

# **First-episode psychosis and schizophrenia**

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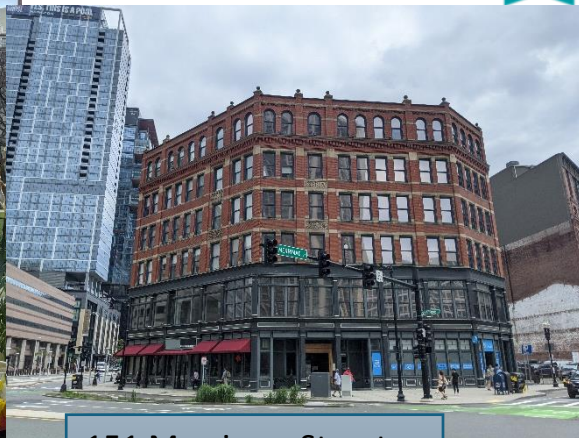
# Disclosures

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- **Psychopharmacology Institute** Speaker honorarium (medical peer education)
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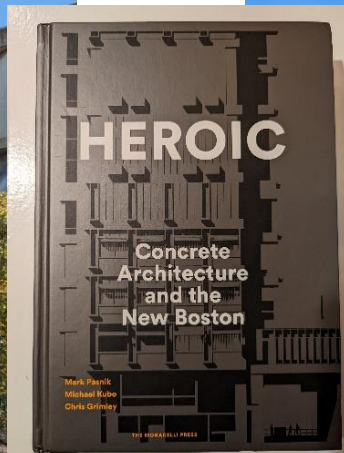
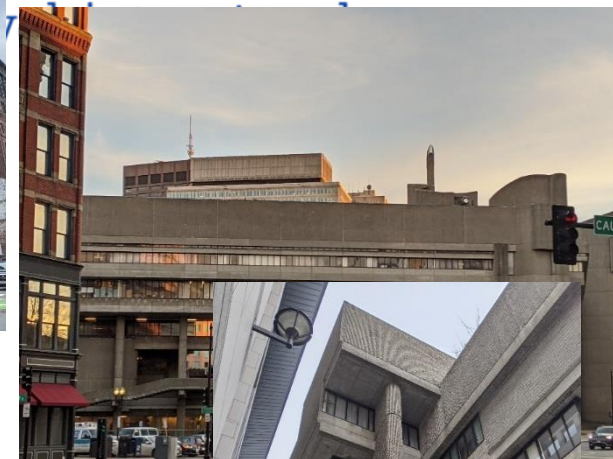
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# Outline

## A. Treatment as prevention

- Staging model of treatment

## B. Stage-based care

- Prodromal phase
- Acute psychosis
- Post-psychotic/chronic phase

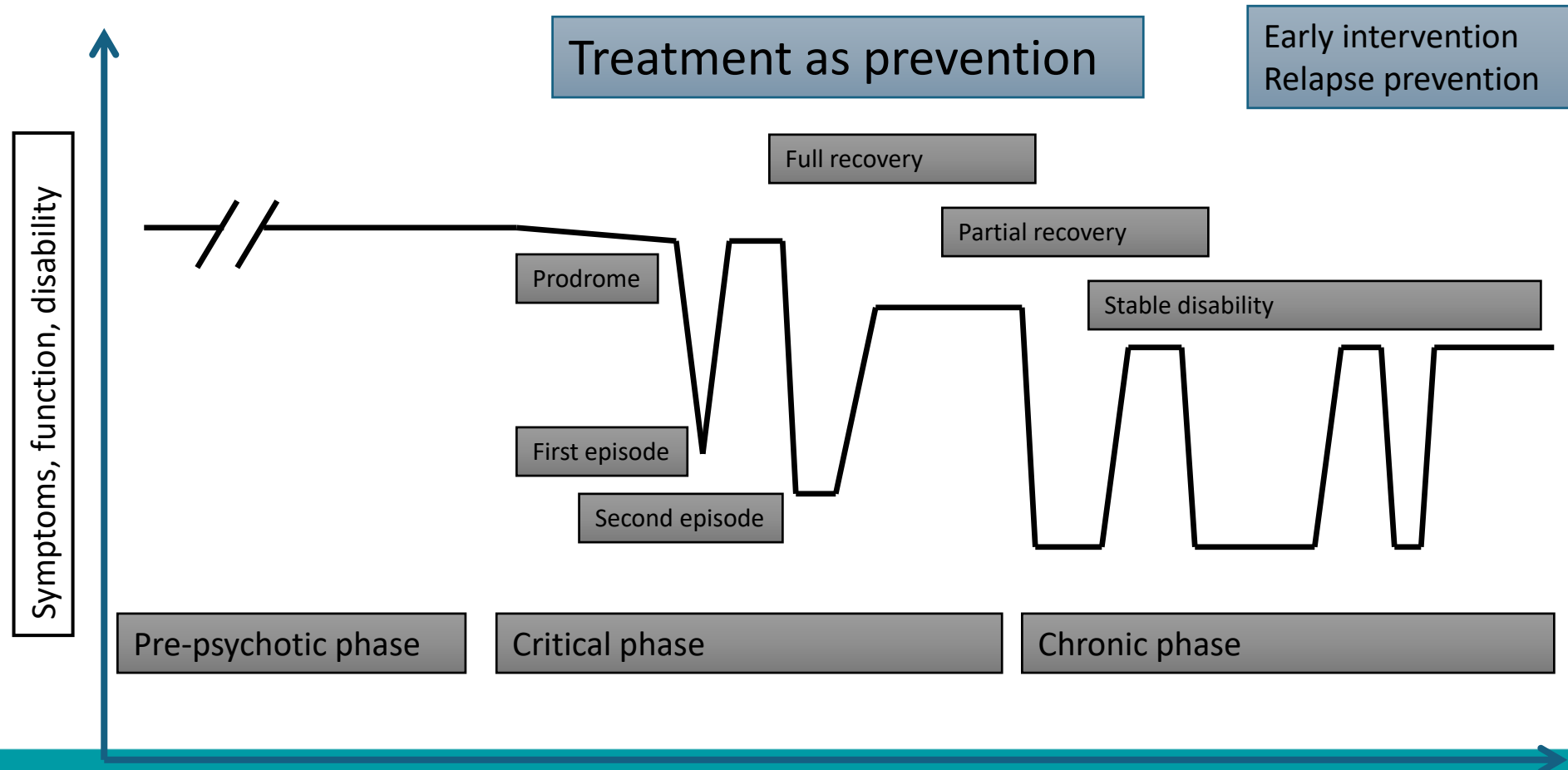
## C. Medical prevention

## D. Reflections



Photo courtesy of Oliver Freudenreich

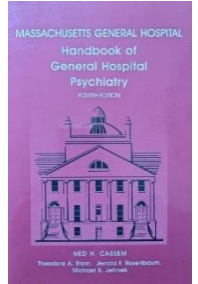
# Natural (?) course of schizophrenia



# Staging in psychiatry

- **Rational for staging**
  - Avoid progression to disease stages where only amelioration is possible
  - Better response to treatments in early stages
  - Earlier treatments are less aggressive
- **Principles**
  - Early intervention to treat patients as early as possible in the disease course
  - Stage-specific care that tailors the interventions to the patient's needs
  - Stepped care that adjusts treatment intensity based on response
- **Works best for “transdiagnostic psychiatry” in early stages**

# Two analogies from medicine



## Neurology

Multiple sclerosis is for many a relapsing-remitting illness with accrued disability over time

## HIV care

Treatment with antiretrovirals as prevention: to prevent secondary infections and to progression of HIV

Treatment as prevention

# Early intervention: reducing DUP

DUP = Duration of Untreated Psychosis

- Prolonged DUP<sup>1,2</sup>
  - Poorer response
  - Worse outcome for cognition<sup>3</sup>
- DUP can be reduced<sup>4</sup>
  - Clinical advantage at baseline, 2-year<sup>4</sup> and 5-year f/u<sup>5</sup>
  - *Sustained* information campaign is key<sup>6</sup>
  - Feasible in United States<sup>7</sup>
- Focus on outliers<sup>8</sup>
- Role of lead-time bias<sup>9,10</sup>



## Marked variability in DUP

|                |          |
|----------------|----------|
| Africa         | 70 weeks |
| Asia           | 49 weeks |
| North America* | 49 weeks |
| Europe         | 39 weeks |
| South America  | 35 weeks |
| Australasia    | 28 weeks |

Salazar de Pablo G et al. Psychol Med. 2024;54:652-662.

\*RAISE median DUP 74 weeks

## Stage-specific care: First-episode psychosis

- **Diagnosis**
  - Some guidelines include MRI in first-episode work-up (German Guideline)<sup>1,2</sup>
- **Treatment**
  - Optimal pharmacotherapy
    - Choose wisely: metabolically safe, mode of delivery (oral versus long-acting injectable)
  - Coordinated specialty care (APA Guideline)<sup>3</sup>
  - Integrated care with proactive medical monitoring
- **Prognosis**
  - Keep DUP short
  - Address comorbidities
  - Non-adherence
- ?Duration of maintenance treatment<sup>2</sup>

### RAISE = Recovery After an Initial Schizophrenia Episode

- Goal
  - Develop early-intervention system in real world fragmented US healthcare system
- NAVIGATE
  - Cluster randomization of 34 clinics in 21 states of NAVIGATE versus community care (CC)
  - Core services: family education, resilience training, supported employment/education, medications<sup>1</sup>
  - N=404
- Results
  - Team-based, multi-component NAVIGATE improved primary outcome variable (QoL) more than CC<sup>2</sup>
  - Effects were better for those with shorter DUP (median 74 weeks)<sup>3</sup>
- Benefits persist in 5-year follow-up<sup>4</sup>

Coordinate Specialty Care

**75 years NIMH  
RAISE project<sup>4</sup>**

<sup>1</sup>Keating D, et al. BMJ Open 2017;7:e013881. <sup>2</sup>Available at [www.awmf.org](http://www.awmf.org), including in English

<sup>3</sup><https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841>

<sup>4</sup><https://www.nimh.nih.gov/news/science-news/2023/raise-ing-the-standard-of-care-for-schizophrenia-the-rapid-adoption-of-coordinated-specialty-care-in-the-united-states>

# Cost of relapse in schizophrenia

- Relapse has **psychosocial toxicity**
  - Loss of job
  - Derailed education
  - Criminal problems
  - Suicide
  - Loss of reputation
  - Loss of social support
- Relapse might be biologically harmful<sup>1</sup>
  - Emergent treatment non-response in 16%
- Sustained remission is basis for accrued treatment benefits over time

**Relapse  
prevention  
(tertiary  
prevention) is  
key goal  
of schizophrenia  
care**

<sup>1</sup>Emsley R et al. J Clin Psychopharmacol. 2013;33(1):80-3.

