Medicating Children:

If Long-term Outcomes Are Considered, Is This An Evidence-Based Practice?

Robert Whitaker
April 2016

Do the Benefits Outweigh The Risks?

1. Stimulants for ADHD
2. Antidepressants in youth
3. Antipsychotics in youth

Mechanism of Action: A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

- Psychiatric medications "create perturbations in neurotransmitter functions."

- In response, the brain goes through a series of compensatory adaptations in order "to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu."

- The "chronic administration" of the drugs then cause "substantial and long-lasting alterations in neural function."

- After a few weeks, the person's brain is now functioning in a manner that is "qualitatively as well as quantitatively different from the normal state."

Source: Hyman, S. "Initiation and adaptation: A paradigm for understanding psychotropic drug action." *Am J Psychiatry* 153 (1996):151-61.

The Compensatory Adaptation with Stimulants

1. Stimulants increase dopamine activity in the brain.

2. For instance, at a therapeutic dose, methylphenidate (Ritalin) blocks the transporters that remove dopamine from the synaptic cleft between neurons and bring it back into the presynaptic neuron.

In Response:

- The presynaptic neurons may begin releasing less dopamine.

- The density of dopamine receptors on the post-synaptic neurons declines.

- Methylphenidate also acts on serotonin and norepinephrine neurons, and that may cause compensatory changes in those two pathways.

These Compensatory Changes May Not Be Reversible

In a study of prepubertal rats exposed to methylphenidate for two weeks, there was a dramatic decrease in the density of dopamine receptors in the striatum that persisted into adulthood.

Source: G. Moll, "Early methylphenidate administration to young rats causes a persistent reduction in the density of striatal dopamine transporters." *J of Child and Adolescent Psychopharmacology* 11 (2001): 15-24

Short-term Benefits of Stimulants for ADHD in Clinical Trials

Stimulants are highly effective in "dramatically reducing a range of core ADHD symptoms such as task-irrelevant activity (e.g., finger tapping, fidgetiness, fine motor movement, off-task during direct observation) and classroom disturbance."

--NIMH investigators in 1995

The Evidence-based Question:

Does this drug-induced change in how the brain works provide a long-term benefit to the child, particularly in regard to functional outcomes? What does the evidence show?

Early Clinical Observations of Stimulants on Global Behavior

• There is a "marked drug-related increase in solitary play and a corresponding reduction in their initiation of social interactions." Russell Barkley, 1978.

• The drug reduces a child's "curiosity about the environment." Nancy Fiedler, 1983.

• At times, the medicated child "loses his sparkle." Till Davy, 1989.

• Medicated children often become "passive, submissive" and "socially withdrawn." UCLA psychologists, 1993.

• Stimulants curb hyperactivity by "reducing the number of behavioral responses." *Oxford Textbook of Clinical Psychology and Drug Therapy.*

Early Observations of Stimulants on Academic Achievement

• Ritalin enhances performance on "repetitive, routinized tasks that require sustained attention," but "reasoning, problem solving and learning do not seem to be positively affected." Alan Sroufe, 1973.

• Ritalin does not produce any benefit on the students' "vocabulary, reading, spelling, or math" and hinders their ability to solve problems. "The reactions of the children strongly suggest a reduction in commitment of the sort that would seem critical for learning." Herbert Rie, 1978.

• "The major effect of stimulants appears to be an improvement in classroom manageability rather than academic performance." Russell Barkley, 1978.

Assessment of Long-term Effects of Stimulants, Early 1990s

"Stimulants do not produce lasting improvements in aggressivity, conduct disorder, criminality, education achievement, job functioning, marital relationships, or long-term adjustment."

-- APA's *Textbook of Psychiatry*, 1994

The NIMH Mounts a Study to Assess Long-term Outcomes

• Known as the Multisite Multimodal Treatment Study of Children With ADHD

• Hailed as the "first major clinical trial" that the NIMH had ever conducted of "a childhood mental disorder."

• At outset, the investigators wrote that "the long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning."

• Diagnosed children were randomized to one of four treatment groups: medication alone, behavioral therapy, medication plus behavioral therapy, or routine community care.

14-Month Results from NIMH's MTA Study

At end of 14 months, "carefully crafted medication management" had proven to be superior to behavioral treatment in terms of reducing core ADHD symptoms. There was a hint that medicated children also did better on reading tests.

Conclusion: "Since ADHD is now regarded by most experts as a chronic disorder, ongoing treatment often seems necessary."

Source: The MTA Cooperative Group, "A 14-month randomized cliniical trial of treatment strategies for attention-deficit/ hyperactivity disorder," *Archives of General Psychiatry* 56 (1999):1073-86.

Three-Year Results from NIMH's MTA Study

At the end of 36 months, "medication use was a significant marker not of beneficial outcome, but of deterioration. That is, participants using medication in the 24-to-36 month period actually showed increased symptomatology during that interval relative to those not taking medication." Medicated children were also slightly smaller, and had higher delinquency scores.

Source: Jensen, "A 3-year follow-up of the NIMH MTA study," *J Amer Academy of Child & Adolescent Psychiatry* 46 (200&):989-1002.

