Assessing the Evidence:

What Science Has To Say About the Prescribing of Atypical Antipsychotics to Children

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Growth in Prescribing of Atypicals to Youth

- In 1987, fewer than 50,000 youth under age 18 (.04 percent of the youth population) were prescribed an antipsychotic drug.
- Today, more than 1% of American youth under age 18 are taking an atypical antipsychotic.

Diagnoses of Youth Prescribed Atypicals

- 38% for disruptive behaviors
- 32% for mood disorders
- 17% for developmental disorders or mental retardation
- 14% for psychotic disorders

Source: M. Olfson, "National trends in the outpatient treatment of children and adolescents with antipsychotic drugs," *Arch Gen Psychiatry* 63 (2006):679-85.

Broadened Use of Atypicals in Youth

Non-psychotic conditions include:

- ADHD
- Impulsivity
- Insomnia
- Aggression
- PTSD
- Obsessive-compulsive symptoms
- Eating disorders
- Poor tolerance of "frustration"

Source: B. Vitiello, "Antipsychotics in children and adolescents," *Eur Neuropsychopharmacol* 19 (2009):629-35; C. Panagiotopoulos, "First do no harm," *J Can Acad Child Adolesc Psychiatry* 19 (2010):124-37.

How Atypicals Act on the Brain

- Atypicals are broad-acting agents.
- They bind with dopaminergic, serotonergic, histaminergic, adrenergic, and muscarinic receptors.
- For the most part, they block these receptors and in that manner hinder the passage of messages along the various neuronal pathways.

Expected Effects From a Drug's Blockade of Receptors

Receptor Type	Adverse Events	Withdrawal Effects
Dopamine	EPS, weight gain, endocrine effects, akathisia, tardive dyskinesia, increased prolactin, sexual or reproductive system dysfunction	Psychosis, mania, agitation, akathisia, dyskinesia
Serotonin	Weight gain, diabetes, increased appetite	EPS, akathisia, psychosis, decreased appetite
Histamine	Weight gain, diabetes, sedation	Agitation, insomnia, anxiety, EPS
Muscarinic	Dry mouth, blurred vision, constipation, urinary retention, diabetes, memory problems cognitive problems, tachycardia, hypertension	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS, akathisia, diarrhea, nausea, vomiting, bradycardia, hypotension, syncope
Adrenergic	Postural hypotension, dizziness, syncope	Tachycardia, hypertension, hypotension, dizziness

EPS=extrapyramidal symptoms. Source: C Correll, "Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents." *J Clin Psychiatry* 69, suppl. 4 (2008): 26-36. Also see C. Correll, "Antipsychotic use in children and adolescents." *J Am Acad Child Adolesc Psychiatry* 47 (2008):9-20.

Atypicals and Brain Shrinkage

Animal studies:

- In macaque monkeys, treatment with either haloperidol or olanzapine for 17 to 27 months led to a "8-11% reduction in mean fresh brain weights" compared to controls.

- The differences (in brain weights and brain volumes) "were observed across all major brain regions, but appeared most robust in the frontal and parietal regions."

Source: Dorph-Petersen. "The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation." *Neuropsychopharmaology* (2005) 30: 1649-1661.

Nancy Andreasen's MRI Study

In 2003, Andreasen reported that schizophrenia was a "progressive neurodevelopmental disorder" characterized by "progressive reduction in frontal white matter volume." This decline in brain volumes was seen in MRI imaging tests.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." *Arch Gen Psych* 60 (2003):585-94.

In 2011, Andreasen reported that this shrinkage was drug-related. Use of the old neuroleptics, the atypical antipsychotics, and clozapine were all "associated with smaller brain tissue volumes," with decreases in both white and grey matter. The severity of illness and substance abuse had "minimal or no effect'" on brain volumes.

Ho, B. "Long-term antipsychotic treatment and brain volumes." *Arch Gen Psychiatry* 68 (2011):128-37.

Nancy Andreasen, former editor of the *American Journal of Psychiatry*, on antipsychotics:

"What exactly do these drugs do? They block basal ganglia activity. The prefrontal cortex doesn't get the input it needs and is being shut down by drugs. That reduces psychotic symptoms. It also causes the prefrontal cortex to slowly atrophy."

--*New York Times*, September 16, 2008

More Evidence That Antipsychotics Shrink the Brain

In a 2012 review of 43 brain-imaging studies of first-episode psychosis, European researchers determined that a loss of gray matter volume was "significantly more severe in medicated patients."

Source: J. Radua. "Multimodal meta-analysis of structural and functional changes in first episode psychosis and the effects of antispychotic medications." *Neuroscience and Biobehavioral Review*, in press as of 9/04/2012.

Short-Term Efficacy Studies

- FDA approved Risperdal, Zyprexa, Seroquel, and Abilify for schizophrenia, bipolar disorder, and irritability in autism.
- In a 2010 review of the literature, investigators found reports of nine "placebo-controlled" randomized studies of these four drugs for psychotic and bipolar disorders.
- The industry-funded studies lasted 3 to 8 weeks.
- While the placebo patients saw the target symptoms improve, those treated with an atypical improved--on the target symptom--to a greater extent.

