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PSYCHIATRY ACADEMY

Schizophrenia & Pharmacological Approaches to Pediatric Mania

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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.

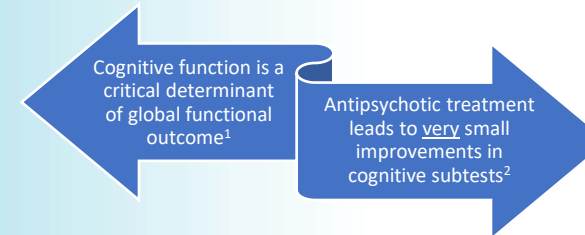
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Overview:

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

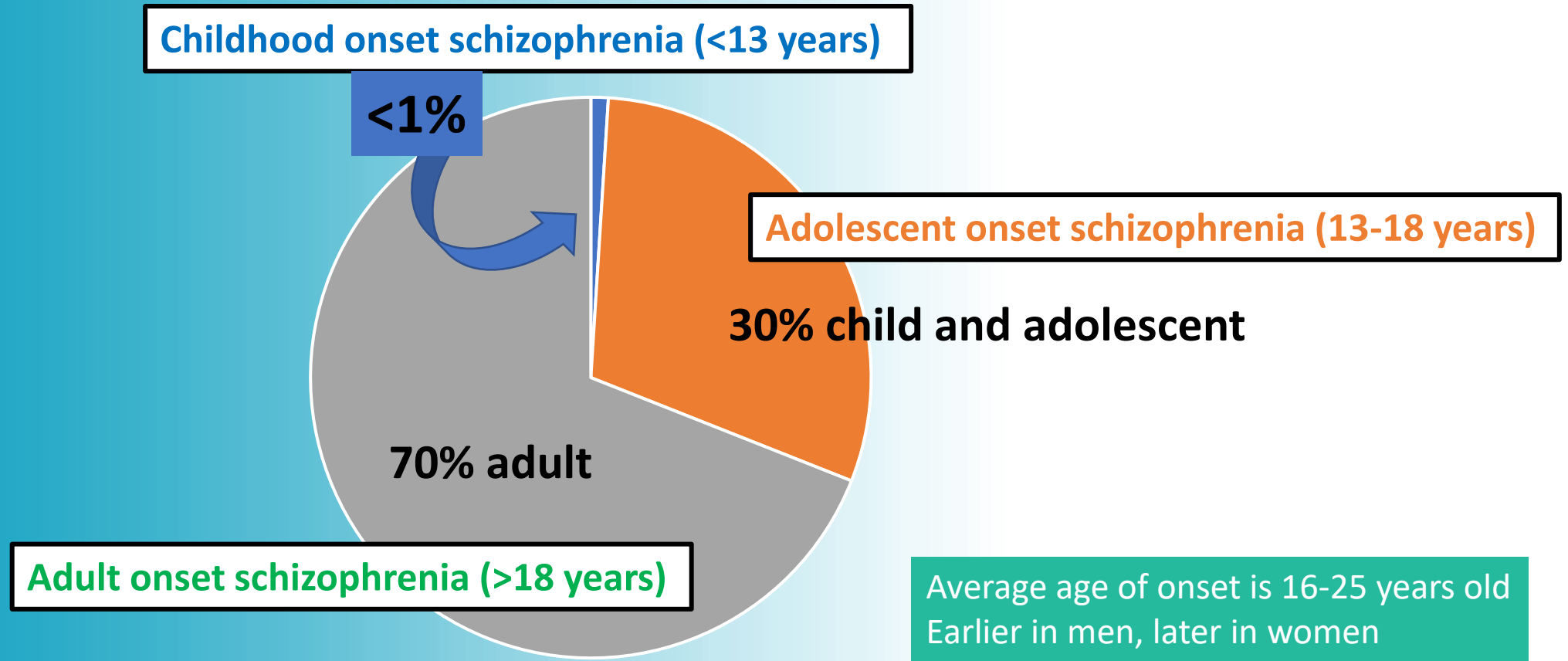


Weight gain is a major adverse event: Metformin and newer agents can help offset metabolic side effects of antipsychotics





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

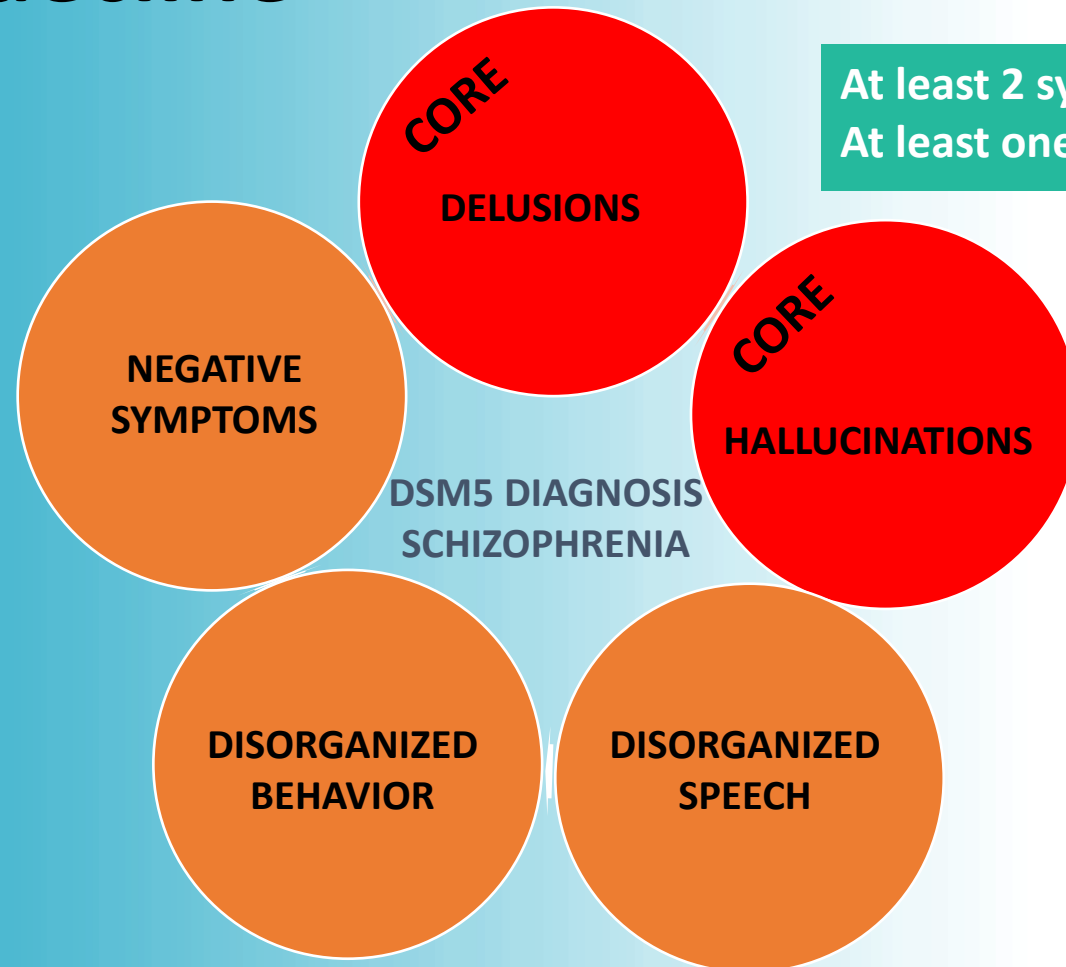


Schizophrenia criteria requires 6-month duration of symptoms and functional decline