Analyzing the 3-Year Results

"The findings . . . were not consistent with views and expectations about medication effects held by many investigators and clinicians in the field. That is, long term benefits from consistent treatment were not documented; selection bias did not account for the loss of relative superiority of medication over time; there was no evidence for "catch up" growth; and early treatment with medication did not protect against later adverse outcomes."

Source: J. Swanson. "Evidence, interpretation and qualification from multiple reports of long-term outcomes in the multimodal treatment study of children with ADHD Part II." *J of Attention Disorders* 12 (2008):15-43.

Six-Year Results from MTA Study

At end of six years, medication use was "associated with worse hyperactivity-impulsivity and oppositional defiant disorder symptoms," and with greater "overall functional impairment."

Source: Molina, "MTA at 8 years," *J Amer Academy of Child & Adolescent Psychiatry 48 (2009):*484-500.

MTA Study Conclusion

"We had thought that children medicated longer would have better outcomes. That didn't happen to be the case. There were no beneficial effects, none. In the short term, [medication] will help the child behave better, in the long run it won't. And that information should be made very clear to parents."

--MTA Investigator William Pelham, University at Buffalo

Daily Telegraph, "ADHD drugs could stunt growth," Nov. 12, 2007.

Canadians Review the Literature, 2002

In a review of 14 studies that lasted a minimum of three months, involving 1,379 youth, Canadian investigators concluded that there is "little evidence for improved academic performance" with stimulants.

Source: R. Sachar, "Attention-deficit hyperactivity disorder," *Canadian Journal of Psychiatry* 47(2002):337-348.

A Meta-Analysis of the Literature, 2005

In a review of 2,287 studies:

There is "no good quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc."

-- Drug Effectiveness Review Project
Oregon Health and Science University, 2005

Source: McDonagh, "Drug class review on pharmacologic treatment for ADHD," 2006. http://www.ohsu.edu/drugeffectiveness

Western Australia's Long-Term Study of ADHD Drugs, 2009

- Medicated ADHD children were ten times more likely than unmedicated ADHD children to be identified by teachers as performing below age level in their school work.
- A small effect size showed worse ADHD symptoms in the medicated group.
- Medicated children had elevated diastolic blood pressure.
- Conclusion: Medication does not translate into long-term benefits to the child's social and emotional outcomes, school-based performance, or symptom improvement.

Source: Western Australian Department of Health, "Raine ADHD study: Long-term outcomes associated with stimulant medication in the treatment of ADHD children," 2009.
http://www.health.wa.gov.au/publications/documents/MICADHD_Raine_ADHD_Study_report_022010.pdf

Study of Long-Term Outcomes in Quebec, 2013

"The increase in medication use is associated with increases in unhappiness and a deterioration in relationship with parents. These emotional and social effects are concentrated among girls, who also experience increases in anxiety and depression. We also see some evidence of deterioration in contemporaneous educational outcomes including grade repetition and mathematics scores. When we turn to an examination of long-term outcomes, we find that increases in medication use are associated with increases in the probability that boys dropped out of school and with marginal increases in the probability that girls have ever been diagnosed with a mental or emotional disorder."

Source: J. Currie. "Do stimulant medications improve educational and behavioral outcomes for children with ADHD?" NBER working paper 19105, June 2013.

Summing Up The Evidence in 2012

"Attention-deficit drugs increase concentration in the short term, which is why they work so well for college students cramming for exams. But when given to children over long periods of times, they neither improve school achievement nor reduce behavior problems . . . to date, no study has found any long-term benefit of attention-deficit medication on academic performance, peer relationships, or behavior problems, the very things we would want most to improve . . . The drugs can also have serious side effects, including stunting growth."

--Alan Sroufe, professor emeritus of psychology at the University of Minnesota

Source: *New York Times*, "Ritalin Gone Wrong," January 28, 2012.

Adverse Effects From ADHD Medications

- **Physical:** Drowsiness, appetite loss, lethargy, insomnia, headaches, abdominal pain, motor abnormalities, tics, jaw clenching, skin problems, liver disorders, weight loss, growth suppression, hypertension, and sudden cardiac death.

- **Emotional:** Depression, apathy, a general dullness, mood swings, crying jags, irritability, anxiety, and a sense of hostility from the world.

- **Psychiatric:** Obsessive-compulsive symptoms, mania, paranoia, psychotic episodes, and hallucinations.

- **Upon Withdrawal:** ADHD symptoms (excitability, impulsivity, talkativeness) may become worse than ever. Behavior may rapidly deteriorate.

In Animal Studies, Stimulants Lead to Abnormal Behavior in Adulthood

- Preadolescent rats exposed to methylphenidate turned into anxious, depressed adult rats, with a "deficit in sexual behavior." Researchers concluded that "administration of methylphenidate" while the rat brain is still developing "results in aberrant behavioral adaptations during adulthood."

- In an overview of animal studies, researchers concluded that adolescent exposure to methylphenidate provokes "persistent neurobhavioral consequences," including less tolerance of stress and decreased sensitivity to natural rewards.

- In monkeys, repeated exposure to low doses of amphetamines caused monkeys to exhibit "aberrant behaviors" that remained long after drug exposure stopped.

