The Evidence is In:

Why We Need to Develop Alternatives to Psychiatric Medications for Children

September 2013

Disclosure

I do not have any commercial interests to disclose.

A Review of the Evidence: Do the Benefits Outweigh The Risks?

1. Stimulants for ADHD
2. Antidepressants in youth

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

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• Medicated children often become "passive, submissive" and "socially withdrawn."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

Six-Year Results from NIMH's 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

One-year ADHD Outcomes in Medicaid Population

- At end of one year, no difference between those received care and those who did not.
- "Compared with children receiving no care, children in specialty mental health clinics were more likely to have high functional impairment at 6- and 12-month follow-ups."

Source: Zima, "Quality of care for childhood attention-deficit/hyperactivity disorder in a managed care Medicaid program." *J Amer Acad of Child & Adolesc Psychiatry* (2010): 49, 1225-1237.

Study of Long-Term Outcomes in Quebec

"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 neurobehavioral 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.

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

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
- The FDA had only approved one SSRI for pediatric use, Prozac.

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.

- At end of 36 weeks, there were 17 suicidal events in children exposed to fluoxetine; one in children randomized to placebo or CBT and who were never exposed to fluoxetine during the trial. (This result was hidden in the published literature.)

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

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.
- In short-term trials, 8.19% of youth with anxiety or depression treated with an antidepressant had a manic or hypomanic reaction, versus .17% in placebo group.
- 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. Olfidani. "Excessive mood elevagtion and behavioral activation 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.

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.
	Increased risk of suicidal acts
	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.

Juvenile Bipolar Disorder: An Iatrogenic Illness

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*

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.

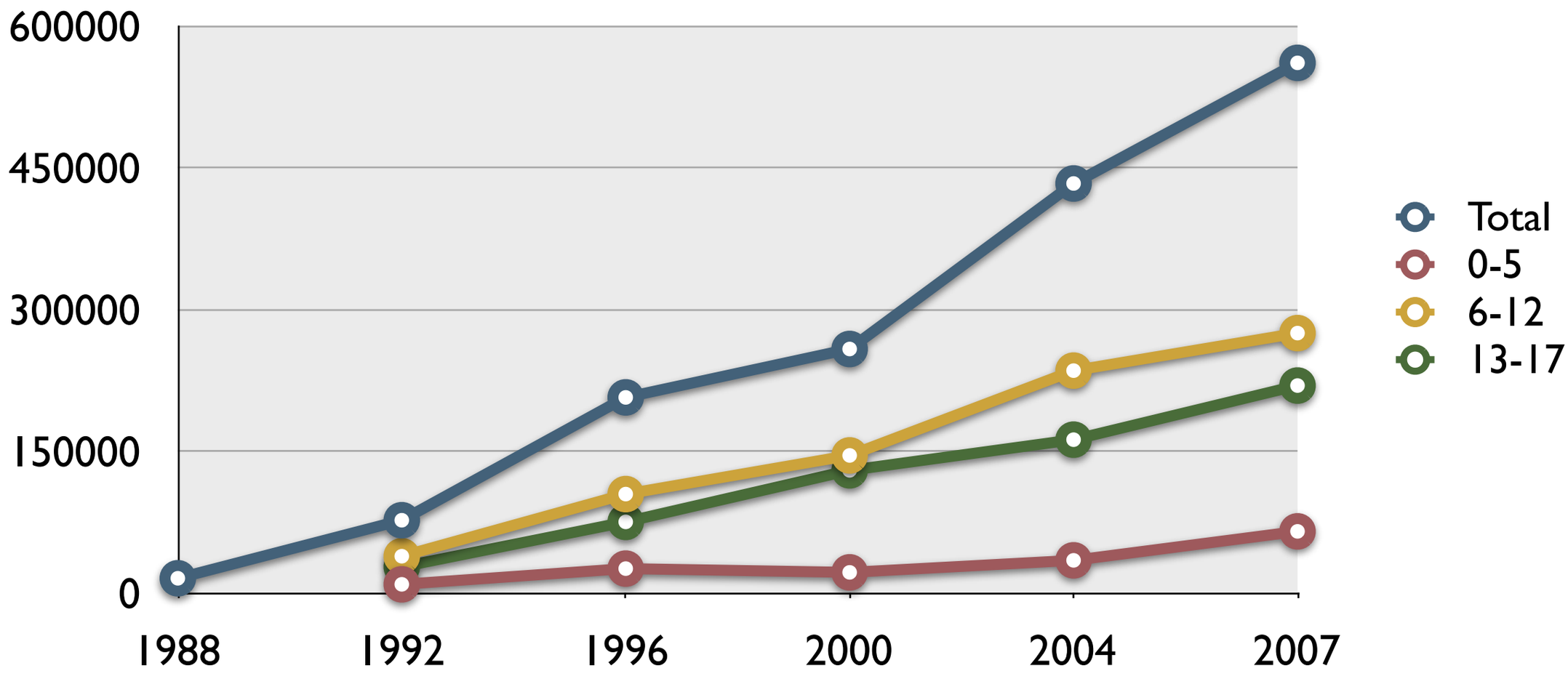
Reviews of Medications for Juvenile Bipolar Disorder

- 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.

Children on SSI Disability Due to Mental Illness in the Prozac Era



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