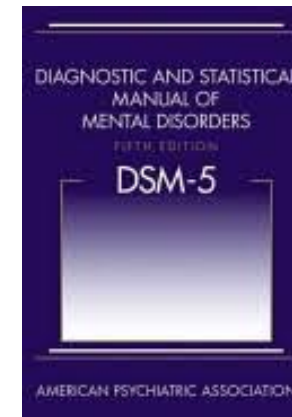


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At least 2 symptoms for one month
At least one is a 'core' symptom



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



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Cognitive performance
is 1-2 SD below age
matched controls¹

Affected areas include:

- attention
- executive function
- memory
- processing speed
- social cognition²

Cognitive decline is:

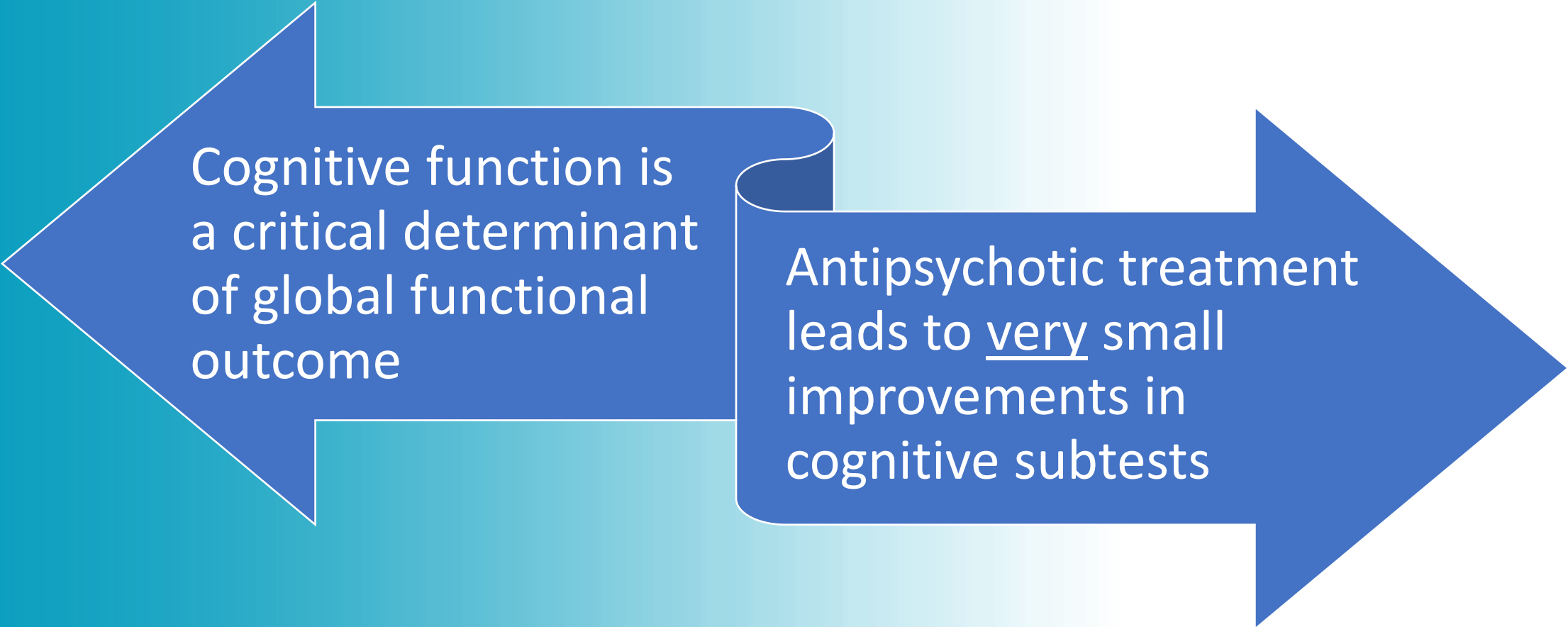
- nearly universal
- present before the onset of psychosis
- worsens during the illness³

**CHRONIC
COGNITIVE
IMPAIRMENT IS
SPECIFIC TO
SCHIZOPHRENIA⁴**

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

A diagram consisting of two large, blue, stylized arrows pointing in opposite directions. The left arrow points left and contains the text 'Cognitive function is a critical determinant of global functional outcome'. The right arrow points right and contains the text 'Antipsychotic treatment leads to very small improvements in cognitive subtests'. The two arrows are connected at their inner ends by a horizontal line, creating a central space.

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:

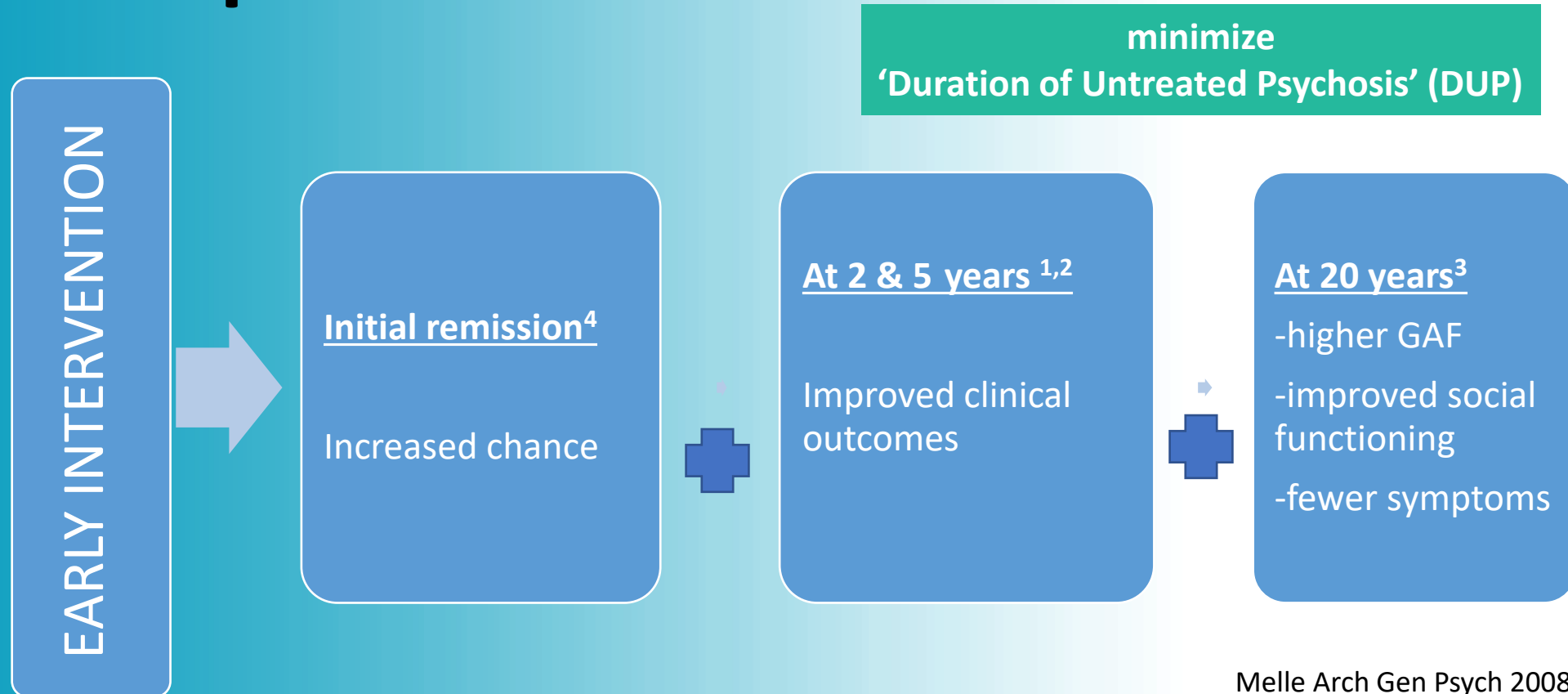


Begin treatment of schizophrenia as soon as possible



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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 Trial¹

SGAs only

Comparable efficacy for:

- olanzapine
- quetiapine
- risperidone

SGA=second generation antipsychotic
FGA=first generation antipsychotic

EUFE²

FGAs and SGAs

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

TEOSS³

FGAs and SGAs
children only

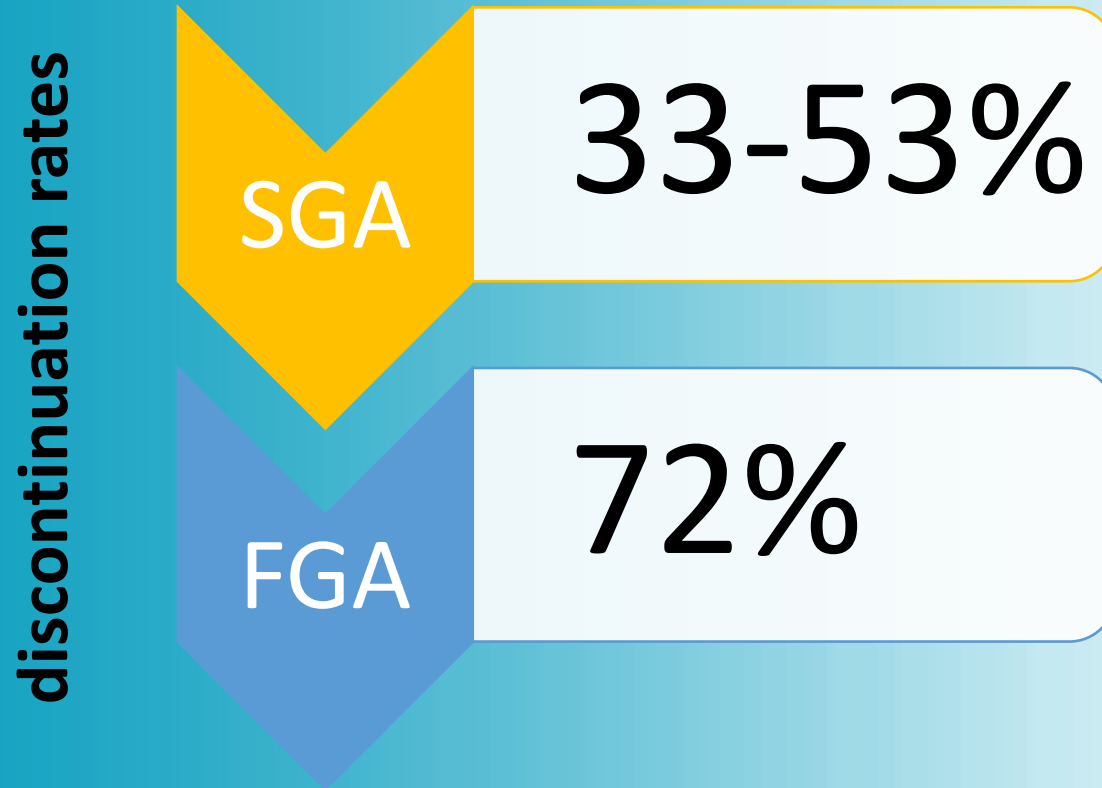
- Comparable efficacy and discontinuation: molindone, olanzapine, risperidone
- Olanzapine had significant weight gain

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**

ZIPRASIDONE TRIAL IN ADOLESCENTS
DISCONTINUED DUE TO LACK OF
EFFICACY

**META-
ANALYSIS**

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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| | | | |
|----------------------|------------------------|------------------------------|--|
| Paliperidone | 3-12mg QD | approved age 12-17 | Active metabolite of risperidone |
| Lurasidone | 40-160mg QD w/ food | approved age 13-17 | Akathisia, less weight gain, more EPS? |
| Asenapine | 2.5-10mg BID SL | approved for bipolar only | Sedation, EPS, weight gain |
| Iloperidone | 1-12mg BID | not approved in children | Sedation, weight gain |
| Brexpiprazole | 2-4mg QD | not approved in children | Partial D2 agonist, akathisia, less weight gain |
| Cariprazine | 3-6mg QD | not approved in children | Partial D2 agonist, akathisia, less weight gain |