# Stage-based care

|                             | GOALS                                                                            | KEY QUESTION                                                                             |
|-----------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <b>Prodromal Phase</b>      | Prevent psychosis<br>Prevent schizophrenia?                                      | Treat with antipsychotic?                                                                |
| <b>Acute Psychosis</b>      | Keep DUP short<br>Achieve initial response and early positive symptoms remission | Which antipsychotic?<br>Problem: early non-response (positive Sx)                        |
| <b>Post-psychotic Phase</b> | Achieve sustained remission<br>Recovery and QOL<br>Prevent morbidity             | Treat for how long?<br>Problems: early relapse and residual Sx (adherence); risk-benefit |

# Prodromal phase

# Prodromal schizophrenia

DSM-5 Attenuated Psychosis Syndrome (APS)\*

CHR = Clinical High Risk

- Prodrome can only be diagnosed in retrospect
  - Transition risk for putatively prodromal patients not 100%<sup>1</sup>
    - 18% after 6 months
    - 22% after 1 year
    - 29% after 2 years
    - 36% after 3 years
- Transition risk prediction in its infancy
  - No Framingham risk score (yet) for selective or indicated prevention
  - Low positive predictive value of positive symptoms (less than 2%)<sup>3</sup>
  - Polygenic risk score enhances prediction (somewhat)<sup>4</sup>
- Majority will not convert (stage 2) but is help-seeking<sup>5</sup>
  - Heterogeneous neurocognitive trajectories<sup>6</sup>
  - NEW Low remission rates (11.4% after 26 weeks), not improved with specialty care<sup>7</sup>
- Increasing appreciation of social determinants of health risk factors
  - Example, deprived environments and cognitive development<sup>8</sup>

**Harmonized criteria for  
Clinical High Risk for Psychosis  
SIPS + CAARMS = PSYCHS<sup>9</sup>**

“Probably at risk but certainly ill”

<sup>1</sup>Fusar-Poli P. Arch Gen Psychiatry. 2012;69(3):220-9. <sup>2</sup>Lin A et al. Am J Psychiatry. 2015;172(3):249-58. <sup>3</sup>Livny A et al. Am J Psychiatry. 2018;175(4):351-8. <sup>4</sup>Muarry GK et al. JAMA Psychiatry. 2021;78(2):210-219. [Clinical Review] <sup>5</sup>Iorfino F et al. JAMA Psychiatry. 2019;76(11):1167-75. Fusar-Poli P et al. JAMA Psychiatry. 2020;77(7):755-764. <sup>6</sup>Gold JM et al. JAMA Psychiatry. 2021;78(8):827-828. <sup>7</sup>McGorry PD et al. JAMA Psychiatry. 2023 (in press). <sup>8</sup>Lewis G et al. JAMA Psychiatry. 2020;77(7):729-36. <sup>9</sup>Salazar de Pablo G et al. JAMA Psychiatry. 2020;77(3):311-20. Corcoran CM et al. JAMA Psychiatry. 2021;78(8):821-822. <sup>9</sup>Woods SW et al. EIP. 2024;18:255-72.

# Early intervention for clinical high risk

IEPA=International Early Psychosis Association<sup>1</sup>  
EPA = European Psychiatric Association<sup>2</sup>

- Assess and treat syndromes (anxiety, depression)
- Benign interventions to delay conversion<sup>1,2</sup>
  - CBT should be first-line treatment
  - Integrated psychological interventions (EDIPPP)<sup>3</sup>
  - Omega-3 fatty acids ineffective;<sup>4</sup> NAC?; minocycline?
- Use of antipsychotics
  - Low-dose second-generation antipsychotic
  - If severe symptomatology
  - *Not* long-term for primarily preventive purpose
- Note: do not treat for pseudo-ADD with stimulants<sup>5,6,7</sup>

Provide needs-based care

Have protocol for client transition from early intervention services<sup>8</sup>

# **ACUTE PSYCHOSIS**

**“Der Ball ist rund und das Spiel dauert 90 Minuten.”  
- Sepp Herberger**

# Antipsychotic choice

- Efficacy<sup>1,2</sup>
  - Antipsychotics not equivalent
    - Clozapine ES 0.88
    - Olanzapine ES 0.59
    - Risperidone ES 0.56
  - Overall efficacy for rest
    - ES 0.33 to 0.50
- Avoid haloperidol in first-episode patients<sup>3</sup>
- LAI superior effectiveness compared to oral medications<sup>4</sup>

**Choose wisely**

**Metabolically low-risk  
Antipsychotics**

INTEGRATE: aripiprazole<sup>5</sup>

**Lowest effective dose<sup>6</sup>**

<sup>1</sup>Smith RC et al. Psychopharmacology. 2019;236(2):545-59. <sup>2</sup>Leucht S et al. Lancet. 2013;382(9896):951-62. Huhn M et al. Lancet. 2019;6736(19):1-13.

<sup>3</sup>Zhu Y et al. Lancet Psychiatry. 2017;4(9):649-705. [network meta-analysis] <sup>4</sup>Eftimiou O et al. Lancet Psychiatry. 2024;11(2):102-111.

<sup>5</sup>McCutcheon RA et al. Lancet Psychiatry. 2025;12(5):384-394. <sup>6</sup>Sabe M et al. J Clin Psychiatry. 2023;84(2):84(2):22r14490.

# SINO trial

## SINO = Schizophrenia in Non-Occidental Participants

- Randomized trial
  - Comparing 7 antipsychotics
    - olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, haloperidol, perphenazine
  - 3,067 adults randomized
- Outcome: 6-week PANSS improvement
- Key findings:
  - Differential efficacy
    - Olanzapine and risperidone best (but not compared to 1<sup>st</sup> generation AP)
    - BUT: differences small
  - Different side effect profile
    - Olanzapine highest risk weight gain and moderate sedation
    - Quetiapine low EPS but moderate metabolic risk
    - Aripiprazole lowest risk prolactin, minimal sedation, low metabolic risk
    - Haloperidol and perphenazine effective but with high EPS; dose of haloperidol was too high
- Largest randomized acute phase trial in schizophrenia
  - Industry-independent head-to-head comparison between 7 antipsychotics
  - Original intent identify genetic markers of treatment response
- Evidence-based guidance for acute schizophrenia
- Broadly aligns with available comparative efficacy and tolerability from CATIE, EUFEST and meta-analyses
  - Preferential use of risperidone and olanzapine for rapid symptoms control
  - Balance efficacy with tolerability
- Trial did not address clozapine, LAIs, or xanomeline-trospium

# A new 4<sup>th</sup> generation antipsychotic

## Non-dopaminergic antipsychotics

- Xanomeline = mAChR M1/M4 agonist
  - Poor oral tolerability (cholinergic syndrome)
  - Long development history
  - Tolerability improved by co-formulating with trospium as KarXT (Karuna)
  - Trospium (brand name Sanctura) = FDA-approved peripheral muscarinic antagonist for overactive bladder
- EMERGENT clinical trials program
  - Phase 2: EMERGENT-1
  - Pivotal phase 3: EMERGENT-2,3
  - Long-term extension: EMERGENT-4,5

## KarXT (brand name Cobenfy)

- FDA-approved Sept 26, 2024 NNT = 5
  - Safe and effective compared to placebo
- Side effect profile
  - GI
  - Metabolic low risk
  - Hypertension?
- Unresolved clinical issues
  - Comparative effectiveness
  - Side effect management
  - Patient selection (including FEP, TRS)
    - Failure of ARISE add-on trial
  - Informed consent

# First-episode psychosis

- Diagnosis
  - Some guidelines include MRI in first-episode work-up (German Guideline)<sup>1,2</sup>
- Treatment
  - Optimal pharmacotherapy
    - Choose wisely: metabolically safe, mode of delivery (oral versus long-acting injectable)
    - Timely move to clozapine if treatment resistance<sup>3</sup>
  - CSC = Coordinated specialty care (APA Guideline)<sup>4</sup>
  - Integrated care with proactive medical monitoring
- Prognosis
  - Keep DUP short
  - Address comorbidities including cannabis
  - Non-adherence
- Unclear: duration of maintenance treatment<sup>2</sup>

**75 years NIMH  
RAISE project<sup>4</sup>**

<sup>1</sup>Keating D, et al. BMJ Open 2017;7:e013881. <sup>2</sup>Available at [www.awmf.org](http://www.awmf.org), including in English

<sup>3</sup>Williams R et al. Br J Psych. 2025 (in press). <sup>4</sup><https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841>

<sup>4</sup><https://www.nimh.nih.gov/news/science-news/2023/raise-ing-the-standard-of-care-for-schizophrenia-the-rapid-adoption-of-coordinated-specialty-care-in-the-united-states>

# Post-Psychotic/ Chronic phase

**“Nach dem Spiel ist vor dem Spiel.”**

**- Sepp Herberger**

# Long-acting antipsychotic medications

- **Relapse risk 20 to 30% lower for LAI compared to oral<sup>1</sup>**
  - 56% reduction in mirror image studies<sup>2</sup>
- **Can be life-saving<sup>3</sup>**
  - 30% lower mortality risk LAI compared to oral antipsychotic
- **Treatment decisions based on facts**
  - LAI gives real-time, accurate information about adherence
  - Avoids family conflict and reduces caregiver burden
  - Reduces polypharmacy
- **Avoids gaps in care during care transitions**
  - First injection prior to hospital discharge, not as outpatient

Antipsychotics are highly effective to prevent relapse

Leucht S et al. Lancet 2012;379: 2063-2071

**NNT = 3**

<sup>1</sup>Tiihonen J et al. JAMA Psychiatry. 2017 Jul 1;74(7):686-693. <sup>2</sup>Kishimoto T et al. Lancet Psychiatry. 2021;8(5):387-404.