Source: D. Fraguas, "Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrums disorders." *Eur Neuropsychopharmacol* (2010), doi:10.1016.

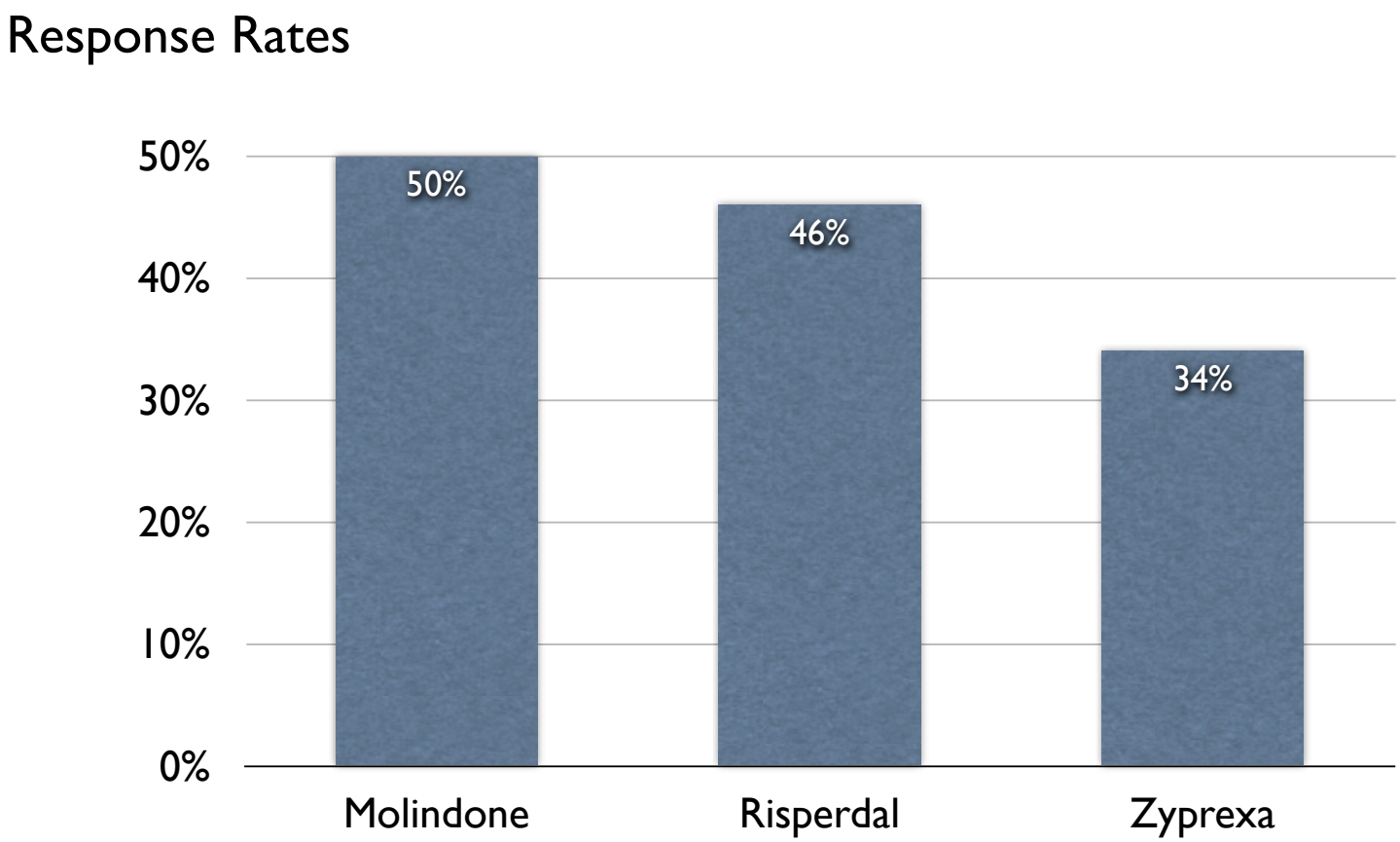
Other Short-Term Studies

Industry-funded trials of atypicals found them effective over the short term for controlling aggression. Many of these studies were conducted in autistic children.

NIMH's TEOSS Trial

- Youth 8 to 19 years old
- No placebo control
- 116 youth randomized to molindone (an older antipsychotic), Risperdal, or Zyprexa.
- Many were on antidepressants and mood stabilizers prior to the study, and were allowed to continue on those drugs.
- Many were prescribed drugs during the trial--anticholinergic agents, propranolol, and benzodiazepines--to counter the side effects of the atypical drugs.

TEOSS: Eight-Week Results



Source: L. Sikich, "Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder." *Am J Psychiatry* 165 (2008):1420-31.

Only 31 of the 76 youth (41%) treated with Risperidone or Zyprexa responded to the drug.

