Medicating Children:

Science, Commerce, and Long-Term Outcomes

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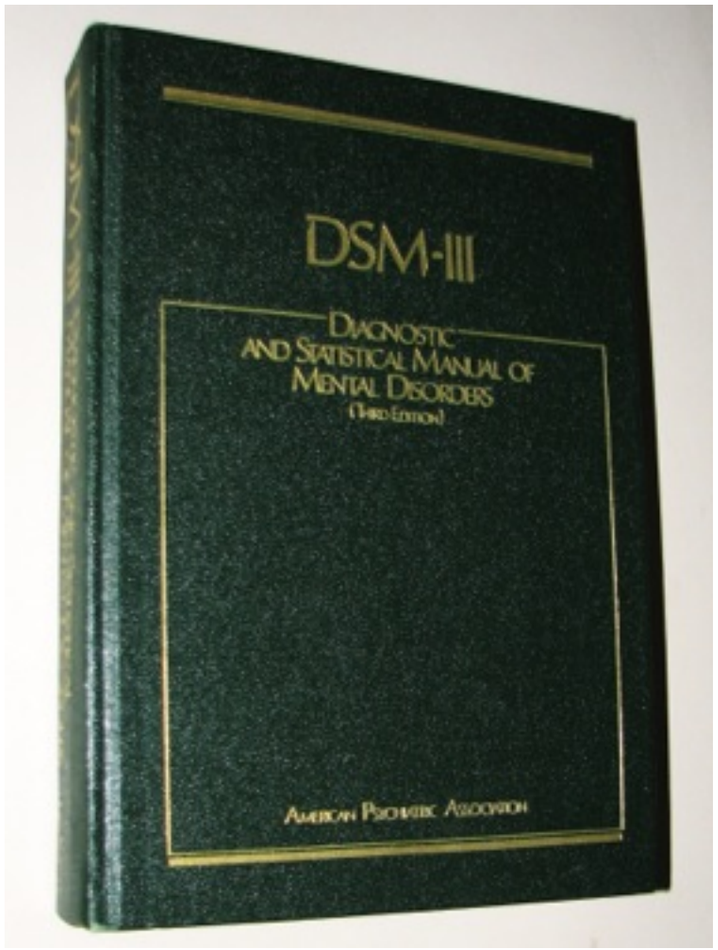
April 2015

The Origins of the Medical Model



DSM III was the "book that changed everything."

