



# Pediatric Schizophrenia

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# Disclosure

Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.

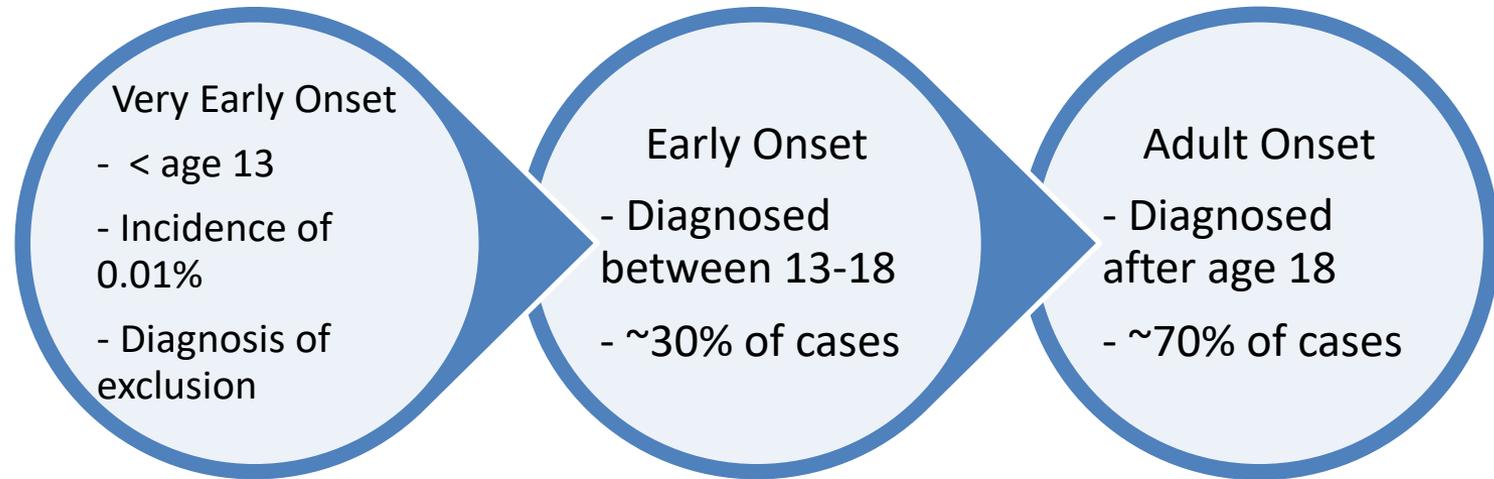
# Learning Objectives

- Learn to recognize the first episode of schizophrenia.
- Understand the relevant psychopharmacologic treatment options for pediatric schizophrenia.
- Understand the relevant psychopharmacologic treatment options of antipsychotic related metabolic side effects.

