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PSYCHIATRY ACADEMY

# Schizophrenia & Pharmacological Approaches to Pediatric Mania

**Janet Wozniak, MD**

Director, Pediatric Bipolar Disorder Research Program

Associate Professor of Psychiatry

Harvard Medical School

Massachusetts General Hospital

**Abigail Donovan, MD**

Director, First Episode and Early Psychosis Program

MGH Schizophrenia Program

Assistant Professor of Psychiatry

Harvard Medical School

Massachusetts General Hospital



# Disclosures

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

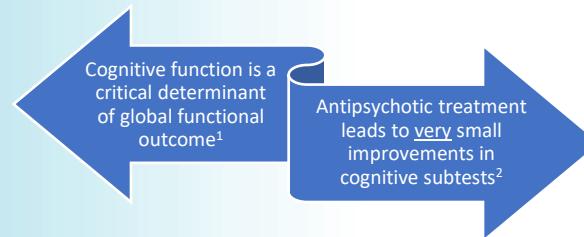
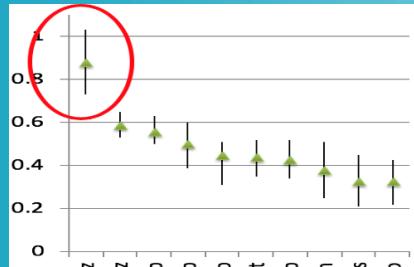
Dr. Janet Wozniak receives research support from the Baszucki Brain Research Fund, PCORI and Demarest Lloyd, Jr. Foundation. In the past, Dr. Wozniak has received research support, consultation fees or speaker's fees from Eli Lilly, Janssen, Johnson and Johnson, McNeil, Merck/Schering-Plough, the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH), Pfizer, and Shire. She is the author of the book, *"Is Your Child Bipolar"* published May 2008, Bantam Books.

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## Overview:

Schizophrenia onsets in adolescence and young adulthood and requires treatment early in course. Antipsychotic medications are first line treatment for schizophrenia and pediatric onset Bipolar Disorder

**Diagnosis:** Schizophrenia is associated with functional and cognitive decline



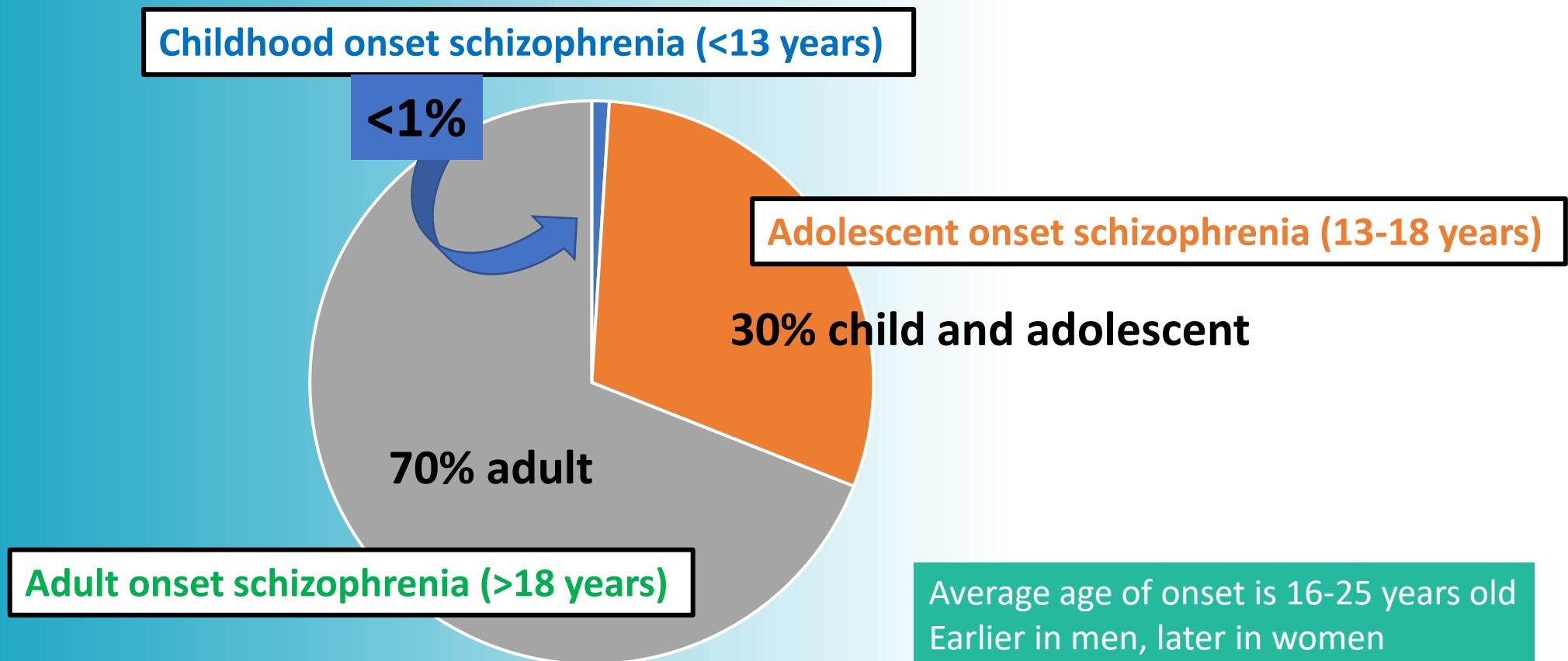
**Treatment:** Pharmacotherapy with antipsychotic medication is required for schizophrenia and pediatric bipolar disorder

**Emerging evidence base guides treatment decisions:** Long-term treatment is required for schizophrenia; bipolar disorder outcomes are better with early effective treatment



**Weight gain is a major adverse event:** Metformin and newer agents can help offset metabolic side effects of antipsychotics

**The lifetime prevalence of schizophrenia is 1% and onset prior to age 13 is rare**

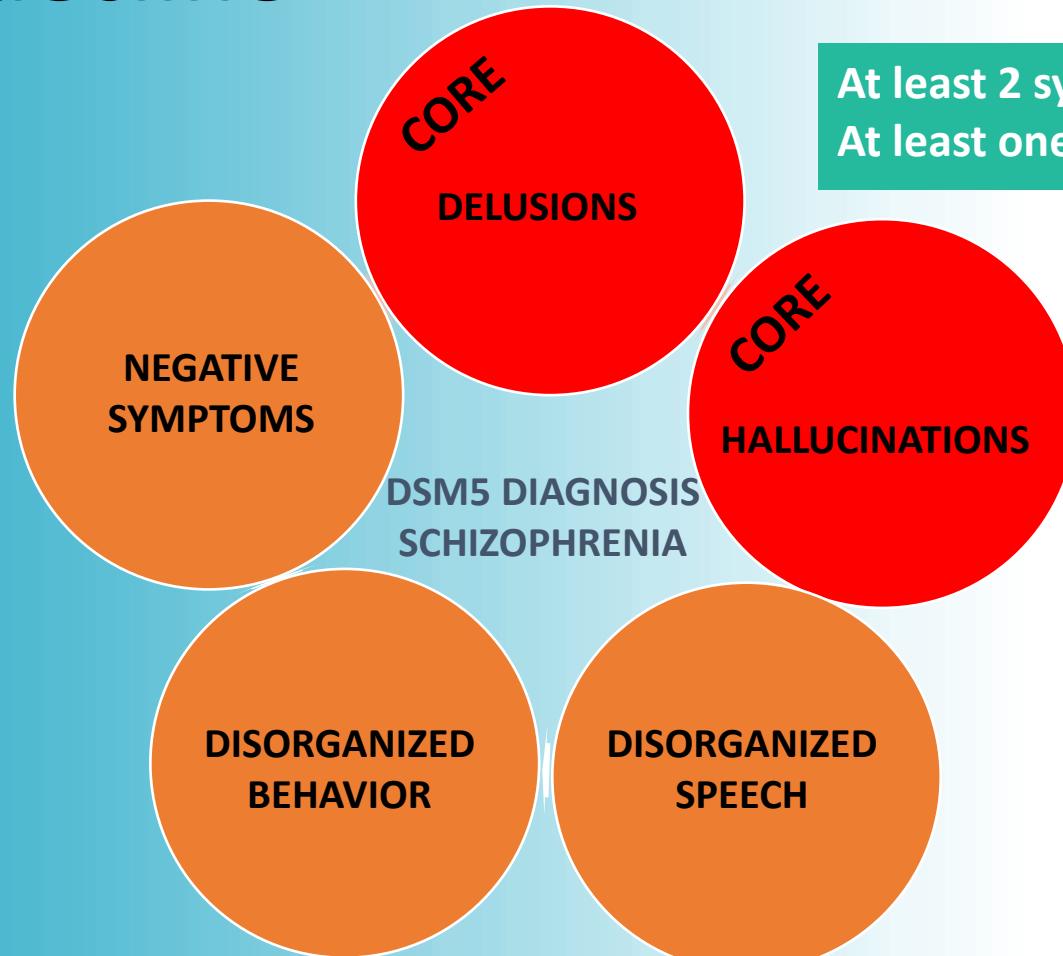




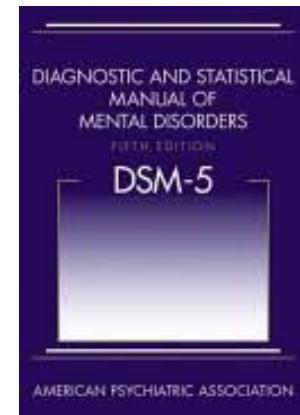
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# Schizophrenia criteria requires 6-month duration of symptoms and functional decline