Reported Adverse Effects

Movement Disorders

- In the one double-blind, randomized study that compared EPS rates for older antipsychotics and the atypical in youth under 18, 56% of those given Zyprexa and 53% of the Risperdal group experienced "substantial" EPS. This was only slightly less than EPS with Haldol.

- Five to 20% of youth experience akathisia in a short trial, which is associated with an increased risk of violence and suicide.

- Researchers at the University of Maryland reported that 10% of youth developed TD within one to two years.

- Spanish investigators reported that 38% of youth on atypicals for more than one year showed signs of mild TD.

Metabolic Dysfunction

- Weigh gain, obesity. Israeli researchers reported that 90% of youth taking Zyprexa and 43% taking Risperdal gained more than 7% of their baseline weight within 12 weeks. Researchers in Cincinnati and British Columbia found that more than 50% of youth exposed to atypicals were overweight or obese.

- Diabetes. Canadian investigators reported that 22% of pediatric patients treated with atypicals had "impaired fasting glucose or type 2 diabetes."

- Elevated triglycerides and LDL-cholesterol (dyslipidemia.)

- Metabolic syndrome. Defined as being obese and developing two other signs of metabolic dysfunction (high blood pressure, dyslipidemia, or high fasting glucose.) Canadian investigators reported that 27% of juvenile patients treated with an atypical for 12 months could be deemed as having a "metabolic syndrome."

- Obesity and drug-induced metabolic changes "can persist over time and not be fully reversible upon drug discontinuation," and thus lead to poor long-term health.

The long-term consequences of metabolic adverse effects, even if drugs are withdrawn:

"Because drug-induced metabolic changes can persist over time and may not be fully reversible upon drug discontinuation, the implications for distal health outcomes can be profound. Age-inappropriate weight gain and obesity increase the risk for a variety of negative outcomes, such as diabetes, hyperlipidemia, and hypertension, which are major risk factors for cardiovascular diseases and reduced quality of life and life expectancy."

-- Benedetto Vitiello, NIMH

Endocrine Dysfunction

Hormonal abnormalities

Spanish investigators reported in 2007 that 49% of youth treated with an atypical for longer than one year had elevated prolactin levels. This can cause breast enlargement and hypogonadism in males, and galactorrhea, amenorrhea, and hirsutism in females.

Elevated prolactin levels may also cause a decrease in libido, sexual dysfunction and decreased bone density.

The decreased bone density "may not be recovered later in life," and thus the child treated with atypicals may end up with a lifelong increased risk of bone fractures.

Other Physical Adverse Effects:

- Elevated levels of liver enzymes.
- Cardiovascular risks include cardiomegaly, tachycardia, arrhythmia, QTc prolongation, heart disease not otherwise specified, and high blood pressure.
- Dizziness, facial flushing, dry mucous membranes, decreased sweating, constipation, urinary retention, headaches, blurred vision and tinnitus.
- Cases of neuroleptic malignant syndrome and pancreatitis, both of which can be fatal, have been reported in pediatric patients.

Emotional and Cognitive Problems

- In TEOSS study, 26% of patients reported being anxious.
- More than half of pediatric patients in some trials reported being sedated, which is associated with "cognitive impairment and decreased mental activity."
- Irritability, depression, emotional lethargy, and decreased concentration.

The Longer-Term Effects of Atypicals on Children

- Efficacy of drugs
- Physical health
- Tardive dyskinesia
- Data from long-term studies of adult patients

The One-Year TEOSS Results

Design

The 54 (of 116) youth who had responded were followed for another 44 weeks.

Results

- 40 of 54 dropped out, mostly because of adverse effects or "inadequate response."
- Those on Risperdal worsened significantly in their functional capacities. Those on Zyprexa worsened slightly in this regard.
- The psychotic symptoms of those on Risperdal or Zyprexa worsened to a small extent.

Source: R. Findling. "Double-blind maintenance safety and effectiveness findings from the treatment of early-onset schizophrenia spectrume (TEOSS) study." *J Am Acad Child & Adolesc Psychiatry* 49 (2010):583-95.

The Bottom Line From the TEOSS Study

Only 14 of the original cohort of 116 patients (12%) responded to an antipsychotic and then stayed on the drug and in the trial throughout the followup period.

The investigators concluded: "Few youths with early onset schizophrenia who are treated with antipsychotic medications for up to a year appear to benefit from their initial treatment choice over the long term."

Poor Global Health

In TEOSS followup study, 83% of the youth suffered an adverse event.

In a survey of 4,140 Medicaid youth on atypicals for a longer period of time, 47 percent suffered from digestive or urogenital problems; 36% had skin, musculoskeletal, or respiratory conditions; and 3% had diabetes.

The University of South Carolina researchers concluded: "The treated cohort exhibits a high incidence and diverse array of treatment-related adverse events."

Source: R. Findling. "Double-blind maintenance safety and effectiveness findings from the treatment of early-onset schizophrenia spectrume (TEOSS) study." *J Am Acad Child & Adolesc Psychiatry* 49 (2010): 583-95. J. Jerrell, "Adverse events in children and adolescents treated with antipsychotic medications." *Hum Psychopharmacol* 23 (2008):283-90.