# Epidemiology

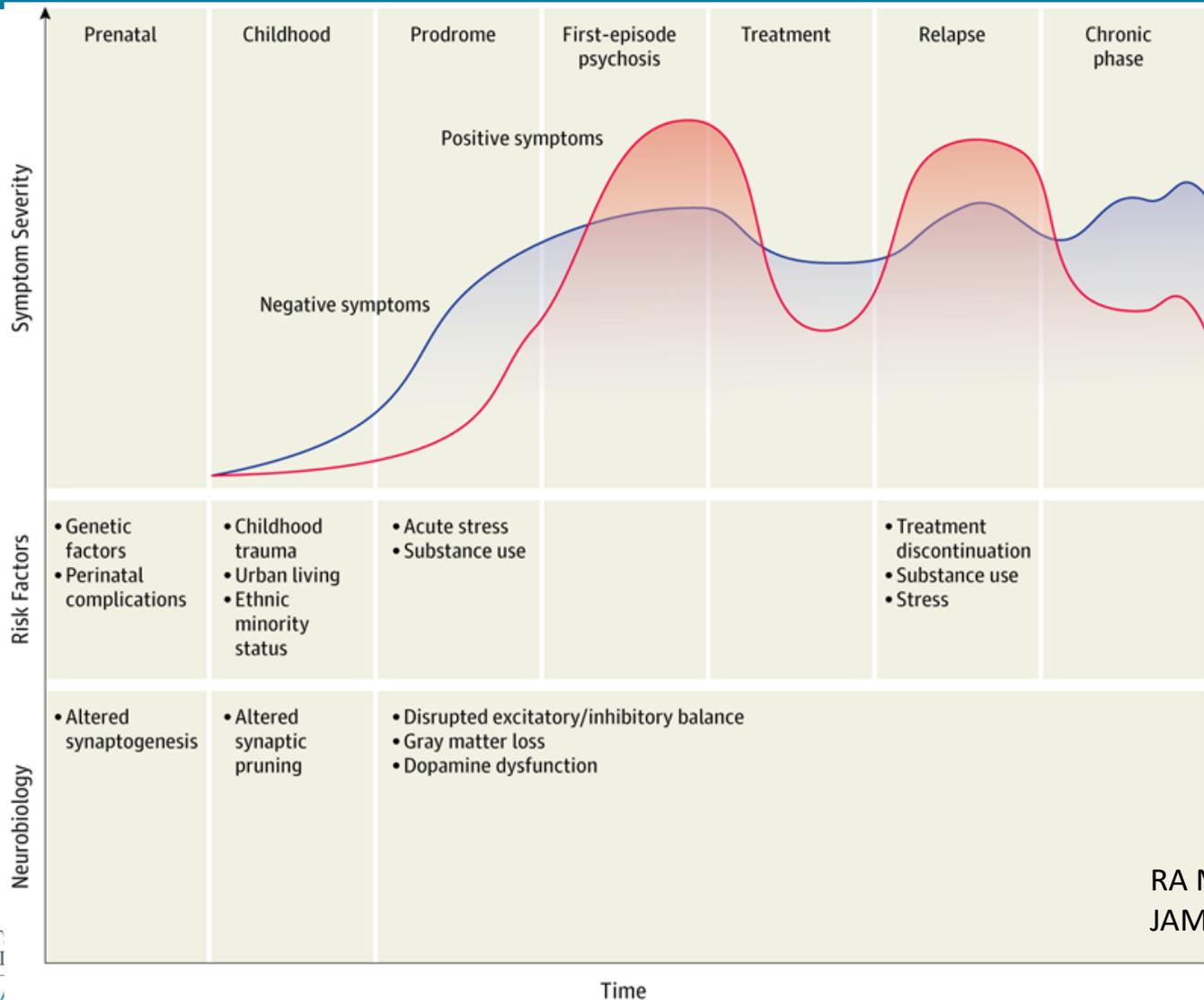
Lifetime prevalence is ~1%.

## 3 Age Groups:



Average age of onset is between 16- 25 years old, earlier in men.

