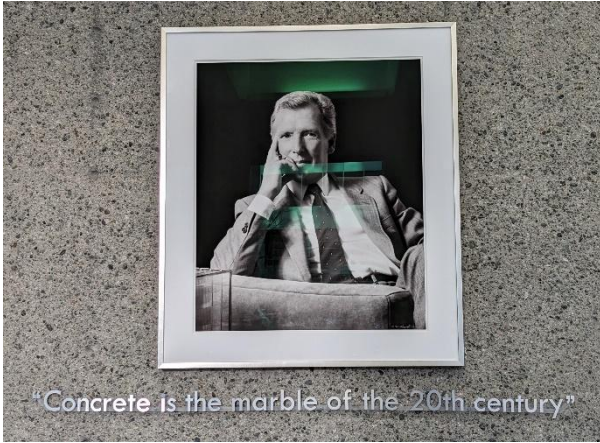
Cruz A and Freudenreich O. Curr Psychiatry. 2018;17(8):44

Clozapine = slow gut⁴

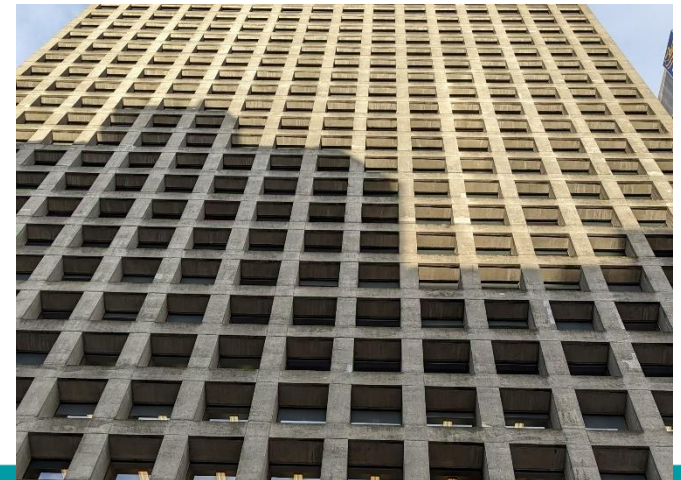
<https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can>

¹de Leon J. Am J Psychiatry. 2005;162(3):627. ²Every-Palmer S. Schizophr Res. 2021 Apr;230:114. ³Every-Palmer S et al. CNS Drugs. 2017 Jan;31(1):75-85.

⁴Every-Palmer S et al. CNS Drugs. 2019 Jan;33(1):81-91.



The optimal clozapine trial



3 questions about a clozapine trial

1. Who should receive clozapine?
2. When should clozapine be offered?
3. What constitutes a good clozapine trial?
 - Duration
 - Clozapine dose

APA Schizophrenia Guideline, 3rd ed

- Assessment and treatment plan
- Psychopharmacology
 - **Clozapine for TRS, suicidality, or aggression**
 - LAIs as a good choice if preferred or if adherence poor or uncertain
 - VMAT-2 inhibitors as treatment of choice for TD
- Psychosocial interventions
 - Coordinated specialty care for first-episode patients

Clozapine indications

FDA indications

1. Treatment-refractory schizophrenia¹
2. Suicidality in schizophrenia²

Other clinical uses

1. Aggression in setting of psychosis³
2. Sensitivity to EPS and tardive dyskinesia
3. Catatonic subtype of schizophrenia
4. Refractory bipolar disorder
5. Cannabis in setting of schizophrenia⁴
6. ?Psychogenic polydipsia

¹Kane J et al. Arch Gen Psychiatry 1988;45:789. ²Meltzer HY et al. Arch Gen Psychiatry 2003;60:82.

³Citrome L et al. Psychiatr Serv 2001;52:1510. ⁴Denissoff A et al. Schiz Bull 2024; 50(6):1287-1294.

Suicide prevention

- High risk of suicide in schizophrenia
 - Risk elevated in early course
 - Risk remains increased throughout life
- High risk for untreated patients
- Pharmacological interventions
 - Long-acting injectable antipsychotics¹
 - Clozapine
 - FDA-approved indication for clozapine²
 - Autopsy study Maryland³
 - 53,144 deaths from 2003 2021 while taking clozapine or olanzapine
 - Suicide risk on clozapine versus olanzapine OR = 0.47;95% CI, 0.26-0.84;p=.011

Psychiatric treatment
as prevention

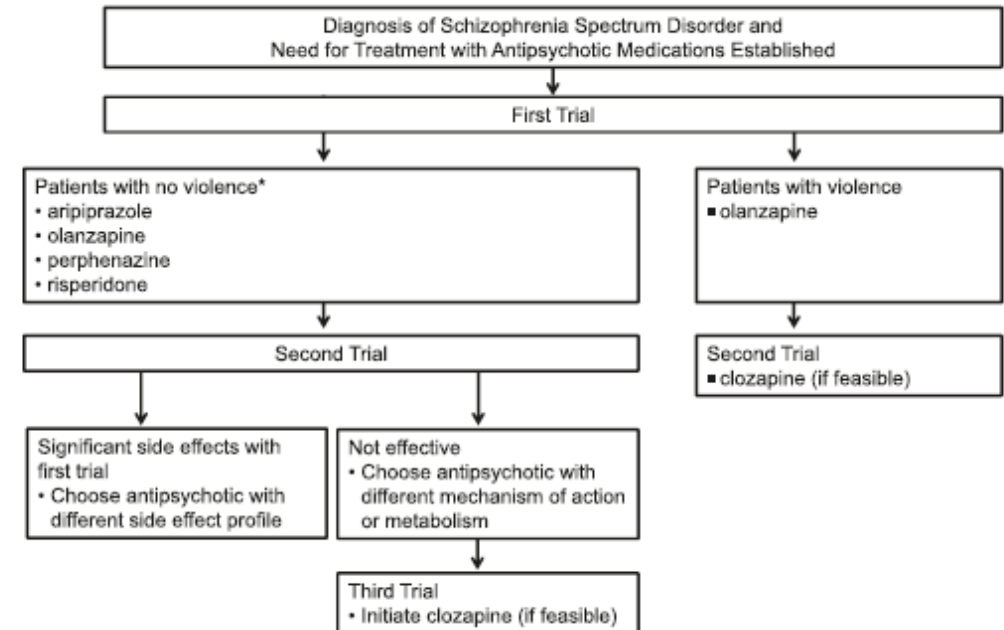
¹Taipale H et al. Schizophr Res. 2018; 197:274-280. ²Meltzer HY et al. Arch Gen Psychiatry. 2003;60(1):82-91. [InterSePT]

³Lee BJ et al. J Clin Psychiatry. 2023;84(3);16-20.

Aggression prevention

- Dangerous triad of psychosis, young male, sociopathy
- RTC
 - Clozapine > olanzapine > haloperidol
 - Conduct disorder

Consider clozapine for prevention of violence in patients with psychosis, particularly if conduct disorder is present



Markota M et al. *Schizophrenia (Heidelb)*. 2024;10(1):74.