At least 2 symptoms for one month  
At least one is a 'core' symptom





# Cognition is impaired in schizophrenia (but not in bipolar disorder)

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:

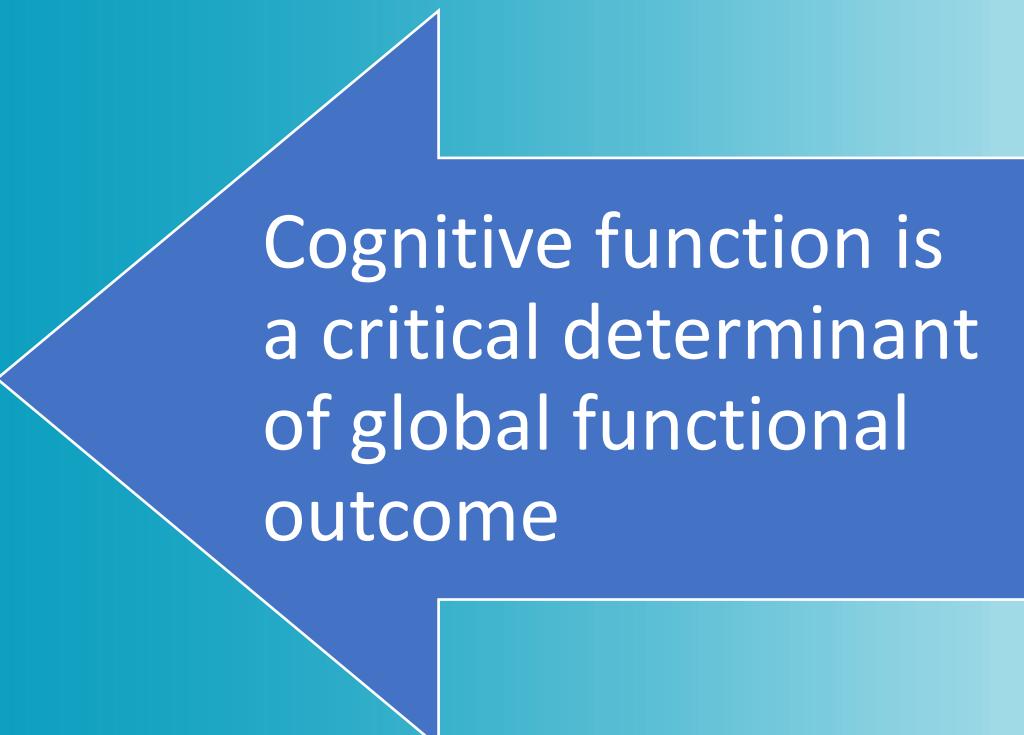
- nearly universal
- present before the onset of psychosis
- worsens during the illness<sup>3</sup>

**CHRONIC  
COGNITIVE  
IMPAIRMENT IS  
SPECIFIC TO  
SCHIZOPHRENIA<sup>4</sup>**

Keefe et al *Schizophr Bull*.2007 912-920; Nuechterlein KH et al. *Schizophr Res* 2004 29-39;  
Kahn et al. *JAMA Psych* 2013 1107-1112; Meier et al *Am J Psychiatry* 2014 91-101



# Cognition in schizophrenia is difficult to target



Cognitive function is a critical determinant of global functional outcome



Antipsychotic treatment leads to very small improvements in cognitive subtests

Kahn JAMA Psychiatry 2013:1107-1112; Frazier JAACAP 2012:496-505



# Acute psychosis and pediatric bipolar disorder require treatment, but:

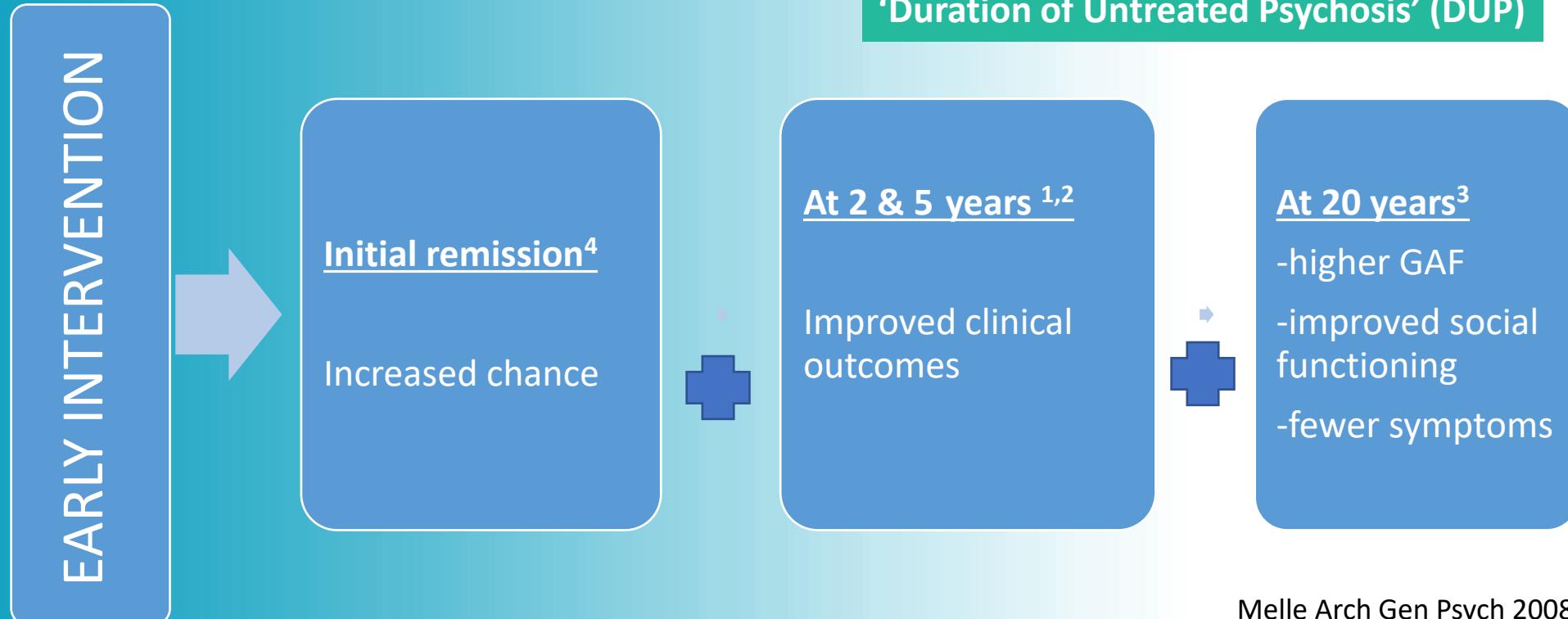


# Begin treatment of schizophrenia as soon as possible



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Melle Arch Gen Psych 2008;634-640  
Larsen Psychol Med 2011;1461-1469  
Cechnicki Psych Res 2014;420-425  
Fraguas Schizophr Res 2014;130-138



# Antipsychotics treat pediatric schizophrenia

Café Trial<sup>1</sup>  
SGAs only

Comparable efficacy for:

- olanzapine
- quetiapine
- risperidone

SGA=second generation antipsychotic  
FGA=first generation antipsychotic

EUFEST<sup>2</sup>  
FGAs and SGAs

- Comparable efficacy: haloperidol, quetiapine, ziprasidone, amisulpride, olanzapine
- SGA's better tolerated: 33-53% vs 72% FGA discontinuation rate