# Phases of Illness

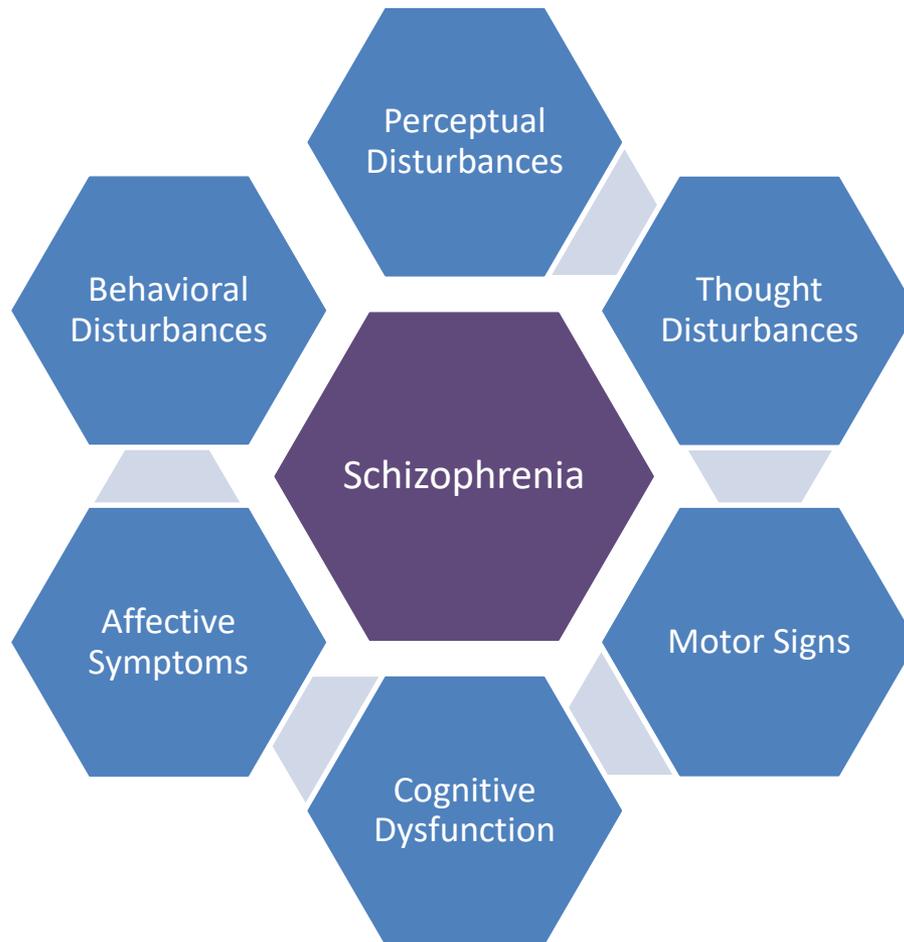


RA McCutcheon et al.  
JAMA Psych 2019

# Diagnosis

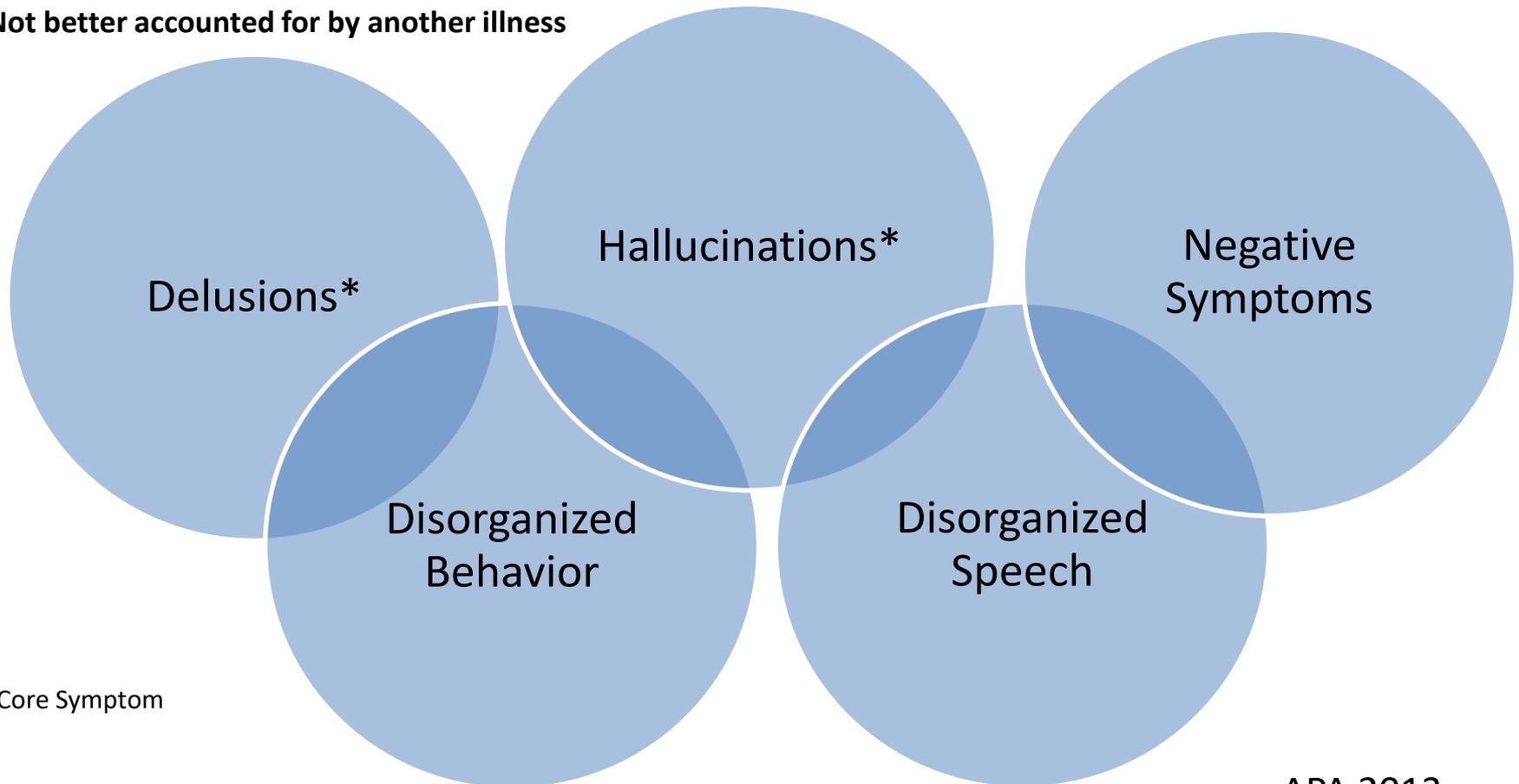
- The history is all we have, so take a good one.
- Get collateral information.
- Always ask about developmental and family hx.
- Drill down on symptoms- avoid the “check-box” approach.
- We use the DSM 5 criteria to diagnose pediatric schizophrenia, but it alone does not ensure an accurate diagnosis.
- Be phenomenological. Use a domain-based approach.