Who should not receive clozapine?

- Unable to reliably obtain mandated blood work
- Unable to establish sufficient adherence
- Severe heart disease*
- History of clozapine-associated agranulocytosis**
- History of clozapine-associated myocarditis**

Successful rechallenge rates

- 128/203 after neutropenia
 - 63.0%, CI, 56.0%-69.6%
- 3/17 after agranulocytosis
 - 17.7%, CI, 4.7%-44.2%
- 11/17 after myocarditis
 - 64.7%, CI, 38.6%-84.7%
- 7/7 after neuroleptic malignant syndrome
 - 100%, CI, 56.1%-100%

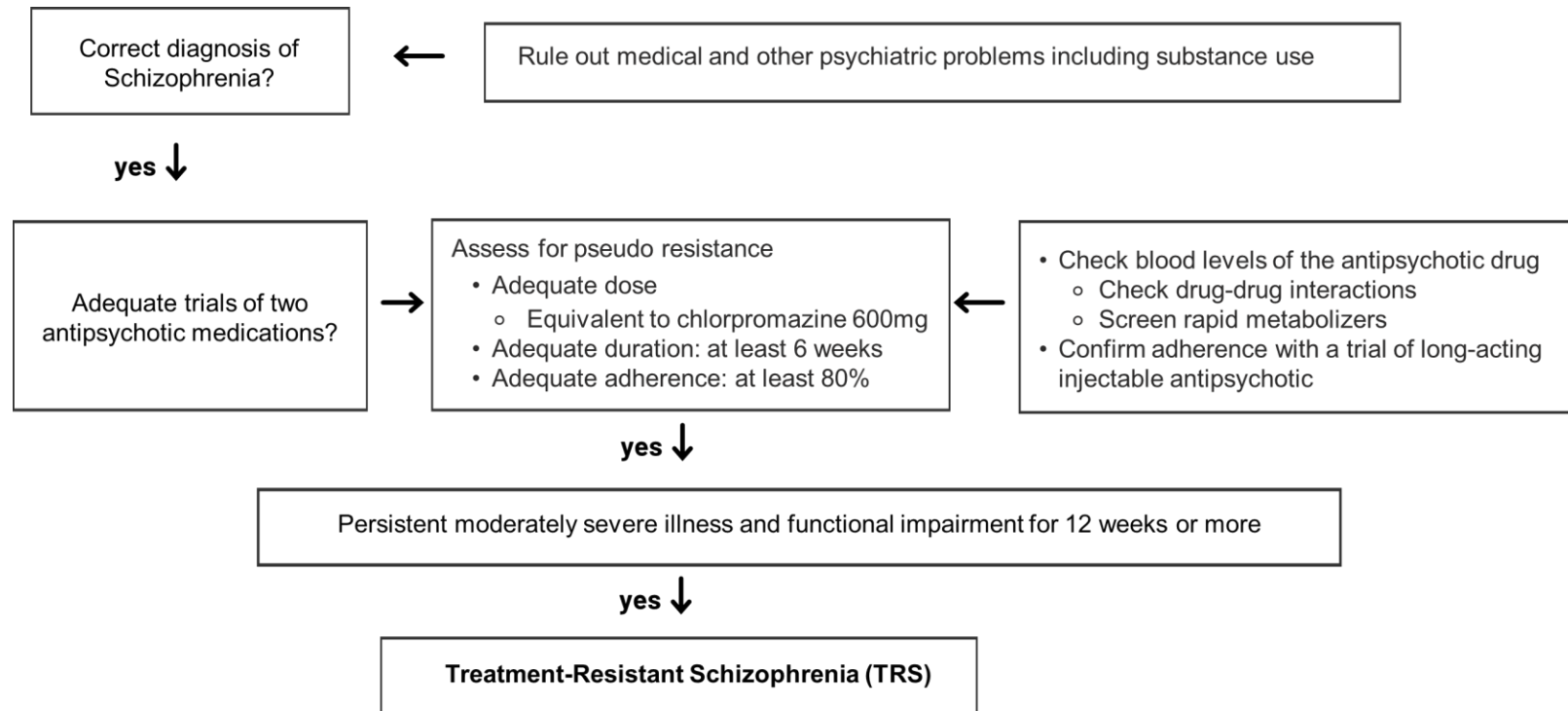
*If patient unable to tolerate tachycardia or orthostatic hypotension

**Rechallenge may be considered with monitoring if psychosis severe and particularly if diagnosis is unclear

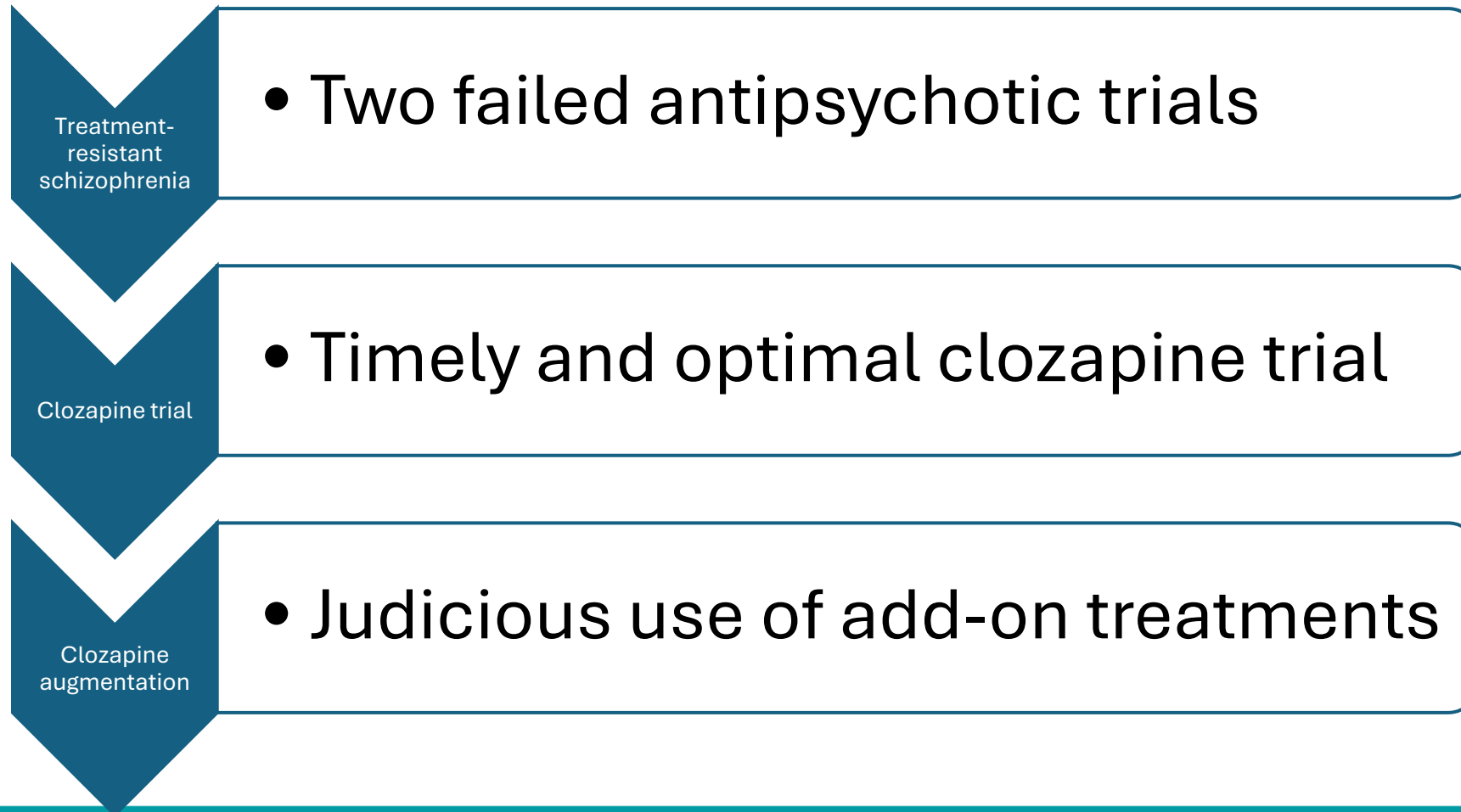
Treatment-resistant schizophrenia (TRS)