<sup>3</sup>Taipale H et al. Schizophr Res. 2018; 197:274-280.

# Patient selection for LAIs

Similar considerations for bipolar disorder, but best established for schizophrenia

## General recommendation

- Any patient who prefers LAIs
- Any patient who takes an antipsychotic

We need to normalize LAIs as a good first-line option, not only as a treatment of last resort for non-adherence.

## Clinical indications

- Early course of illness<sup>1</sup>
  - Better efficacy in shorter illness duration<sup>2</sup>
  - Reduces suicide risk by half<sup>3</sup>
  - Suicide risk highest in first 5 years of illness<sup>4</sup>
- Violence and arrests/incarceration prevention<sup>5</sup>
- Comorbid cannabis use<sup>6</sup>
- Patients with chaotic and unstructured lives
- Patients with cognitive impairment and limited support
- Patients who are ambivalent but willing to accept an LAI
- Anyone with numerous hospitalizations
- Families with high conflict around medications

<sup>1</sup>Kane JM et al. JAMA Psychiatry. 2020;77(12):1217-1224. <sup>2</sup>Kim S et al. J Clin Psychiatry. 2021;82(1):20m13446. <sup>3</sup>Huang CY et al. 2021 May 3;4(5):e218810.

<sup>4</sup>Kurdyak P et al. Schizophr Bull. 2021;47(3):864-74. <sup>5</sup>Bell Lynam K et al. J Clin Psychiatry. 2021;82(2):20m13356. <sup>6</sup>Denissoff A et al. Schiz Bull. 2024;50(6):1287-1294.

## Why would you not want to use an LAI?

### Real world use of LAIs

#### Good reasons

- Treatment-resistant schizophrenia
  - Clozapine
- Stable on medication not available as LAI
  - Lithium for bipolar disorder
- Contraindications
  - Catatonia
  - EPS sensitivity

#### Bad reasons

- I am on the inpatient side
- I cannot get it approved
- There are too many choices
- I do not have a system to help me
- It is coercive
- The patient would not want it
- I don't even know how to give it
- It is too expensive

# The strong case for LAIs for SMI care

- Relapse prevention core goal for schizophrenia and bipolar care
- LAIs are effective tools to prevent relapse
- Relapse prevention saves lives
- Adjust your attitude
  - Oncology thought experiment
- Acquire skills
  - Know the choices
  - Learn how to talk about them
- Arrange supportive environment
  - All hands-on deck approach
    - Interdisciplinary
  - True care continuum
    - ED, inpatient units, outpatient clinics
  - Reduce barriers and pain points in system

Oncology thought experiment:  
Imagine you see an oncologist ...

# Selection of LAIs

- It has gotten complicated!
  - Injection interval decision<sup>1,2</sup>
  - Administration techniques
    - Newtonian fluids
- Seek consultation or refer
- Consider setting up injection clinic
- Join a learning health collaborative

<https://mghaccess.org/>

“How long is too long?”  
The best injection interval is a  
clinical decision.  
Less frequent clinic visits is not  
automatically better.

<sup>1</sup>Dotson SJ et al. J Clin Psychiatry. 2023 May 31;84(4):23com14680.

<sup>2</sup>Najarian D et al. Int J Neuropsychopharmacol. 2022;25(3):238-251.

# Long-acting antipsychotic medications

| Drug                                                                                                                                            | Dose strengths                                                                                                             | Dose (IM) & Frequency                                                                                  | Notes                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Haloperidol decanoate<br>[HALDOL DECANOATE]                                                                                                     | Vials 50mg/ml<br>Vials 100mg/ml                                                                                            | 50 - 200 mg monthly<br>Other dose intervals are possible                                               | Initiation: overlap with oral antipsychotic<br>Loading dose strategy possible<br>Maintenance dose equals 20 x oral dose                                                                                                                                                                                                                                                                                                           |
| Fluphenazine decanoate<br>[PROLIXIN DECANOATE]                                                                                                  | Vials 25mg/ml                                                                                                              | 6.25 - 25 mg every 2 weeks<br>Other dose intervals are possible                                        | Initiation: overlap with oral antipsychotic                                                                                                                                                                                                                                                                                                                                                                                       |
| Risperidone microspheres<br>[RISPERDAL CONSTA]<br>[RYKINDO]                                                                                     | 12.5mg, 25 mg, 37.5 mg, 50 mg<br>12.5 mg to 50 mg                                                                          | 12.5-50 mg every 2 weeks                                                                               | Initiation: 3 week overlap with oral antipsychotic<br>Main release of drug occurs 3 weeks after injection<br>50 mg every two weeks corresponds to 4 mg/d oral (50 mg is highest IM dose)                                                                                                                                                                                                                                          |
| Risperidone long-acting suspension<br>[PERSERIS]<br><br>[UZEDY]                                                                                 | 90 mg, 120 mg<br><br>50 mg to 250 mg                                                                                       | 90 or 120 mg monthly <u>subcutaneously</u><br><br>Monthly or every two months<br><u>subcutaneously</u> | For subcutaneous use<br>90 mg corresponds to 3 mg/d oral<br>120 mg corresponds to 4 mg/d oral                                                                                                                                                                                                                                                                                                                                     |
| Paliperidone palmitate<br>[INVEGA SUSTENNA] [ERZOFRI]<br><br>[INVEGA TRINZA]<br><br>[INVEGA HAYFERA]                                            | 39 mg, 78 mg, 117 mg, 156 mg, 234 mg; ERZOFRI also as 351 mg<br><br>273 mg, 410 mg, 546 mg, 819 mg<br><br>1092 mg, 1560 mg | 39-234 mg monthly<br><br>273-819 mg every 3 months<br><br>1092 – 1560 every 6 months                   | Loading dose of 234 mg [deltoid!] to initiate (no oral overlap needed), 2 <sup>nd</sup> dose one week later, the monthly. Alternatively, ERZOFRI 351 mg loading dose, followed by monthly dosing<br>156 mg monthly corresponds to 9 mg/d oral<br>Every 3 months dose can be used after 4 months of monthly injections<br>546 mg corresponds to 9 mg/d oral<br><br>After 4 months of Sustenna or after one 3-month cycle of Trinza |
| Olanzapine pamoate<br>[ZYPREXA RELVREVV]                                                                                                        | 150 mg, 210 mg, 300 mg, 405 mg                                                                                             | 150 or 300 mg every 2 weeks<br>405 mg monthly                                                          | No overlap with oral antipsychotic (higher initiation doses)<br>Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDSS)*<br>300 mg monthly corresponds to 10 mg/d oral                                                                                                                                                                                                                            |
| Aripiprazole monohydrate<br>[ABILIFY MAINTENA]<br><br>[ABILIFY ASIMTUFI]                                                                        | Vials 200 mg/ml.<br><br>Pre-filled syringe                                                                                 | 160mg- 400mg monthly<br><br>960 mg (720mg) every two months                                            | Initiation: 2 week overlap with oral antipsychotic<br>300 mg corresponds to 10 mg/d oral; 400 mg to 15 mg/d                                                                                                                                                                                                                                                                                                                       |
| Aripiprazole lauroxil<br>[ARISTADA]                                                                                                             | 441 mg, 662 mg, 882 mg, 1064 mg                                                                                            | 441,662,882 mg every 4 weeks<br>882 mg every 6 weeks<br>1064 mg every 2 months                         | Initiation: 3 week overlap with oral antipsychotic or with initiation regimen<br>Inject rapidly due to non-Newtonian fluid characteristics<br>Only lowest dose of 441 mg dose can be given in deltoid<br>441 mg monthly corresponds to 10 mg/d oral<br>662 mg monthly or 1064 mg every two months corresponds to 15 mg/d oral<br>882 mg monthly corresponds to 20 mg/d oral (highest IM dose)                                     |
| Oral test dose required for all antipsychotic if patient has never been exposed to IM antipsychotic<br>*See REMS website for olanzapine pamoate |                                                                                                                            |                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                   |

## Poor response to first-line antipsychotic

- Move to clozapine timely<sup>1</sup>
  - Clozapine proficiency!<sup>2</sup>
- Risks of not prescribing clozapine
  - Accruing psychosocial toxicity
    - Including failure to prevent suicide and violence
  - “End-stage” brain disease with poor function
  - Polypharmacy
  - Higher mortality<sup>3</sup>
- Some patients prefer clozapine!<sup>4</sup>



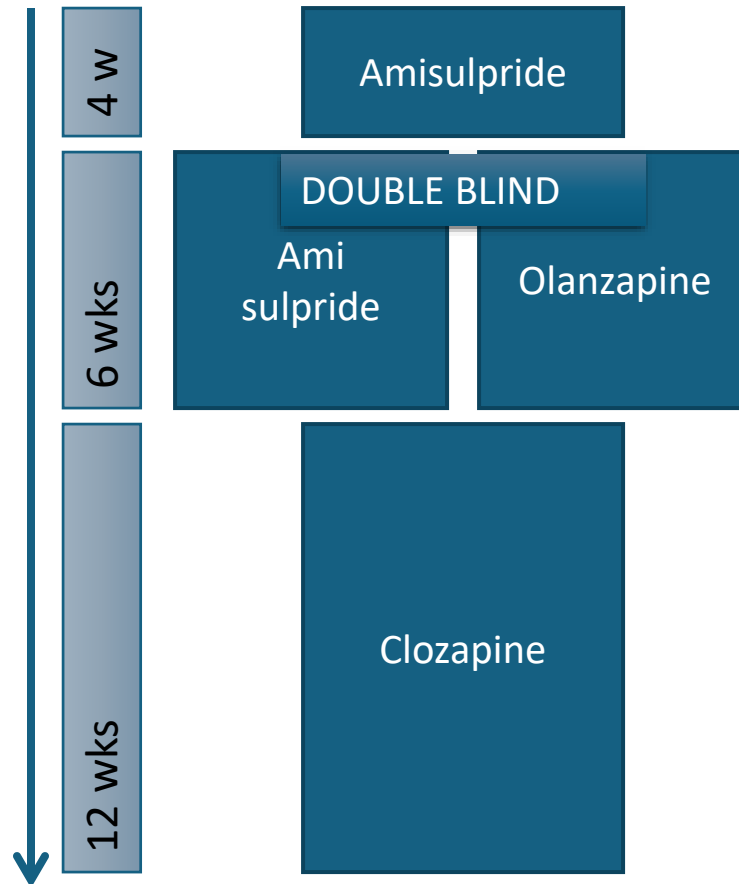
<sup>1</sup>Kahn RS et al. Lancet Psychiatry. 2018; 5(10):797-807. <sup>2</sup>Zarzar TR. JAMA Psychiatry. 2024;81(7):639-640.

