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GENERAL HOSPITAL

PSYCHIATRY ACADEMY

# Schizophrenia Diagnosis and Treatment

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# Disclosures



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Mirah – Investor (spouse)



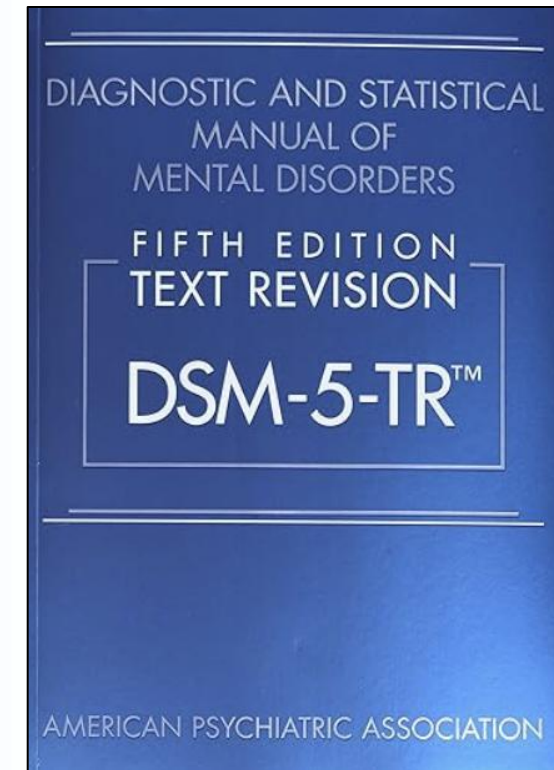
# Outline

- Diagnostic criteria for schizophrenia
- Phases of illness in the first episode of schizophrenia
  - Acute Psychotic Phase
  - Post Psychotic Phase



# DSM 5-TR: Schizophrenia

- Two Criterion A symptoms for one month:
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Disorganized behavior
  - Negative symptoms
- One must be a “core symptom”
- Functional decline
- Total duration of symptoms: 6 months





# Cognition

- Cognitive performance is 1-2 SD below age-matched controls<sup>1</sup>
- Affected areas include: attention, executive function, memory, processing speed, social cognition<sup>2</sup>
- Cognitive decline is nearly universal, present before the onset of psychosis, and worsens during the early illness<sup>3,4,5</sup>
- Chronic impairment is specific to schizophrenia- not seen in bipolar disorder or depression<sup>4,5,6</sup>

1. Keefe et al. Schizophr Bull. 2007;912-920. 2. Nuechterlein KH et al. Schizophr Res. 2004;29-39. 3. Kahn RS et al. JAMA Psych. 2013;70(10):1107-1112. 4. Mollon J et al. JAMA Psychiatry. 2018;75(3):270-279. 5. Zanelli J et al. Am J Psychiatry. 2019;176(10):811-819. 6. Meier MH et al. Am J Psychiatry. 2014;171(1):91-101.



