

Medicating ADHD:

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

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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

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?

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.

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

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 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 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.

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-occurring 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

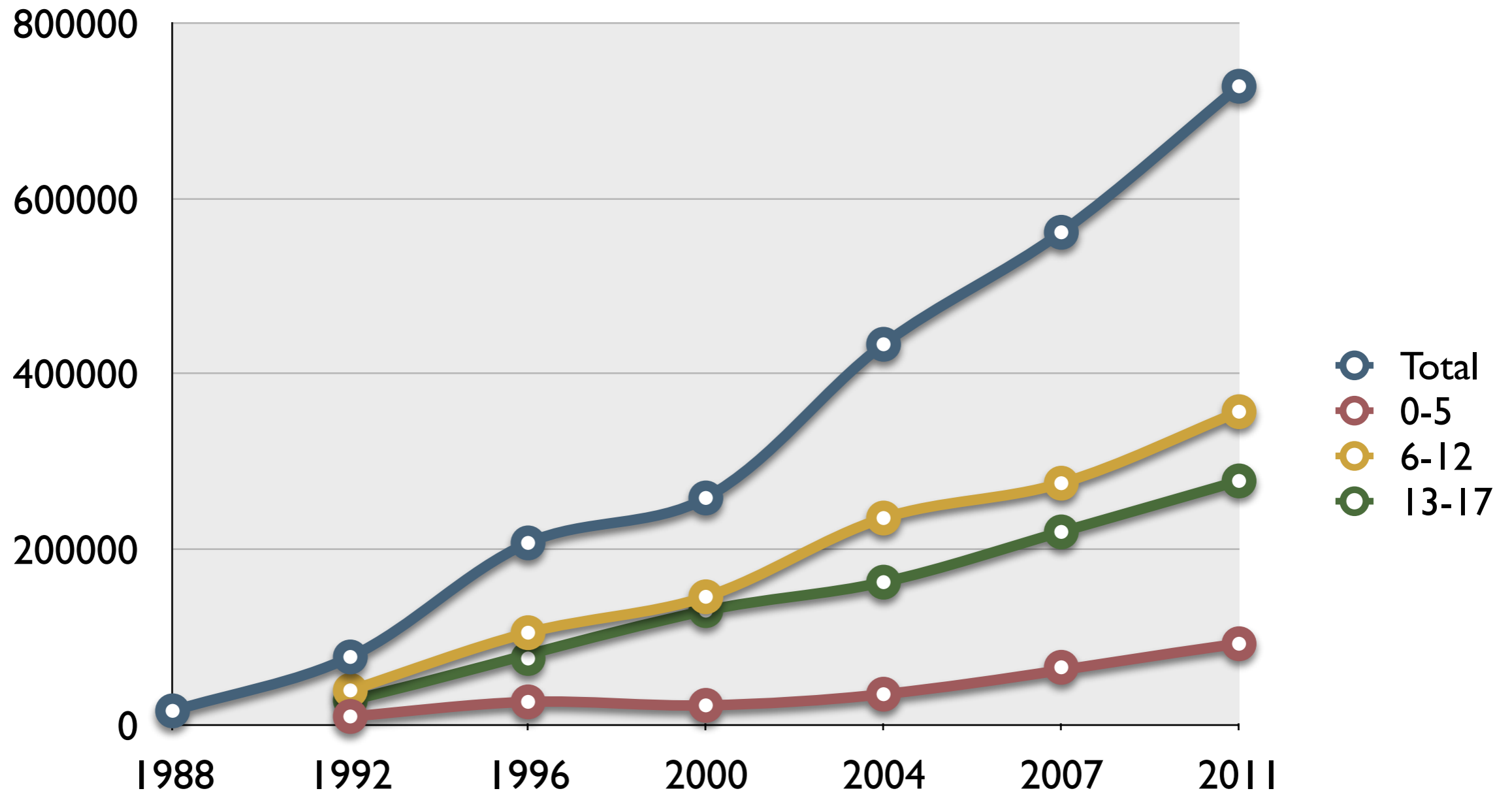
Spanish Investigators: Time To Rethink Use of Stimulants

“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.

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.