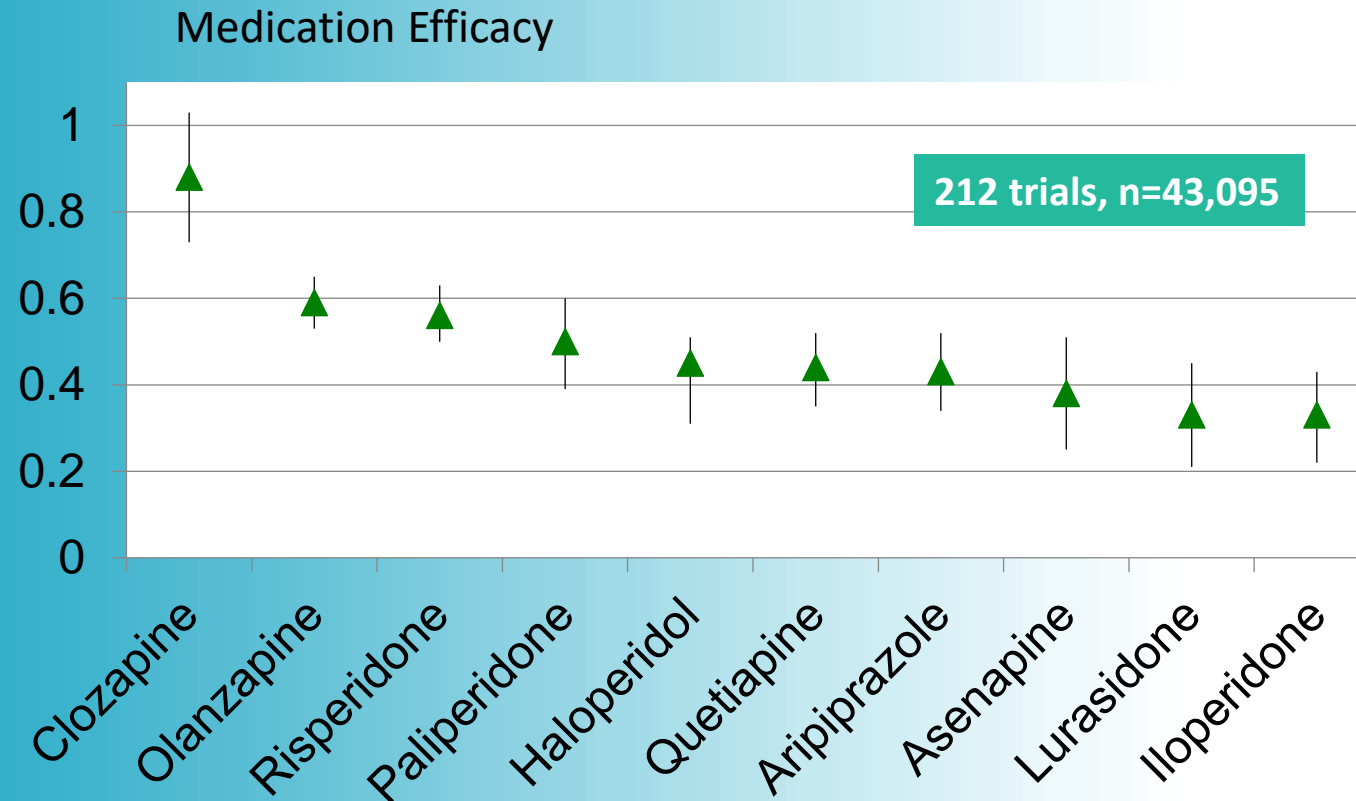
Also lumataperone a.k.a., Caplyta

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



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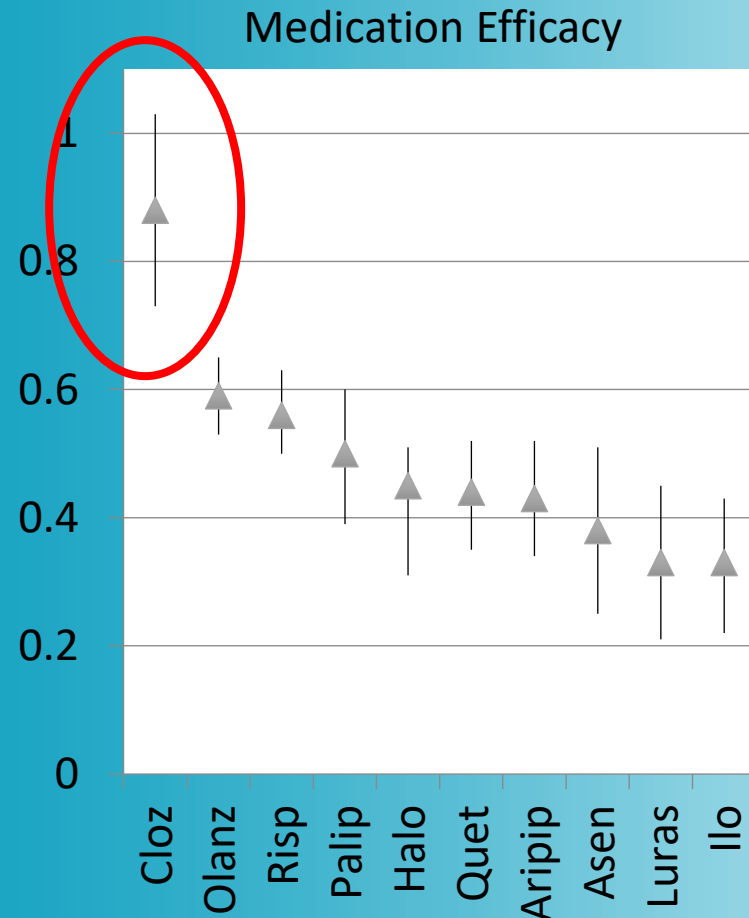
Leucht *Lancet* 2013;951-962