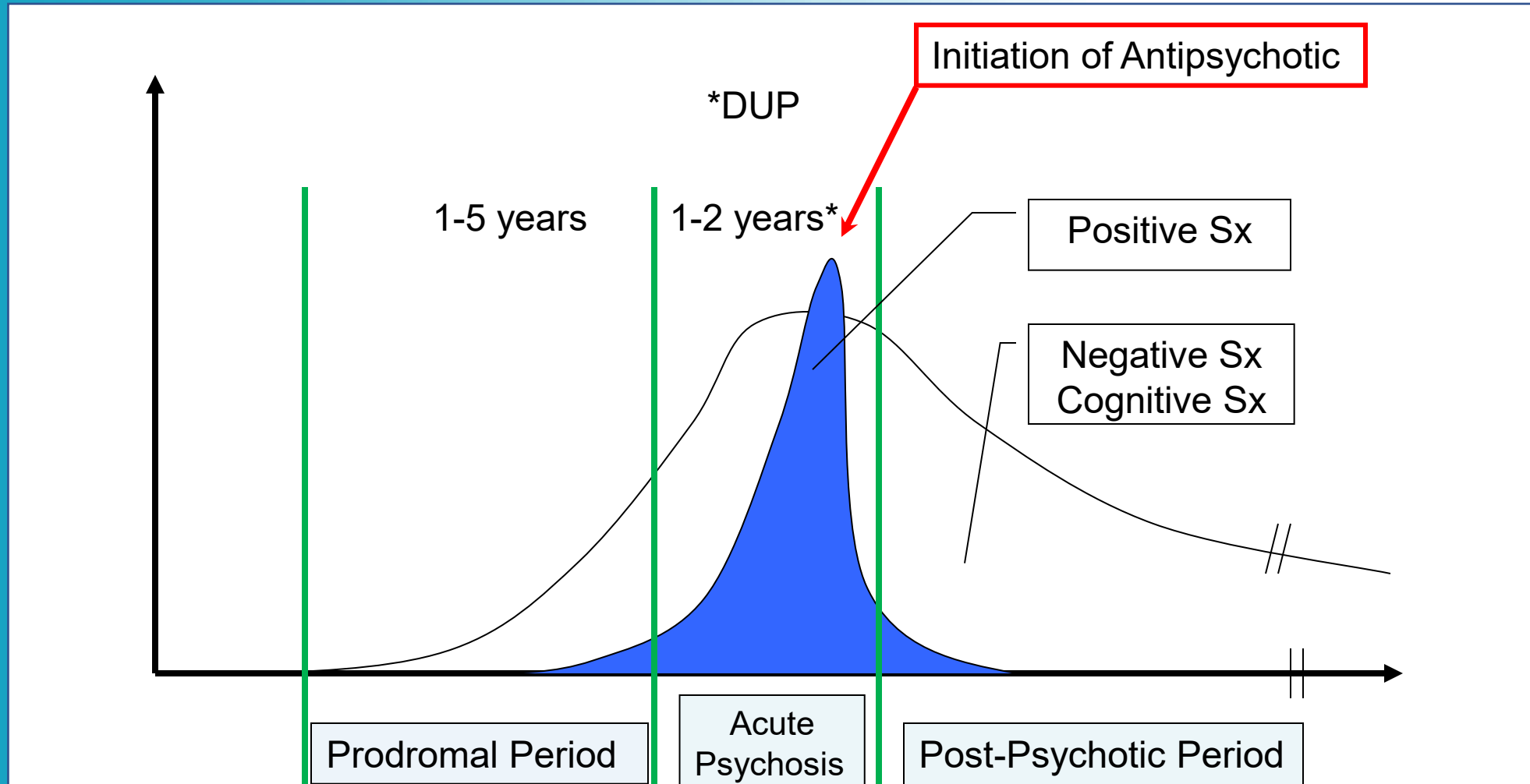
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# Phases of Illness

# Phases of Illness





# Phases of Illness

	<b>GOALS</b>	<b>KEY QUESTIONS</b>
<b>Prodromal Phase</b>	Prevent schizophrenia	What treatments work?
<b>Acute Psychosis</b>	Keep DUP short Achieve early remission of symptoms	Which antipsychotic? When to switch?
<b>Post-psychotic Phase</b>	Achieve sustained remission Promote recovery & QOL Prevent morbidity	Treat for how long? How do we prevent morbidity?