Tardive Dyskinesia

- Researchers at the University of Maryland School of Medicine reported that 3 percent of the 116 pediatric patients they studied developed TD within six to 12 months of exposure to an atypical, and that 10 percent did so after one to two years.

- Spanish investigators reported that 38% of children and adolescents on atypicals for longer than one year showed signs of mild TD.

- TD may be more reversible in children than in adults if the drug is withdrawn. However, adults who develop TD show signs of a permanent global decline in brain function. It is associated with emotional disengagement, psychosocial impairment, and a decline in memory, visual retention, and the capacity to learn.

Source: I. Wonodi, "Tardive dyskinesia in children treated with atypical antipsychotic medications." *Mov Disord* 22 (2007):1777-82. P. Laita, "Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents." J Child Adolesc Psychopharmacol 17 (2007):487-502.

Functional Decline Associated with Drug-Induced Brain Shrinkage

In 2003 and 2005, Andreasen reported that the brain shrinkage in adult schizophrenia patients was associated with a worsening of negative symptoms, increased functional impairment, and, after five years, cognitive decline.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." *Arch Gen Psych* 60 (2003):585-94. Andreasen, N. "Longitudinal changes in neurocognition during the first decade of schizophrenia illness." *International Congress on Schizophrenia Research* (2005):348.

Long-Term Outcomes in Adults

Martin Harrow's 20-year study of psychotic patients

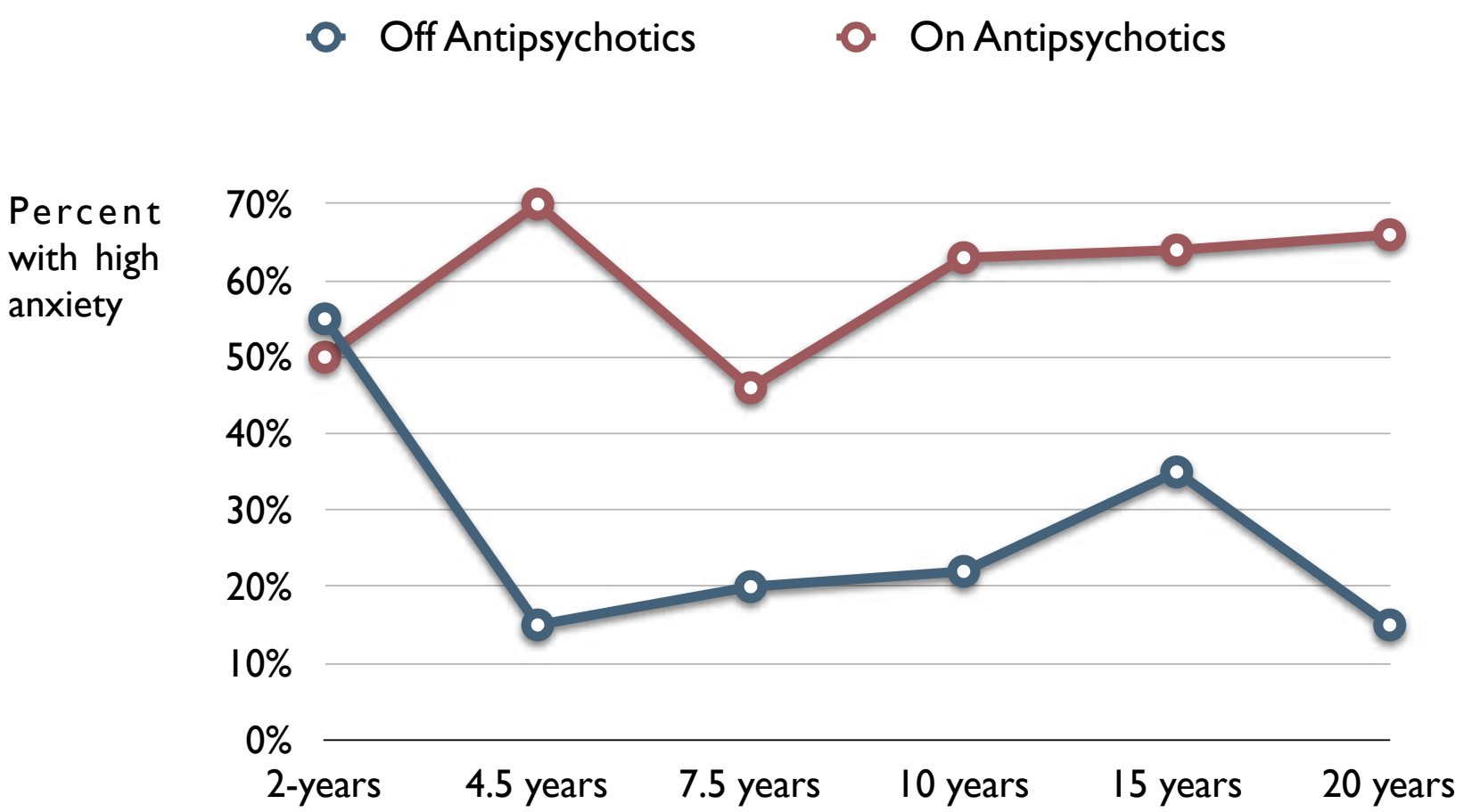
Patient Enrollment

- 64 schizophrenia patients
- 81 patients with other psychotic disorders
  - 37 psychotic bipolar patients
  - 28 unipolar psychotic patients
  - 16 other milder psychotic disorders