TEOSS<sup>3</sup>  
FGAs and SGAs  
children only

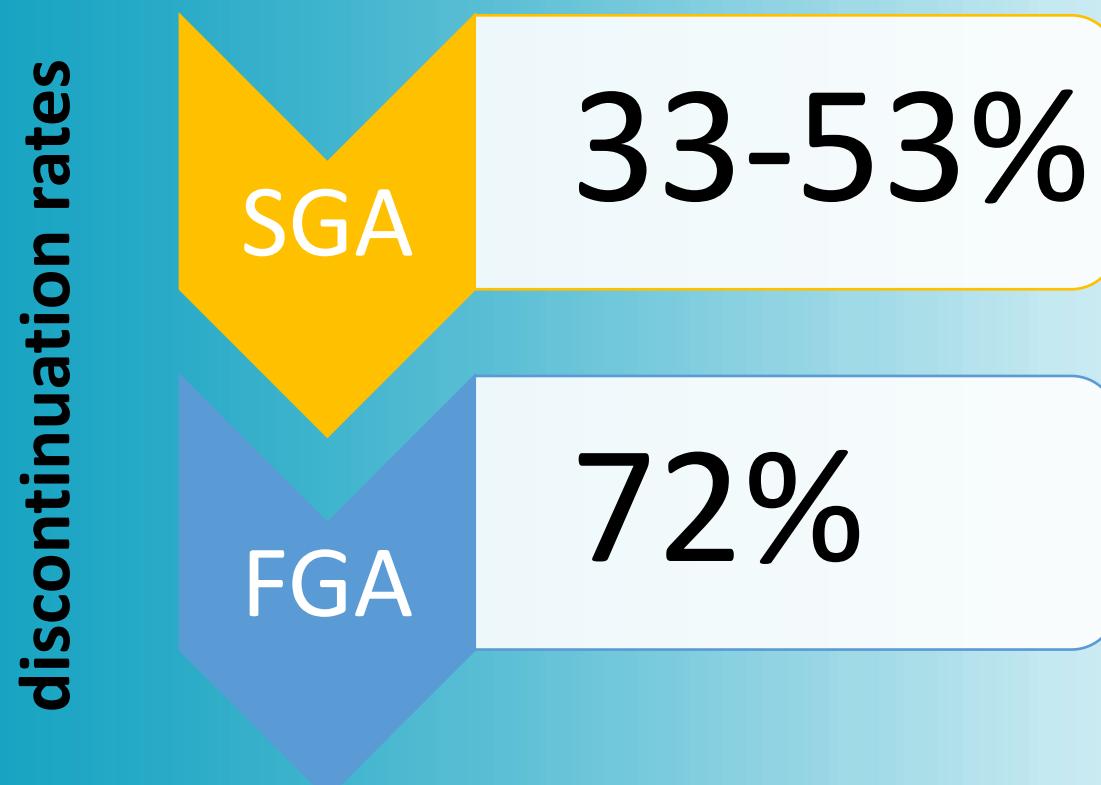
- Comparable efficacy and discontinuation: molindone, olanzapine, risperidone
- Olanzapine had significant weight gain

McEvoy Am J Psychiatry 2007;1050-1060

Kahn Lancet 2008;1085-1097

Sikich Am J Psychiatry 2008;1420-1431

# SGAs are better tolerated than FGAs, with lower discontinuation rates



SGA=second generation antipsychotic  
FGA=first generation antipsychotic

# Ziprasidone is effective for adults with schizophrenia, but not for adolescents



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TERMINATED  
TRIAL

META-  
ANALYSIS

ZIPRASIDONE TRIAL IN ADOLESCENTS  
DISCONTINUED DUE TO LACK OF  
EFFICACY

ZIPRASIDONE (AND ASENAPINE) FARE  
WORSE THAN OTHERS

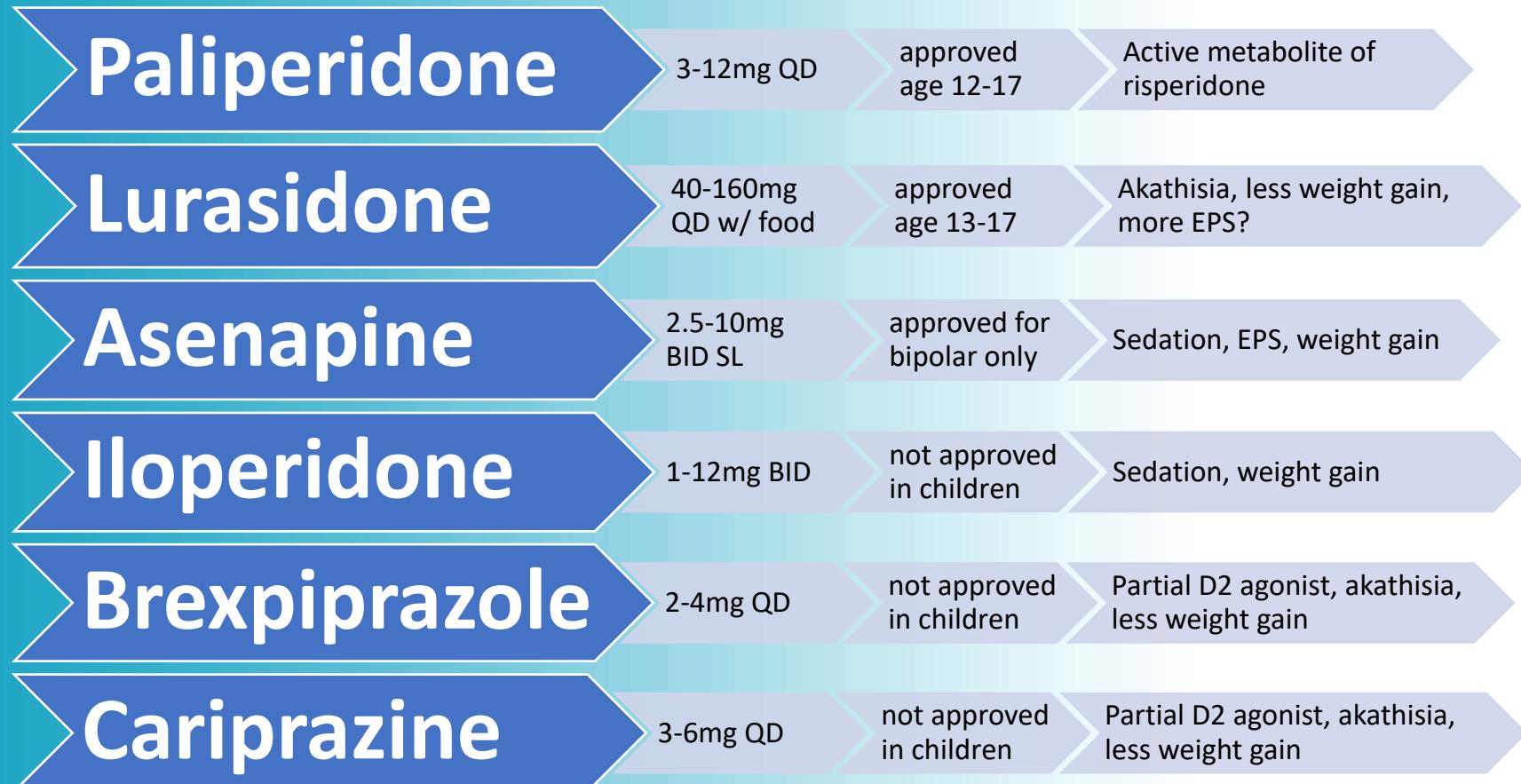
Findling Child Adolesc Psychopharmacol.2013;23(8):531-544  
Pagsberg J Am Acad Adolesc Psychiatry 2017;56(3):191-202