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# Acute Psychosis



# Which antipsychotic to use?

## You Must Choose Wisely

Efficacy

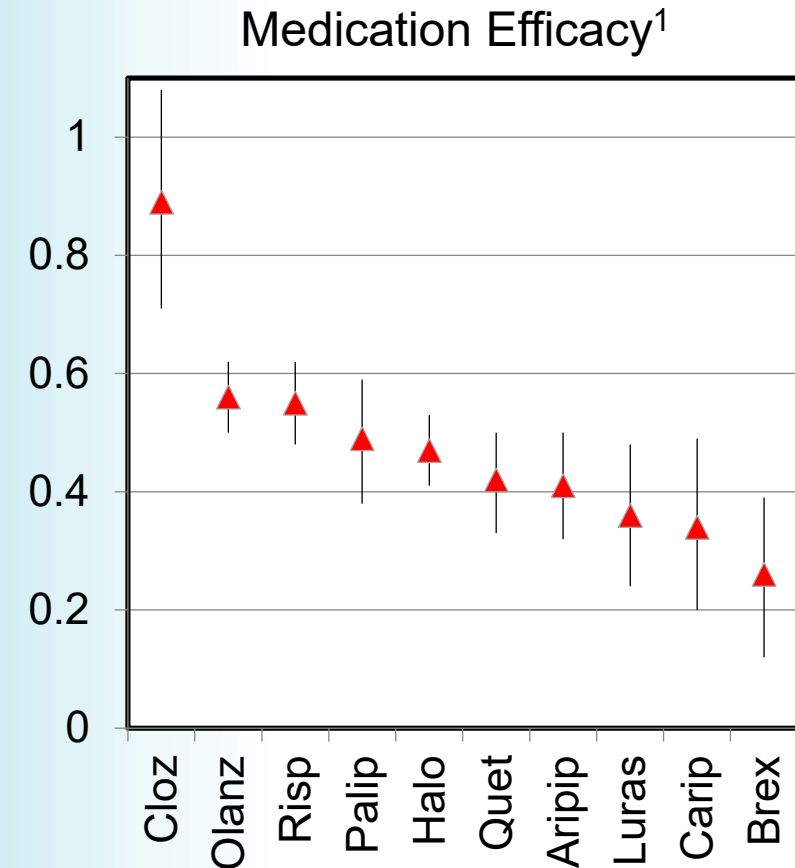
Metabolic  
Impact

LAI  
Availability



# Efficacy

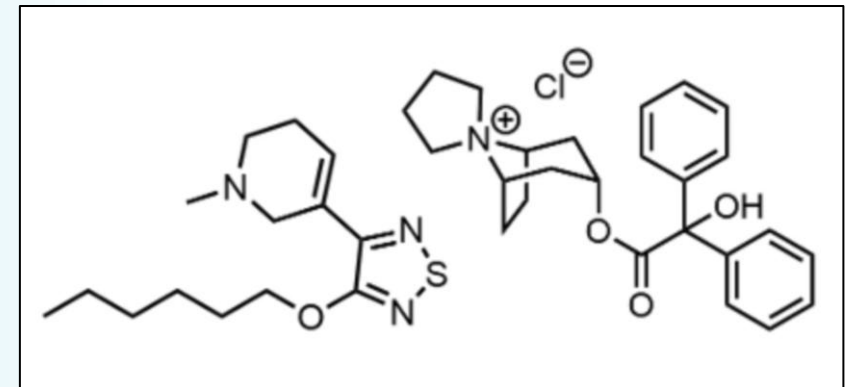
- Meta-analysis, 32 antipsychotics: FGAs, SGAs, Clozapine<sup>1</sup>
- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than the rest (small effect size)
- All others had similar efficacy
- Comparable meta-analysis in youth had similar findings but ziprasidone had inferior efficacy<sup>2</sup>



1. Huhn et al. Lancet. 2019;394(10202):939-951. 2. Pagsberg et al. J Am Acad Child Adolesc Psychiatry. 2017;56(3):191-202.

# Xanomeline + Trospium

- Novel mechanism of action
  - Muscarinic agonist ( $M_1$  &  $M_4$ ) + peripheral muscarinic antagonist
  - Treats psychosis by modulating cholinergic tone
  - Upstream from where FGAs & SGAs work
- Approved in adults only
- Studies underway in FEP and adolescents





# Metabolic Impact

## Long Term Metabolic Effects of Antipsychotics<sup>1</sup>

High	Med	Low	Very Low
<ul style="list-style-type: none"><li>• Clozapine</li><li>• Olanzapine</li></ul>	<ul style="list-style-type: none"><li>• Risperidone</li><li>• Paliperidone</li><li>• Quetiapine</li></ul>	<ul style="list-style-type: none"><li>• Aripiprazole</li><li>• Cariprazine</li><li>• Asenapine</li></ul>	<ul style="list-style-type: none"><li>• Lurasidone</li><li>• Ziprasidone</li><li>• Lumateperone<sup>2</sup></li><li>• Xanomeline / Trospium<sup>3</sup></li></ul>