# Domains of Schizophrenia



# DSM 5 Criteria

- At least 2 symptoms (1 must be a core symptom) for 1 month
- Total duration of symptoms of 6 months with functional decline
- Not better accounted for by another illness



\*Core Symptom

# Cognitive dysfunction is a core feature of Schizophrenia

- Deficits can be up to 2 SDs less than age-matched, healthy controls.
- Present before illness onset and worsens during active illness.
- Affected areas:
  - Attention
  - Executive Function
  - Memory
  - Processing Speed
  - Social Cognition

Mesholam-Gately, et al. Neuropsych, 2009.  
Brewer, et al. Schizo Bull, 2006.  
Nuechterlein, et al. Schizo Res, 2004.

# Cognitive dysfunction



Predicts illness  
development and  
functional outcome



Antipsychotics do not  
substantially improve  
cognitive functioning.

Fett et al. Neuro Bio Rev 2011.

Frazier et al. JAACAP 2012. [www.mghcme.org](http://www.mghcme.org)

# Early treatment is critical

Prompt detection and initiation of antipsychotic medication.



**MINIMIZE THE DUP!**

# What are the options?

- Second Generation (“Atypical”) Antipsychotics
  - 11 agents
  - 6 have FDA approval in pediatric populations
  - 1<sup>st</sup> line recommendation given better tolerability
- First Generation (“Typical”) Antipsychotics
  - 6 FDA approved agents

# Risperidone

- FDA Approved for ages 13-17
- Antagonism at 5HT<sub>2A</sub>, D<sub>2</sub>, alpha 1+2, H<sub>1</sub>
- Dosing
  - Initial: 0.5 mg
  - Target: 3 mg
  - Range: 0.5-6 mg
- Forms: tablet, liquid, ODT, LAI
- 1 LAI formulation- Consta
- Higher risk of hyperprolactinemia

# Paliperidone

- Active metabolite of risperidone
- FDA approved for ages 12-17 years old
- Dosing:
  - Initial: 1.5-3 mg
  - Target: 3-6 mg/d (<51kg)  
3-12 mg/d (>51kg)
  - Range: 1.5-12 mg/d
- Forms: extended release tab (cannot cut), LAI
- 2 LAI formulations- Sustenna, Trinza

# Aripiprazole

- FDA approved for ages 13-17
- Partial agonist at D2 and 5HT1A; 5HT2A antagonist. Long half-life (72 hours).
- Higher Cmax for pediatric patients
- Steady state achieved after 14 days
- Dosing:
  - Initial: 2-5 mg
  - Target: 10 mg
  - Max: 30 mg
- Forms: Tab, ODT, acute IM, LAI
- LAI formulations: Maintena, Aristada, Initio

# Olanzapine

- FDA approved for ages 13-17
- D2 and 5HT2A antagonism, as well as 5HT2C, 5HT3, 5HT5, D1-4, H1, Alpha 1, GABA<sub>A</sub>, beta adrenoreceptors, M1-5.
- Higher risk of weight gain/metabolic disturbance
- Dosing:
  - Initial: 2.5- 5 mg
  - Target: 10 mg
  - Max: 20 mg (higher doses are used)
- Forms: Tabs, ODT, IM, LAI