<sup>3</sup>Taipale H et al. World Psychiatry. 2020;19(1):61-8. [mghcme.org](https://mghcme.org)

<sup>4</sup>Parkes S et al. Schizophr Bull Open. 2022;3(1):sgac042, <https://doi.org/10.1093/schizbullopen/sgac042>

# 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 2<sup>nd</sup> line antipsychotic

## Duration of untreated psychosis

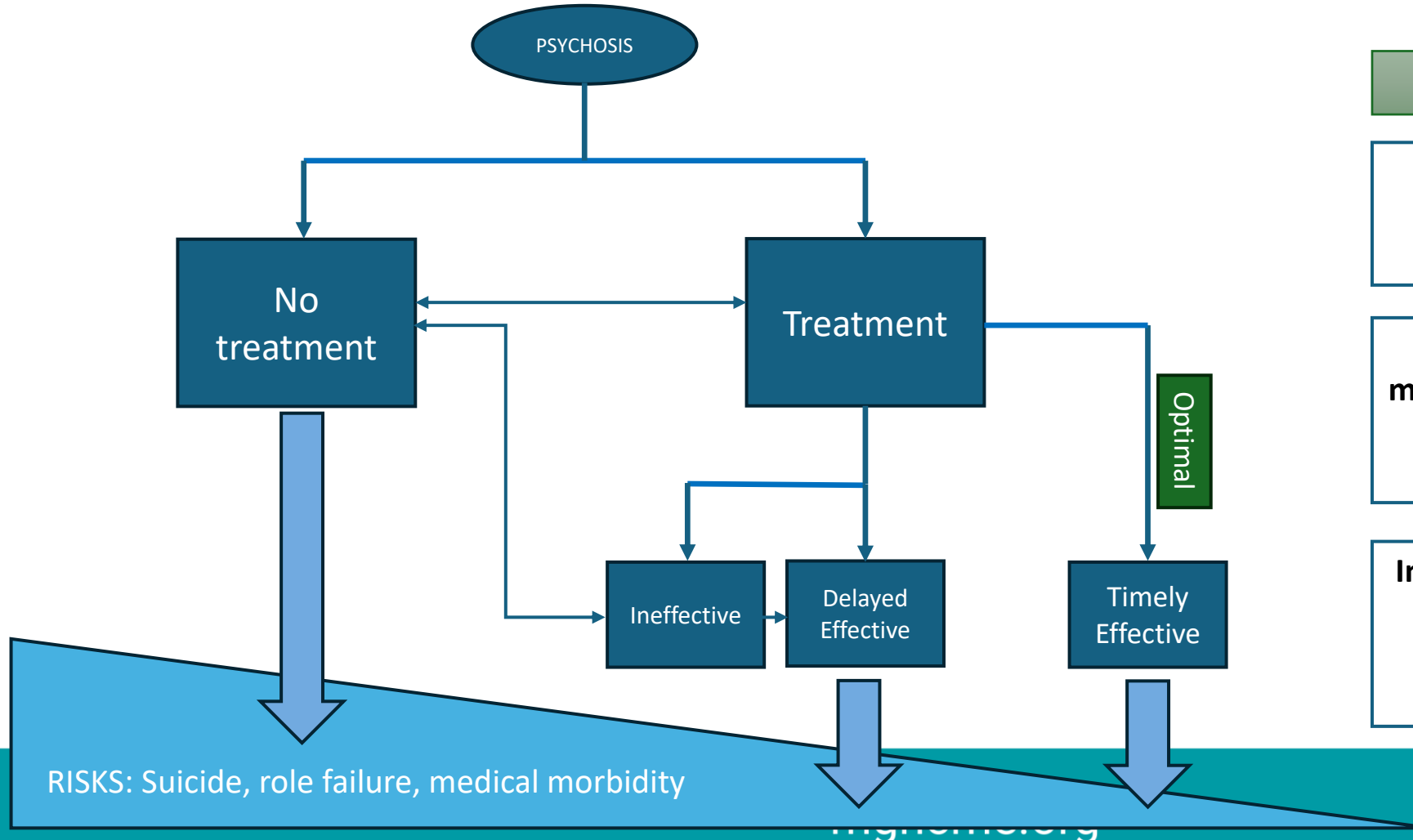
- Avoids delays in TRS!
  - Longer DUP associated with worse response
  - Psychosis associated with suicide risk (mortality reduction)

## Relapse prevention

- Excellent for relapse prevention<sup>1</sup>
  - Relapse associated with worse response
- Good choice after relapse in first-episode patients already<sup>2</sup>

Should we introduce clozapine after one failed treatment?

# Psychiatric treatment as prevention



## Key points about prevention

Psychiatric treatment prevents psychosocial toxicity from delayed treatment and relapse.

Psychiatric treatment prevents medical morbidity and mortality: there is no medical health without psychiatric health.

Ineffective treatment given over time, even if given with great sincerity, remains ineffective treatment.

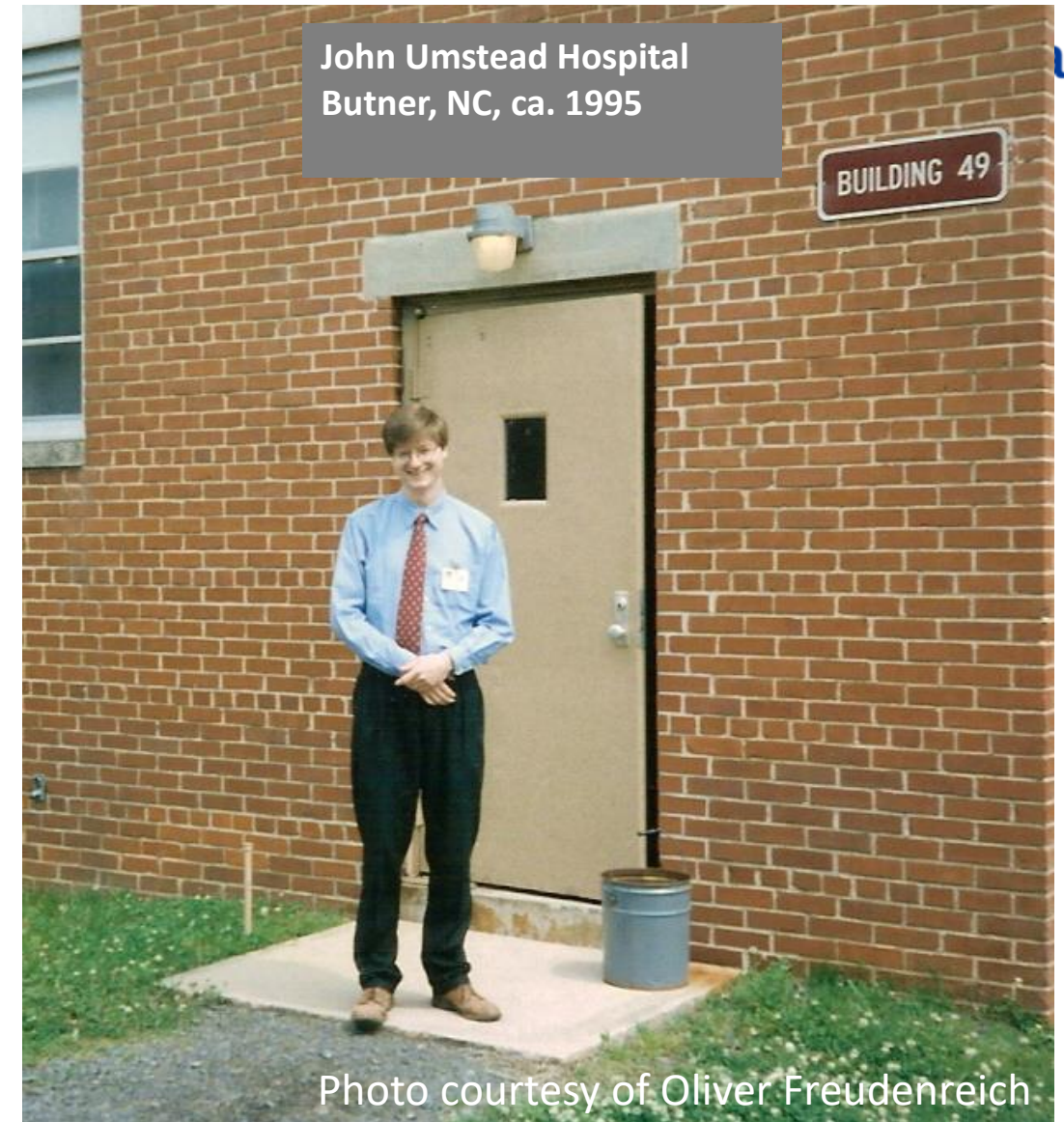


# Medical prevention



# Smoking and SMI

- **Continued higher rates of smoking**
  - Patient with schizophrenia want to quit
  - Smoking cessation is more difficult
- **Psychopharmacology is needed**
  - Varenicline is effective and better than the patch<sup>1</sup>
  - Varenicline is safe in our patients<sup>2</sup>
  - Maintenance treatment may be needed<sup>3</sup>
- **Provider education alone insufficient<sup>4</sup>**
- **Opt-out nudge as default for smoking cessation**



John Umstead Hospital  
Butner, NC, ca. 1995

Photo courtesy of Oliver Freudenreich

<sup>1</sup>Evins AE et al. Psychiatric Services 2021; 72(1):7–15. <sup>2</sup>Anthenelli RM et al. Lancet. 2016;387(10037):2507-20. [EAGLES trial]

<sup>3</sup>Evins AE et al. JAMA. 2014;311(2):145-154. <sup>4</sup>Evins AE et al. Psychiatr Serv. 2023;74(4):365-373.