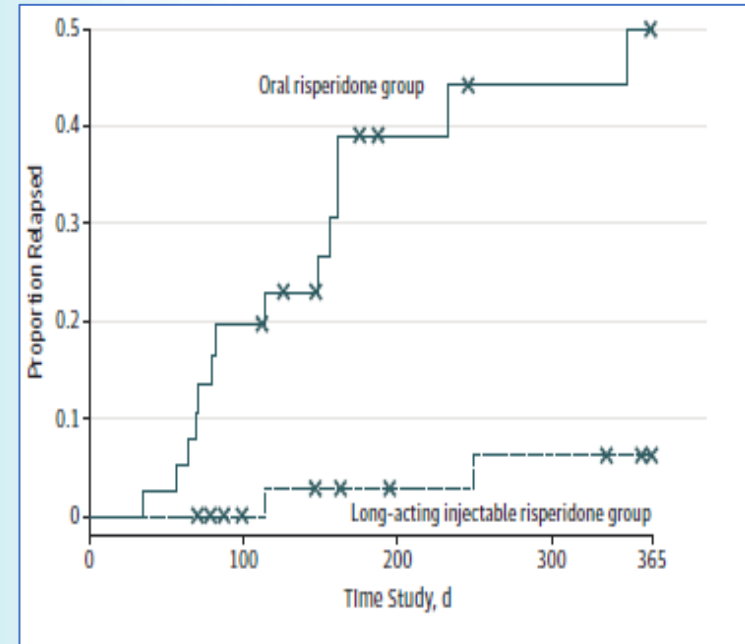
1. Burschinski A, et al. *World Psychiatry*. 2023;22:116-128. 2. McIntyre RS, et al. *Am J Psychiatry*. 2024;181:26-38.  
3. Kaul I, et al. *JAMA Psychiatry*. 2024;81(8):749-756.



# LAI in FEP

- LAIs increase adherence & allow for easier detection of non-adherence
- May be especially beneficial in FEP:
  - Improved positive symptoms<sup>1</sup>
  - Fewer relapses & hospitalizations<sup>2</sup>
- LAIs are life saving
  - 30% decrease in mortality<sup>3</sup>
  - 47% decrease in death by suicide<sup>4</sup>

Time to Relapse after First Episode



**Offer routinely as first-line  
maintenance choice**

1. Subotnik KL et al. JAMA Psychiatry. 2015;72(8):822-829. 2. Szmulewicz AG et al. Nature Mental Health 2025;3:421-428. 3. Taipale H et al. Schizophr Res. 2018;197:274-280. 4. Huang CY et al. JAMA Netw Open. 2021 May3;4(5):e218810.



# Bottom Line

- Given that efficacy is generally similar between most agents, start with any antipsychotic, except olanzapine or clozapine (PORT Guidelines<sup>1</sup>)
- Engage in shared decision making with the patient<sup>2</sup>
  - Consider efficacy
  - Consider metabolic effects and other side effects
  - Consider LAI availability

1. Buchanan RW et al. Schizophr Bull. 2010;36(1):71-93. 2. McCutcheon RA et al. Lancet Psychiatry. 2025;12(5):384-394.



# When to switch antipsychotics?

- Clinical improvement is slow
  - Positive symptoms can take 2-4 weeks to show initial response, and longer to show full response<sup>1</sup>
  - Negative symptoms and cognitive symptoms can take months to show response, complete resolution is unlikely
- If there is minimal improvement after 4 weeks on a therapeutic dose, consider switching<sup>1</sup>

1. APA Practice Guideline for the Treatment of Patients with Schizophrenia, 2020.



# Clozapine

- ~20% of FEP patients will not respond to FGAs or SGAs<sup>1</sup>
- Patients with 2 failed trials should be offered clozapine
  - REMS discontinuation → less burdensome monitoring requirements<sup>2</sup>
- Clozapine is the only FDA-approved medication for treatment resistant schizophrenia
- Clozapine is associated with lower all-cause mortality compared to other antipsychotics<sup>3</sup>
- Clozapine can be used safely in youth, but youth are more sensitive to its side effects<sup>4</sup>