# Newer antipsychotic medications offer additional options for treatment



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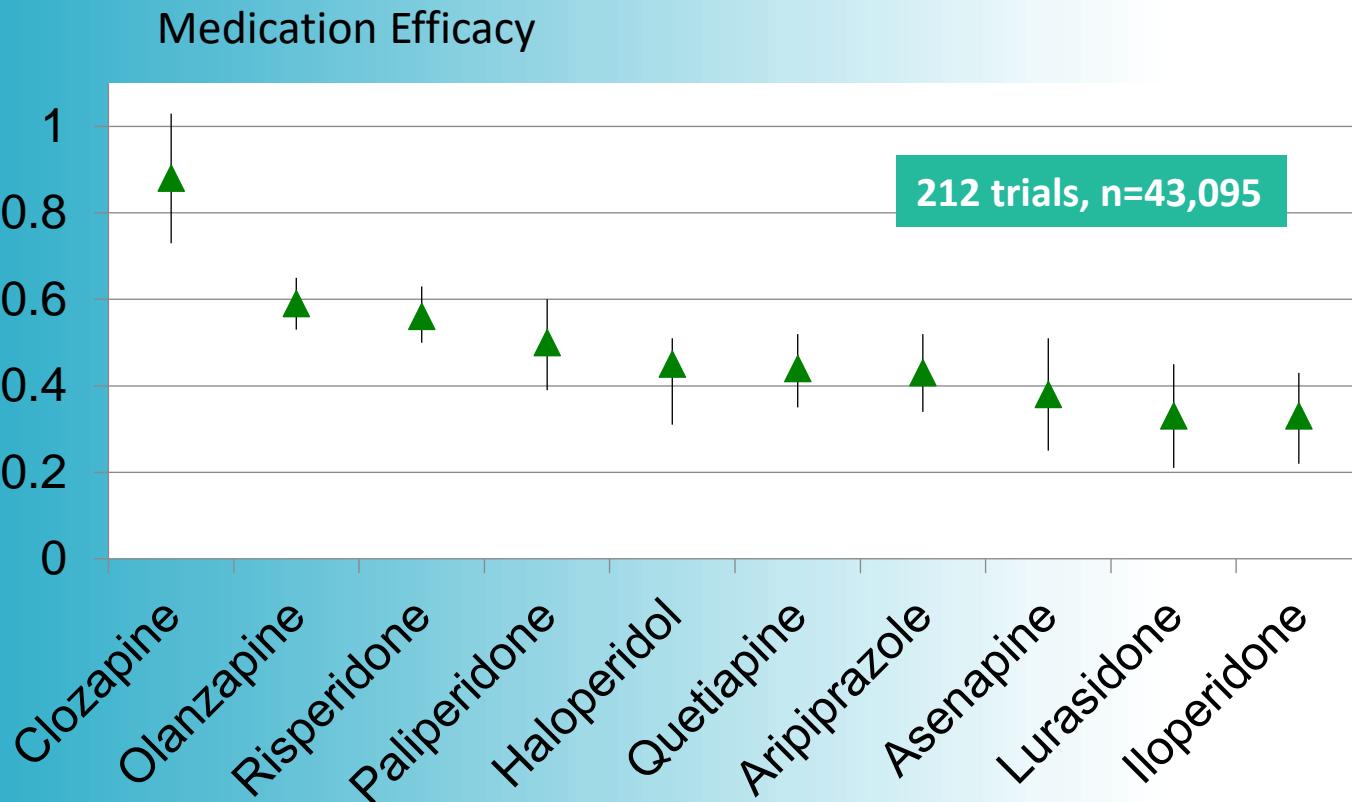
Also lumataperone a.k.a., Caplyta

# Large meta-analysis shows the comparative efficacy of first-generation antipsychotics (FGA), second-generation antipsychotics (SGA) and Clozapine



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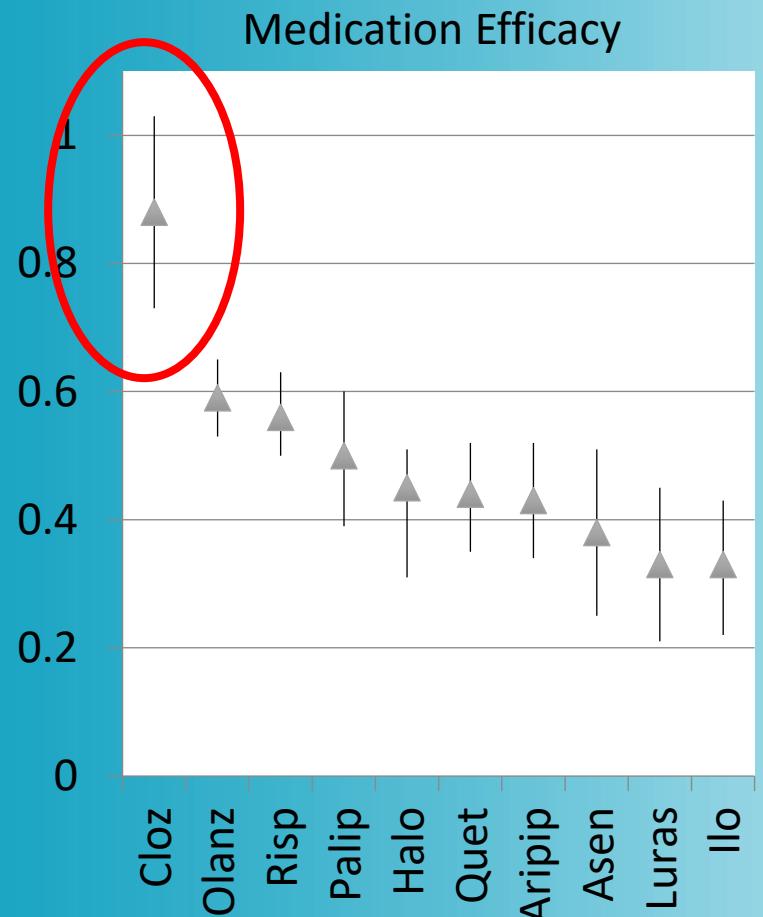
Leucht *Lancet* 2013;951-962

# Large meta-analysis shows the comparative efficacy of antipsychotic medications (FGA, SGA, Clozapine)



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- Clozapine was significantly more effective than the others

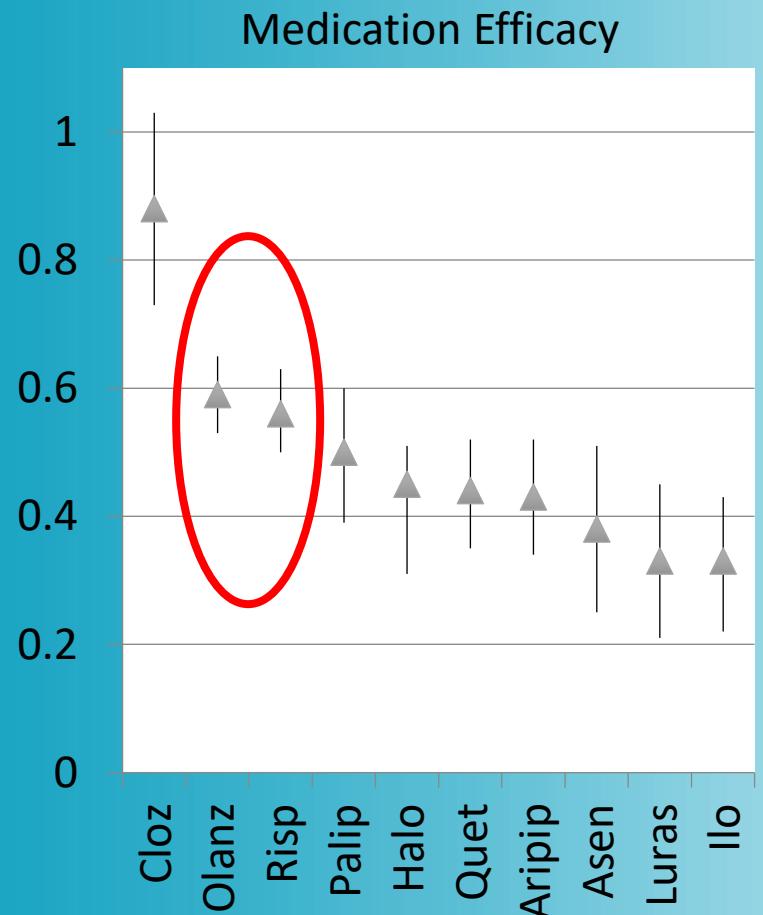
Leucht *Lancet* 2013;951-962

# Large meta-analysis shows the comparative efficacy of antipsychotic medications (FGA, SGA, Clozapine)



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- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than most

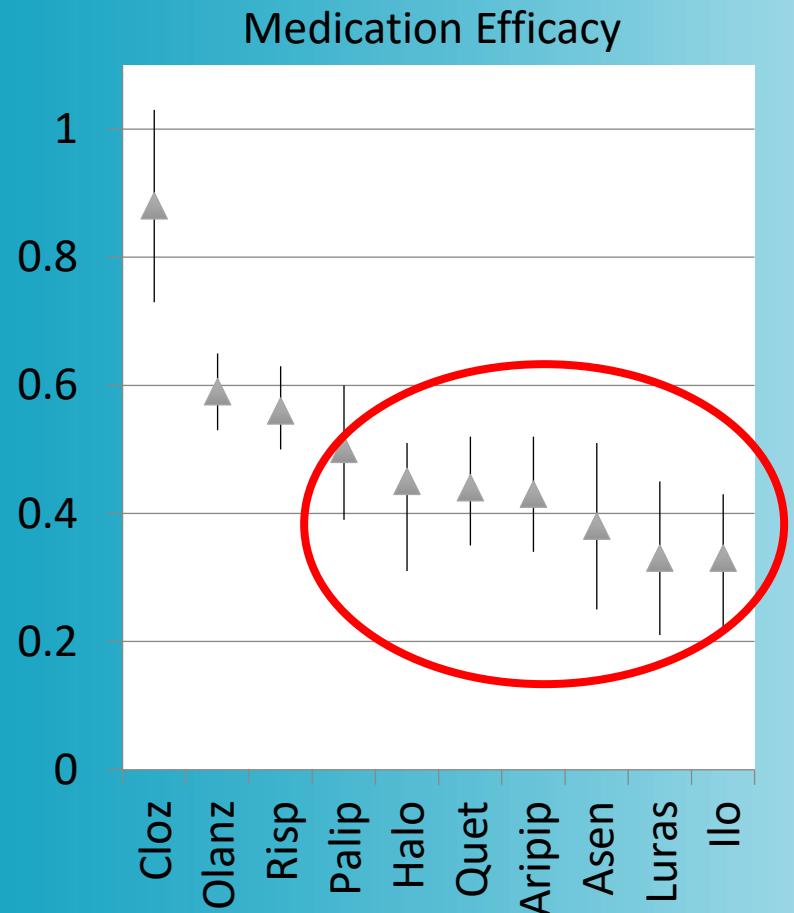
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# Large meta-analysis shows the comparative efficacy of antipsychotic medications (FGA, SGA, Clozapine)