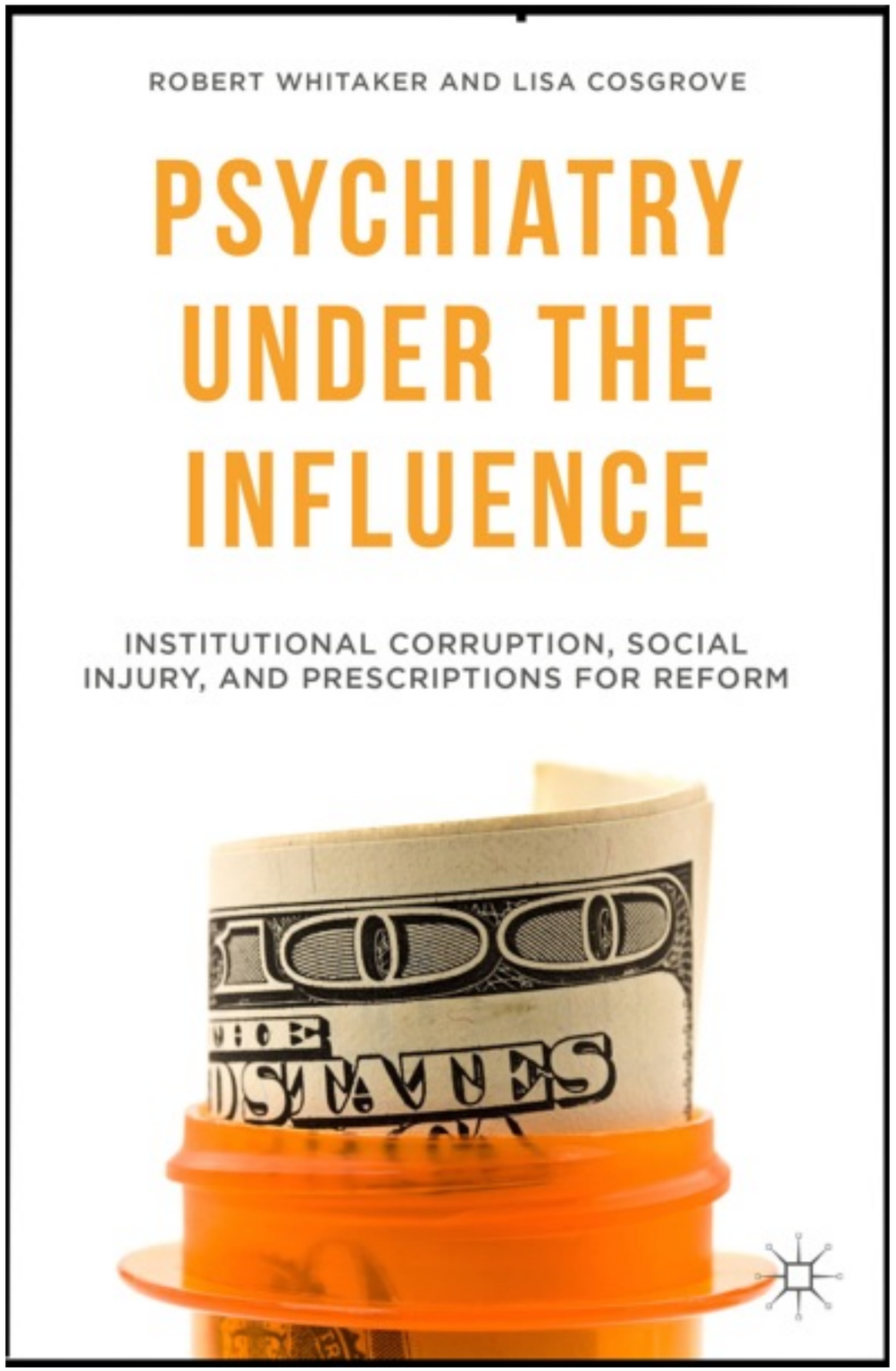
—Jeffrey Lieberman
American Psychiatric Association President

The DSM III Universe (1980)

Conception: Mental disorders are diseases of the brain, which are best treated by medications.

"The major psychiatric illnesses are diseases. They should be considered medical illnesses, just as diabetes, heart disease, and cancer are . . . (each) different illness has a different specific cause . . . There are many hints that mental illness is due to chemical imbalances in the brain and that treatment involves correcting these chemical imbalances."

Nancy Andreasen
Editor-in-Chief of the *American Journal of Psychiatry*
Writing in her book, *The Broken Brain, 1984*