# Proactive medical management

- Iatrogenic complications
  - Antipsychotic-induced weight gain
  - But: worst outcomes in untreated patients with schizophrenia<sup>1,2</sup>
- **Choose wisely - prevent**
  - Prefer metabolically low-risk antipsychotics, if possible
  - Switch to low-risk antipsychotics, if possible
  - Discontinue contributing medications, if possible
- **Screen and monitor – detect and treat early**
  - Guideline-concordant monitoring
  - Treat identified medical morbidity
- **Proactive (preventive) treatment – blunt and mitigate**
  - Add behavioral interventions, if available<sup>3</sup>
  - **Add metformin with high-risk antipsychotics**<sup>4,5</sup>
  - **Use GLP-1 agonists?**<sup>6</sup>

## 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.

Stogios M et al. JAMA Psychiatry. 2026 (in press):  
-Semaglutide, liraglutide, topiramate, metformin, exenatide effective  
-Metformin and semaglutide over 5% weight loss

<sup>1</sup>Vermeulen JM et al. Schizophr Bull. 2019;45(2):315-29. <sup>2</sup>Taipale H et al. World Psychiatry. 2020;19(1):61-8.

<sup>3</sup>Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]

<sup>4</sup>Fitzgerald I et al. Evid Based Ment Health. 2022;25(1):15-22. Carolan A et al. Schizophr Bull. 2025 Sep 8;51(5):1193-1205.

<sup>6</sup>Fink-Jensen and Correll CU. Acta Psychiatr Scand. 2024;150(6):1-3. [Editorial]

# GLP-1 agonists: a paradigm shift

- Antipsychotic-induced weight gain must be managed well
  - Medical morbidity and mortality
  - Weight stigma
    - Blaming patients
    - Ignoring weight gain
  - One size does not fit all (low-intensity, life-style insufficient for some)<sup>1</sup>
  - Shift to multidisciplinary obesity treatment paradigm<sup>2</sup>
- GLP-1 agonists are most effective weight loss medications
  - Do we need to become comfortable prescribing them, just like with metformin?
  - Are these life-long drugs?
  - Fast-moving field
    - Expanding indications: OSA (FDA),<sup>3</sup> SUD<sup>4</sup>
    - Suicide risk?<sup>5</sup>
    - The search for synergy, including preventing muscle loss

Goodbye, Ozempic

-The Atlantic, June 27, 2023

<sup>1</sup>Ard JD et al. JAMA. 2024;332(1):16-18. [Editorial] <sup>2</sup>Samuels JM et al. JAMA Surgery. 2024;159(8):841-842.

<sup>3</sup>Malhotra A et al. NEJM. 2024;391(13):1193-1205. <sup>4</sup>Leggio L et al. Nat Med. 2023;29:2993-5. [Editorial]

<sup>5</sup>Wang W et al. Nat Med. 2024;30(1):168-176.

# GLP-1 agonists for schizophrenia

HISTORI = Handling Increased Somatic Treatment-related Obesity in Related psychotic Illnesses  
COaST = Clozapine Obesity and Semaglutide Treatment

## Strong evidence base

- Pivotal liraglutide trial<sup>1+</sup>
  - Put GLP-1 for schizophrenia on the map
  - Note: published in 2017 (!)
- Landmark HISTORI semaglutide trial<sup>2\*+</sup>
  - Shift to semaglutide
  - Prediabetes and overweight/obese
  - Second-generation antipsychotics
  - Effective and safe
- Semaglutide trials in high-risk groups
  - COaST trial (clozapine)<sup>3</sup>
  - “Danish study” (clozapine, olanzapine)<sup>4</sup>

## Implications

- From risk reduction to active obesity treatment
  - Beyond metformin
  - Need for new guidelines
- Psychiatric disorders as metabolic disorders
  - Brain health as key aspect of schizophrenia care
  - See for example SGLT-2 inhibitors and reduced dementia risk

<sup>1</sup>Larsen JR et al. JAMA Psychiatry. 2017 Jul 1;74(7):719-728.

<sup>2</sup>Ganeshalingam AA et al. JAMA Psychiatry. 2026;82(11):1065-1074.

<sup>3</sup>Siskind D et al. Lancet Psychiatry. 2025;12(7):493-503.

<sup>4</sup>Sass MR et al. JAMA Psychiatry. 2026;83(2):128-138.

# Semaglutide for clozapine patients

COaST = Clozapine Obesity and Semaglutide Treatment

## 1. Methods

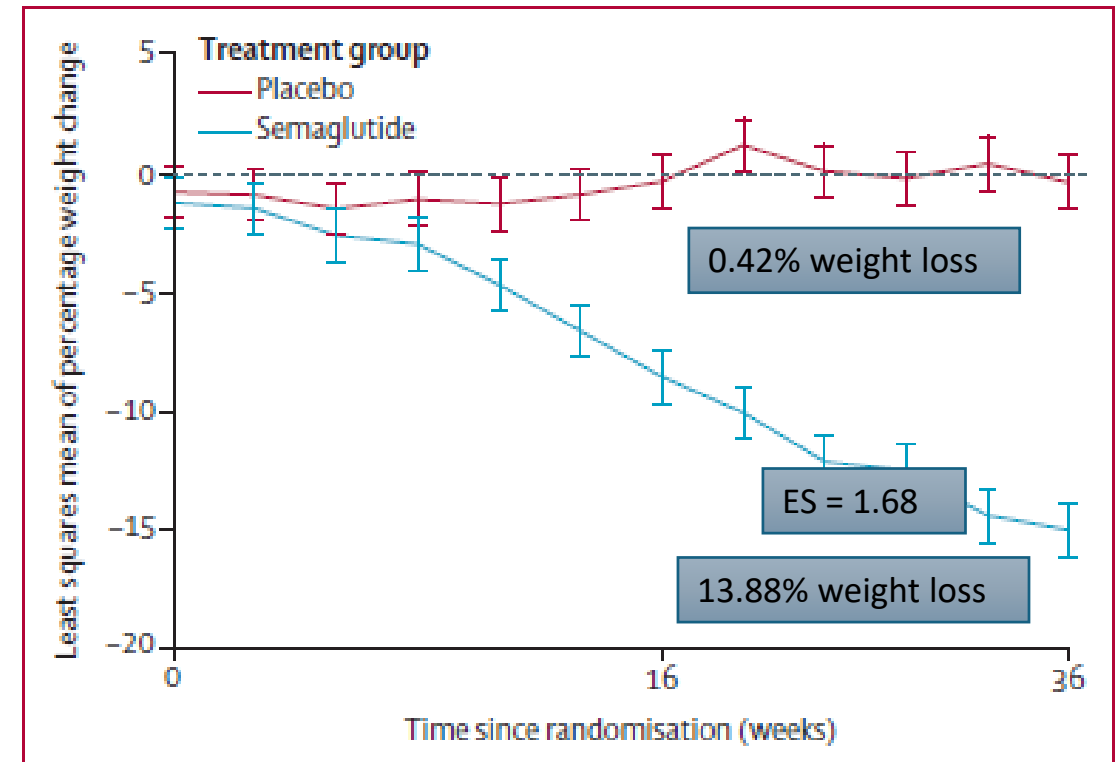
- Schizophrenia patients on clozapine from Queensland, Australia
- Obese and stable
- 36-week phase 2 RCT with blinding
- Semaglutide 2 mg SQ every week