- Consensus guidelines on diagnosis and terminology developed by TRRIP Working Group
 - Clinical sub-specifiers for positive, negative, cognitive symptom domains
 - Time-course (i.e., early, medium, late onset)
 - Ultra-treatment resistant (i.e., clozapine)
- Minimum requirements for TRS:
 - Current symptoms
 - Symptom threshold at least moderate severity (rating scale!)
 - Symptom duration at least 12 weeks
 - Functional impairment at least moderate (rating scale!)
 - Adequate treatment
 - At least two trials of at least 6 weeks of at least 600 CPZ-EQ
 - At least 80% adherence

Diagnosis of TRS



Stepped care for TRS



Clozapine baseline visit

- Physical exam
 - Vital signs
 - ECG if possible
 - Weight
- Baseline measures for clozapine eligibility
 - ANC at least 1,500/microL
 - BEN: ANC at 1,000/microL
- Set up clozapine monitoring schedule
 - ANC
 - Myocarditis
 - Metabolic abnormalities

Clozapine titration

- Starting Dose: 12.5 mg once daily or twice daily.
- Use cautious titration and divided dosage schedule.
- Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated.
- Target dose (Caucasian): 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks.
- Subsequent increases: increase in increments of 100 mg or less, once or twice weekly.
- Maximum daily dose: 900 mg

The titration scheduled is determined by the patient!

Age/frailty
Ethnicity
Medical comorbidities
Living circumstances

de Leon J et al. *Pharmacopsychiatry*. 2022;55(2):73-86.

de Leon J et al. *J Clin Psychopharmacol*. 2025;45(3):179-196.

Clozapine and TDM

- Therapeutic drug monitoring (TDM)
 - Possible: one metabolite only, with 10% activity
 - Underutilized and misunderstood
 - Large inter-individual variability
- Efficacy
 - Therapeutic range¹
 - Low range 50 to 150 mg TDD
 - Medium 200 to 300 mg TDD
 - High 350 to 450 mg TDD
 - No established upper limit for efficacy; target 450 if resistance
- Safety
 - ECG slowing at higher range²
 - Dose-related (i.e., level-related) seizure risk

***1 in 3 TRS
patients
have
subtherapeutic
drug levels.**

**Clozapine only
(not active moiety)**

¹VanderZwaag C et al. Am J Psychiatry 1996;153:1579. ²Freudenreich O et al. Biol Psychiatry. 1997;15;42:132. Freudenreich O. Current Psychiatry. 2009 March;8(3):78. [Pearls]
Schoretsanitis G et al. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. [Consensus statement] *McCutcheon R et al. Acta Psychiatr Scand. 2018;137(1): 39–46.

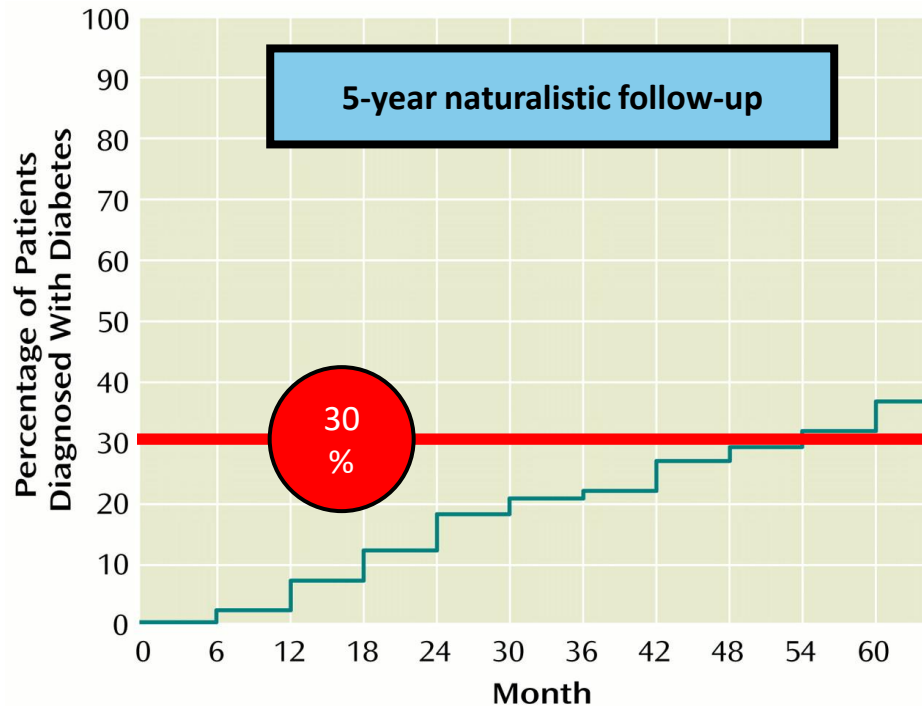
What is an adequate clozapine trial?

- Adequate adherence
 - May need to work with patient and hope for virtuous cycle
- Adequate dose or rather blood level
 - TDM is critical for clozapine use
- Adequate duration
 - Symptomatic benefit should become apparent after a few weeks on a therapeutic dose
 - Functional benefits will accrue only over time

I try to get a 3 to 6 months commitment from patients.

Maintenance treatment with clozapine

ELMHC clozapine cohort



Henderson DC et al. Am J Psychiatry. 2000;157(6):975-981.