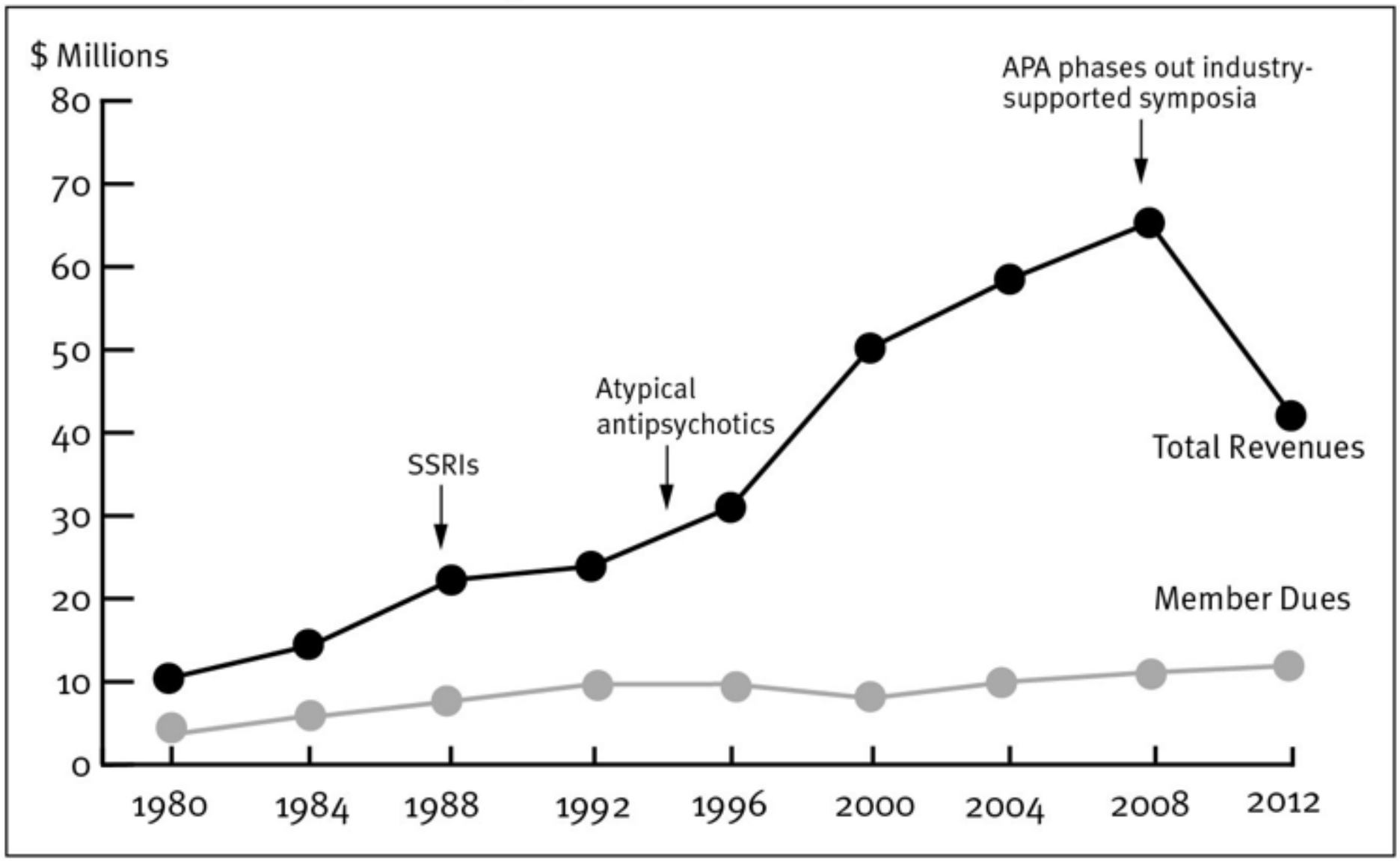


Economies of Influence:

1. Pharmaceutical money
2. Psychiatry' s guild interests

Pharma Money Flowed to the APA

APA's Annual Revenues, 1980–2012



Source: APA's annual financial reports, 1980–2012.

Examples of Funding by Pharmaceutical Companies To APA

- "Scientific" symposiums at APA's annual meeting were now "sponsored" by pharmaceutical companies.

- Pharmaceutical companies provided grants to psychiatrists from Europe, Asia and South America to attend APA's annual meetings (and thus learn about this new paradigm of care).

- Pharmaceutical firms paid for media training programs for psychiatrists throughout the United States. These programs taught the psychiatrists how to speak about the medical model to the public.

- Pharmaceutical companies funded APA's PR campaigns in United States, which regularly repeated this message: Disorders are diseases of the the brain, they under recognized and undertreated, and medications are highly effective.