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

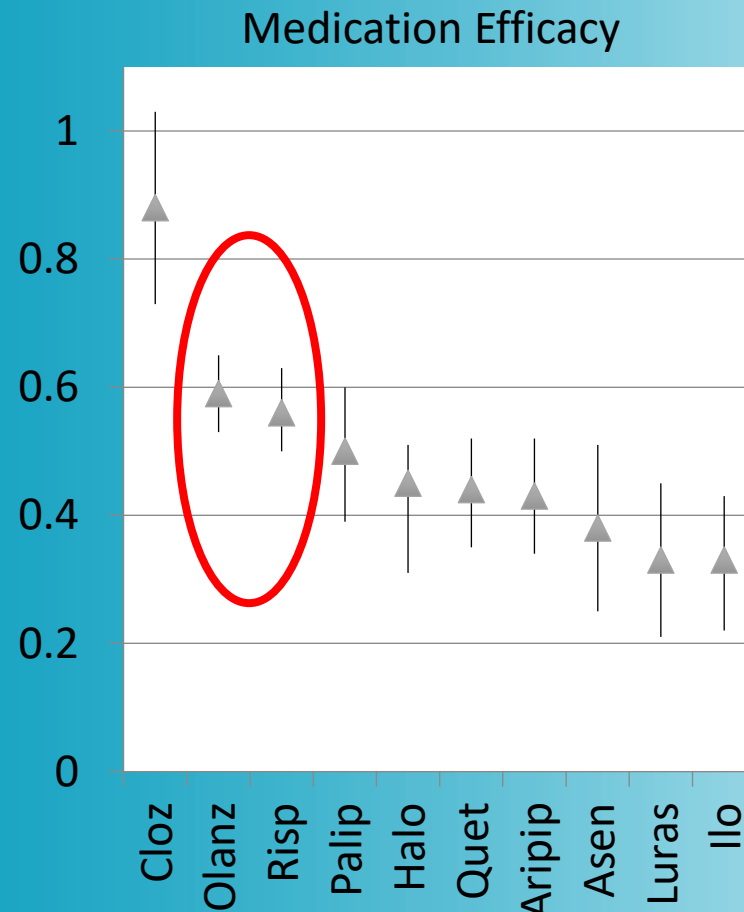
Leucht *Lancet* 2013;951-962

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

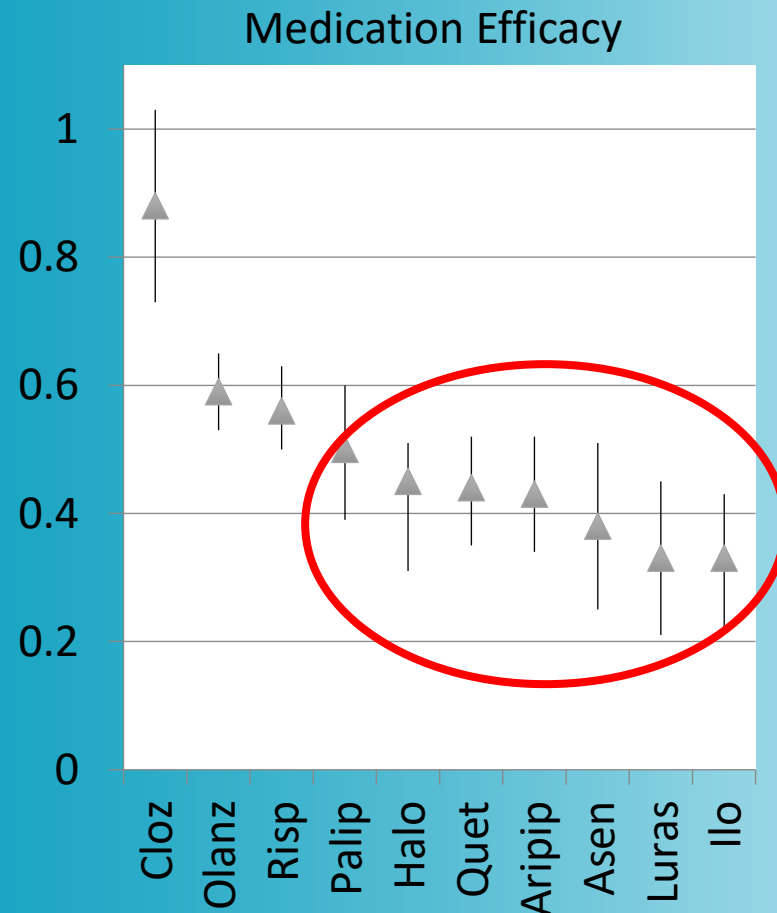
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- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than most
- All others had similar efficacy

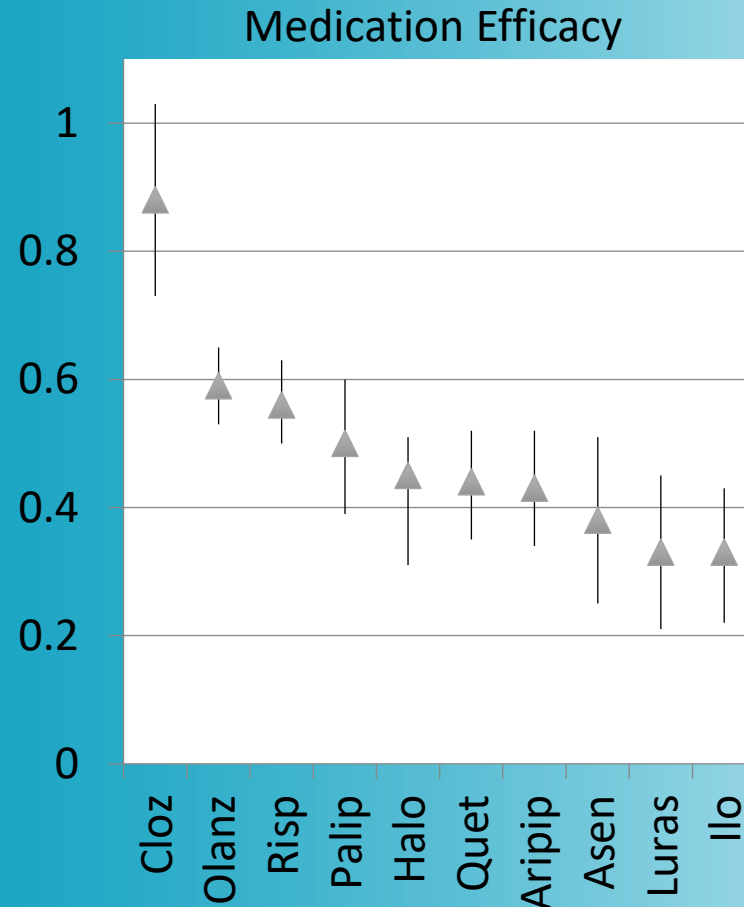
Leucht *Lancet* 2013;951-962

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

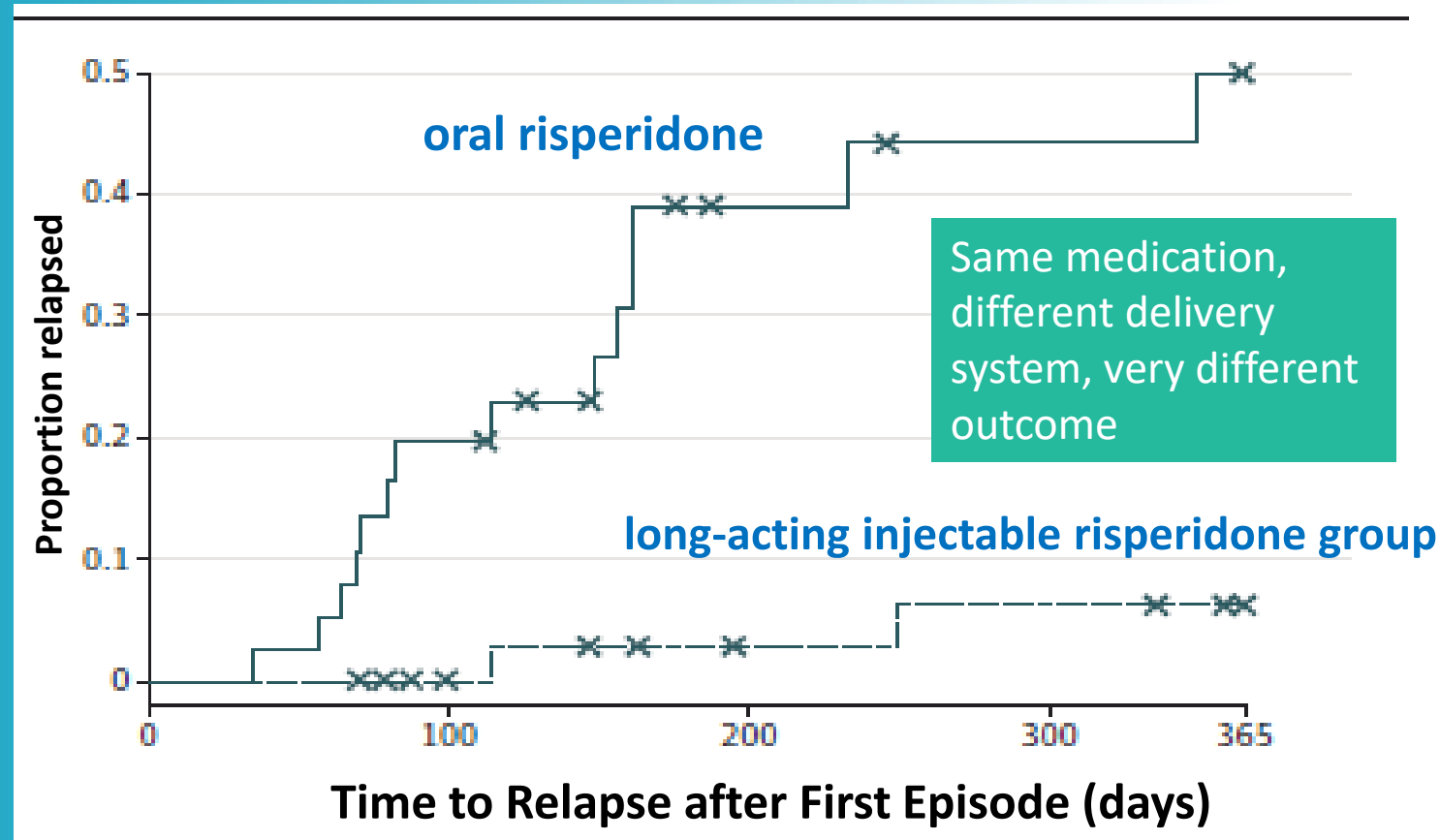
Encourage
patients to
consider a long
acting injectable
(LAI) antipsychotic
early on