# Quetiapine

- FDA approved for ages 13-17
- Weaker antagonism at D2 and 5HT2A, strong alpha 1 blocker, H1
- Dosing:
  - Initial: 25 mg
  - Target: 400-800 mg/d
  - Max: 800 mg (higher doses used)
- Forms: tabs, XR (?less sedation)
- Monitoring of TSH, eye exam recommended

# Lurasidone

- FDA approved for ages 13-17
- Antagonist of D2, 5HT2A, 5HT7, partial agonist at 5HT1A
- Dosing:
  - Initial: 20-40 mg/d
  - Target: 40-80 mg/d
  - Max: 80 mg (up to 160 mg/d used)
- Forms: tabs (should be taken w/ 350 calories)

# Clozapine

- Not FDA approved for pediatric SCZ, but has shown superior efficacy compared to other neuroleptics
- “Broad spectrum” neuroleptic
- Dosing:
  - Initial: 12.5-25 mg/d
  - Target: 150-350 mg/d (follow levels)
  - Max: 900 mg/d
- Forms: tabs, ODT
- Requires monitoring of ANC due to risk of agranulocytosis (younger age = higher risk)
- Higher risk of seizure, myocarditis

# Ziprasidone and Asenapine not effective for adolescent schizophrenia

## Findling et al, 2013

- Ziprasidone
- 6 week RDBPCT followed by 26 week OLE
- Flexible dosing 40-160 mg/d
- No statistically significant separation from placebo aside from PANSS + scale

## Findling et al, 2015

- Asenapine
- 8 week RDBPCT followed by 26 week OLE
- 5 or 10 mg/d fixed dosing
- PANSS did not separate from placebo

# Newer antipsychotics

## Iloperidone

- Not FDA approved for teens with SCZ
- 1-12 mg BID
- D2 + 5HT2A antagonism
- Sedation/weight gain

## Brexipiprazole

- Not FDA approved for teens with SCZ
- 2-4 mg/d
- Partial D2 agonist
- Less weight gain
- Akathisia

## Cariprazine

- Not FDA approved for teens with SCZ
- 1.5-6 mg/d
- Partial agonist at D2/3, 5HT1A, low affinity for 5HT2C/alpha 1a
- Less weight gain
- Akathisia

## Lumateperone

- Not FDA approved for teens with SCZ
- 42 mg/d
- Novel mechanisms
- Less peripheral side effects.

# FGAs

- FDA Approved Agents:
  1. Chlorpromazine
  2. Haloperidol
  3. Perphenazine
  4. Thioridazine
  5. Thiothixene
  6. Trifluoperazine

First episode trials have shown reduced rates of discontinuation of SGAs compared to FGAs.

# So many options...How do I choose?

## Consider:

- Illness Features
- Side effect profile
- Patient/Family Preference
- Cost
- Availability

Start with any antipsychotic

\*except olanzapine and clozapine (per PORT guidelines)

Consider a long-acting injectable antipsychotic

Buchanan RW. Schizophr Bull 2010.

# Offer LAI as first-line maintenance medication

## SEVERAL OPTIONS

- risperidone
- paliperidone
- aripiprazole
- olanzapine
- haloperidol
- fluphenazine