Greatly decreased life expectancy

Natural causes: 85%

Unnatural causes: 15%

Two main medical causes:

#1 Cardiovascular disease

#2 Cancer

Medical monitoring

- ANC monitoring
- Troponin and CRP for the first 4 to 8 week
- Weight at every visit for the first 6 months, then at least quarterly
- Fasting glucose, HbA1c, and lipid panel 4 months after treatment initiation, then at least annually
 - Global Delphi Guideline: weight/waist Q 3 mos, HbA1c/HDL Q6-12 mos
- Establish if patients meets criteria for metabolic syndrome 4 months after treatment initiation, then at lease annually
- Need to adopt population-based management (spread-sheet)

Stage-specific care

Stage 1 (Clinical high-risk)

- High index of suspicion (functional decline, withdrawal, distress)
- Offer needs-based psychosocial care
- Treat identifiable comorbidities; avoid antipsychotics

Stage 2 (first-episode psychosis)

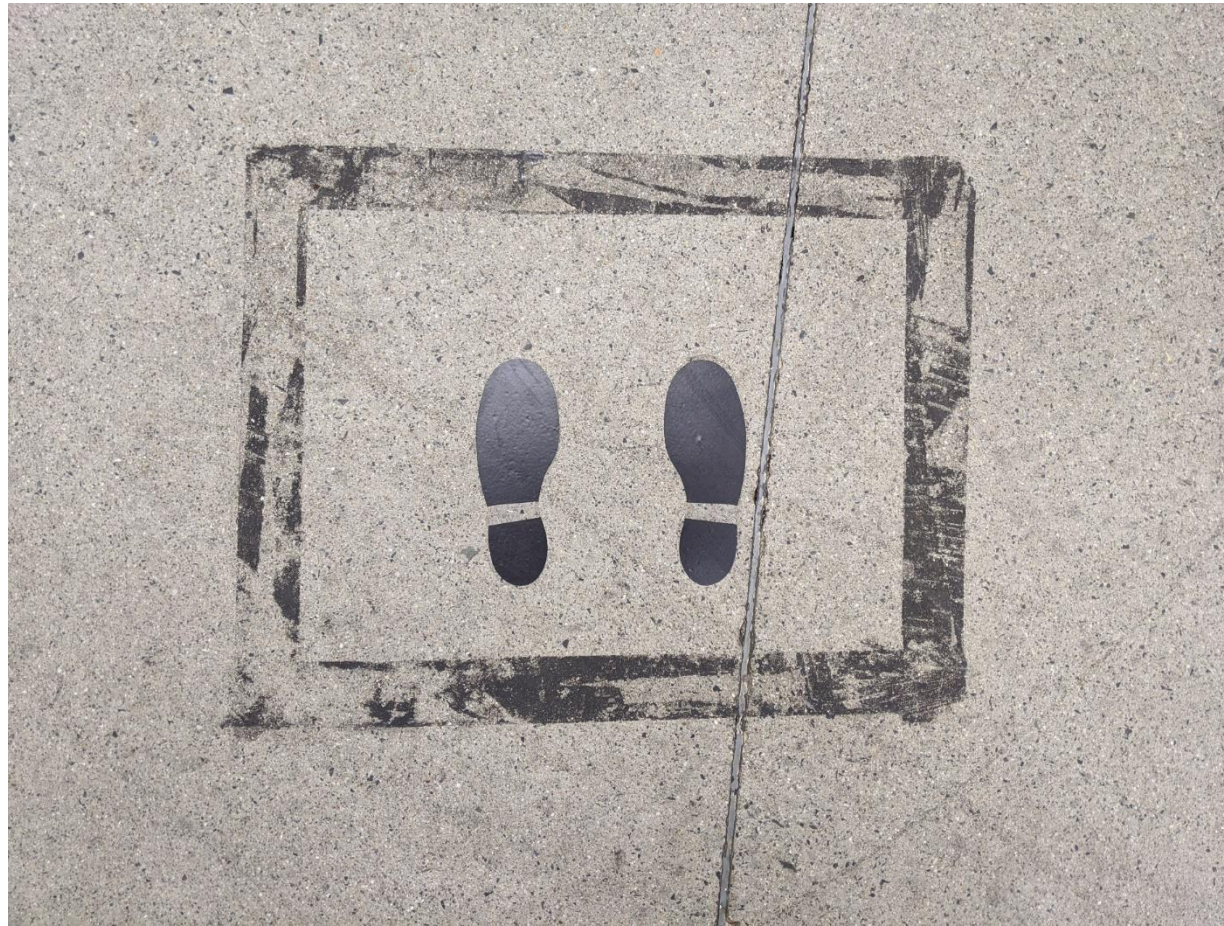
- Reduce duration of untreated psychosis
- Use low doses of antipsychotics to minimize side effects
- Offer coordinated specialty care
- Offer LAIs and clozapine if no symptomatic remission in 3-6 months

Stage 3 and 4

- Retain optimistic stance
- Focus on quality of life and vocational rehabilitation
- Pay attention to physical health

TRS as failed term
Difficult-to-treat schizophrenia
Palliative psychiatry

Intermission



Clinical vignettes with Q&A

3 clinical scenarios

1. When should you offer clozapine to patient with schizophrenia?
2. What do you do if somebody continues to gain weight during treatment?
3. What do you do if somebody does not get better with clozapine alone?

Timing of a clozapine trial

CASE: Helmut is a 55-year-old immigrant from Germany. He has been treated with haloperidol decanoate since his early 20s but does not remember details. He seems to have a forensic history (assault while psychotic). On MSE, he experiences positive symptoms, and he appears withdrawn. His AIMS score is 7. He does not work and lives in a group home. He is adherent to his monthly injections.

Should you consider clozapine for this patient?

- A. No. He has been ill for too long to benefit from clozapine.
- B. No. The risk of clozapine complications increases with age.
- C. Yes. He is a good clozapine candidate.
- D. Maybe. Only if his family pushes for a clozapine trial, you should consider it.

Patients to prioritize for clozapine

- Patients with chronic schizophrenia and poor illness course and function
- First-episode patients with treatment-resistance
- Patients with a forensic history due to psychosis and aggression
- Patients with a schizophrenia spectrum disorder and suicidality
- Patients with catatonic symptoms or EPS sensitivity

Clozapine for first-episode schizophrenia

- **PROS**
 - Avoids delay in refractory patients
 - High-dose strategy for risperidone or olanzapine of limited value in refractory patients¹
 - Better tolerability in selected patients
 - Reduced risk for TD
 - Reduced mortality over time²
 - Excellent for relapse prevention^{3,4}
- **CONS**
 - Generally good response to first-line antipsychotics in first-episode patients (“fail-first” strategy)⁵
 - No disease-modifying properties
 - High propensity for metabolic problems
 - Agranulocytosis risk; myocarditis risk

¹Agid O et al. Eur Neuropsychopharmacol. 2013 Sep;23(9):1017-22. ²Taipale H et al. World Psychiatry. 2020;19(1):61-68.

³Efthimiou O et al. Lancet Psychiatry. 2024 Feb;11(2):102-111. ⁴Taipale H et al. Lancet Psychiatry. 2025;12(2):122-130.

⁵Freudenreich O and McEvoy JP. Clin Schizophr Relat Psychoses 2012;6:115.