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



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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</i> quetiapine | 500 mg |

Lieberman Am J Psychiatry 2003;160(8):1396-1404

Schooler N Am J Psychiatry 2005;162(5):947-953

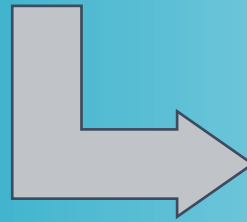
Consider switching to another medication after 6 weeks of adequate dosage If the effect is insufficient



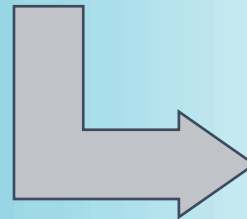
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CLINICAL IMPROVEMENT IS SLOW



Positive symptoms take weeks to resolve



**Negative symptoms and
cognitive symptoms
won't resolve**

AACAP Guidelines

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)

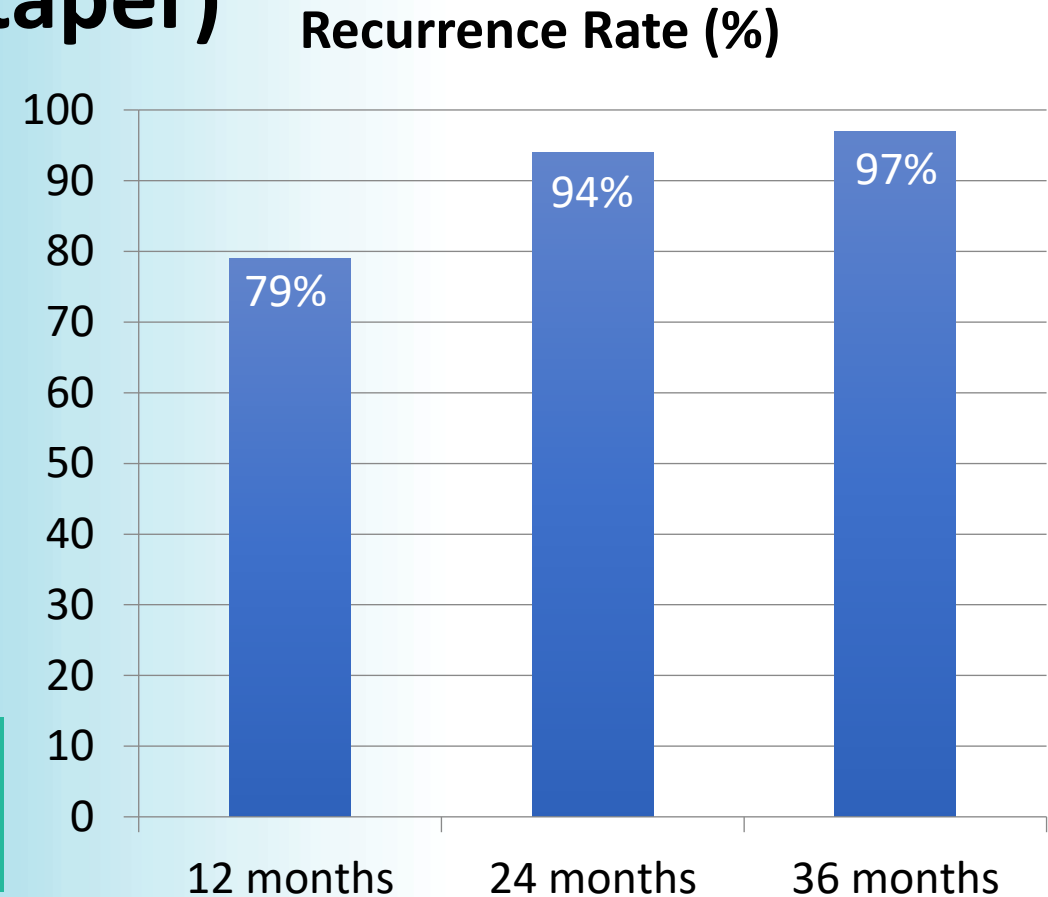


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- First episode patients
- Stable for 2 years
- Tapered gradually from antipsychotic medication
- Followed for 3 yrs., open label