- Median age of 22.9 years at index hospitalization
- Previous hospitalization
  - 46% first hospitalization
  - 21% one previous hospitalization
  - 33% two or more previous hospitalizations

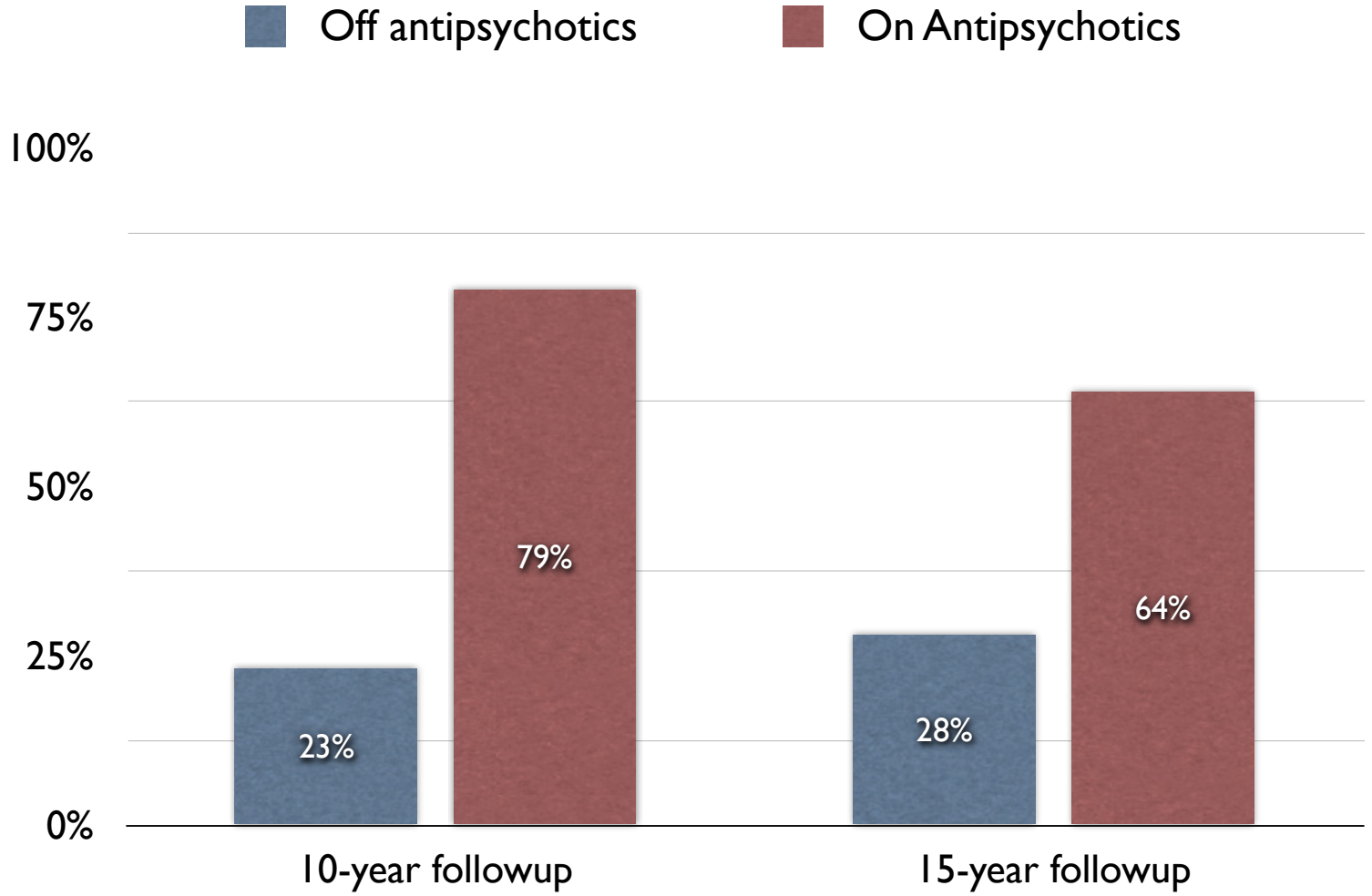
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Anxiety Symptoms of Schizophrenia Patients