Source: S. Castner. "Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys," *Neuropsychopharmacology* 20 (1999):10-28; E. Marco, "Neurobehavioral adaptations to methylphenidate," Neuroscience and Behavioral Reviews 35 (2011):1722-1739. W. Carlezon, "Enduring behavioral effects of early exposure to methylphenidate in rats," *Biological Psychiatry* 54 (2003):1330-37; C. Bolanos, "Methylphenidate treatment during pre-and periadolescence alters behavioral responses to emotional stimuli at adulthood," *Biological Psychiatry* 54(2003):1317-29.

Summary of Animal Studies

"Adolescent exposure to methylphenidate seems to provoke persistent neurobehavioral consequences: long-term modulation of self-control abilities, decreased sensitivity to natural and drug reward, and enhanced stress-induced emotionality."

E. Marco. "Neurobehavioral adaptations to methylphenidate." *Neuroscience and BioBehavioral Reviews* 35 (2011):1722-1739.

Conversion to Bipolar Illness

Stimulants can induce mania and psychosis

- In a Canadian study, six percent of ADHD children treated with stimulants for an average of 21 months developed psychotic symptoms.
- In a study of 195 bipolar children, Demitri Papolos found that 65% had "hypomanic, manic and aggressive reactions to stimulant medications."
- University of Cincinnati reported that 21 of 34 adolescent patients hospitalized for mania had been on stimulants "prior to the onset of an affective episode."

Source: Cherland, "Psychotic side effects of psychostimulants," *Canadian Journal of Psychiatry* 44 (1999):811-13. Papolos, "Bipolar disorder, co-occuring conditions, and the need for extreme caution before initiating drug treatment." *Bipolar Child Newsletter* 1 (Nov. 1999). DelBello, "Prior stimulant treatment in adolescents with bipolar disorder," *Bipolar Disorders* 3 (2001):53-57.

Stimulants Can Induce Mood Swings That Are Basis for Bipolar Diagnosis

Stimulant-induced symptoms		Bipolar Symptoms	
Arousal	Dysphoric	Arousal	Dysphoric
Increased energy Intensified focus Hyperalertness Euphoria Agitation, anxiety Insomnia Irritability Hostility Hypomania Mania Psychosis	Somnolence Fatigue, lethargy Social withdrawal Decreased spontaneity Reduced curiosity Constriction of affect Depression Emotional lability	Increased energy Intensified goal-directed activity Agitation Severe mood change Decreased need for sleep Irritability Destructive outbursts Increased talking Distractibility Hypomania Mania	Sad mood Loss of energy Loss of interest in activities Social isolation Poor communication Feelings of worthlessness Unexplained crying

Harm-Benefit Ratio of Stimulants

Benefits	Harms
Short-term improvement of ADHD symptoms	No long-term benefit on any domain of functioning
Possible short-term improvement in reading	Physical, emotional and psychiatric adverse effects
	Risk of drug-induced conversion to juvenile bipolar disorder
	Risk of aberrant behavior in adulthood

Counterpoint One

- Through a review of a Swedish national registry, investigators identified 25,656 patients 15 years and older diagnosed with ADHD, and assessed their use of stimulants from 2006 through 2009.

- Researchers found that patients were more likely to commit crimes during period when they stopped taking stimulants (31% increased rate for men; 41% for women.)

- Conclusion: "These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD."

Source: P. Lichtenstein. "Medication for attention-deficit hyperactivity disorder and criminality." *NEJM* 367 (2012):2006-2014.

The Flaw With the Swedish Study

Medication use:

- 1,057 of 25,656 patients (4.2%) used stimulants continuously during the four years.
- 13,558 patients (52.8%) used stimulants sporadically during the four years.
- 11,041 patients (43%) didn't use stimulants at all during the four years.

Findings:

- "In patients who had both treatment and non-treatment periods, the risk of being convicted of a crime was significantly increased."

The Flaw:

- There is no crime data specific to the group that never used stimulants during the study period. A more revealing finding would be to report the crime rates for each of these three groups.

Counterpoint Two

- In 2012, Shire Pharmaceuticals funded a study, led by its medical director, that reviewed studies of long-term outcomes, at least two years in length, for ADHD that had been published since 1980.

- Shire manufactures Vyvanse, Adderall XR and Intuniv, three drugs commonly prescribed for ADHD.

- The researchers reported that there were 29 reports of favorable outcomes for treated ADHD in the literature, on some measure or another, when compared to patients who weren't treated, and 20 reports of no benefit or worse outcomes for treated ADHD. (The data has to be carefully parsed to see this.)

- They concluded: "Treatment for ADHD improved long-term outcomes compared with untreated ADHD."

Source: M. Shaw. "A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder." BMC Medicine10 (2012):99.

Reasons to Question the Study

- Evident financial conflict of interest by investigators
- Biased methodology. In comparison of treated to untreated ADHD, the researchers included studies that compared treated patients to "pretreatment baseline," i.e. studies that in fact had no untreated patients. Sixty-two percent of their comparison studies were of studies of this type.
- These findings are in contrast to the meta-analysis of the literature by the Drug Effectiveness Review Project, which is a consortium of investigators from different universities that receives no funding from pharmaceutical companies.