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- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than most
- All others had similar efficacy

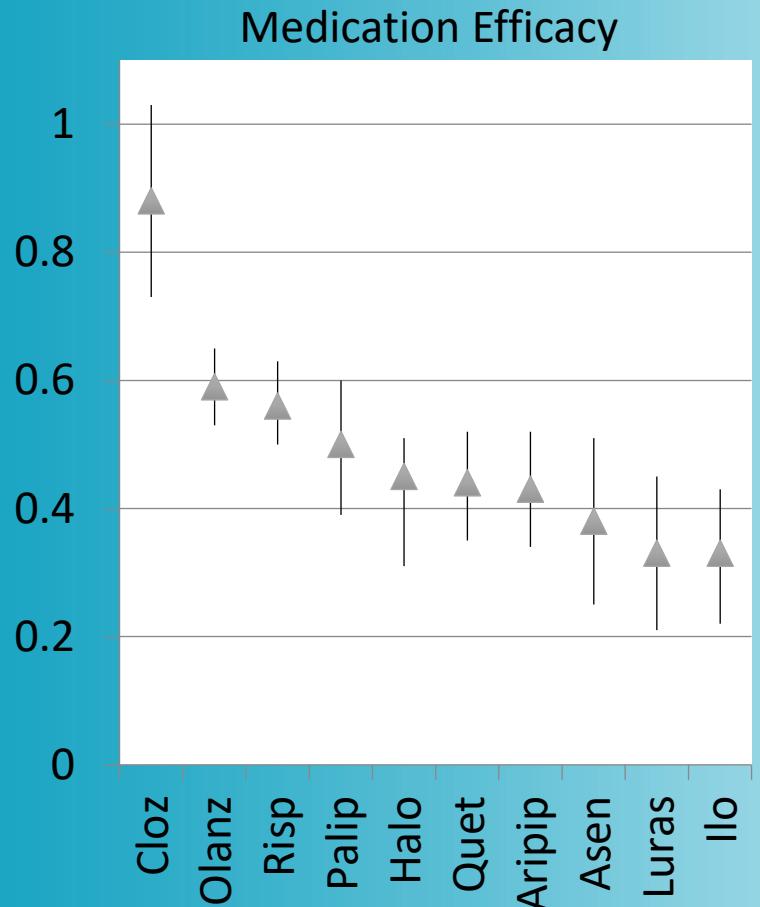
Leucht *Lancet* 2013;951-962

# Large meta-analysis shows the comparative efficacy of antipsychotic medications (FGA, SGA, Clozapine)



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- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than most (small effect size)
- All others had similar efficacy
- Haloperidol had highest all cause discontinuation

Leucht *Lancet* 2013;951-962



# Studies showing similar efficacy allow flexibility in medication choice

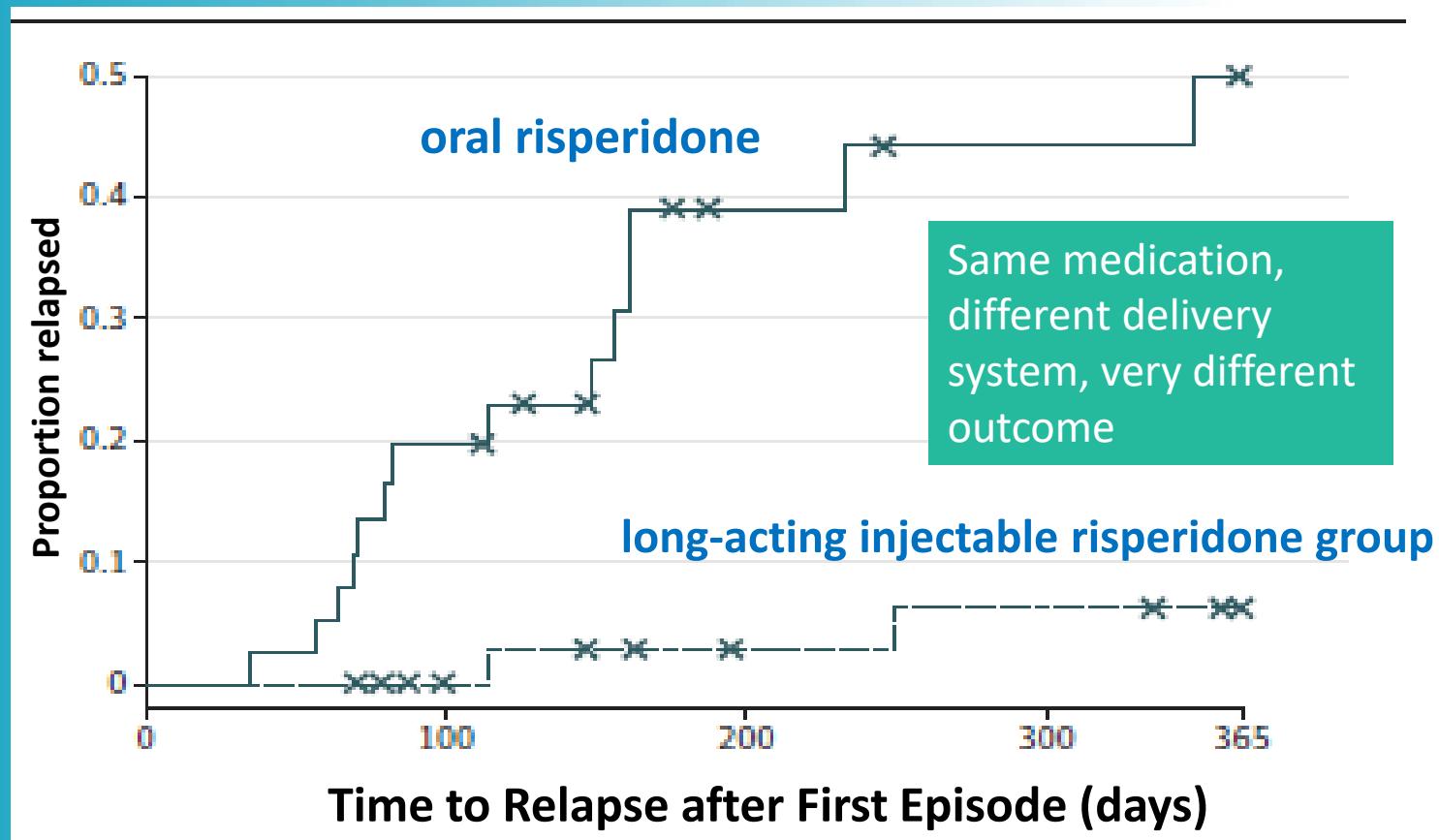
Start with any  
antipsychotic  
\*except olanzapine  
or clozapine per  
PORT Guidelines

Consider  
individual side  
effect profiles and  
patient  
preferences

Encourage  
patients to  
consider a long  
acting injectable  
(LAI) antipsychotic  
early on

Buchanan *Schizophr Bull* 2010;36:71

# Long Acting Injectable (LAI) formulations of antipsychotic medications prevent relapse in schizophrenia



Subotnik JAMA Psychiatry 2015;72(8):822-829

# First episode patients respond to lower doses of antipsychotics



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Daily Target Dose for First Episode Patients

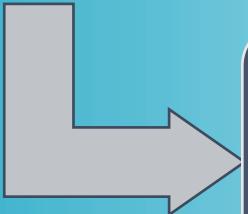
haloperidol	2.1 mg
aripiprazole	10 mg
olanzapine	11.7 mg
risperidone	2.4mg
<i>except quetiapine</i>	500 mg

Lieberman Am J Psychiatry 2003;160(8):1396-1404  
Schooler N Am J Psychiatry 2005;162(5):947-953

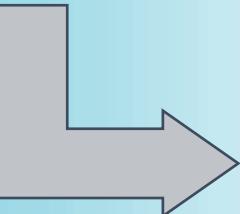
# Consider switching to another medication after 6 weeks of adequate dosage If the effect is insufficient