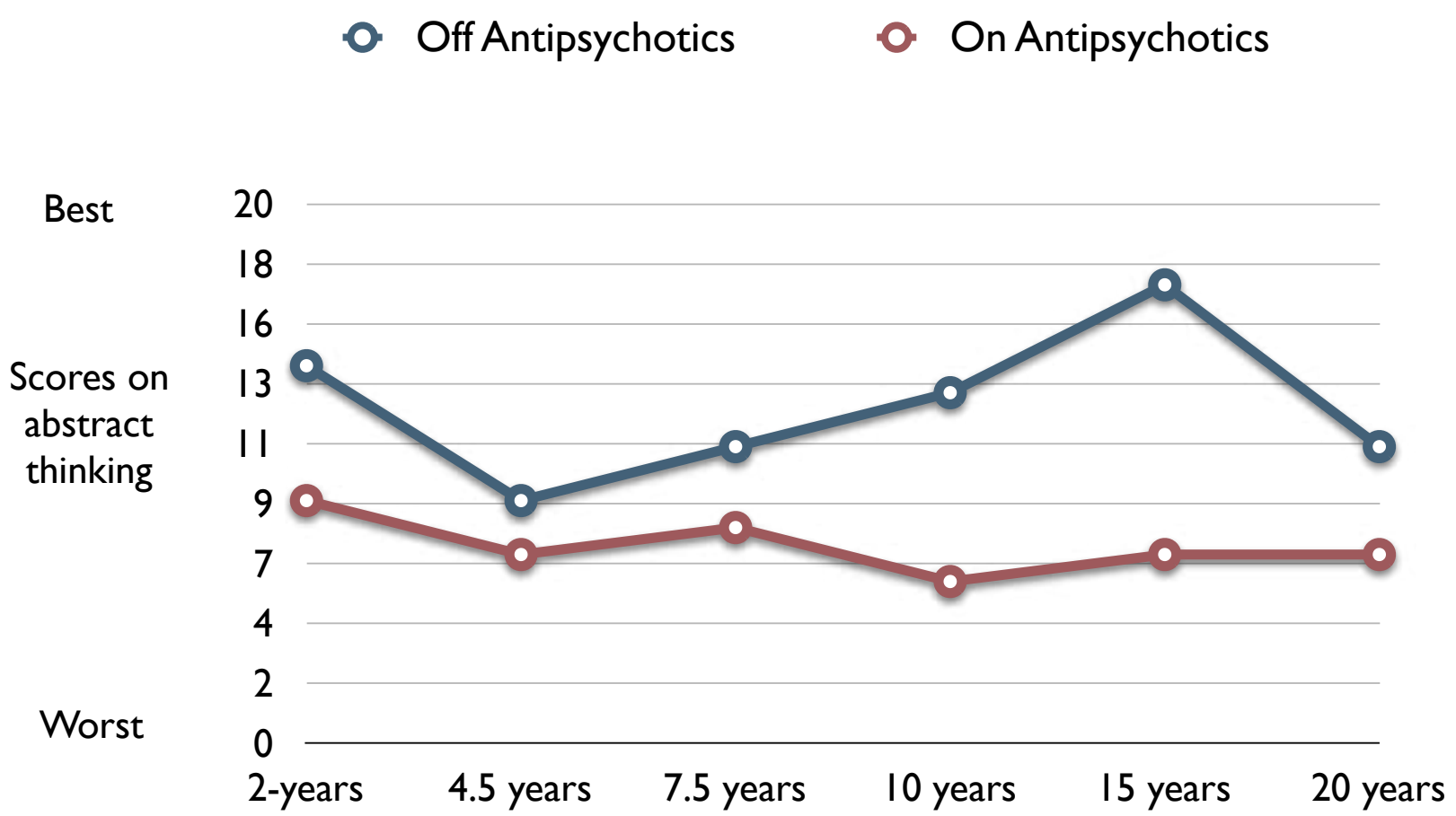
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