## ADHERENCE

- increases adherence
- allows for easier detection of non-adherence

## BENEFICIAL IN EARLY EPISODE

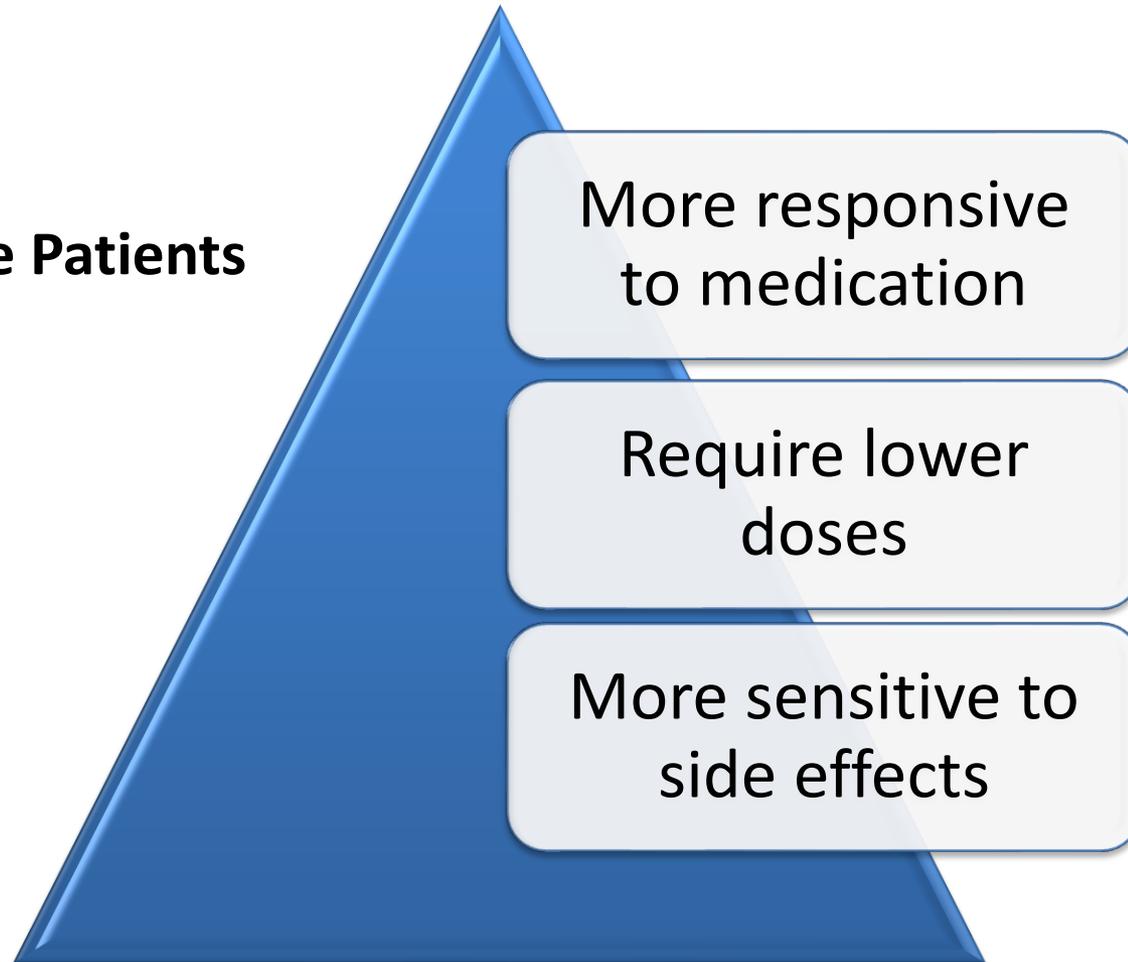
- Decrease in exacerbations
- Significant delay in time to 1<sup>st</sup> hospitalization
- Reduced time to relapse
- Reduction in hospitalization rate

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

Subotnik JAMA Psychiatry 2015  
Correll, et al. J Clin Psych 2016  
Kane, et al. JAMA Psych 2020

# First episode patients require careful dosing

**First-Episode  
vs.  
Multi-Episode Patients**



# When to Switch?

**After 6 weeks of adequate dosage if the effect is insufficient.**

**Clinical improvement is gradual**

**Positive symptoms can take weeks to resolve**

**Negative symptoms and cognitive symptoms may not resolve**

# Another Plug for Clozapine

- 20% of patients will not respond to FGAs or SGAs
- Patients with 2 failed trials should be offered clozapine.
  - The only antipsychotic agent for which there is established superiority over other agents.
- Childhood-onset schizophrenia (COS) is a more severe form of the disorder.
- Progression to the use of clozapine should be considered in COS.

Kumra et al, Biol Psychiatry 2008;  
Sporn et al, JAACAP 2007;  
Kane, J. Psych Congress, 2016.