Pharma Money Also Flowed to Academic Psychiatrists

Examples of Pharmaceutical Payments to Thought Leaders in Psychiatry

Academic Psychiatrist	Affiliation	Pharmaceutical Company	Amount
Joseph Biederman	Professor at Harvard Medical School	Janssen	$1.6 million (2000–2007)
Frederick Goodwin	Former NIMH Director	GlaxoSmithKline	$1.2 million (2000–2008)
Melissa DelBello	Associate Professor at Univ. of Cincinnati	Astra Zeneca	$418,000 (2003–2007)
Karen Wagner	Director of Child Psychiatry at Univ. of Texas	GlaxoSmithKline	$160,000 (2000–2005)

Source: Senator Charles Grassley, "Disclosure of Drug Company Payments to Doctors," 2008.

What Thought Leaders Do

They create the common wisdom

- Serve on committees that establish diagnostic boundaries
- Conduct clinical trials of new drugs in trials funded by drug companies
- Author articles on those reports (often ghostwritten)
- Speak about the validity of the disorders and efficacy of treatments at scientific symposiums, CME courses, and other professional forums.
- Set clinical practice guidelines
- Write psychiatric textbooks
- Are quoted by the media as the "experts" in this field

At 2008 Annual Meeting of American Psychiatric Association, 373 speakers told of having a collective total of 888 consulting agreements with pharmaceutical companies, and 483 agreements to serve on “speaker’s bureaus” at pharmaceutical firms.

Financial Conflicts of Interest in DSM-IV and DSM-5 Members

	On DSM IV	On DSM 5
Task Force	57%	69%
Work Panels		
Anxiety	81%	57%
Eating disorders	83%	50%
Mood disorders	100%	67%
Sleep disorders	50%	100%
Schizophrenia/psychotic disorders	100%	83%

Source: L. Cosgrove. "A comparison of DSM-IV and DSM-5 panel members' financial associations with industry." *PLoS Med* 9 (2012):e1001190.

"Our field as a whole is progressively being purchased lock, stock, and barrel by the drug companies: this includes the diagnoses, the treatment guidelines, and the national meetings."

—Psychiatrist Daniel Carlat, 2007

Did "Economies of Influence" Affect the Story that American Psychiatry Told to the World?

- Are mental disorders due to chemical imbalances?
- Did it affect the setting of diagnostic boundaries?
- How did it affect reporting of results from trials of psychiatric drugs?

What the American Public was Told About Low Serotonin and Depression

1981: "Researchers believe clinical depression is caused by a chemical imbalance in the brain." University of Chicago psychiatrist Herbert Meltzer, in interview with Associated Press.

1988. Antidepressants "restore the chemical imbalance scientists have linked to many depressions." John Talbott, former president of the American Psychiatric Association (APA), in interview with the *St. Petersburg Times*.

2001: "We now know that mental illnesses--such as depression or schizophrenia--are not 'moral weaknesses' or 'imagined' but real diseases caused by abnormalities of brain structure and imbalances of chemicals in the brain." -- APA President Richard Harding, in article in *Family Circle* magazine.

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2001: Antidepressants “restore brain chemistry to normal.” Future APA President Nada Stotland, in Family Circle magazine.

2005: A psychiatrist is a “specialist specifically trained to diagnose and treat chemical imbalances.”--APA press release.

2005: “Antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain.” APA’s “Let’s Talk Facts About Depression” brochure.

2014: “Research has shown that imbalance in neurotransmitters like serotonin, dopamine and norepinephrine can be corrected with antidepressants.” --National Alliance on Mental Illness.