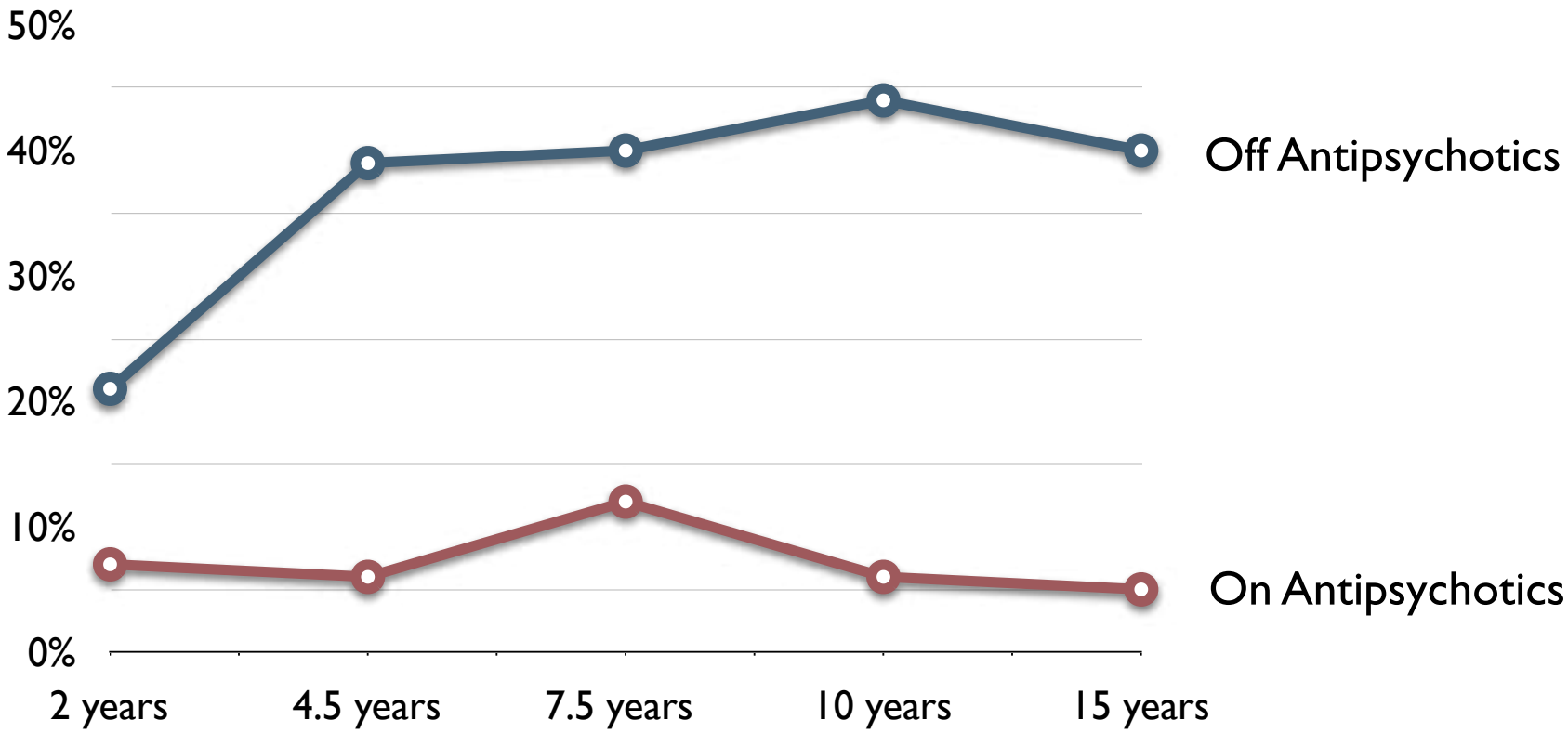
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Cognitive Function of Schizophrenia Patients



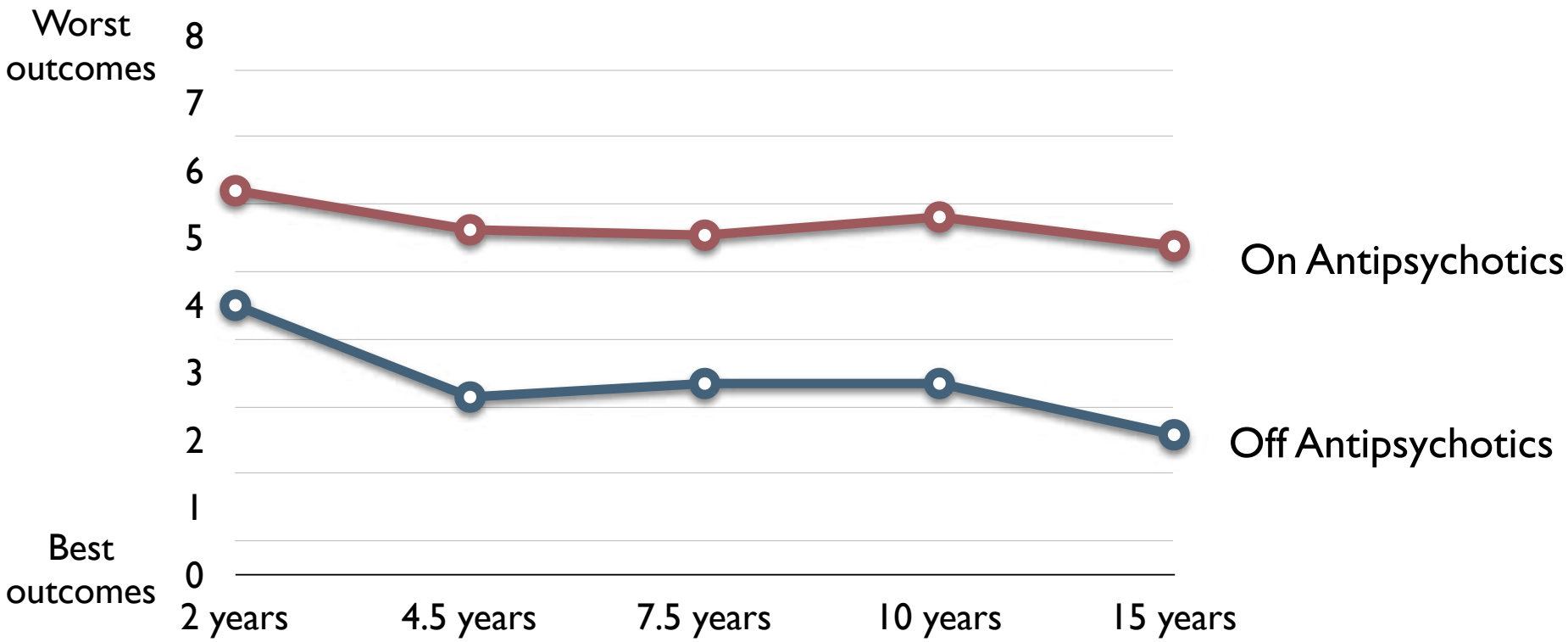
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Long-term Recovery Rates for Schizophrenia Patients