## CLINICAL IMPROVEMENT IS SLOW



Positive symptoms take weeks to resolve



Negative symptoms and  
cognitive symptoms  
won't resolve

# 20% of first episode patients will not respond to FGAs or SGAs and should be offered clozapine



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Consider clozapine after 2 failed trials

Clozapine is the only antipsychotic agent for which there is established superiority over other agents

For treatment refractory schizophrenia:

66% improved clozapine

33% improved haloperidol and olanzapine

Kumra Biol Psychiatry 2008;524

# Most patients with schizophrenia and pediatric bipolar disorder need long-term treatment and are at risk of relapse if medication is discontinued



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Use lowest effective dose to minimize adverse events

After prolonged remission, a *small* number may be able to discontinue medication

Change from 2001 guidelines which emphasized *intermittent treatment or discontinuation*

AACAP Schizophrenia Guidelines 2013

# Relapse rates with medication discontinuation are high (even with gradual medication taper)

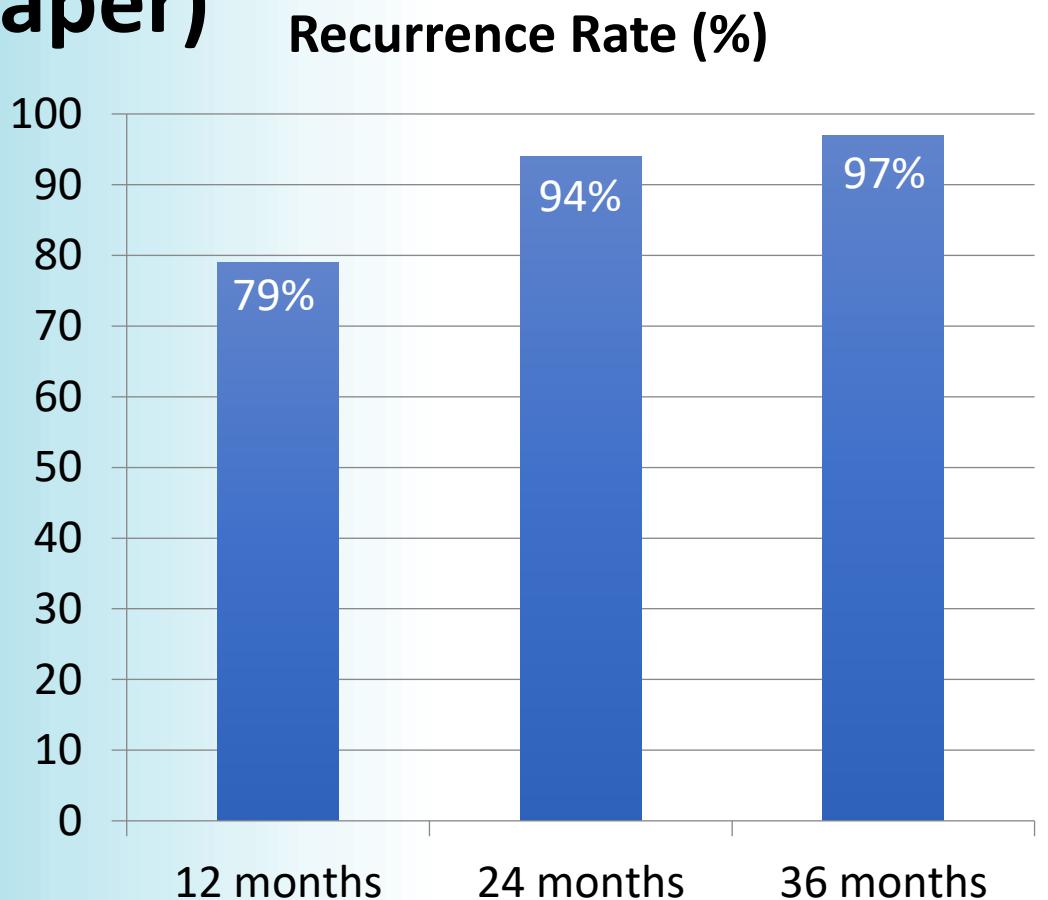
- First episode patients
- Stable for 2 years
- Tapered gradually from antipsychotic medication
- Followed for 3 yrs., open label

Encourage first episode patients to stay on medication



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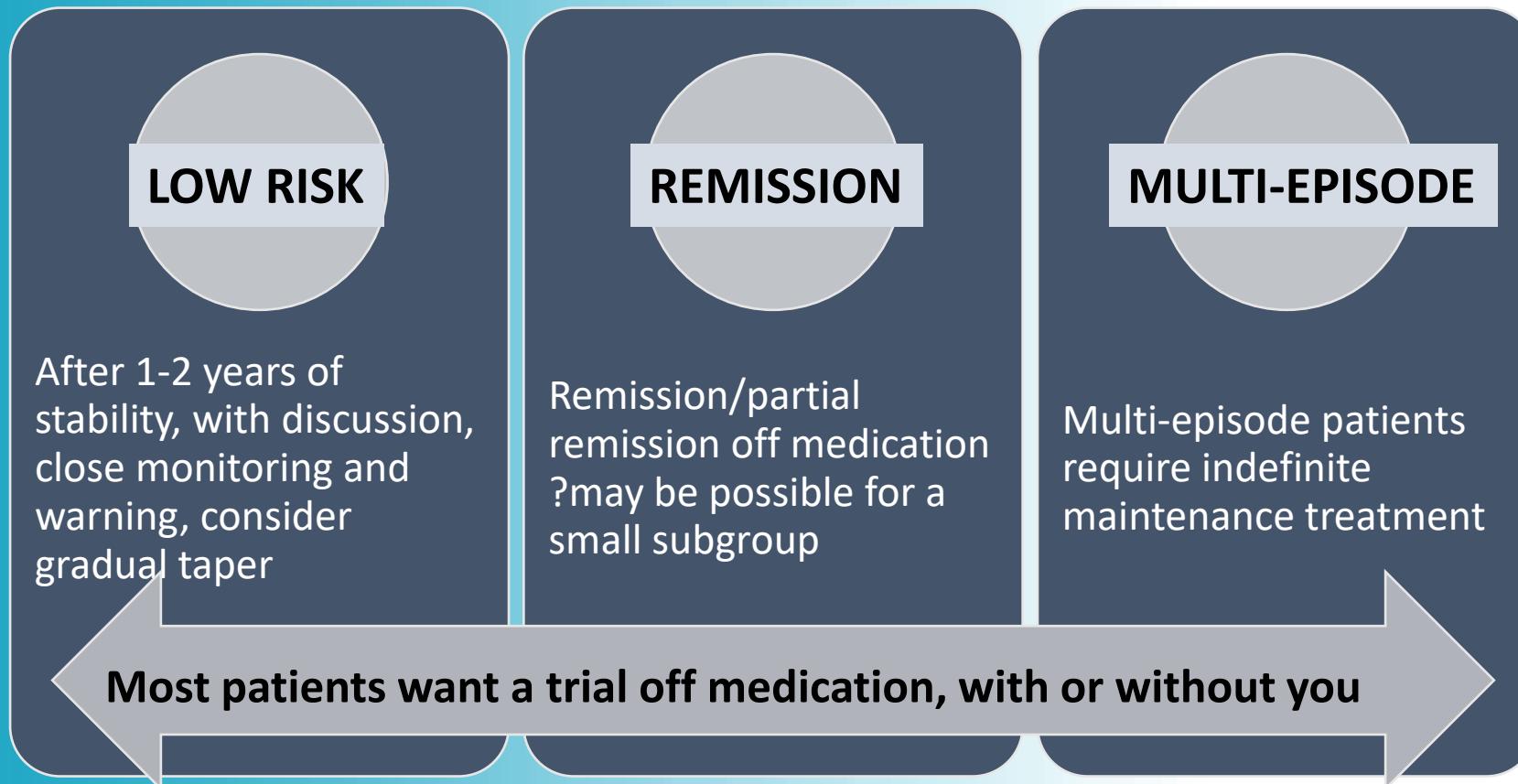
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Emsley J Clin Psychiatry 2012