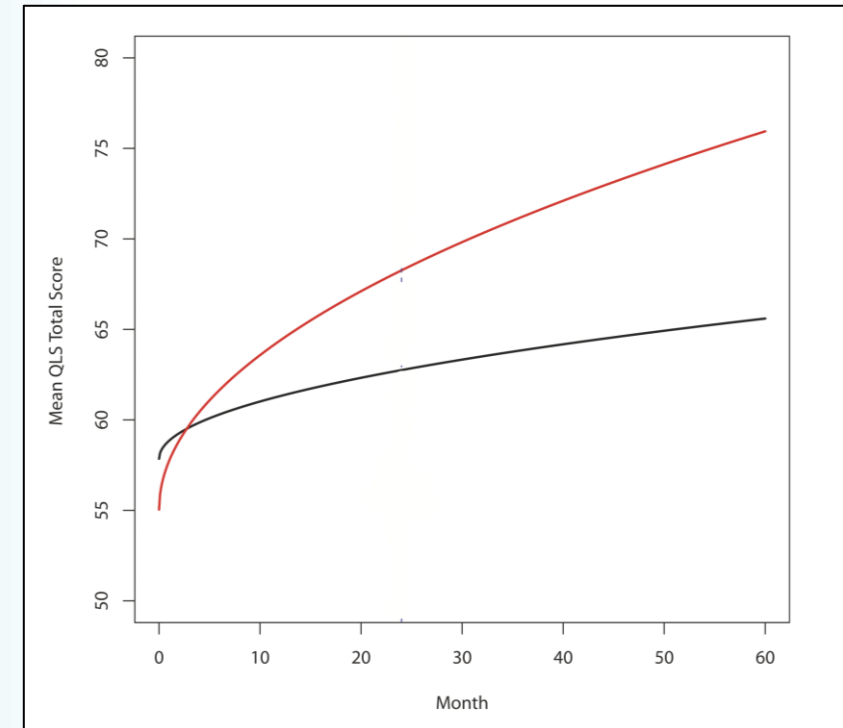
1.. Zhu Y,et al Eur Neuropsychopharmacol. 2017;27(9):835-844. 2. Donovan et al. Psychiatr Serv.. 2026. In Press. 3. Vermeulen JM et al. Schizophr Bull. 2019;45(2):315-329. 4. Sporn AL et al. J Am Acad Child Adolesc Psychiatry. 2007;46(10):1349-1356.



# Beyond Medication: Coordinated Specialty Care (CSC)

- Core components<sup>1</sup>:
  - Specialized psychopharmacology
  - Individual therapy: Individual Resiliency Training
  - Family Psychoeducation
  - Supported Employment and Education
- Benefits:
  - Lower risk of relapse and hospitalization<sup>2</sup>
  - Greater symptomatic improvement<sup>2</sup>
  - Improved functioning and quality of life<sup>1,2</sup>
  - Lower suicide rate<sup>3</sup>

Mean Quality of Life Score<sup>4</sup>



1. Kane JM et al. Am J Psychiatry 2016;173(4):362-72. 2. Correll C et al. JAMA Psychiatry. 2018;75(6):555-565. 3. Chan S et al. JAMA Psychiatry. 2018;75(5):458-464. 4. Robinson DB et al. Schizophr Bull. 2022;48(5):1021-1031.



# Post-Psychotic Phase

- Treatment question:
  - How long do you treat the first episode?
  - How do we prevent morbidity?