# Long term maintenance treatment is the rule for treating first episode schizophrenia

## LOW RISK

After 1-2 years of stability, with discussion, close monitoring and warning, consider gradual taper

## REMISSION

Remission/partial remission off medication may be possible for a small subgroup

## MULTI-EPIISODE

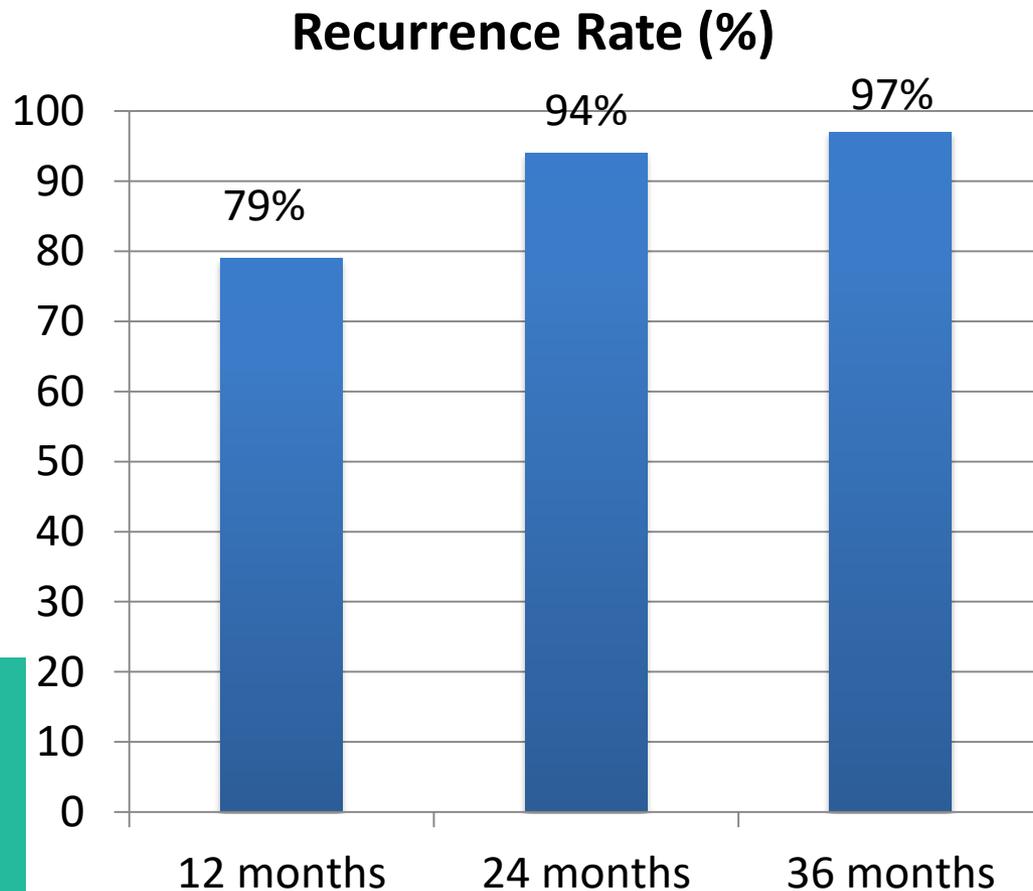
Multi-episode patients require indefinite maintenance treatment

**Most patients want a trial off medication, with or without you**

# Higher relapse rates with medication discontinuation

- First episode patients
- Stable for 2 years
- Tapered gradually from antipsychotic medication
- Followed for 3 yrs, open label

Encourage first episode patients to stay on medication



Emsley J. Clin Psychiatry, 2012.

# Metabolic Monitoring

## Baseline:

- BMI
- Labs: Fasting glucose, lipids, BP
- Family history of obesity, DM, CVD, HTN