Spanish Investigators: Time To Rethink Use of Stimulants

"These drugs are the same stimulants whose harmful consequences are well known in other uses in adults. In this paper we have carried out an exhaustive review of the sources from scientific evidence regarding the short and long term effectiveness of the medication . . . The result is disappointing and should lead to a modification of the [Clinical Practice Guidelines] to the use of drugs as tools of last resort, in a small number of cases and limited and short periods of time."

--Miguel Valverde Eizaquirre

Source: M. Valverde. "Outreach and limitations of the pharmacological treatment of Attention Deficit Disorder with Hyperactivity (ADHD) in children and adolescents and Clinical Practice Guidelines: A literature review." *Rev Asoc Esp. Neuropsiq* 34 (2014):37-74.

What the Public is Told About Longer-Term Use of Stimulants

ADHD Parents Medication Guide

To help families make important decisions about treatment, the National Institute of Mental Health began a large treatment study in 1992 called the Multimodal Treatment Study of Children with ADHD. Data from this 14-month study showed that stimulant medication is most effective in treating the symptoms of ADHD, as long as it is administered in doses adjusted for each child to give the best response—either alone or in combination with behavioral therapy. This is especially true when the medication dosage is regularly monitored and adjusted for each child.

Published by: *American Academy of Child and Adolescent Psychiatry*

Antidepressants for Children Prior to Prozac Era

Studies of tricyclics: "There is no escaping the fact that research studies certainly have not supported the efficacy of tricyclic antidepressants in treated depressed adolescents." --*Journal of Child and Adolescent Psychology,* 1992

The Corruption of the Scientific Literature in Pediatric Antidepressant Trials

Pediatric trials of antidepressants:

- Biased by design
- Published results didn't square with actual data
- Adverse events were downplayed or omitted
- Negative studies went unpublished or were spun into positive ones

"The story of research into selective serotonin reuptake inhibitor use in childhood depression is one of confusion, manipulation and institutional failure."

--*Lancet*, 2004

Source: Editorial, "Depressing research," *Lancet* 363 (2004):1335.

FDA's 2004 Report on SSRI Pediatric Trials

- 12 of 15 pediatric trials of SSRIs failed to show short-term efficacy for the drug
- The FDA rejected the applications of six manufacturers seeking pediatric labeling for SSRIs
- Although the FDA approved Prozac for pediatric uses, the trials were biased by design.

Source: T. Laughren, "Background comments for Feb. 2 2004 meeting of psychopharmacological drugs advisory committee, Jan. 4, 2004. Accessed at FDA.gov.

The British View of SSRIs in Children

- In 2003, the Medicines and Health Regulatory Agency essentially banned the use of SSRIs, except for fluoxetine (Prozac), in patients under 18 years old.
- *Lancet* editorial, 2004: These drugs are "both ineffective and harmful in children."
- *British Medical Journal,* 2004: "Recommending [any antidepressant, including Prozac] as a treatment option, let alone as first line treatment, would be inappropriate."

Source: Editorial, "Depressing research," *Lancet* 363 (2004):1335. Jureidini, "Efficacy and safety of antidepressants for children and adolescents," *Brit Med Journal* 328 (2004):879-83.

The TADs Controversy

Reported Results: Fluoxetine is Effective

After 12 weeks, 62% response for fluoxetine versus 35% for placebo.

The Critics' View

The reported benefits only occurred in the unblinded arm of the study; in blinded arm, fluoxetine failed to perform better than placebo on Children's Depression Rating Scale.

Significantly more psychiatric adverse events in fluoxetine-treated group; researchers failed to fully report on negative data.

Six children on fluoxetine attempted suicide; versus one on placebo.

Suicide Data From TADS Study

	At 12 Weeks		12 to 36 Weeks		Total	
Initial Randomization	**Suicidal Ideation**	**Suicidal Attempts**	**Suicidal Ideation**	**Suicidal Attempts**	**Suicidal Ideation**	**Suicidal Attempts**
Non-Drug						
Placebo	5	0	1	6	6	6
CBT	4	1	0	2	4	3
Total Non-Drug	9	1	1	8	10	9
Fluoxetine						
Fluoxetine	9	3	1	3	10	6
Fluoxetine Plus CBT	3	2	3	1	6	3
Total Fluoxetine	12	5	4	4	16	9

Source: B. Vitiello. "Suicidal events in the treatment for adolescents with depression." *J Clin Psychiatry* 70 (2009): 741–7.

Conclusion

There is no "evidence of medication-induced behavioral activation as a precursor" to a suicidal event.

Source:B. Vitiello. "Suicidal events in the treatment for adolescents with depression." *J Clin Psychiatry* 70 (2009): 741–7.

The TADS Suicide Data By Drug Exposure

	At 12 Weeks		12 to 36 Weeks		Total	
	Suicidal Ideation	Suicidal Attempts	Suicidal Ideation	Suicidal Attempts	Suicidal Ideation	Suicidal Attempts
Non-Drug						
Placebo	3	0	0	0	3	0
CBT	4	1	0	0	4	1
Total Non-Drug	7	1	0	0	7	1
Fluoxetine						
Randomized to Placebo	2	0	1	6	3	6
Randomized to CBT				2		2
Randomized to Fluoxetine	9	3	1	3	10	6
Randomized to Fluoxetine Plus CBT	3	2	3	1	6	3
Total on Drug	14	5	6	12	19	17

Source:B. Vitiello. "Suicidal events in the treatment for adolescents with depression." *J Clin Psychiatry* 70 (2009): 741–7.