# How long to treat?

Patients with schizophrenia whose symptoms improved with antipsychotics should continue to be treated with antipsychotics

APA  
Guidelines<sup>1</sup>

Some people with a brief episode of psychosis or an uncertain diagnosis may not require ongoing antipsychotic treatment

Individuals with clear diagnostic features of schizophrenia will likely have poorer outcomes if medications are stopped

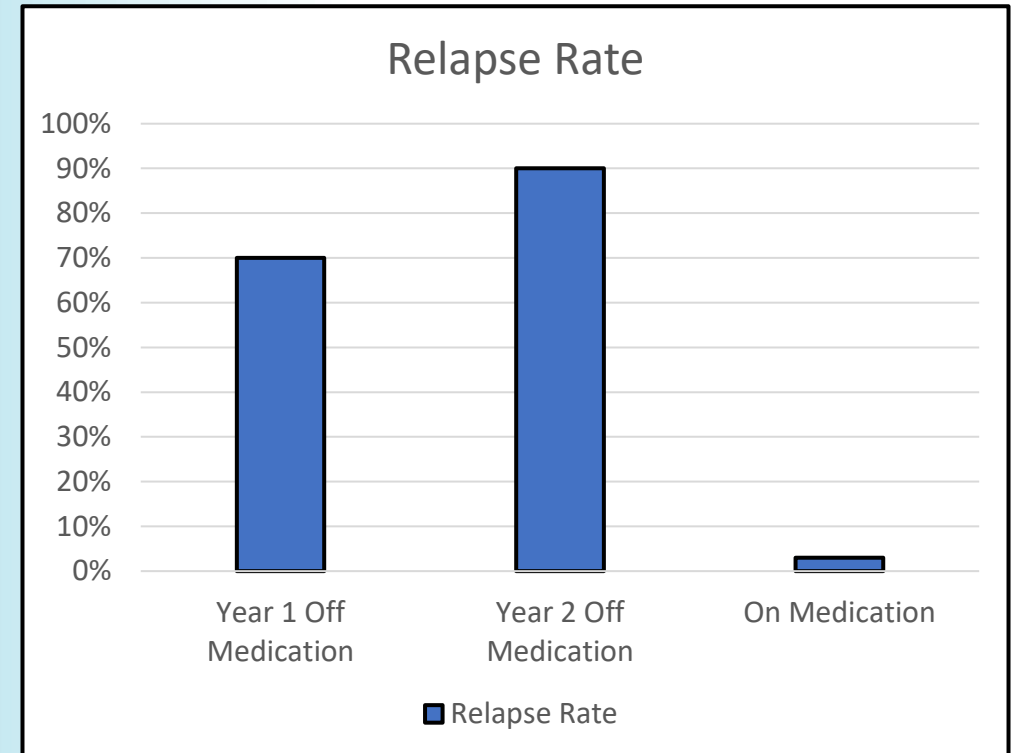
Poor outcomes: persistent psychosis<sup>2</sup>, treatment failures<sup>3</sup>, increased risk of death<sup>3</sup>

1. APA Practice Guideline for the Treatment of Patients with Schizophrenia, 2020. 2. Hui C et al. Lancet Psychiatry. 2018;5:432-442. 3. Tiihonen J et al. Am J Psychiatry. 2018;175:765-773.



# Relapse Off Medication

- Systematic review of planned medication discontinuation after a first episode of non-affective psychosis
- All participants had symptomatic remission at the time of medication discontinuation
- Relapse rates:
  - 70% at 1 year off medication
  - 90% at 2 years off medication
  - 3% at 1 year for those on medication



Zipursky RB et al. Schizophr Res. 2014;152(2-3):408-414.



# Why does relapse matter?

- Relapse creates social toxicity
- Relapse creates neurotoxicity

## After Relapse:

- It takes longer to respond to medication<sup>1</sup>

- Higher doses are often needed<sup>1</sup>

- Fewer people have a favorable treatment response<sup>1,2,3</sup>

- Early relapse predicts poor long-term outcomes<sup>4</sup>

Relapse Prevention Is Key

1. Takeuchi H et al. Neuropsychopharmacology. 2019;44(6):1036-1042. 2. Emsley R et al. J Clin Psychopharmacology 2013;33(1):80-83.  
3. Emsley R et al. Schizophr Res. 2012;138(1):29-34. 4. Hui C et al. Lancet Psychiatry. 2018;5:432-442.