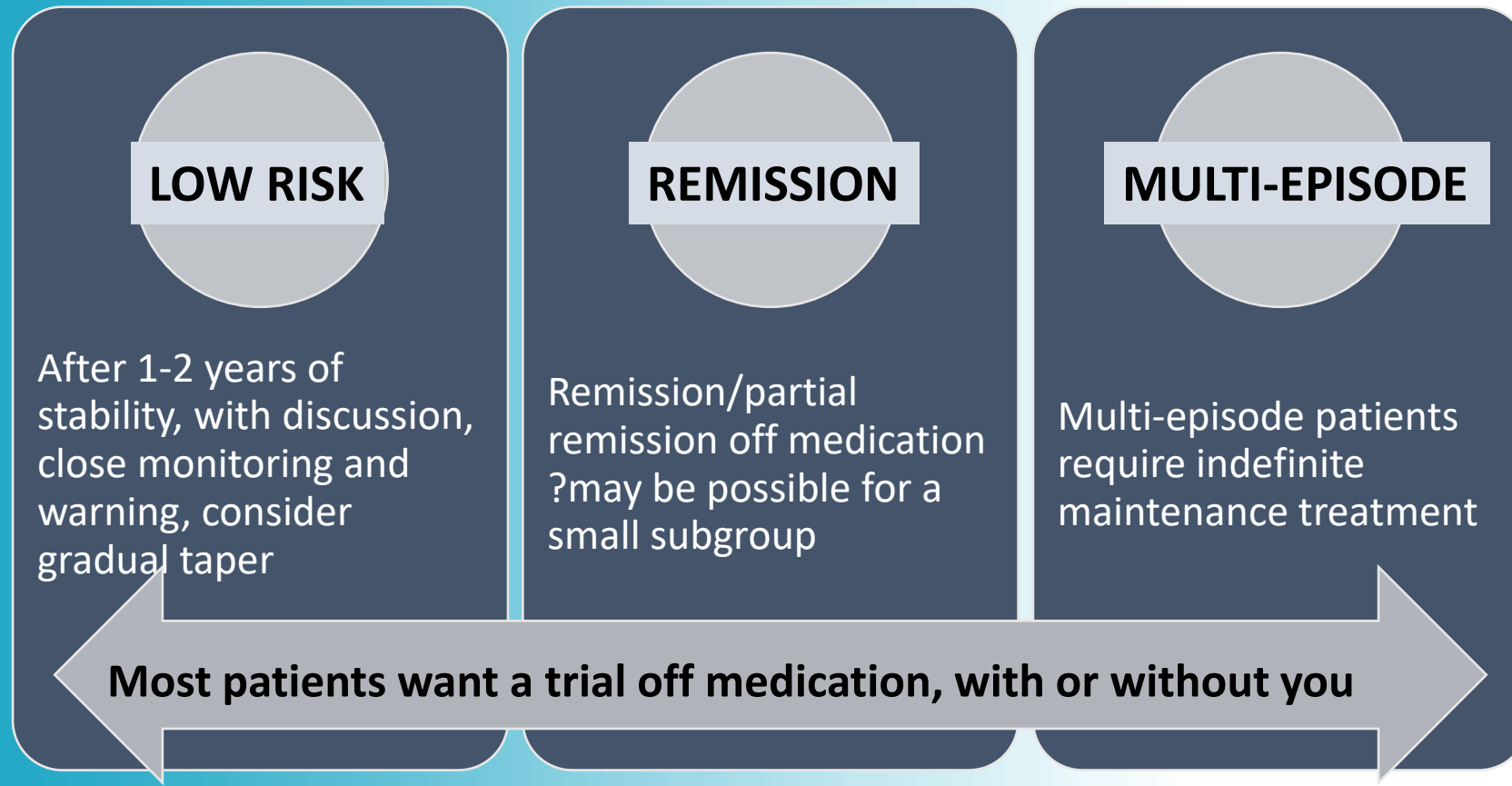
Encourage first episode patients to stay on medication



Emsley J Clin Psychiatry 2012



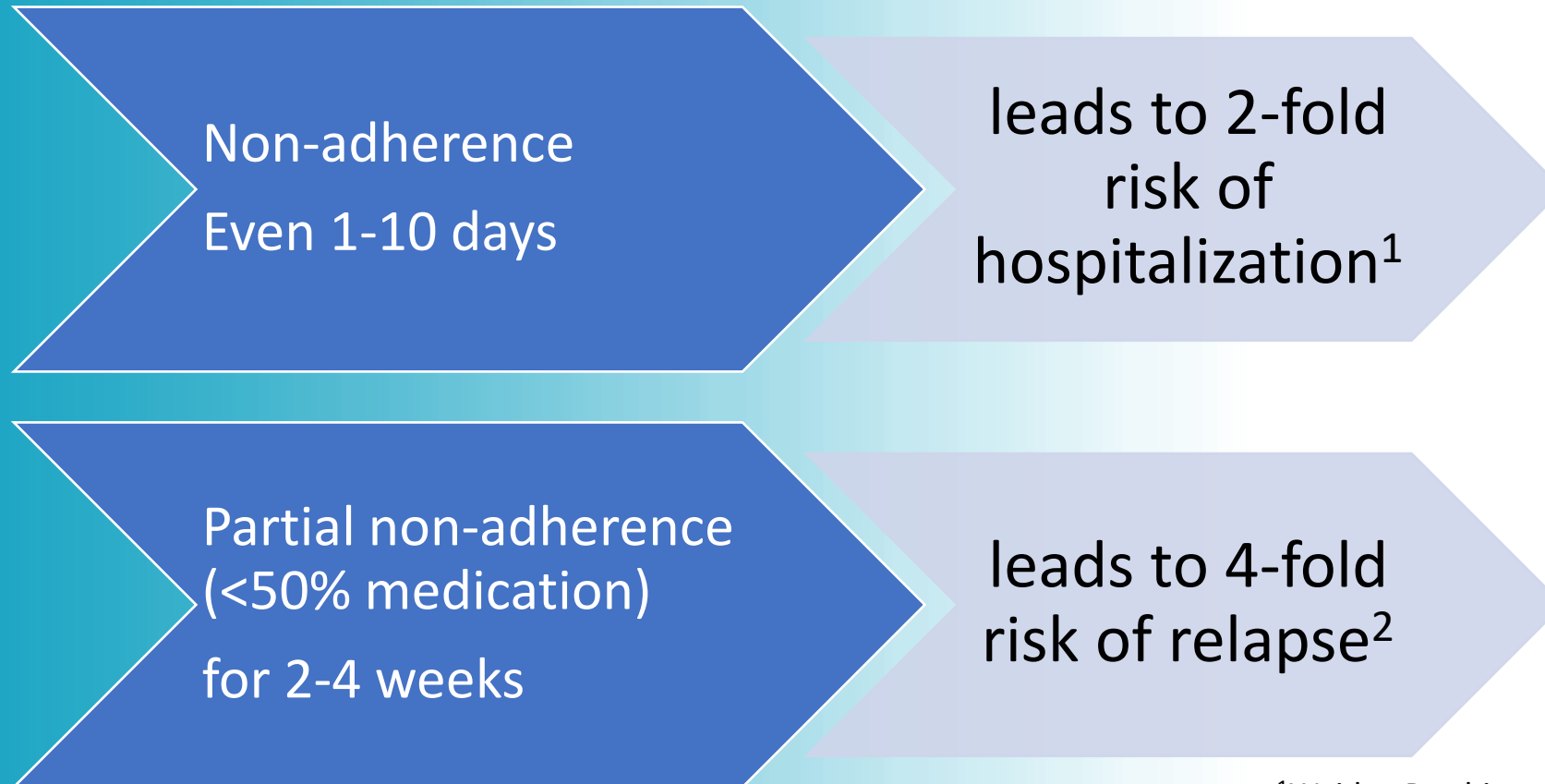
Long term maintenance treatment is the rule for treating first episode schizophrenia