Adverse Effects of SSRIs in Children

- **Physical:** Insomnia, sexual dysfunction, headaches, gastrointestinal problems, dizziness, tremors, nervousness, muscle cramps, muscle weakness, seizures, and akathisia (associated with increased risk of suicide).
- **Emotional/Psychiatric:** Psychosis, mania, behavioral toxicity, panic attacks, anxiety, apathy, an emotional dulling. Also, doubling of risk of suicidal acts.

Long-Term Risks With SSRIs in Children

- Conversion to bipolar diagnosis.
- Apathy Syndrome
- Cognitive Impairment
- Sexual dysfunction in adulthood

Source: Faedda, "Pediatric onset bipolar disorder," Harvard Review of Psychiatry 3 (1995):171-95. Geller, "Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder," *Amer J of Psychiatry* 158 (2001):125-7.

Pediatric Bipolar in the Literature Prior to the Use of Stimulants and Antidepressants

- 1945, Charles Bradley: Pediatric mania is so rare that "it is best to avoid the diagnosis of manic-depression." --*Journal of Pediatrics*
- 1950, Louis Lurie: "Observers have concluded that mania does not occur in children."--*Journal of Pediatrics*
- 1952, Barton Hall: "Manic-depressive states are illnesses of the maturing or matured personality."--*Nervous Child*
- 1960, James Anthony: "Occurrence of manic depression in early childhood has yet to be demonstrated."--*Journal of Child Psychology and Psychiatry*

The Discovery of Juvenile Bipolar Illness -- The First Case Studies

- 1976, Washington University: At least three of five children diagnosed with mania had been treated with a tricyclic or Ritalin prior to becoming manic. --*American Journal of Diseases of Childhood.*

- 1980, Massachusetts General Hospital: At least seven of nine children diagnosed with manic-depressive illness had been previously treated with amphetamines, methylphenidate, or other medications to affect behavior. -- *Journal of Pediatrics*

- 1982, UCLA: Twelve of 60 adolescents treated with antidepressants turned "bipolar" within three years; this is seen as evidence that antidepressants can "unmask" the disease.-- *Archives of General Psychiatry*

The SSRI-to-Bipolar Pathway

- In first pediatric trial of Prozac, 6% of treated children suffered a manic episode; none in placebo group.
- In study of antidepressant-induced mania for all ages, Yale University investigators found the risk highest in those under 13 years of age.
- Harvard University researchers find that 25% of children treated for depression convert to bipolar within four years.
- Washington University researchers report that within 10 years, 50% of prepubertal children treated for depression convert to bipolar illness.

Source: Emslie, "A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression," *Arch of General Psychiatry* 54 (1997):1031-37. Martin, "Age effects on antidepressant-induced manic conversion," *Arch of Pediatrics & Adolescent Medicine* 158 (2004):773-80. Faedda, "Pediatric onset bipolar disorder," *Harvard Review of Psychiatry* 3 (1995): 171-95. Geller, "Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder," *Amer J of Psychiatry* 158 (2001):125-7.

Confirming the Stimulant and SSRI Pathways to Juvenile Bipolar Illness

- University of Louisville researchers report that 49 of 79 juvenile bipolar patients (62%) had been treated with an antidepressant prior to their becoming manic.

- Demitri Papolos reports that 83% of 195 bipolar children had been initially diagnosed and treated for another psychiatric disorder; two-thirds had been exposed to an antidepressant.

- At the Luci Bini Mood Disorders Clinic in New York City, 84% of the bipolar children treated between 1998 and 2000 had been exposed to other psychiatric drugs before bipolar diagnosis. "Strikingly, in fewer than 10% [of the cases] was diagnosis of bipolar disorder considered initially," the investigators wrote.

Source: Cicero, "Antidepressant exposure in bipolar children," *Psychiatry* 66 (2003):317-22. Papolos, "Antidepressant-induced adverse effects in juvenile-onset bipolar disorder," paper presented at the Fifth International Conference on Bipolar Disorder, June 12-14, 2003, Pittsburgh, Pa. Faedda, "Pediatric bipolar disorder," *Bipolar Disorders* 6 (2004):305-13.

Long-Term Outcomes for Medicated Juvenile Bipolar Patients are Poor

- Washington University: Juvenile bipolar patients exhibit symptoms "similar to the clinical picture reported for severely ill, treatment-resistant adults."

- Demitri Papolos reported that 87% of his 195 juvenile bipolar patients suffered from "ultra, ultra rapid cycling."

- At Luci Bini clinic in NYC, 66% of juvenile patients were "ultra, ultra rapid cyclers," and another 19% from rapid cycling only a little bit less extreme.

- University of Pittsburgh: Early onset bipolar patients are symptomatic 60% of time, and shift polarity on average 16 times per year.