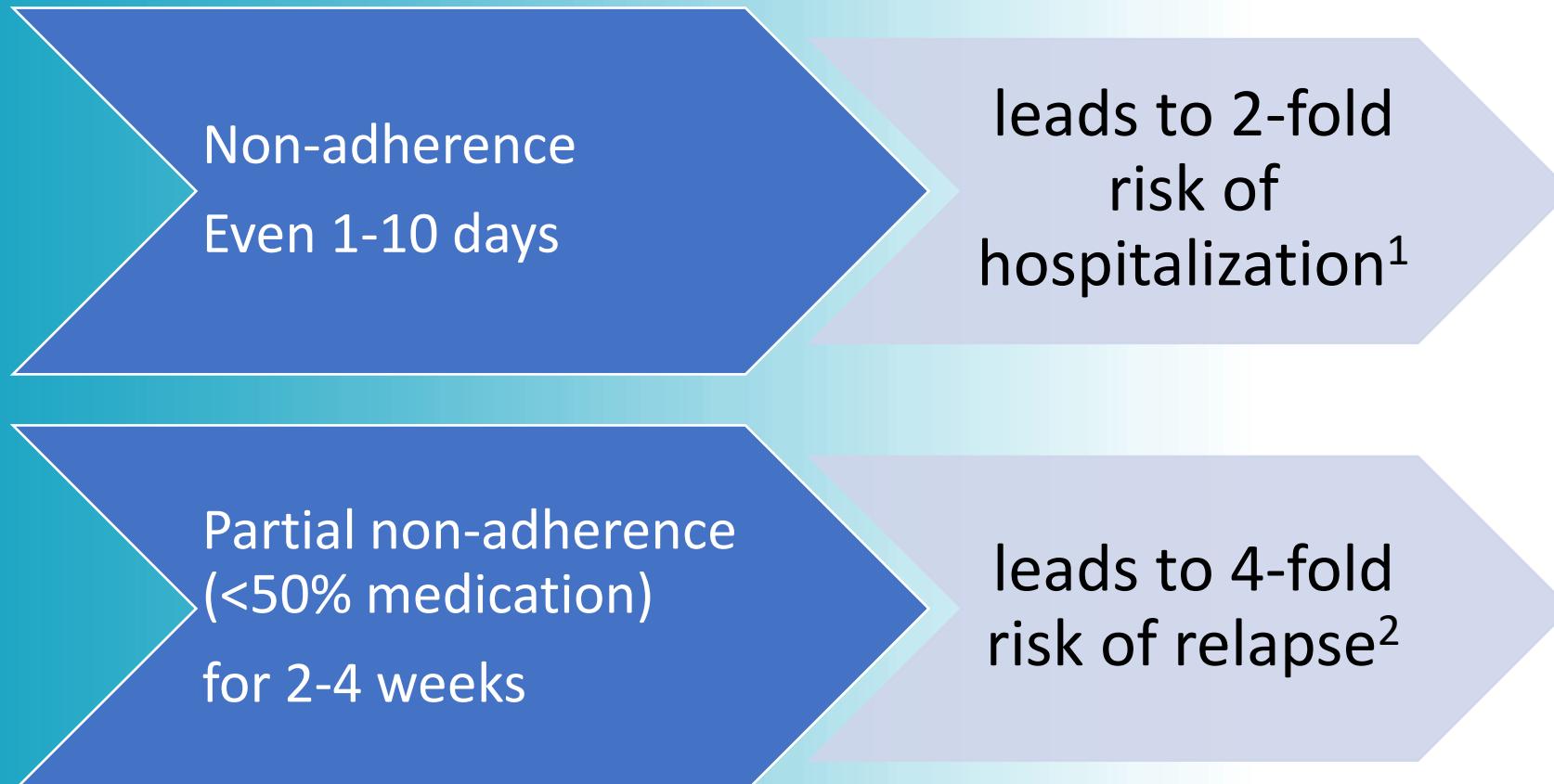
# Long term maintenance treatment is the rule for treating first episode schizophrenia



Goff Am J Psychiatry 2017;174:840-849



# Even brief or partial non-adherence adversely affects outcomes in schizophrenia



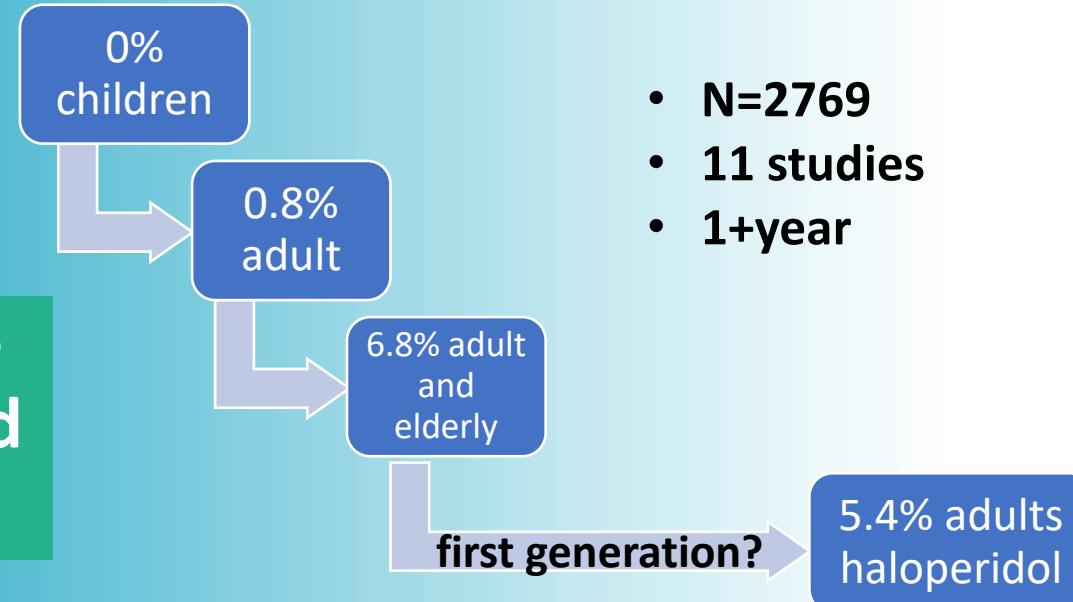
<sup>1</sup>Weiden Psychiatry Serv 2004;55(8):886-891

<sup>2</sup>Subotnik Am J Psych 2011;168(3):286-292

# Tardive dyskinesia is dreaded, but low risk

(although data is limited by small sample sizes, low doses and limited durations)

The weighted mean annual incidence of tardive dyskinesia **for second generation antipsychotics (SGAs):**



**A lower risk for tardive dyskinesia is associated with SGAs versus FGAs**

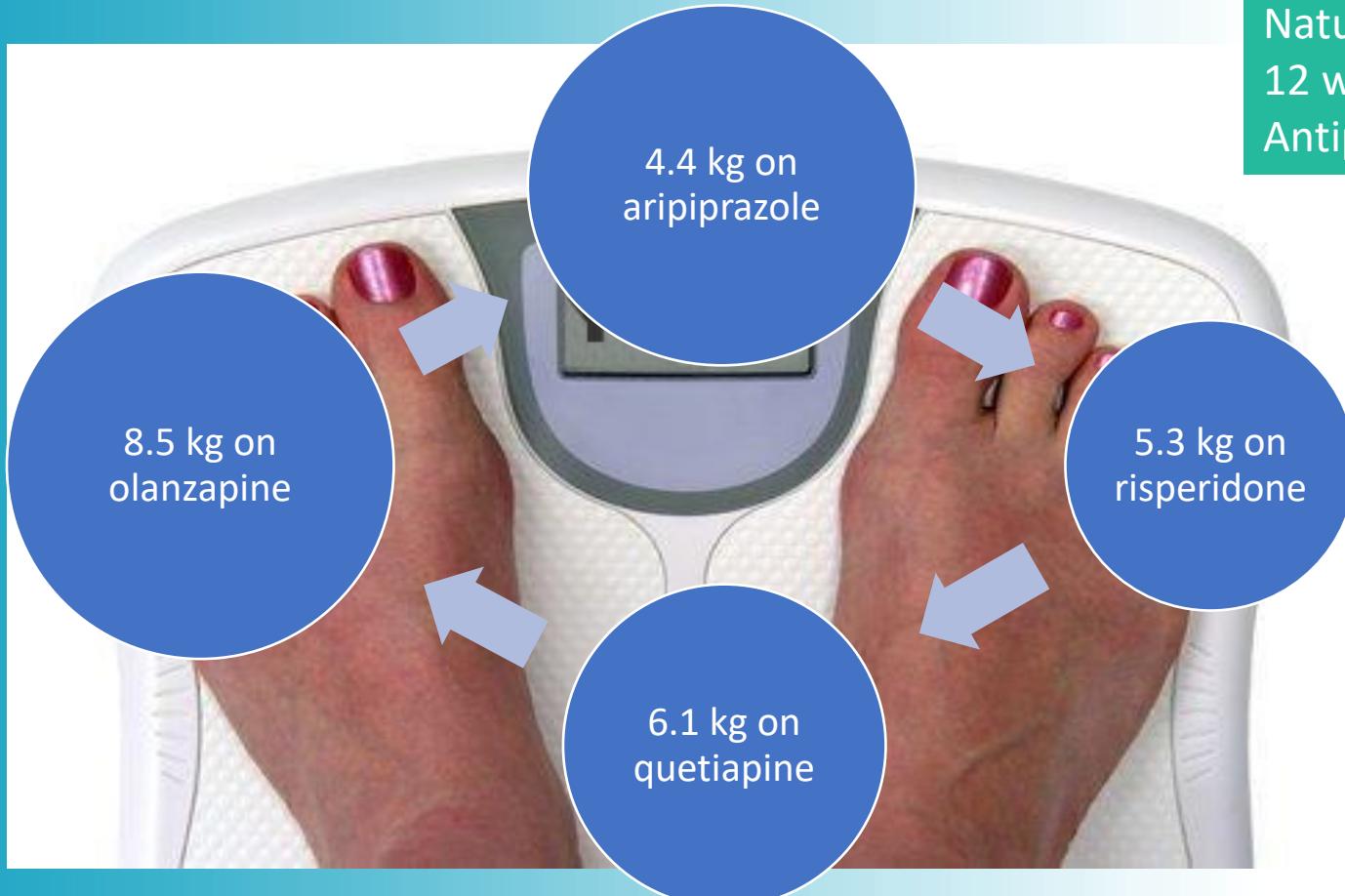
Correll Am J Psych 2004



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# Children may be particularly prone to weight gain with treatment