## 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

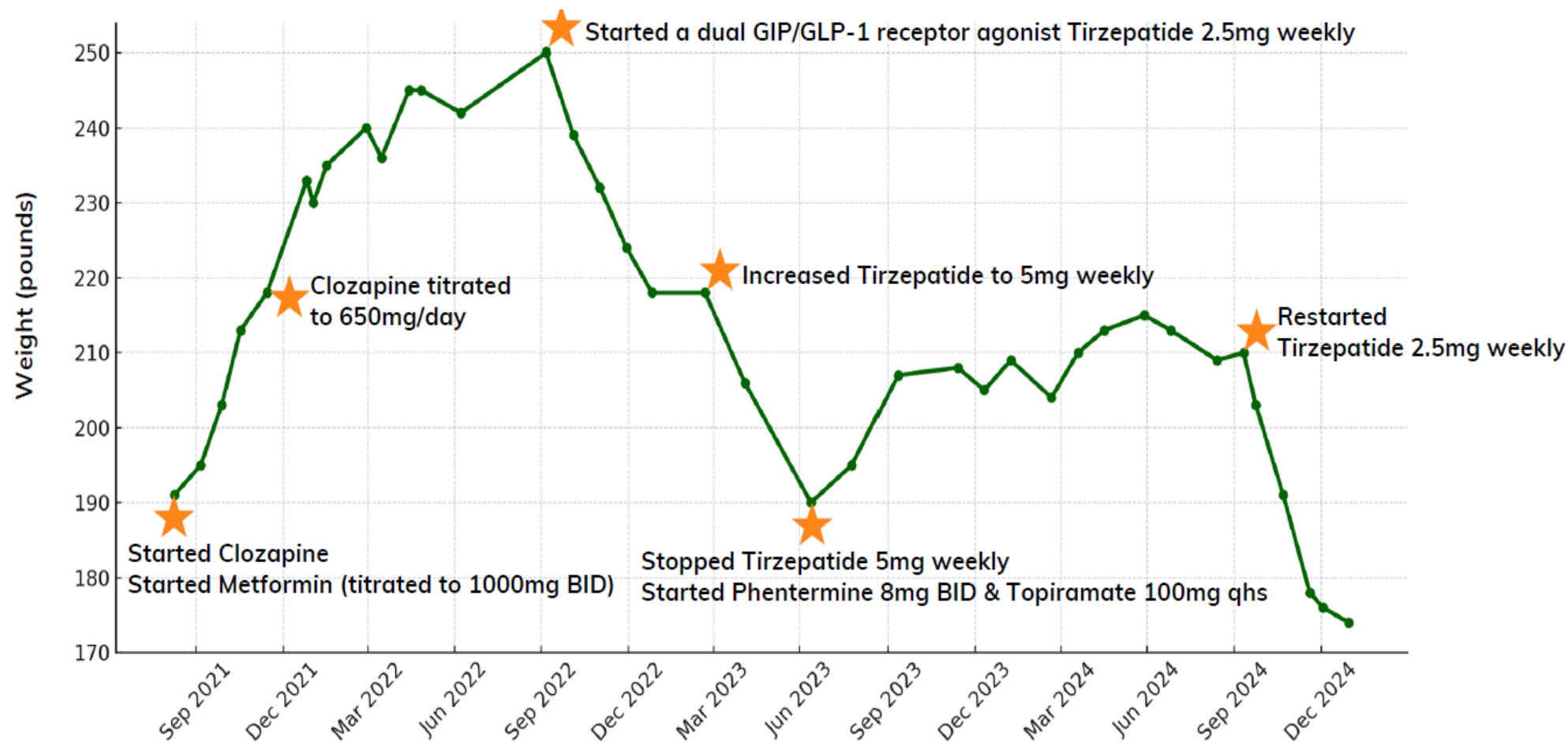
## 3. Significance

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



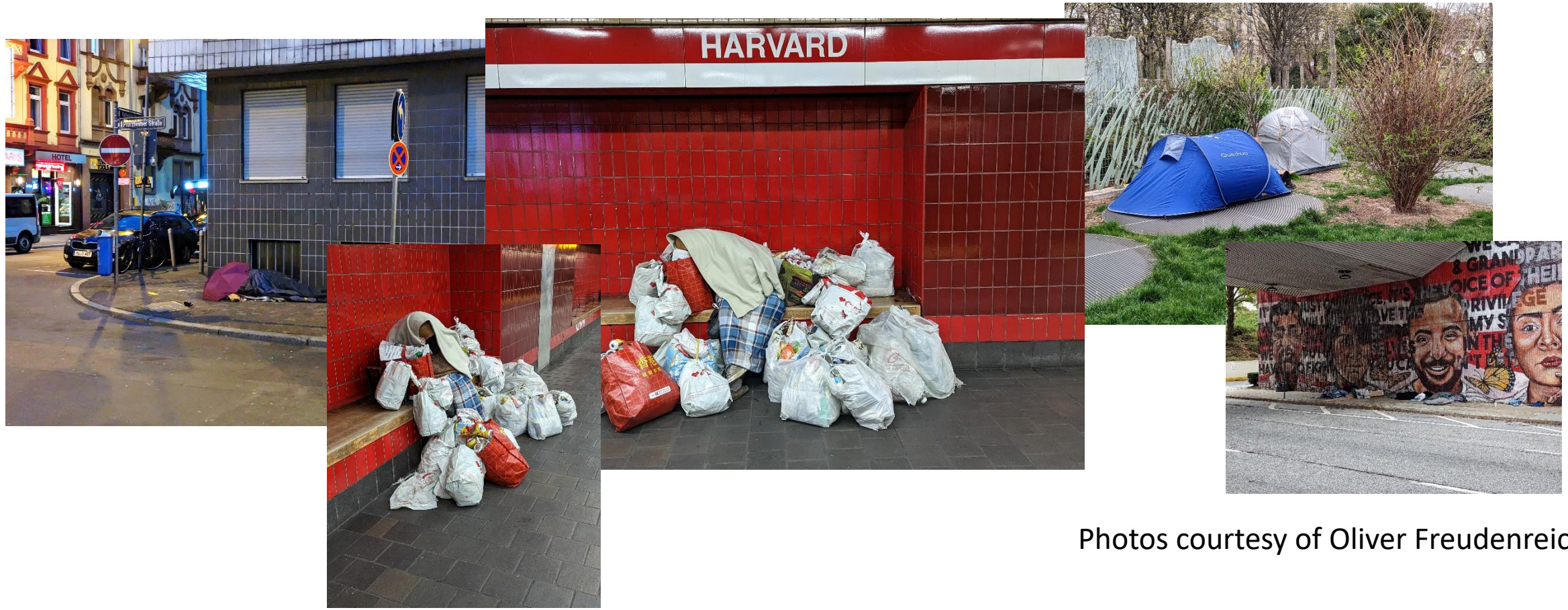
Percent weight change over 36 weeks

## CASE: GLP-1 agonist in clozapine-treated patient





# Reflections: How are we doing?



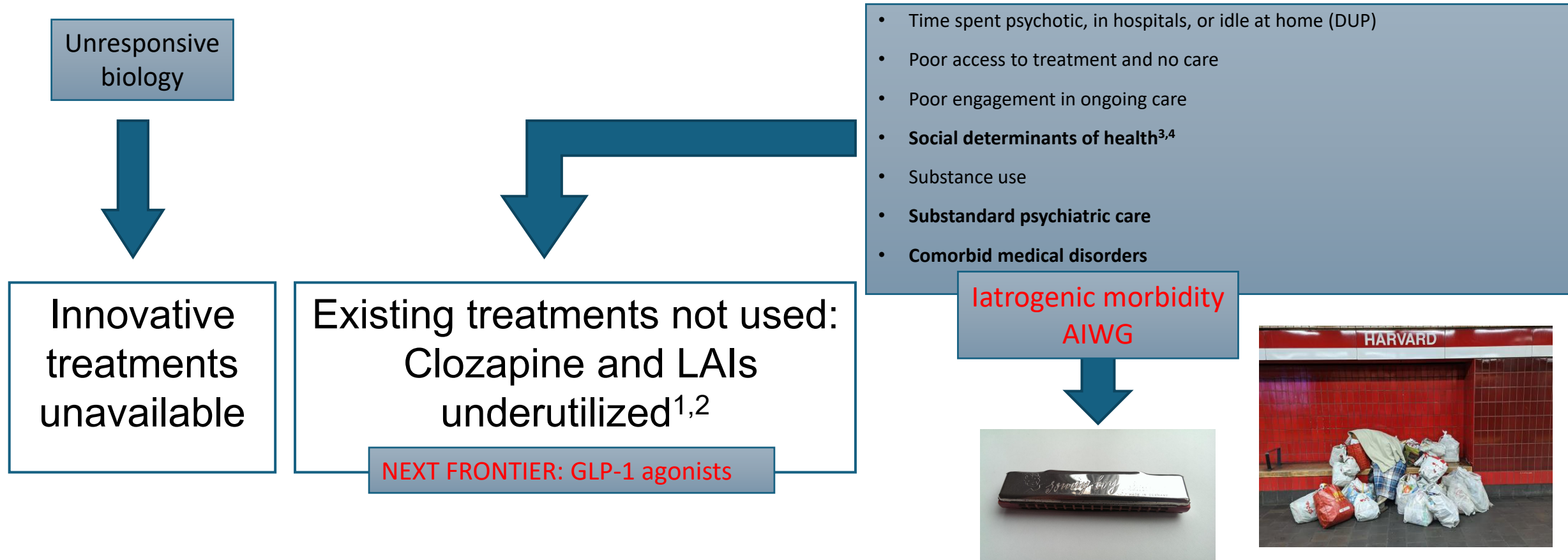
Photos courtesy of Oliver Freudenreich

# Suffolk County Study

- **Suffolk County Mental Health Project**
  - Epidemiological first-episode study
  - Eastern, semirural county of Long Island
  - First-episode cohort recruited from 12 inpatient units 1989-1995
    - Baseline 591 patients with at least one follow-up
    - 6 follow-up time points
    - 311 patients available for 25-year follow-up
- **25-year, naturalistic follow-up**
  - Most common outcome pattern: no remission and no recovery for schizophrenia
    - Intermittent remissions and recoveries for non-schizophrenia psychosis
    - Cross-sectional recovery at 25 years: 14% (SSD) versus 28% (other psychosis)
    - Worse outcome for Black compared to white
  - More effective treatments needed for schizophrenia
  - More efforts geared towards mid-life for schizophrenia patients

However beautiful  
your strategy, you  
should occasionally  
look at the results.