Source: Geller, "Child and adolescent bipolar disorder," *Journal of the American Academy of Child & Adolescent Psychiatry* 36 (1997):1168-76. Papolos, "Antidepressant-induced adverse effects in juvenile-onset bipolar disorder," paper presented at the Fifth International Conference on Bipolar Disorder, June 12-14, 2003, Pittsburgh, Pa. Faedda, "Treatment-emergent mania in pediatric bipolar disorder," *Journal of Affective Disorders* 82 (2004):149-58. Birmaher, "Course and outcome of bipolar spectrum disorder in children and adolescents," *Development and Psychopathology* 18 (2006): 1023-35.

Reviews of Medications for Juvenile Bipolar Disorder

- Washington University: At end of two years, mood stabilizers, lithium, stimulants, and antidepressants all failed to help bipolar youth fare better. Those treated with an antipsychotic "were significantly less likely to recover than those who did not receive a neuroleptic."

- Hayes, a medical consulting firm, in 2008: "Our findings indicate that at this time, anticonvulsants [mood stabilizers] and atypical antipsychotics cannot be recommended for children diagnosed with bipolar disorders."

Source: Geller, "Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype," *American Journal of Psychiatry* 159 (2002):927-33. Press release, "Hayes says new treatments for pediatric bipolar disorder not ready for prime time," December 3, 2008, hayesinc.com.

Other Long-Term Worries

- Long-term SSRI use may lead to an apathy syndrome, now dubbed "tardive dysphoria."
- Long-term SSRI use may be associated with memory impairment and other cognitive impairments.
- Long-term SSRI use may lead to persistent sexual dysfunction, even after the antidepressant is withdrawn. This problem has been dubbed PSSD (post SSRI sexual dysfunction.)

Harm-Benefit Ratio of SSRIs In Children

Benefits	Harms
In TADS study, fluoxetine showed a benefit over placebo at the end of 12 weeks.	Most SSRIs fail to provide a benefit over placebo on the target symptom of depression
	Physical, emotional and psychiatric adverse effects
	Risk of drug-induced conversion to juvenile bipolar disorder, and possible lifelong disability.
	Risk of drug-induced apathy, cognitive impairment, and sexual dysfunction in adulthood.

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.

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.

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.

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.

