Medicating Children and Adolescents

Is This an Evidence-Based Practice?

Short-term Benefits of Stimulants for ADHD

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

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

Long-Term 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.

- 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.

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

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

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.
- 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

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.

Long-Term Risks With Stimulants

- Desensitized brain-reward system?
- Increased risk of addiction?
- Conversion to bipolar diagnosis: 10% to 25% now convert

Source: "Bolla," The neuropsychiatry of chronic cocaine abuse," *J of Neuropsychiatry and Clinical Neurosciences* 10 (1998):280-9. Castner, "Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys," *Neuropsychopharmacology* 20 (1999):10-28. Carlezon, "Enduring behavioral effects of early exposure to methylphenidate in rats," *Biological Psychiatry* 54 (2003):1330-37. Biederman, "Attention-deficit hyperactivity disorder and juvenile mania," *J of the American Academy of Child & Adolescent Psychiatry* 35 (1996):997-1008.

Antidepressants and 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
- Usage: In 1988, one in 250 children under 19 years of age taking an antidepressant

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 Report on SSRI Pediatric Trials

- 12 of 15 pediatric trials of SSRIs failed to show 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 highly 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.

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.

Long-Term Risks With SSRIs in Children

- Apathy Syndrome
- Cognitive Impairment
- Conversion to bipolar diagnosis; 25% to 50% of long-term users convert.

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 Stimulant-to-Bipolar Pathway, Part One

Stimulants can induce mania and psychosis

- In Canadian study, six percent of ADHD children treated with stimulants for 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.

The Stimulant-to-Bipolar Pathway, Part Two

Stimulants can induce mood swings used to diagnose bipolar

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

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 Iatrogenic Pathways to Juvenile Bipolar Illness

Surveys of Juvenile Bipolar Patients

- 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 reported 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.

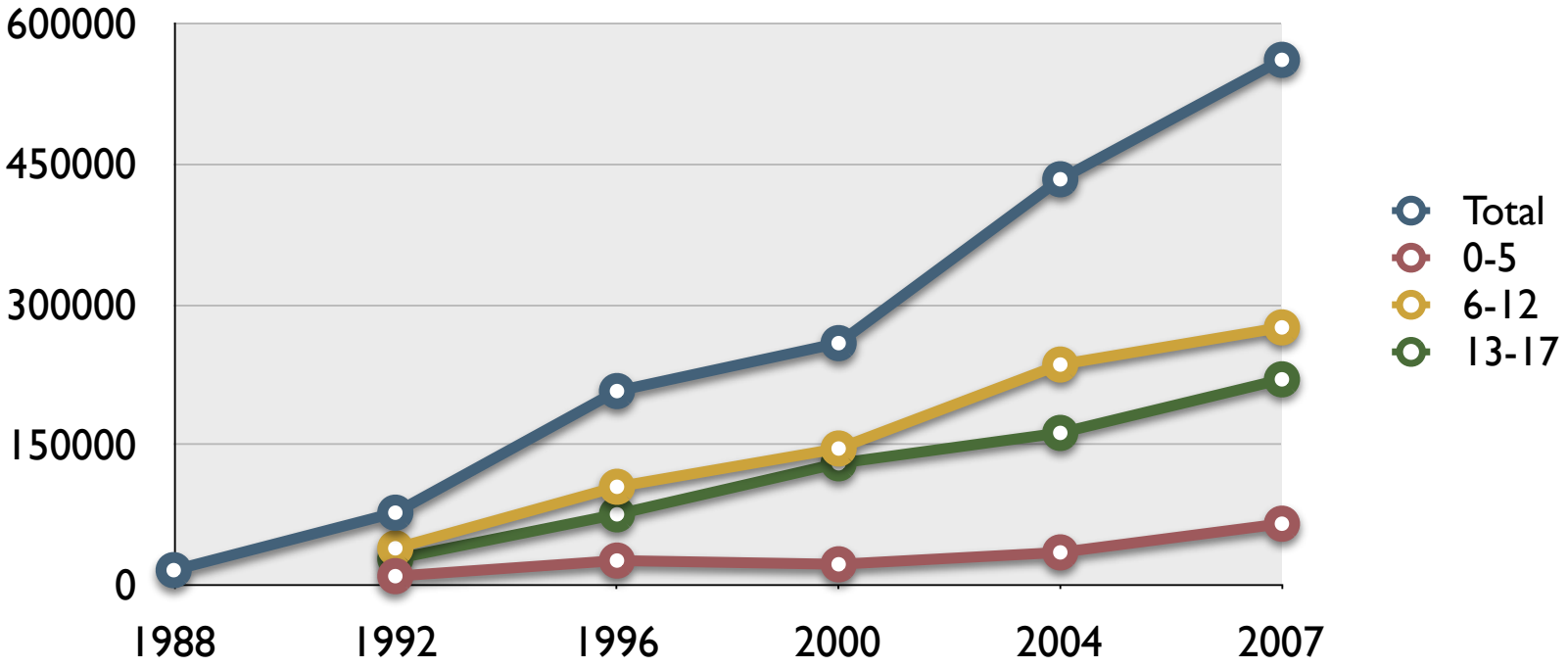
Reviews of Medications for Juvenile Bipolar Disorder