# Contributors to poor outcomes



**Social (structural) interventions have greater impact on outcomes than molecular advances.<sup>5</sup>**

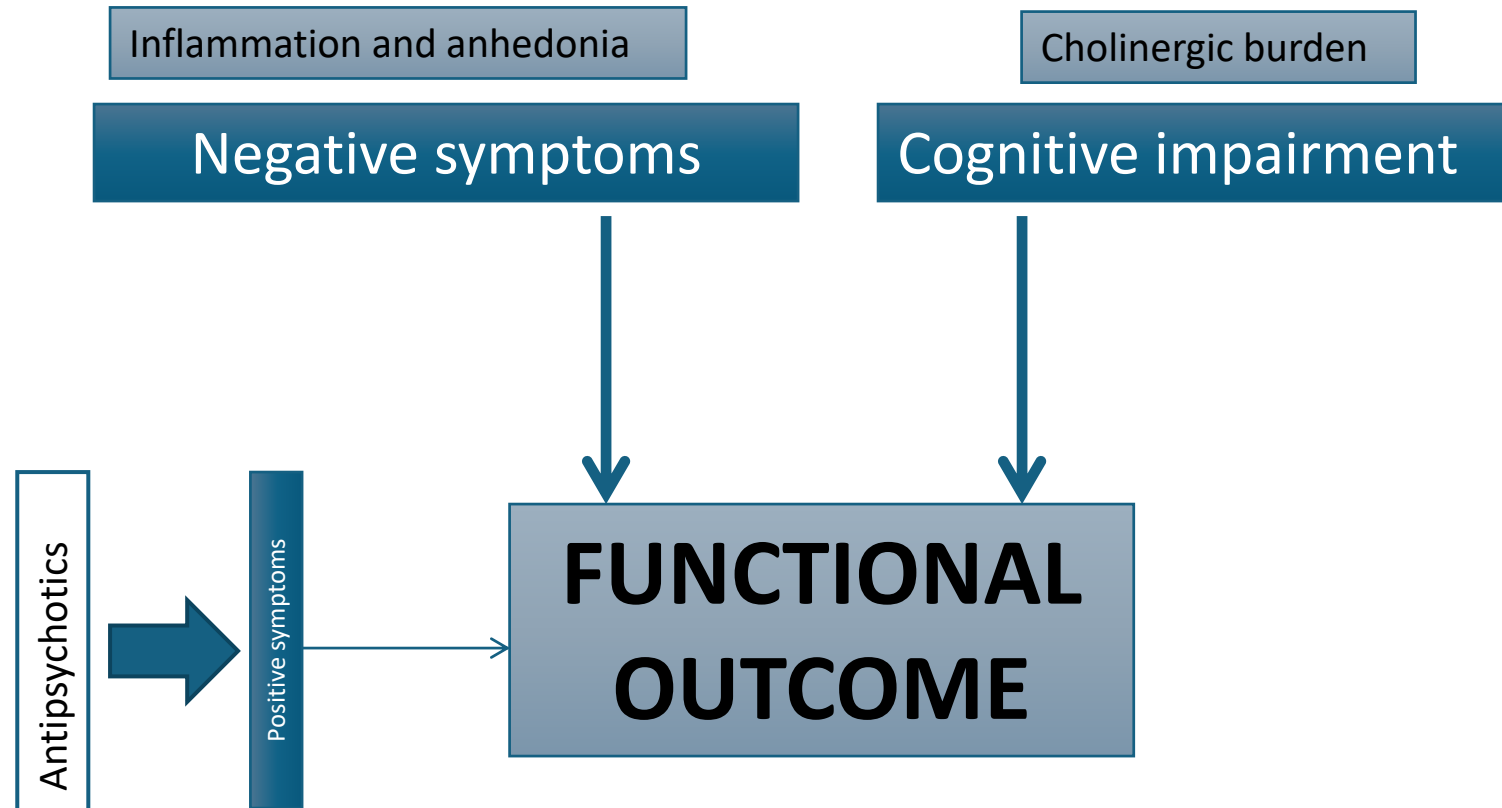
<sup>1</sup>Kelly DL et al. Psychiatr Serv. 2018;69(2):224-227. <sup>2</sup>Torrey EF and Lieberman J. Psych Serv. 2025;76(1):90-92.

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

# New FDA drug approvals

- 2021: Olanzapine plus samidorphan [brand name Lybalvi]
- 2021: IM paliperidone palmitate LAI for every 6 months [brand name Invega Hayfera]
- 2022: Dexmedetomidine [brand name Igalmi]
- 2023: IM risperidone LAI for every 2 weeks [brand name Rykindo]
- 2023: SC risperidone LAI for every one or two months [brand name Uzedyl]
- 2023: IM aripiprazole for every two months [brand name Abilify Asimtufii]
- 2023: Deutetrabenazine extended release [brand name Austedo XR]
  - Once-daily formulation of deutetrabenazine 6 mg, 12 mg 24 mg
- 2023: Brexpiprazole [brand name Rexulti]
  - Supplemental indication for agitation associated with Alzheimer's disease
- 2024: Deutetrabenazine extended release [brand name Austedo XR]
  - New dose strengths 30 mg, 36, mg, 42 mg, 48 mg
- 2024: IM paliperidone palmitate LAI for every 4 weeks [brand name Erzofri]
  - High dose of 351 mg for one-time loading
- 2024: KarXT (xanomeline + trospium) [brand name Cobenfy]
- 2025: Arpiprazole oral film [brand name Mezofy]
- **2026: Milsaperidone [brand name Bysanti]**
  - Active metabolite of iloperidone (interconvert in vivo)
  - Consider a regulatory move for patent exclusivity if LAI or once-a-day adjunct for depression approved
- **2026: Lumateperons [brand name Caplyta]**
  - Supplemental indication for relapse prevention in schizophrenia

# Symptom domains and functional outcome



“All organizations are perfectly designed to get the results they get!

- Don Berwick, MD (and others)

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.<sup>5</sup> “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.

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

## Second Opinions for Diagnoses of Psychotic Disorders: Delivering Stage-Specific Recommendations

Carol Lim, M.D., M.P.H., Abigail L. Donovan, M.D., Sophie Freudenreich, Corinne Cather, Ph.D., Sarah Maclaurin, P.M.H.N.P., Oliver Freudenreich, M.D., F.A.C.L.P.

**Objective:** The impact of obtaining second-opinion consultations on diagnoses of schizophrenia spectrum disorders was evaluated.

**Methods:** A retrospective chart review was conducted for 177 patients referred to a psychosis consultation service at an academic medical center from January 1, 2017, to October 1, 2023; these consultations aimed to clarify a diagnosis of psychosis. Diagnoses made before and after consultations were compared, and treatment recommendations resulting from the consultation visit were summarized.

**Results:** Among patients without a preconsultation diagnosis of schizophrenia, 28% (N=28 of 100) received

a postconsultation diagnosis of schizophrenia. Among 62 patients with a postconsultation diagnosis of treatment-resistant schizophrenia (TRS), 56% (N=35) received this diagnosis only after consultation. Nearly all of these patients were advised to begin taking clozapine, and electroconvulsive therapy was less commonly recommended.

**Conclusions:** Expert consultation facilitates timely identification and optimal treatment of schizophrenia and its more severe subtype, TRS.

*Psychiatric Services 2024; 75:1035–1038; doi: 10.1176/appi.ps.20230623*

Lim C et al. Psychiatr Serv. 2024;75(10):1035-1038.

# The Underuse of Clozapine and Long-Acting Injectable Antipsychotics

E. Fuller Torrey, M.D., and Jeffrey Lieberman, M.D.

Schizophrenia is among the most devastating and costly human diseases. The public face of the failure to appropriately treat schizophrenia includes approximately 100,000 homeless individuals with schizophrenia and related psychoses and 200,000 incarcerated individuals with similar diagnoses. Clozapine and long-acting injectable antipsychotics are among the most effective treatments, but both are markedly underused. The following organizations should

take responsibility for fixing this problem: National Institute of Mental Health, Patient-Centered Outcomes Research Institute, Substance Abuse and Mental Health Services Administration, Centers for Medicare and Medicaid Services, U.S. Food and Drug Administration, American Psychiatric Association, and patient and family advocacy groups.

*Psychiatric Services* 2025; 76:90–92; doi: 10.1176/appi.ps.20240110

# REMS – gone but not forgotten

## Key points about post-REMS age

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

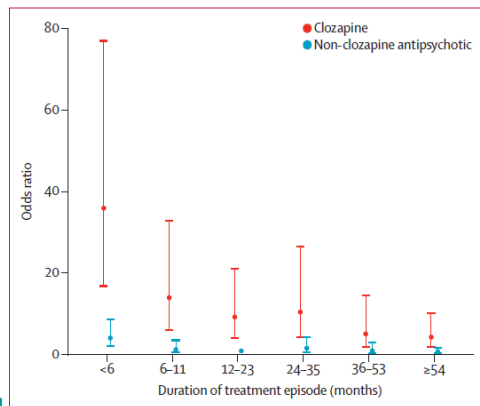


Figure 2: Odds ratio for developing agranulocytosis during various treatment durations