Clozapine as first-line treatment

- Chlorpromazine trial¹
 - N=160
 - 52 weeks
 - Remission: CPZ 79%, CLZ 81%
 - Earlier remission with CLZ
- 9-year follow-up²
 - Comparable amounts in remission (78%), intermediate (8%), or relapsed states (14%)
 - Tardive dyskinesia: 2/8 (25%) CPZ; 1/21 (4.8%) CLZ ($p=0.02$).
 - More patients randomized to CLZ remained on it (26%) compared to CPZ (10%) ($p=0.01$)

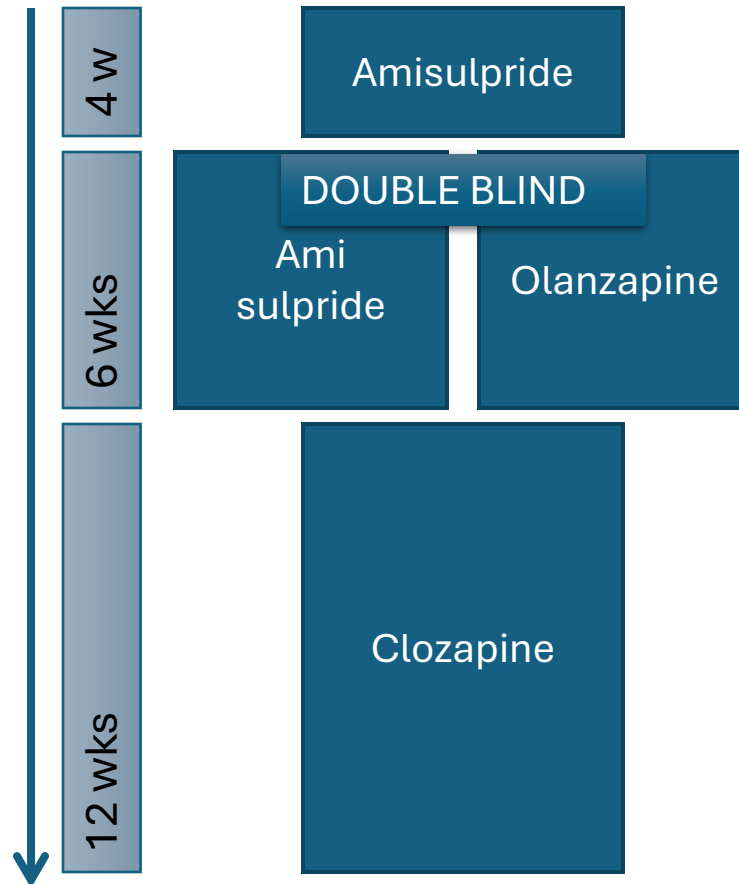
¹Lieberman JA et al. Neuropsychopharmacology 2003;28(5):995-1003.

²Girgis RR et al. Br J Psychiatry 2011;199(4):281-288.



Stepped care: early use of clozapine

OPTiMiSE = Optimization of Treatment and Management of Schizophrenia in Europe



- Good overall *remission* rate after 10 weeks of treatment
 - 2/3 of patients
- 56% responded in four weeks to amisulpride
- No added benefit from switching to olanzapine
- Some benefit from switching to clozapine (25%) but not as good as responders

Essentially confirmed in SMART-CAT*

Clozapine as 2nd line antipsychotic

Duration of untreated psychosis

- Avoids delays in TRS!
 - Longer DUP associated with worse response
 - Psychosis associated with suicide risk (mortality reduction)

Relapse prevention

- Excellent for relapse prevention¹
 - Relapse associated with worse response
- Good choice after in first-episode patients already²

Should we introduce clozapine after one failed treatment?

Clozapine and weight gain

CASE: You successfully transitioned Helmut to clozapine. He feels tired from clozapine, and he drools but “looks better” and feels better. Religiously, you monitor his weight at each visit which keeps increasing.

Which add-on option do you consider next?

- A. Metformin
- B. Aripiprazole
- C. Topiramate
- D. Bupropion plus naltrexone

The need to focus on mortality



The day the music died

Metabolic prevention

- A. [Choose wisely, if you can – prevent]
- B. Screen and monitor – detect
 - Very frequent monitoring early¹
 - Quarterly weight/waist; HbA1c every 6 to 12 months
- C. Prevent/blunt weight gain – mitigate/treat
 - Add behavioral management
 - [Switch antipsychotics]
 - Add prophylactic metformin
 - Add weight loss medications
 - Topiramate²
 - Next frontier: GLP-1 agonists

Proactive (preventive)
prescribing
for weight loss

Irish metformin guideline

Adult mental health



ORIGINAL RESEARCH

Metformin in the management of antipsychotic-induced weight gain in adults with psychosis: development of the first evidence-based guideline using GRADE methodology

Ita Fitzgerald ^{1,2} Jean O'Connell,^{3,4} Dolores Keating,⁵ Caroline Hynes,⁶ Stephen McWilliams,^{7,8} Erin K Crowley⁹

- Consider as early intervention for AIWG
 - If significant weight gain after one month
 - Use for any antipsychotic
- Target dose 2000 mg/day
- Starting dose 500 mg twice daily with food
- Monitor renal function
- Monitor B12



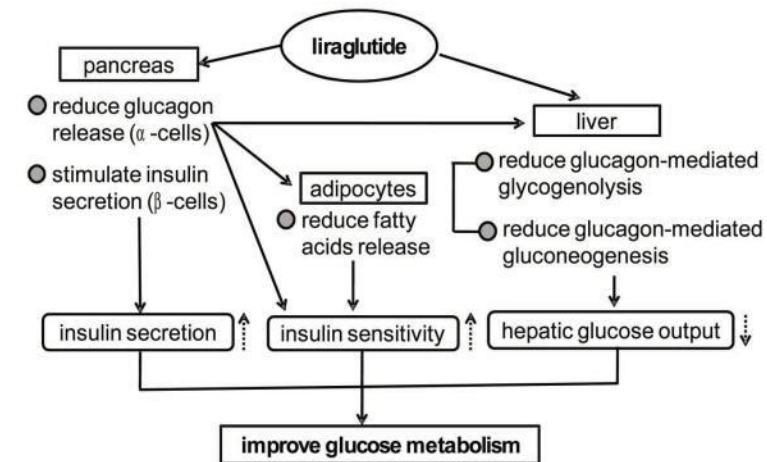
GLP-1 = glucagon-like peptide-1
GIP = glucose-dependent insulintropic polypeptide

Incretin mimetics

Weight loss + improved glucose control

- Antipsychotics increase glucagon¹
- Newer class (2010) of glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist)
 - Incretin hormone effect
 - Tirzepatide also agonizes a second hormone, GIP
 - Triagonists: GLP-1 + GIP + glucagon receptor
 - Low risk of hypoglycemia
 - Adding **bimagrumab** to prevent muscle loss²
- Medications
 - “Hot” new medication class for weight loss
 - Semaglutide³
 - 16% weight loss in 68-week trial with weekly injection
 - Liraglutide⁴
 - First GLP-1 agonist studied in schizophrenia
 - Loss of metabolic benefit once stopped⁵

Stimulate insulin release in response to meal
Decrease glucagon secretion
Decrease hepatic gluconeogenesis
Delay gastric emptying
Promote central satiety/reduce appetite



Yanai H et al. J Med Cases. 2011;2(2):76-80.