## BMI:

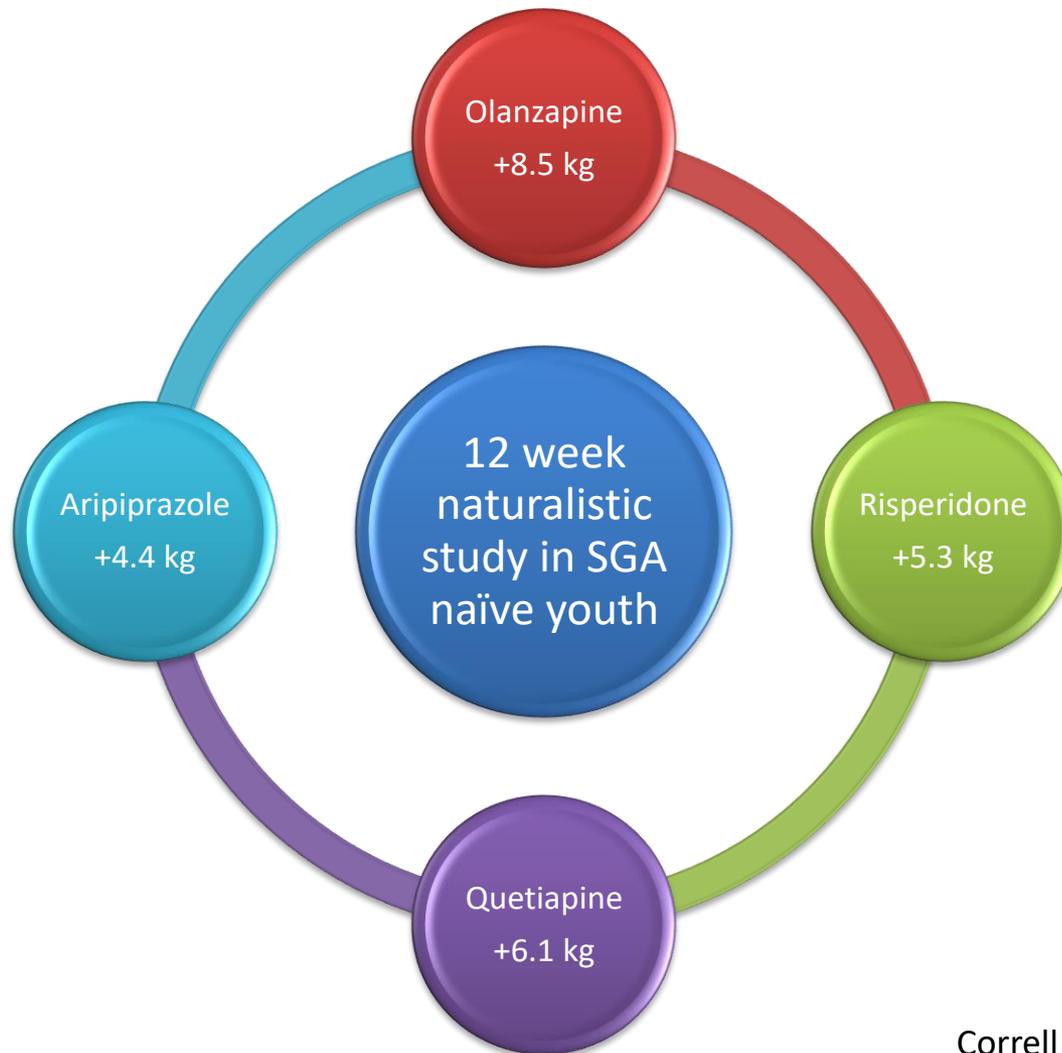
- check at 4, 8, and 12 weeks
- Every 3 months thereafter

## Labs

- Baseline
- At 3 months
- Then annually if normal\*

**Intervene for abnormalities**

# Children are more vulnerable to weight gain with antipsychotics



# Metformin

## Mechanism of action

Decreases hepatic production and GI absorption of glucose

Increases peripheral glucose utilization

Modulation of hypothalamic appetite regulatory centers

## Safety

- Rare lactic acidosis
- B12 deficiency
- GI

Does not cause hypoglycemia

## Dosing

Start with 500 mg daily or BID (comes in XR form)

Target dose is 2000 mg/d

Aroda J Clin Endocrinol Metab 2016.  
Zheng J Clin Psychopharmacol 2015.  
Yerevanian et al, Curr Obes Rep 2019

# What is Coordinated Specialty Care?

- Team-based, multi-modal approach to treating FEP.
- Collaborative, recovery-oriented approach.
- Most effective for non-affective psychoses in youth age 15-25 within 5 years of illness onset.
- Services offered during or shortly after FEP are effective for improving clinical and functional outcomes and quality of life.

Goldstein, A.B. and Azrin, S.T., 2014.

RAISE Study: Kane JM, et al. Am J Psychiatry 2016.

THANK YOU!

[www.massgeneral.org/schizophrenia](http://www.massgeneral.org/schizophrenia)