

A Brief History of ADHD and Outcomes with Medication

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History of Diagnosis

- Attention deficit disorder was identified as a discrete disorder in 1980, when the American Psychiatric Association published the third edition of its Diagnostic and Statistical Manual (DSM-III).
- This was renamed attention-deficit hyperactivity disorder in a revised edition of DSM-III, published in 1987.
- Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity.

- Diagnosis arises primarily from teacher complaints, as “only a minority of children with the disorder exhibit symptoms during a physician’s office visit.” (*Harvard Review of Psychiatry*, 2009).
- The youngest children in a classroom are 30% more likely to be diagnosed than the oldest children.
- Between 2007-2009, 9% of children five to 17 years old in the United States had been diagnosed with ADHD. For boys, 12.3% had been so diagnosed (U.S. Department of Health and Human Services.)

The Biology of ADHD

- 1991: “Attempts to define a biological basis for ADHD have been consistently unsuccessful. The neuroanatomy of the brain, as demonstrated by imaging studies, is normal.”
Gerald Gordon, pediatric neurologist.
- 1997: “Efforts to identify a selective neurochemical imbalance (in ADHD children) have been disappointing.”
Textbook of Neuropsychiatry.
- 1998: “After years of clinical research and experience with ADHD, our knowledge about the cause or causes of ADHD remain largely speculative.” NIH Consensus Development Conference statement.

- 2012: “The vast majority of neuroimaging studies to date demonstrate relative, quantitative differences between ADHD and [typically developing controls] that are neither sufficiently large nor specific enough to be useful on a case-by-case basis as a diagnostic or treatment biomarker.”

On confound of medication:

“Notably absent from structural neuroimaging literature examining biomarkers of ADHD are treatment studies which contrast morphometric differences before and after medication treatment. To our knowledge, no controlled trials have examined the effect of stimulant medication on structural brain abnormalities in youth with ADHD, suggesting a critical area for future research.”

Consensus report of the APA Work Group on Neuroimaging Markers of Psychiatric Disorders.

How Stimulants Work

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.
3. Cocaine acts on the brain the same way, and with similar potency.
4. Methylphenidate clears more slowly from the brain than cocaine, and thus it blocks dopamine reuptake for hours, as opposed to cocaine's relatively brief disruption of this function.

How the Brain Is Changed by Methylphenidate

- The density of dopamine receptors on the postsynaptic neurons declines.
- The amount of dopamine metabolites in the cerebrospinal fluid drops, evidence that the presynaptic neurons are releasing less dopamine.
- Methylphenidate also acts on serotonin and norepinephrine neurons, and that causes similar compensatory changes in those two pathways.

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.

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 clinical 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

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

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

One-year 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.

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.

Animal Studies of Stimulants

- Repeated exposure to low doses of amphetamines caused monkeys to exhibit “aberrant behaviors” that remained long after drug exposure stopped.
- Various rat studies suggested that lengthy exposure to methylphenidate might cause the dopaminergic system to become permanently desensitized.
- 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.”

Source: S. Castner, “Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys,” *Neuropsychopharmacology* 20 (1999):10-28; 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.

Long-Term Risks With Stimulants

- Desensitized brain-reward system?
- Conversion to bipolar diagnosis: 10% to 25% now convert (in U.S.)

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.

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 that the brain's dopaminergic system will become desensitized
	Risk of drug-induced conversion to juvenile bipolar disorder

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.

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

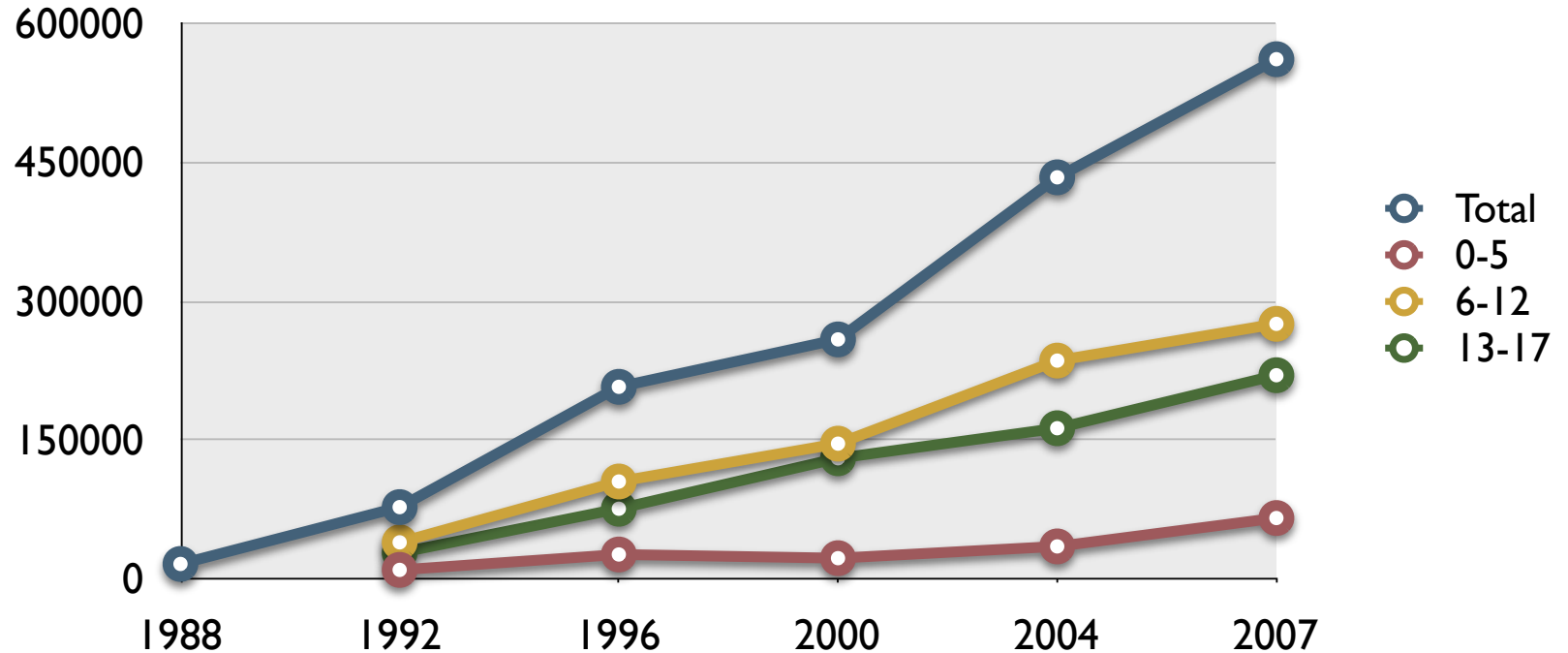
- In 2012, Shire Pharmaceuticals funded a study, which was led by its medical director, that reviewed studies of long-term outcomes, at least two years in length, for ADHD that had been published since 1980.
- Shire manufactures Vyvanse, Adderall XR and Intuniv, three drugs commonly prescribed for ADHD.
- 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 Medicine 10 (2012):99.

Reasons to Question the Study

- Evident conflict of interest by investigators
- No citations of source studies
- 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.

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.