¹Aslanoglou D et al. Translational Psychiatry. 2021;11(1):59. ²Heymsfield SB et al. JAMA Netw Open. 2021;4(1):e2033457.

³Wadden TA et al. JAMA. 2021;325(14):1403-1413. [STEP-3 trial. NCT03611582] ⁴Larsen FR et al. JAMA Psychiatry. 2017;74(7):719-728.

⁵Svensson CK et al. Acta Psychiatr Scand. 2019;1139(1):26-36. [One-year follow-up] Jakubowska A et al. Endocrinol Metab. 2024;39:12-22.

Semaglutide for clozapine patients

COaST = Clozapine Obesity and Semaglutide Treatment trial

1. Methods

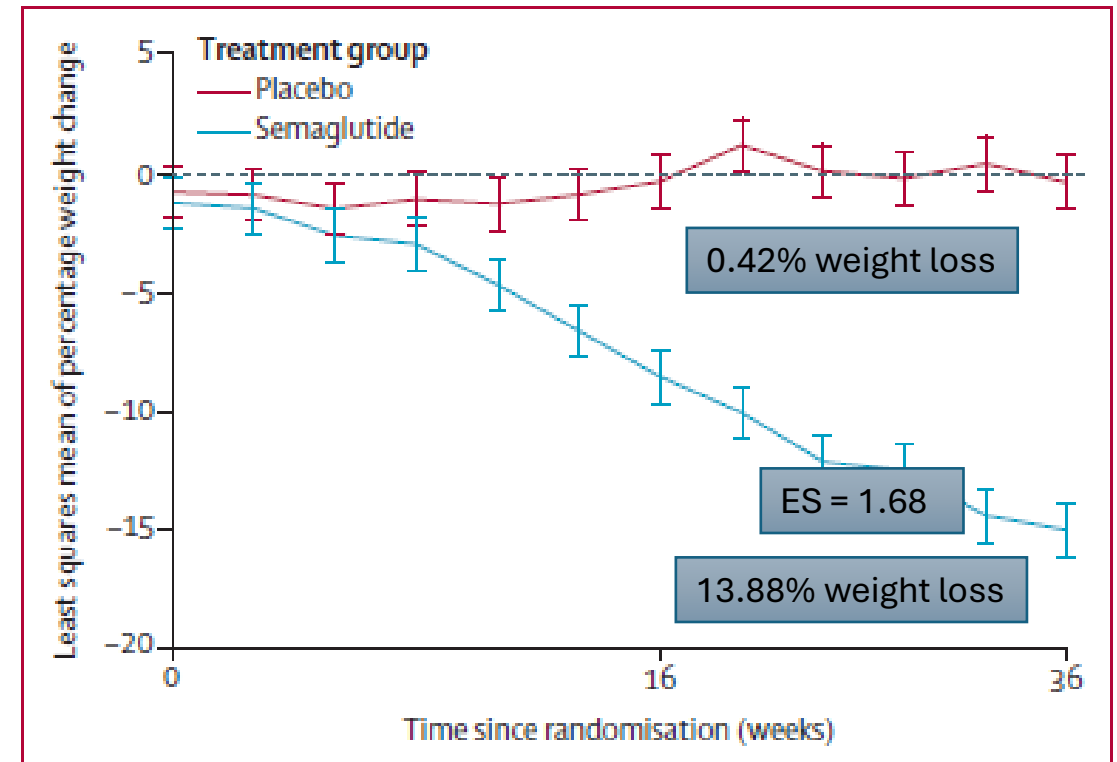
- Schizophrenia patients on clozapine from Queensland, Australia
- Obese and stable
- 36-week phase 2 RCT with blinding
- Semaglutide 2 mg SQ every week

2. Results

- N=31 (premature end of enrollment)
- Effective
 - Primary: weight loss (15.2 kg, majority 5 to 10%)
 - Secondary: HBA1c improvement (5.4 → 5.0%)
- Safe (psychiatric and medical)
 - Stable psychopathology
 - Stable clozapine levels and low constipation rate