## 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<sup>1</sup>
  - International Delphi<sup>2</sup>

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

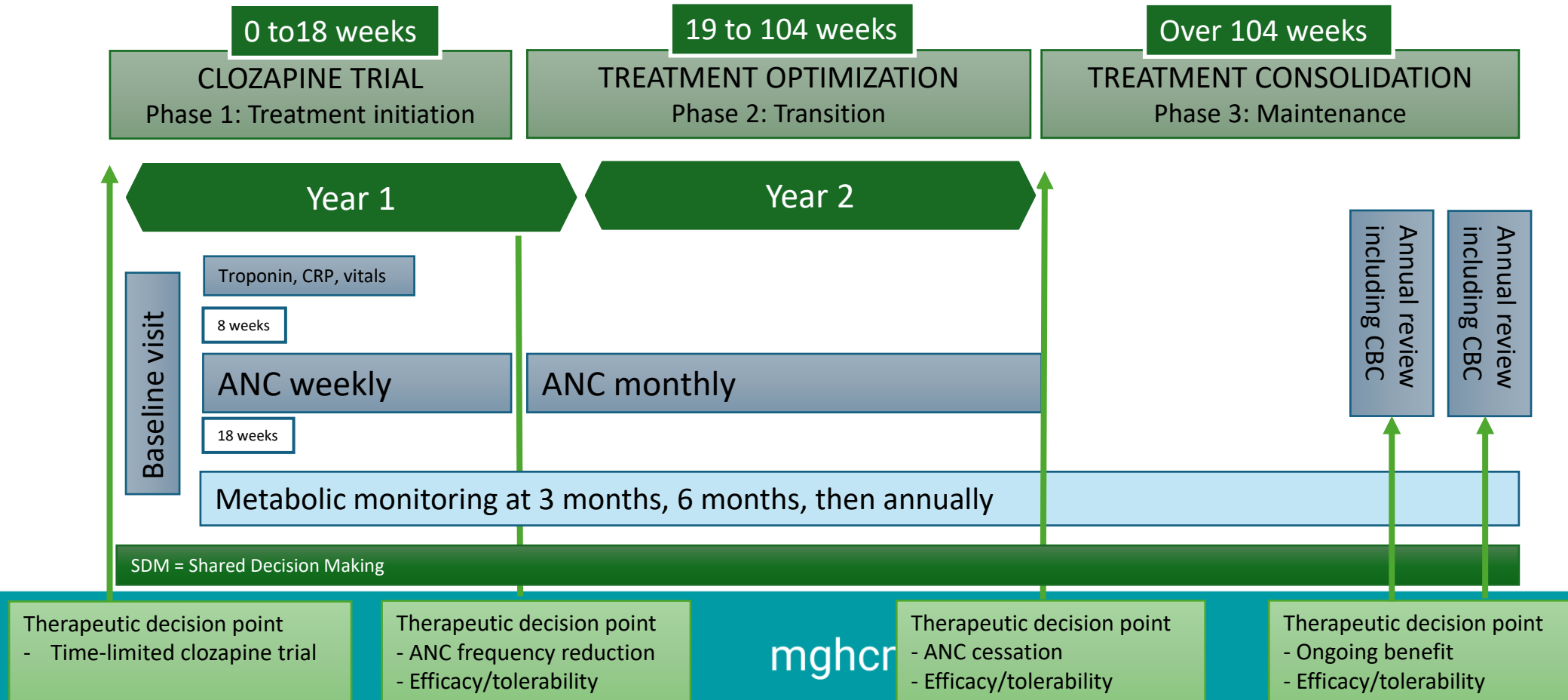


Response to the U.S. Department of Health and Human Services RFI: Making America Healthy  
Again: Chronic Disease Prevention and Treatment

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.

# Form follows function

## TREATMENT PHASES



## 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.”**

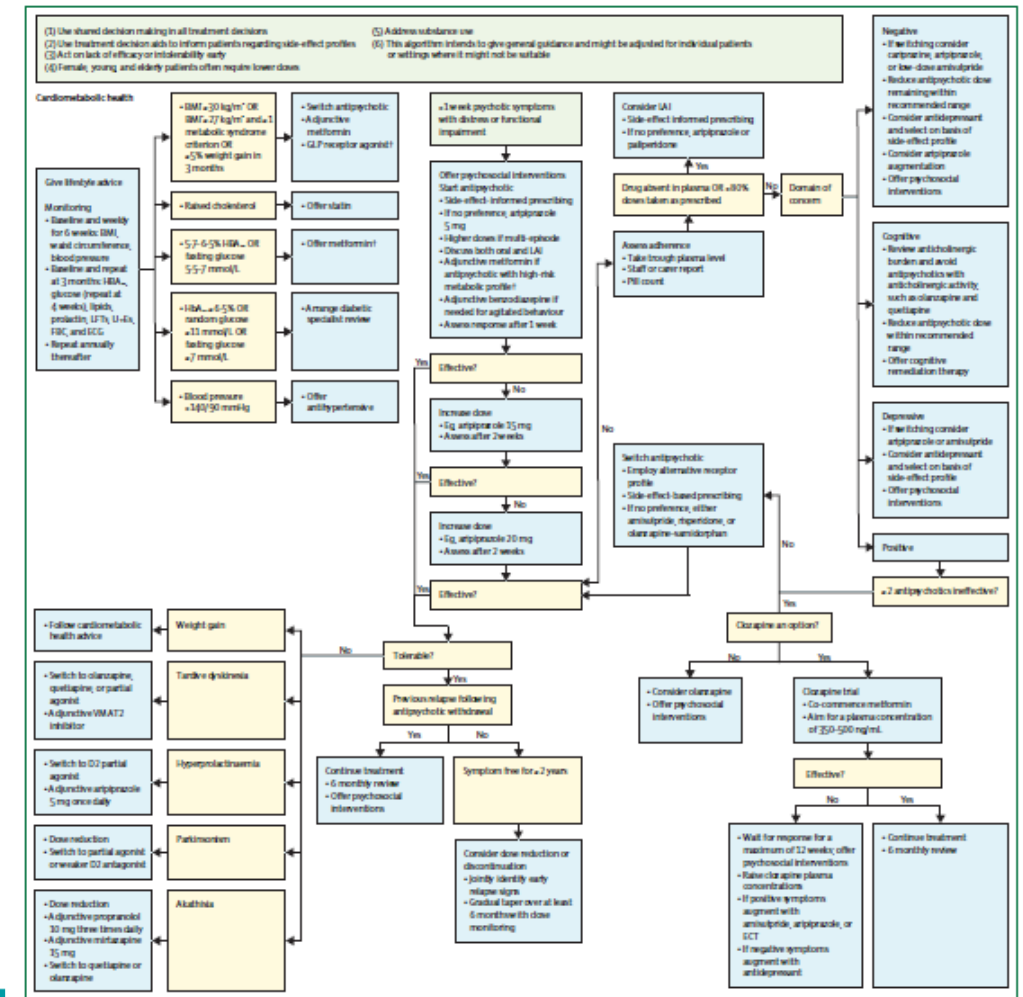
Opportunity for service expansion

Opportunity for first-episode like movement for TRS

# INTEGRATE guidelines for schizophrenia

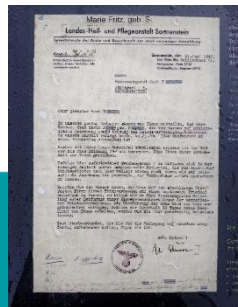
International guidelines for the algorithmic treatment

- Consensus guideline for psychopharmacology
- Areas of focus
  - Metabolic health from treatment initiation
  - Timely assessment and management of non-response
  - Symptom domain-specific interventions
  - Mitigation of side effects
  - Prompt use of clozapine in cases of treatment resistance



# Epilogue

Humanism in medicine



Tiergartenstrasse 4

Thibault GE. Acad Med. 2019;94:1074–1077.

mgn



Photos courtesy of Oliver Freudenreich

# Commitment to professionalism

## Reflective practice

### Accompaniment and solidarity

|                                                           |                                                                                                                                           |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Primacy of patient welfare<br>Reject patient as commodity | Serve the interest of the patient<br>Guard against market forces, societal pressures, and administrative exigencies                       |
| Patient autonomy<br>Give patients a voice                 | Respect patient autonomy<br>Empower patients to make informed decisions about their care                                                  |
| Social justice<br>Offer “asylum”                          | Promote justice in healthcare system<br>Work toward fair resource distribution<br>Work actively to eliminate discrimination in healthcare |

Collaborative advocacy to effect change in extreme health care environment.\*

Kontos N, Querques J, Freudenreich O. Acad Psychiatry. 2006;30(3):218-26.

Freudenreich O and Kontos N. Psychosomatics. 2019;60(3):246-254.

Freudenreich O, Kontos N, Querques J. Psychiatr Ann. 2021;51(6):272-277.

\*Primm AB and Norris DM. Psychiatr Serv. 2026;77(7):678-680. [Moral injury and ethical dilemmas in extreme environments]

# Global warming is dangerous for humans

## History

### Chicago heat wave of 1995

- ~1,000 dead
- "Social disaster"

### Paris heat wave of 2003

- ~15,000 dead
- Unprepared population

### BC heat dome of 2021

Schizophrenia risk factor, 3-times higher risk of death

## Environmental Outcomes

Increase in extreme temperatures

People outside temperature niche

Crop failure and mass migration

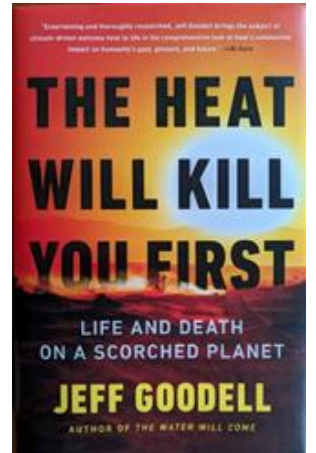
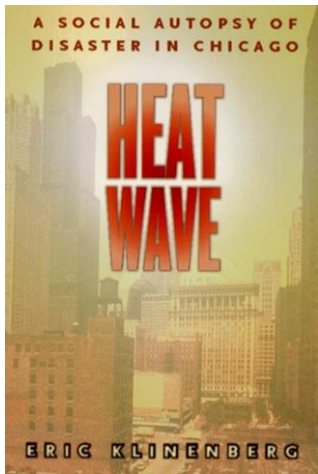
Fires and air pollution

## Increased Mortality

Increase in heat-related deaths

Heat-aggression hypothesis: violent crime rates higher if hot outside

Increased suicide rate



## Homework: Draw (climate) action Venn diagram



<https://www.ayanaelizabeth.com/climatevenn>

WATCH DR. JOHNSON'S  
TED TALK ABOUT CLIMATE ACTION

<https://www.youtube.com/watch?v=VsOJR40M0as&t=11s>

### PICK AN AREA OF INTEREST TO YOU

Disaster psychiatry  
Med-psych integration  
Immigrant health  
Medical education  
Political advocacy

# Thank you!

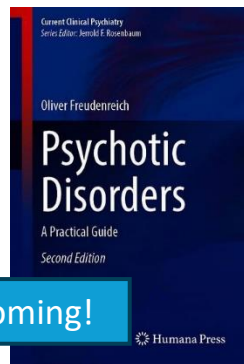
## Websites

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

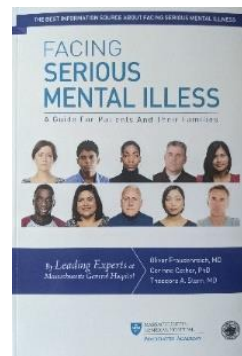
<https://www.uptodate.com/contents/guidelines-for-prescribing-clozapine-in-schizophrenia>

## Article

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



3<sup>rd</sup> edition coming!



John Umstead Hospital, Butner, NC, ca. 1995