- 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.

The Epidemic in Children

Children on SSI Disability Due to Mental Illness



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

Atypicals in Youth 6 to 17 Years Old

- 4.2% of Medicaid youth prescribed an antipsychotic in 2004
- .9% of privately insured prescribed an antipsychotic in 2006
- Only 3.3% of prescriptions for schizophrenia or schizoaffective disorder

Source: Crystal, S. "Broadened Use of Atypical Antipsychotics," *Health Affairs*, 2009

Adverse Effects With Atypicals

- University of Maryland: Nine percent of children treated with antipsychotics for median time of 484 days developed tardive dyskinesia.
- Side effects include metabolic dysfunction, obesity, type-II diabetes, hormonal abnormalities, movement disorders, cardiovascular problems, emotional blunting, sedation, and cognitive problems. Adverse events worse in children and adolescents than in adults.
- Possible brain shrinkage and likely cognitive decline long-term.
- Early death

Source: Wonodi, I. "Tardive dyskinesia in children treated with atypical antipsychotic medications," *Movement Disorders* 22 (200&);1777-82. Jerrell, J. "Adverse events in children and adolescents treated with antipsychotic medications," *Human Psychopharmacology,* June 23, 2008, 283-90. Moreno, "Metabolic effects of second-generation antipsychotics in bipolar youth," *Bipolar Disorders* 12 (2010):172-84. Vitiello, "Antipsychotics in children and adolescents," E*uropean Neuropsychopharmacology* 19 (2009):629-35.

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

The Evidence for Long-Term Use Of Psychotropics in Children

American Academy of Child and Adolescent Psychiatry, 2009

- Three long-term studies cited
  - The MTA results for ADHD at 24 months, which showed that those withdrawn from drugs saw their ADHD symptoms spike. The paper doesn't cite the 3-year and 6-year MTA results.
  - Zoloft for obsessive-compulsive disorder. Study was for one year, and was not placebo-controlled.
  - Zoloft for major depression. Study was for 24 weeks and was not placebo-controlled.

Source: AACAP, "Practice parameter on the use of psychotropic medication in children and adolescents," *J Am Acad Child Adolescent Psychiatry* 48 (2009):961-73.

Summing up the Evidence

1. Stimulants for ADHD

a) short-term efficacy
b) no long-term efficacy
c) risk of long-term harm

2. Antidepressants for Depression

a) except for Prozac, no short-term efficacy
b) risk of long-term harm

3. The bipolar boom

a) iatrogenic pathways to diagnosis
b) poor long-term outcomes

Long-term Worries With Psychotropics

- Increased risk of disability (bipolar pathway)
- Physical ailments
- Emotional lethargy
- Cognitive decline
- Early death