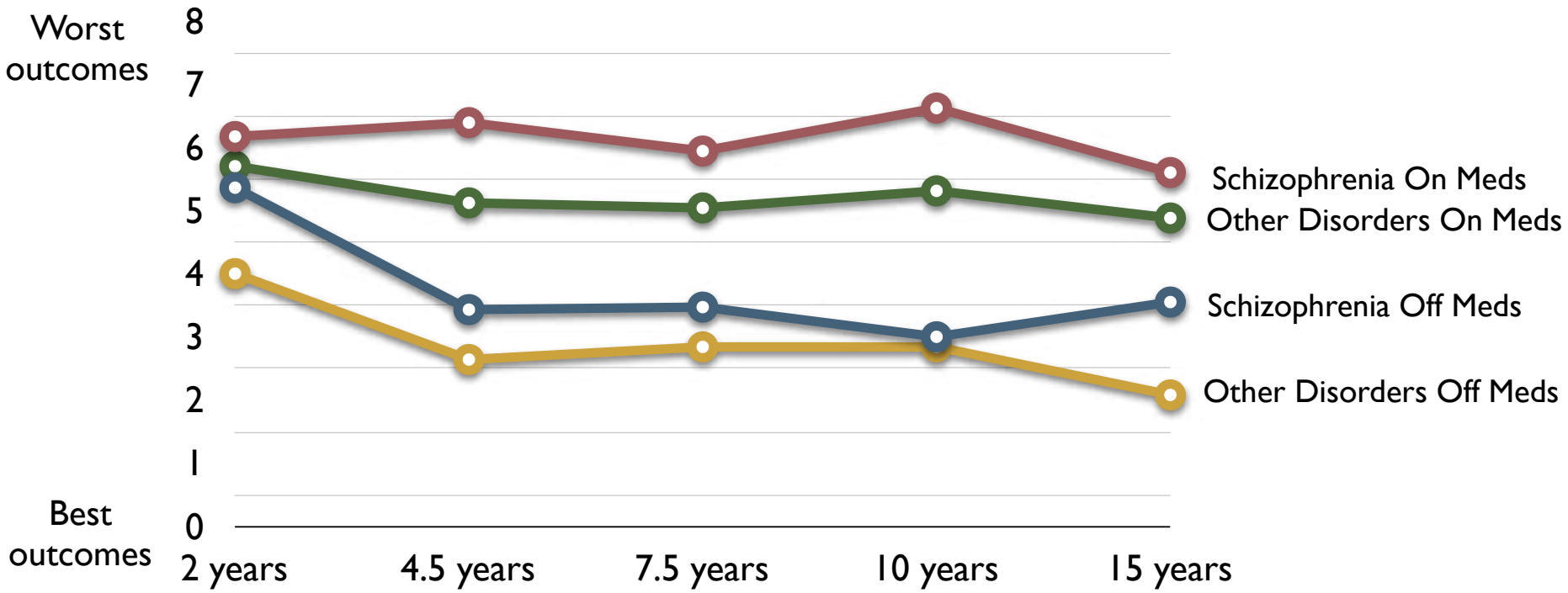
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Global Adjustment of "Other Psychotic" Patients



Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Global Adjustment of All Psychotic Patients



Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Early Death

- Since the introduction of the atypicals, the mortality rate for schizophrenia patients has notably worsened.

- The seriously mentally ill are now dying 15 to 25 years earlier than normal. They are dying from cardiovascular ailments, respiratory problems, metabolic illness, diabetes, kidney failure, and poor global physical health.

- How long will children placed on atypicals be expected to live if kept continuously on the drugs?

Source: M. Morgan, "Prospective analysis of premature mortality in schizophrenia in relation to health service engagement." *Psychiatry Res* 117 (2003):127-35. S. Saha, "A systematic review of mortality in schizophrenia," *Arch Gen Psych* 64 (2007).1123-32; M. Joukamaa, "Schizophrenia, neuroleptic medication, and mortality." *Br J Psychiatry* 1888 (2006):122-27. C. Colton, "Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states." *Prev Chronic Dis* 3 (April 2006).

Final Question

If we were children, would we want to be put on an atypical antipsychotic, for whatever presumed reason?