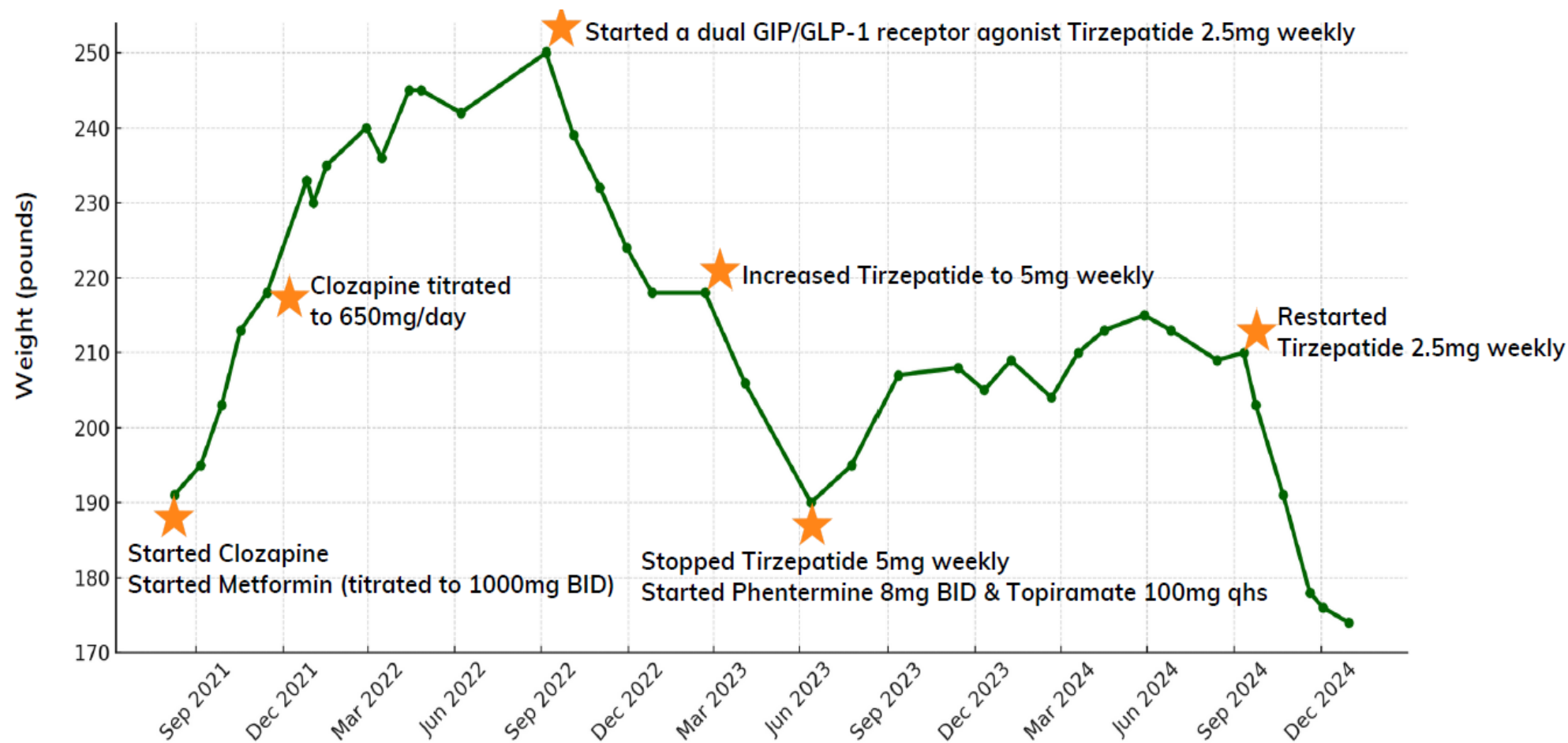
3. Significance

- First RCT of newer GLP-1 in metabolically high-risk psychiatric population
- As effective as in general population and psychiatrically safe



Percent weight change over 36 weeks

CASE: GLP-1 agonist in clozapine-treated patient



Lim C et al. MGB 13th Annual Public and Community Psychiatry Symposium 2025.

Lim C et al. Prim Care Companion CNS Disord. 2025;27(4):25cr03952.

Clozapine-resistance

CASE: After a few month of clozapine treatment, the group home contacts you and reports that Helmut continues to make psychotic statements and lacks motivation. He also seems depressed to them and self-medicates with beer, starting in the afternoon. They wonder if you can add something.

Which medication is least helpful as an augmentation agent?

- A. Risperidone
- B. Aripiprazole
- C. Sertraline
- D. Topiramate

Clozapine augmentation

- ECT has good efficacy for TRS
 - One half to two thirds of patients improve if ECT is added¹
 - Is this truly an augmentation strategy?
- Medication augmentation strategies are limited^{2,3,4}
 - Aripiprazole
 - Clozapine plus medium-dose aripiprazole (10 – 15 mg) prevents hospitalizations⁵
 - Improves metabolic profile
 - SSRI antidepressants
 - For demoralization, dysphoria, depression, negative symptoms, SI
 - Mood stabilizers
 - For aggression and suicidality
 - Topiramate⁶
 - Benefit for psychopathology and weight
- Unclear role of muscarinic agonists for TRS

Do not forget to
deprescribe if
possible.

¹Lally J et al. Schizophr Res. 2016;171(1-3):215-224. ²Correll CU et al. JAMA Psychiatry. 2017;74(7):675-84.

³Wagner E et al. Schizophr Bull. 2020;46(6):1459-1470. [Expert Consensus TRRIP Working Group] ⁴Carr R et al. Mol Psychiatry. 2026 (in print)

⁵Tiihonen J et al. World Psychiatry. 2025;24(2):250-259. ⁶Correll CU et al. J Clin Psychiatry. 2016;77(6):e746-56.

KarXT for TRS

- Rational
 - TRS as biologically heterogeneous
 - Muscarinic modulation represents a new mechanism of action
 - Broader efficacy beyond psychosis (cognition)
 - Clozapine has muscarinic properties¹
- Clinical trials
 - EMERGENT leads to FDA-approval for schizophrenia
 - ARISE phase 3 add-on trial failed²
- Case reports and case series
 - Anecdotal evidence³
 - Texas state hospital experience
 - Frequent discontinuation for lack of efficacy and poor (GI) tolerability⁴
 - Commentary: implementation mistakes⁵

¹Morrison PD et al. J Psychopharmacol. 2025;39(4):297-300. ²<https://www.psychiatrictimes.com/view/cobeniv-as-add-on-treatment-for-schizophrenia-fails-to-meet-primary-endpoint-in-phase-3-arise-trial>

³Went NS et al. Front Psychiatry. 2026;16:1679678. ⁴Vadiei N and Crismon ML. Front Psychiatry. 2026;16:1736922. ⁵Price MZ and Price RL. Front Psychiatry. 2026;17:1807080. [Commentary]

Non-pharmacological augmentation

- Substance use
 - Common, course-destabilizing
 - Alcohol use disorders
- Psychiatric comorbidities¹
 - Agoraphobic avoidance, worry, self-esteem, insomnia
 - Dimensions of psychopathology
 - Affective symptoms
 - Negative symptoms
 - Cognitive symptoms
- Medical comorbidities
 - Improving physical health through intervention²



Ancillary CBT for:

- ✓ Residual psychosis
- ✓ Negative symptoms
- ✓ Depression

Personalized approach with psychological/psychosocial interventions³

¹Freeman D et al. Schizophr Res. 2019;211:44-50. ²Ilyas A et al. Br J Psychiatry. 2017;211:194-96.

Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]

³Ramirez J and Correll UC. J Clin Psychiatry. 2026;87(2):1-4. [Life after clozapine]

TRS and clozapine – dirty little secrets

- **Clozapine efficacy is limited**

- Spectrum of response
 - Rarely restitutio ad integrum
 - Partial response (average 25% symptom reduction) is typical¹
 - Ineffective in perhaps as many as 50% of patients with TRS²
- Not effective for negative or cognitive symptoms which drive functional impairments
- Not effective if risk for (partial) non-adherence is high

- **Medical disease burden is high**

- Diabetes, hyperlipidemia, intestinal obstruction^{3,4}
- Underappreciated: pneumonia⁵ and aspiration pneumonia⁶

¹Siskind D et al. Can J Psychiatry. 2017;62:772-777. ²Porcelli S et al. Neuropsychopharmacol. 2012;22:165-182.

³Stroup TS et al. Am J Psychiatry. 2016;173:166-73. ⁴Partanen JJ et al. mghome.org 2024;181(10):879-892.

⁵Luykx JJ et al. JAMA Psychiatr. 2024 Oct 1;81(10):967-975. ⁶De Leon H et al. World Psychiatry. 2020;19(1):120-1.