# Bottom Line: Maintenance Treatment

- Strongly encourage long-term treatment at the lowest effective dose
- Most patients ask for a trial off medication
  - They will do it with or without you
- After 2 years of stability, for low-risk patients, after significant discussion, consider gradual taper over at least 6 months, with close monitoring<sup>1</sup>
- A small subgroup of patients may maintain remission/partial remission off medication<sup>2</sup>
- Multi-episode patients will need indefinite maintenance treatment

1. McCutcheon RA et al. Lancet Psychiatry. 2025;12(5):384-394. 2. Goff et al. Am J Psychiatry 2017;174:840-849.



# Morbidity and Mortality

- Schizophrenia is associated with a 20-year decrease in life expectancy<sup>1</sup> & a 4-fold increase in mortality<sup>2</sup>
  - Mortality gap may be getting wider over time<sup>3</sup>
- Premature mortality is due to cardiovascular disease (#1), respiratory disease, infections and cancers<sup>3,4</sup>

**We MUST be part of closing the mortality gap**

1. Druss BG, et al. *Med Care*. 2011;49(6):599-604. 2. Revier CJ, et al. *J Nerv Ment Dis*. 2015;203(5):379-386. 3. Ward MC, et al. *JAMA Psychiatry*. 2019;76(7):759-760. 4. Olfson M, et al. *JAMA Psychiatry*. 2015;72(12):1172-1181.



# Preventing Morbidity: Antipsychotic-Induced Weight Gain

- Almost all FGA/SGA antipsychotics show weight gain after extended use<sup>1</sup>
  - Weight gain more pronounced in antipsychotic-naïve patients<sup>2</sup>
  - Not universally dose dependent- individual antipsychotics have their own dose-response curves<sup>3</sup>
- Rapid early on, plateaus over time (6 months-1 year)<sup>1</sup>
- Decreased insulin sensitivity & lipid changes develop rapidly (2-4 weeks)<sup>4,5</sup>
- Early monitoring is key

1. Burschinski A, et al. *World Psychiatry*. 2023;22:116-128. 2. Bak M, et al. *PLoS One*. 2014;9(4):e94112. 3. Sabe M, et al. *J Clin Psychiatry*. 2023.84(2):22r14490. 4. Cao H, et al. *J Psychiatr Res*. 2020;129:265-271. 5. Zhang Y, et al. *J Clin Psychiatry*. 2020;81(3):19M12785.



# Monitoring

- Baseline monitoring: BMI, waist circumference, glucose, HbA1c, lipids
- Ongoing monitoring:
  - Weight at every visit
  - HbA1c and lipids at regular intervals, particularly early on, annually thereafter
- “Perfect is the enemy of good enough”
  - Non-fasting labs are acceptable<sup>1</sup>
- Telehealth requires innovative monitoring

1. Mora S, et al. *JAMA Intern Med.* 2019;179(7):898-905.



# Metformin

## Safety

- Rare lactic acidosis
- May be associated with B12 deficiency

## Dosing

- Target Dose:<sup>1</sup>
- Youth <50kg: 1000 mg TDD
- Youth >50kg: 2000 mg TDD
- Give with food

## Efficacy

- Significant decrease in weight, BMI, HbA1c, lipids<sup>2</sup>
- Most effective prior to development of obesity<sup>3</sup>

## Initiation

- Co-initiation:<sup>4</sup>
- High-risk antipsychotic
- Moderate-risk antipsychotic + health risk factor

1. Correll CU et al. *World Psychiatry*. 2020;19:69-80. 2. Zheng W, et al. *J Clin Psychopharmacol*. 2015;35(5):499-509. 3. Chen H, et al. *J Clin Psychiatry*. 2024;85(1):23M14894. 4. Carolan A, et al. *Schizophr Bull*. 2024. Dec 9:sbae205.



# Summary

- Key treatment goals for the first episode of schizophrenia
  - Antipsychotic selection
    - Efficacy, metabolic impact, LAI availability
  - Beyond medication: Coordinated Specialty Care
  - Encourage maintenance treatment for most patients
  - Monitoring and intervention to prevent morbidity



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# Thank You

## **MGH Psychosis Clinical and Research Program**

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