Goff Am J Psychiatry 2017;174:840-849



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



¹Weiden Psychiatry Serv 2004;55(8):886-891

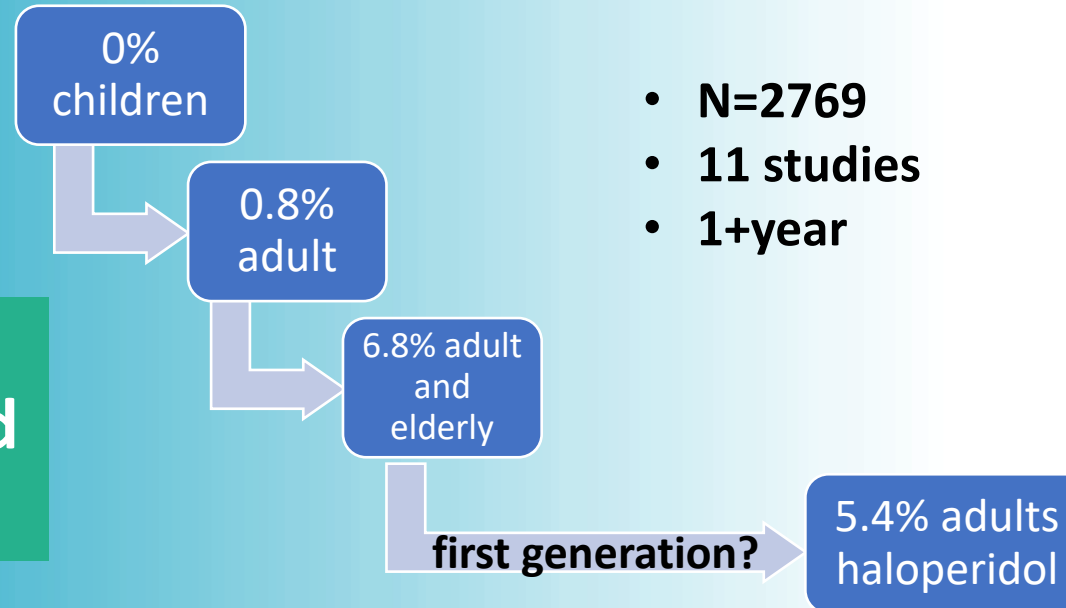
²Subotnik Am J Psych 2011;168(3):286-292



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):



- N=2769
- 11 studies
- 1+year

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



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 deficiency¹
- Most common side effects: GI (N/V 14%, diarrhea 7%²)

Dosing

- Target dose 2000 mg TDD (with food)

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

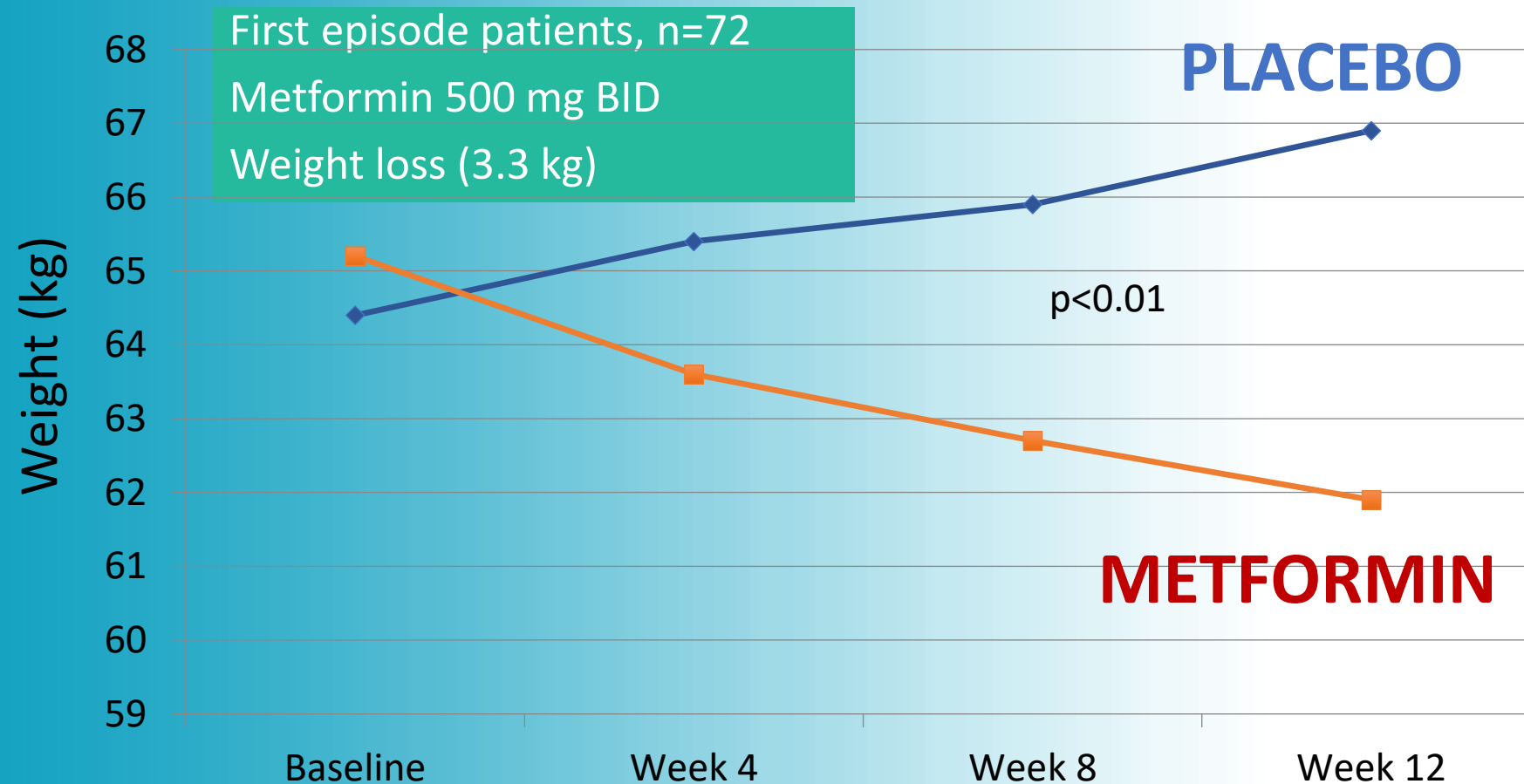
2. Zheng J Clin Psychopharmacol 2015;35:499-509

Metformin leads to weight loss and improved insulin sensitivity in schizophrenia



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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

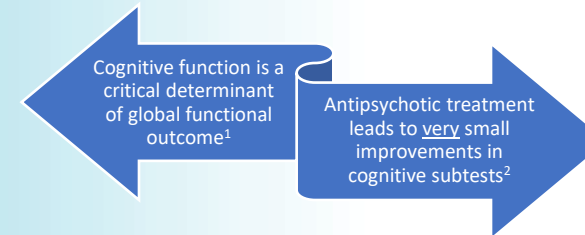
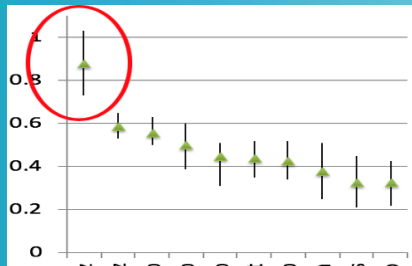
- FDA approved for weight management
- Injection 2.4mg weekly, increase to this slowly
- GI side effects common
- Do not use in patients with personal or fam hx of medullary thyroid c or with multiple endocrine neoplasia type 2 (MEN 2)
- Adults with obesity BMI>30
- Adults overweight BMI>27 with at least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



Overview:

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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



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