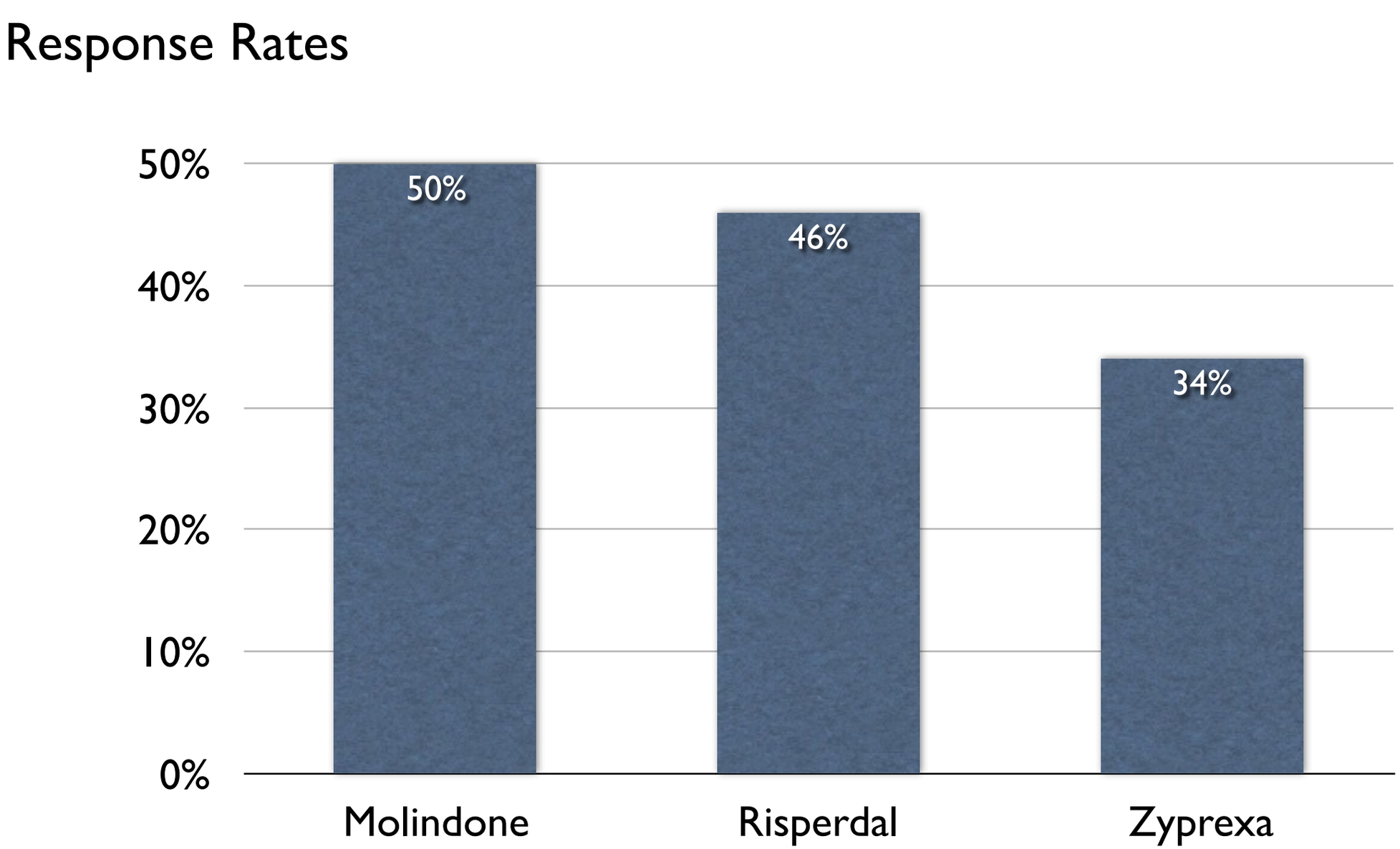
Other Short-Term Studies

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.

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.

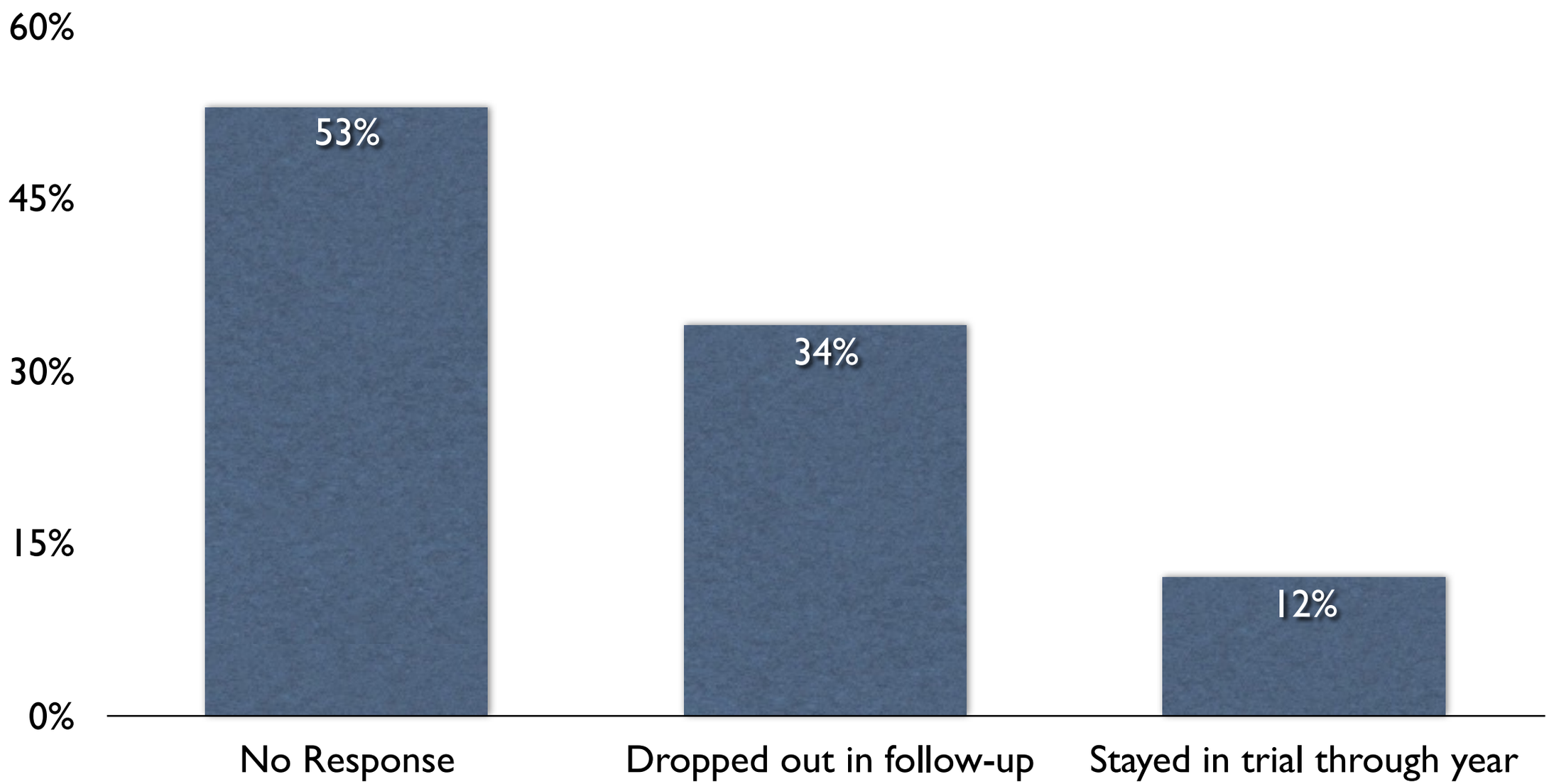
Source: R. Findling. "Double-blind maintenance safety and effectiveness findings from the treatment of early-onset schizophrenia spectrume (TEOSS) study." *J Am Acad Child & Adolesc Psychiatry* 49 (2010):583-95.

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.”