Stopping clozapine

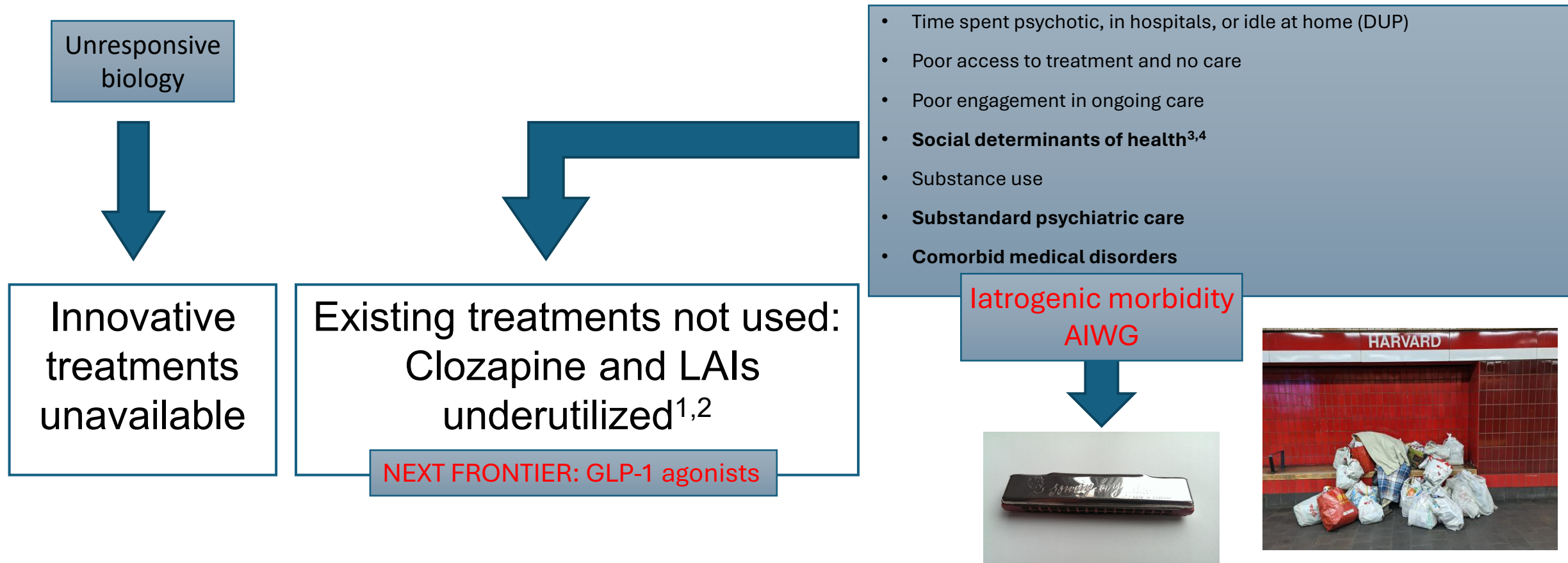
- If you can, taper over 1 to 2 weeks
 - Hyperbolic taper if elective discontinuation
- Clozapine withdrawal¹
 - Cholinergic rebound
 - Experienced by 50% of patients
 - Headache, sweating, nausea, vomiting, diarrhea
 - Rapid onset psychosis
 - Add anticholinergic or chlorpromazine
 - Catatonia following stopping clozapine
 - Add benzodiazepine, followed by ECT
 - Serotonergic discontinuation syndrome
- Monitor ANC after stopping
 - ANC according to patient's schedule if for lack of efficacy
- If you can, re-institute clozapine²
 - Second best option is olanzapine

Do not forget to support patients and their families who you took off clozapine.²

¹Blackman G et al. *Schizophr Bull.* 2026;48(1):176-189.

²Oloyede E et al. *BMC Psychiatry.* 2023;23:413.

Contributors to poor outcomes



Social (structural) interventions have greater impact on outcomes than molecular advances.⁵

¹Kelly DL et al. Psychiatr Serv. 2018;69(2):224-227. ²Torrey EF and Lieberman J. Psych Serv. 2025;76(1):90-92.

³Barry S et al. Psychiatr Serv. 2024;75(8):733-739. ⁴Wheatley MC. Premier J Public Health 2024;1:100008. ⁵Farmer PE et al. PLoS Med. 2006;3(10):e449.

POC ANC testing for clozapine

- Adoption rates at outpatient clinics
 - Freedom Trail Clinic (January 2023 to April 2025)
 - 60% (120/199) patients used at least once
 - PCRPs clinics (August 2024 to April 2025)
 - 22% (10/45) patients used at least once
- Patient survey from both clinics (n=86; April 2025)
 - Regular users (8%): High satisfaction with fingerstick
 - Infrequent users (36%): Half preferred venipuncture.
 - Never users (56%): Many unaware initially; after education, one-third still preferred venipuncture and resisted changing their care, viewing venipuncture as more comfortable, convenient, and less painful.
- Implementation barriers
 - Lack of reimbursement mechanisms
 - Clinician burden
 - Infrastructure and workflow challenges

Introducing new practices requires strategic planning around patient preferences, clinic workflow, staffing, administrative support, and sustainable reimbursement

Need for clozapine-capable clinics*

- Every patient with schizophrenia who has residual symptoms deserves to be offered a time-limited clozapine trial
- The goal is EARLY (not as treatment of last resort) and ROUTINE use of clozapine for any eligible patient
- The goal is SAFE use of clozapine
- You cannot do this alone but need a TEAM

You need to be “The man in the arena.”

Opportunity for service expansion

Opportunity for first-episode like movement for TRS

Citizenship in a Republic

It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. **The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.**



MGH Treatment-resistant schizophrenia (TRS) Service

MGH TRS ACCESS

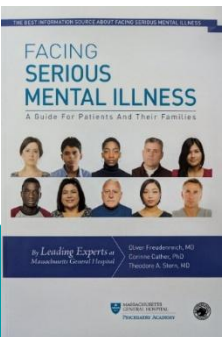
<https://mghaccess.org/>

- **Director**
 - Oliver Freudenreich, MD, FACLP
- **Mission**
 - To improve the care of patients with treatment-resistant schizophrenia
- **Goals**
 - **Innovate:** More effective and safer treatments
 - **Integrate:** Fewer silos and more partners
 - **Instruct:** Easier access to consultation
 - **Influence:** Disseminate knowledge



Lim C, Donovan AL, Freudenreich S, Cather C, MacLaurin S, Freudenreich O. Second opinions for diagnoses of psychotic disorders: delivering stage-specific recommendations. Psychiatr Serv. 2024;75(10):1035-1038.

mghaccess.org



Thank you!

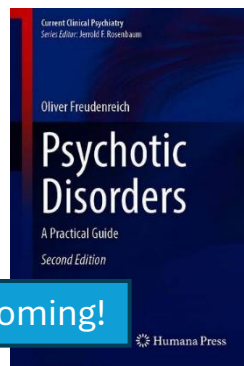
Websites

Freudenreich O and McEvoy JP. Guidelines for prescribing clozapine in schizophrenia. UpToDate

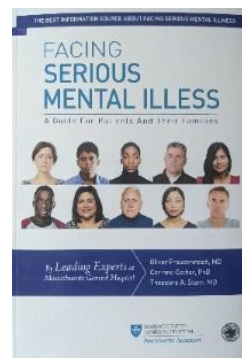
<https://www.uptodate.com/contents/guidelines-for-prescribing-clozapine-in-schizophrenia>

Article

Donovan AL et al. Clozapine monitoring: form follows function. Psych Serv. 2026;77(5):470-473



3rd edition coming!



John Umstead Hospital, Butner, NC, ca. 1995