Naturalistic study  
12 weeks  
Antipsychotic naïve youth

Correll JAMA 2009;1765-1773



# Monitor BMI at 4, 8, 12 weeks and every 3 months

## Monitor labs baseline and annually

### Baseline:

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

### BMI:

- check at 4, 8, 12 weeks
- every 3 months thereafter

### Labs

- Baseline, at 3 months, then annually if normal

Intervene for abnormalities



# Co-treat with metformin

## Mechanism of Action

- Does not cause hypoglycemia
- Decreases hepatic production & GI absorption of glucose
- Increases peripheral glucose utilization

## Safety

- Rare lactic acidosis: more likely with excessive alcohol use
- May be associated with B12 deficiency<sup>1</sup>
- Most common side effects: GI (N/V 14%, diarrhea 7%)<sup>2</sup>

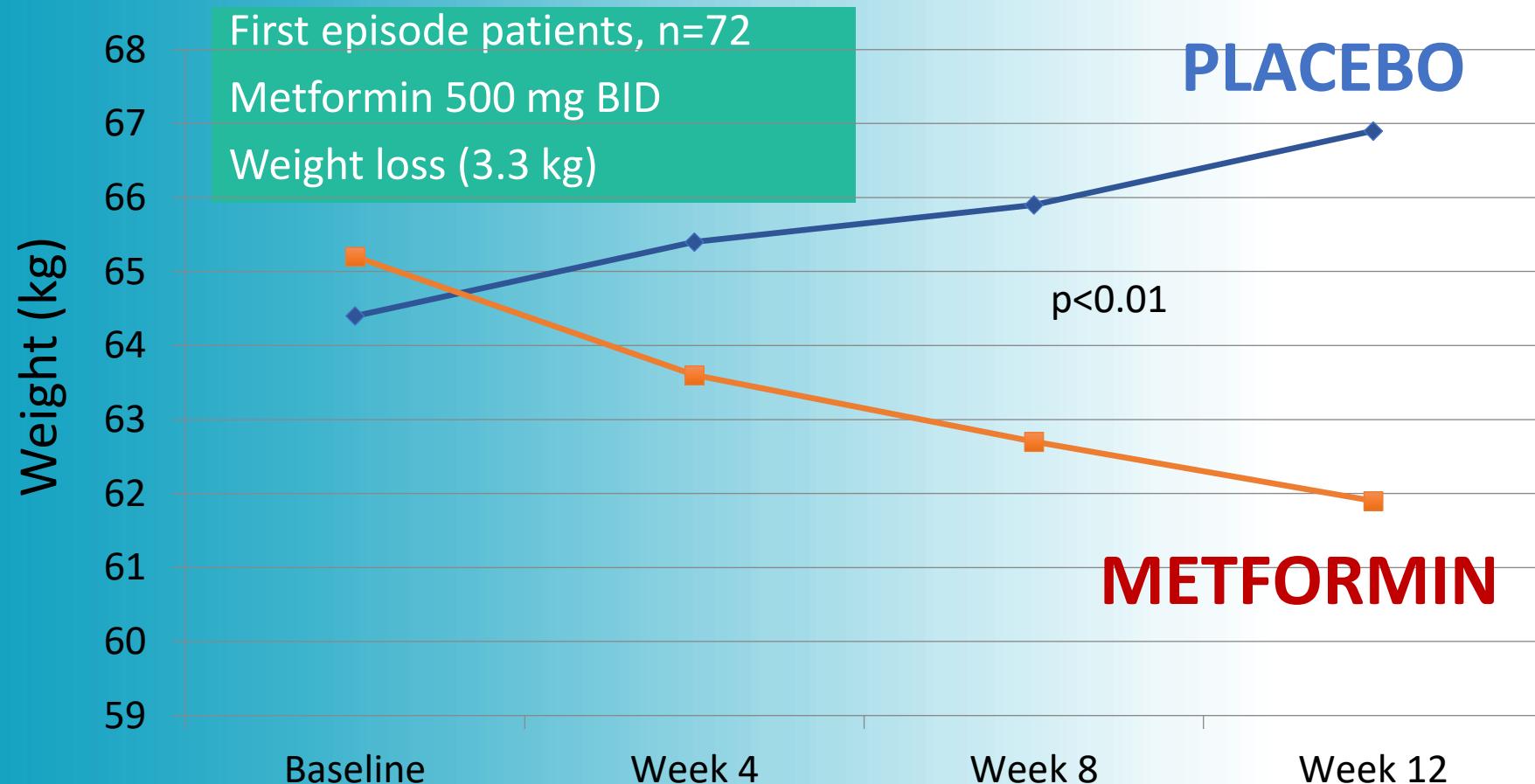
## Dosing

- Target dose 2000 mg TDD (with food)

1. Aroda J Clin Endocrinol Metab 2016;101(4):1754-61

2. Zheng J Clin Psychopharmacol 2015;35:499-509

# Metformin leads to weight loss and improved insulin sensitivity in schizophrenia



Wang Schizophr Res 2012;138:54-7

# Can we co-treat with newer agents?: GLP-1 Agonists



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## Mechanism of Action

- Mimics glucagon-like peptide-1 (GLP-1)
- Targets brain regulation of appetite and food intake
- Glucagon-like peptide-1 (GLP-1) released from gut enteroendocrine cells controls meal-related glycemic excursions through augmentation of insulin and inhibition of glucagon secretion. GLP-1 also inhibits gastric emptying and food intake, actions maximizing nutrient absorption while limiting weight gain.
- Activating GLP-1 receptors in the pancreas, which leads to enhanced insulin release and reduced glucagon release-responses that are both glucose-dependent-with a consequent low risk for hypoglycemia.
- Glucagon-like peptide 1 (GLP-1) is a hormone that is encoded in the proglucagon gene. It is mainly produced in enteroendocrine L cells of the gut and is secreted into the blood stream when food containing fat, protein hydrolysate, and/or glucose enters the duodenum

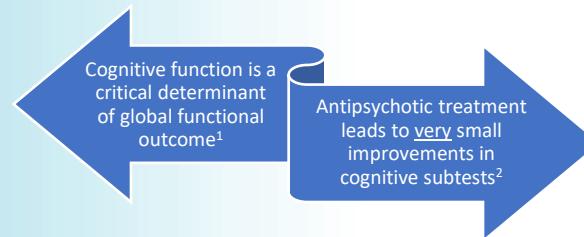
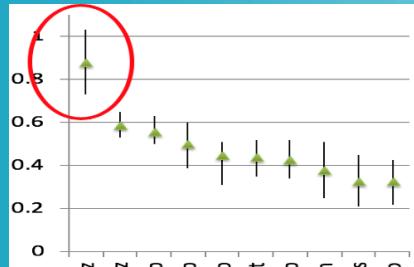
## Example: semaglutide

- FDA approved for weight management
- Injection 2.4mg weekly, increase to this slowly
- GI side effects common
- Do not use in patients with personal or fam hx of medullary thyroid c or with multiple endocrine neoplasia type 2 (MEN 2)
- Adults with obesity BMI>30
- Adults overweight BMI>27 with at least one weight-related condition (htn, type2 diabetes, high cholesterol)

## Overview:

Schizophrenia onsets in adolescence and young adulthood and requires treatment early in course. Antipsychotic medications are first line treatment for schizophrenia and pediatric onset Bipolar Disorder

**Diagnosis:** Schizophrenia is associated with functional and cognitive decline



**Treatment:** Pharmacotherapy with antipsychotic medication is required for schizophrenia and pediatric bipolar disorder

**Emerging evidence base guides treatment decisions:** Long-term treatment is required for schizophrenia; bipolar disorder outcomes are better with early effective treatment



**Weight gain is a major adverse event:** Metformin and newer agents can help offset metabolic side effects of antipsychotics