Harm vs. Benefit in Teoss Trial



Reported Adverse Effects of Atypicals In Youth

- Movement disorders
- Metabolic dysfunction
- Endocrine dysfunction
- Emotional and cognitive blunting
- High rates of tardive dyskinesia

Poor Global Health of Youth Treated With Atypicals

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.

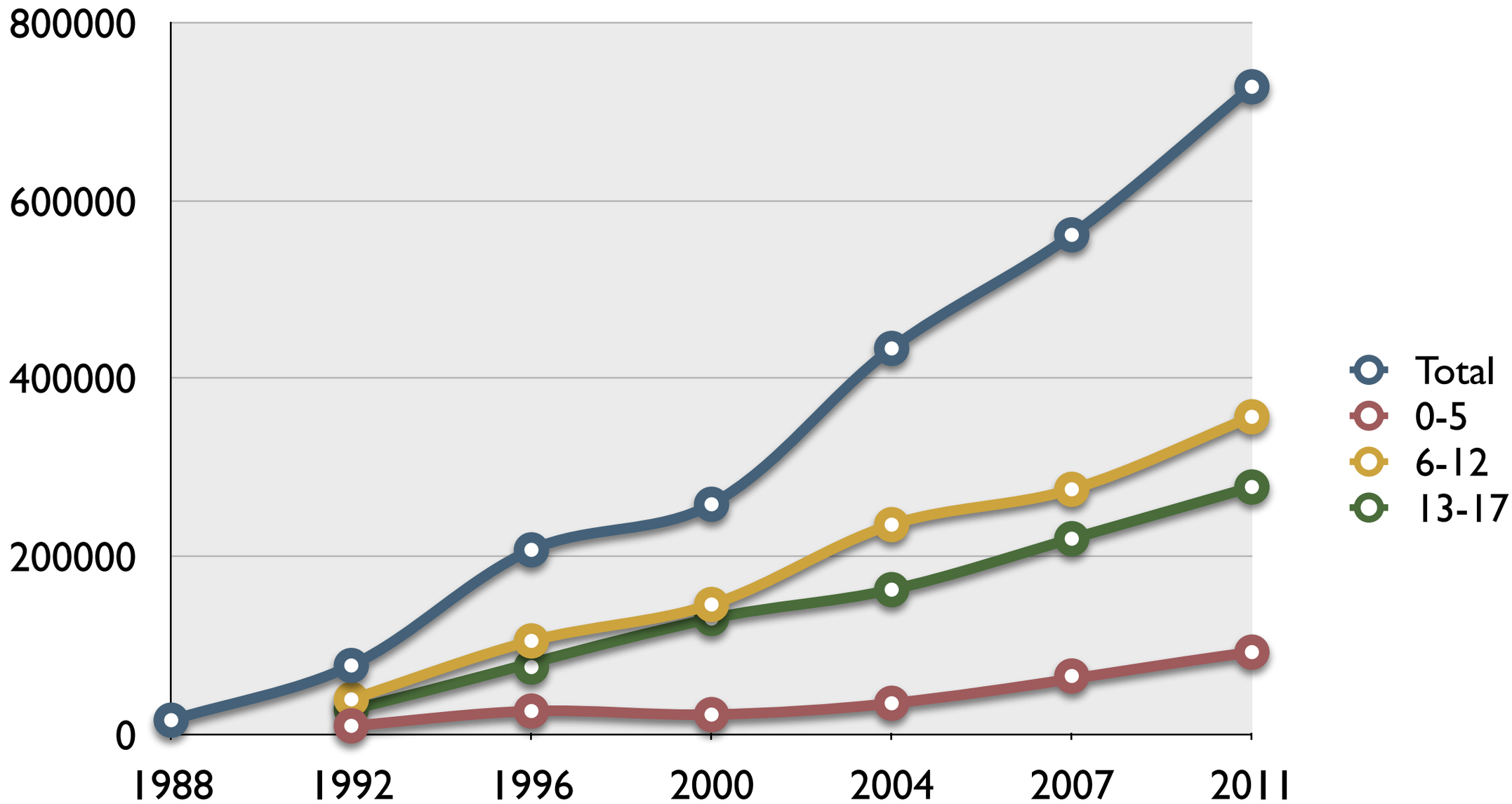
- TD may be more reversible in children than in adults if the drug is withdrawn. However, adults who develop TD show signs of a permanent global decline in brain function. It is associated with emotional disengagement, psychosocial impairment, and a decline in memory, visual retention, and the capacity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

Harm-Benefit Ratio of Atypicals In Children

Benefits	Harms
Improvement in symptoms of schizophrenia and bipolar disorder over the short-term.	Atypicals impair the normal functioning of numerous neurotransmitters.
Curbing aggression and other difficult behaviors over the short-term.	Brain volume loss, which in adult schizophrenia patients is associated with cognitive impairment and functional decline.
	Movement disorders, metabolic dysfunction, endocrine dysfunction, cardiovascular problems, and poor global health.
	Risk of tardive dyskinesia.
	Emotional and cognitive impairments.

U.S. Children on Government Disability Due to Mental Illness, 1987-2011



Prior to 1992, the government's SSI reports did not break down recipients into subgroups by age. Source: Social Security Administration reports, 1988-2007.