2014

Websites:

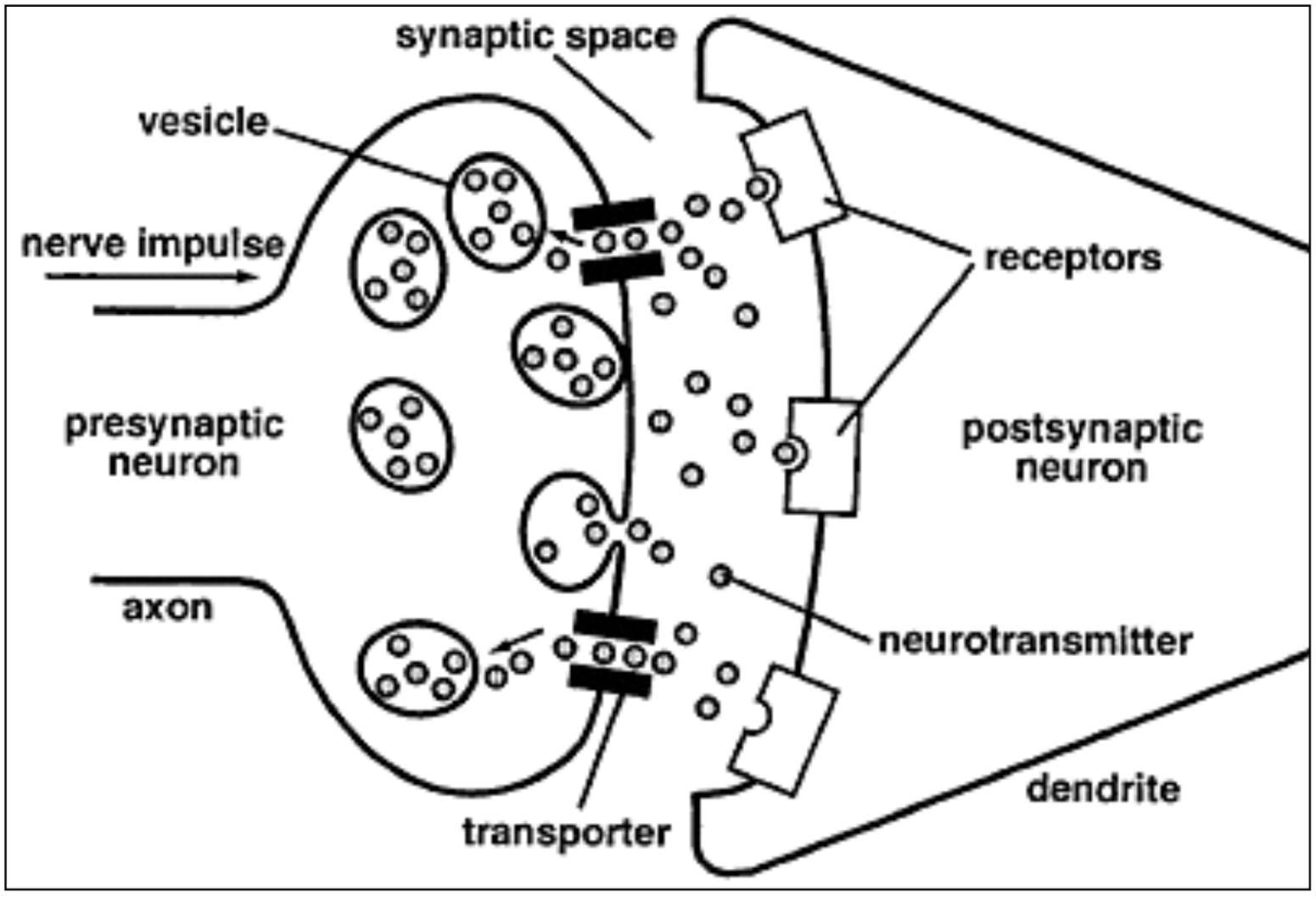
"Antidepressant medications work to restore proper chemical balance in the brain." -- Balanced Mind Parent Network

"Depression is caused by a chemical imbalance in the brain." -- Depression and Bipolar Support Alliance.

"Research has shown that imbalance in neurotransmitters like serotonin, dopamine and norepinephrine can be corrected with antidepressants." --National Alliance on Mental Illness.

Reviewing the Science:
Investigating the Low-Serotonin Theory of Depression

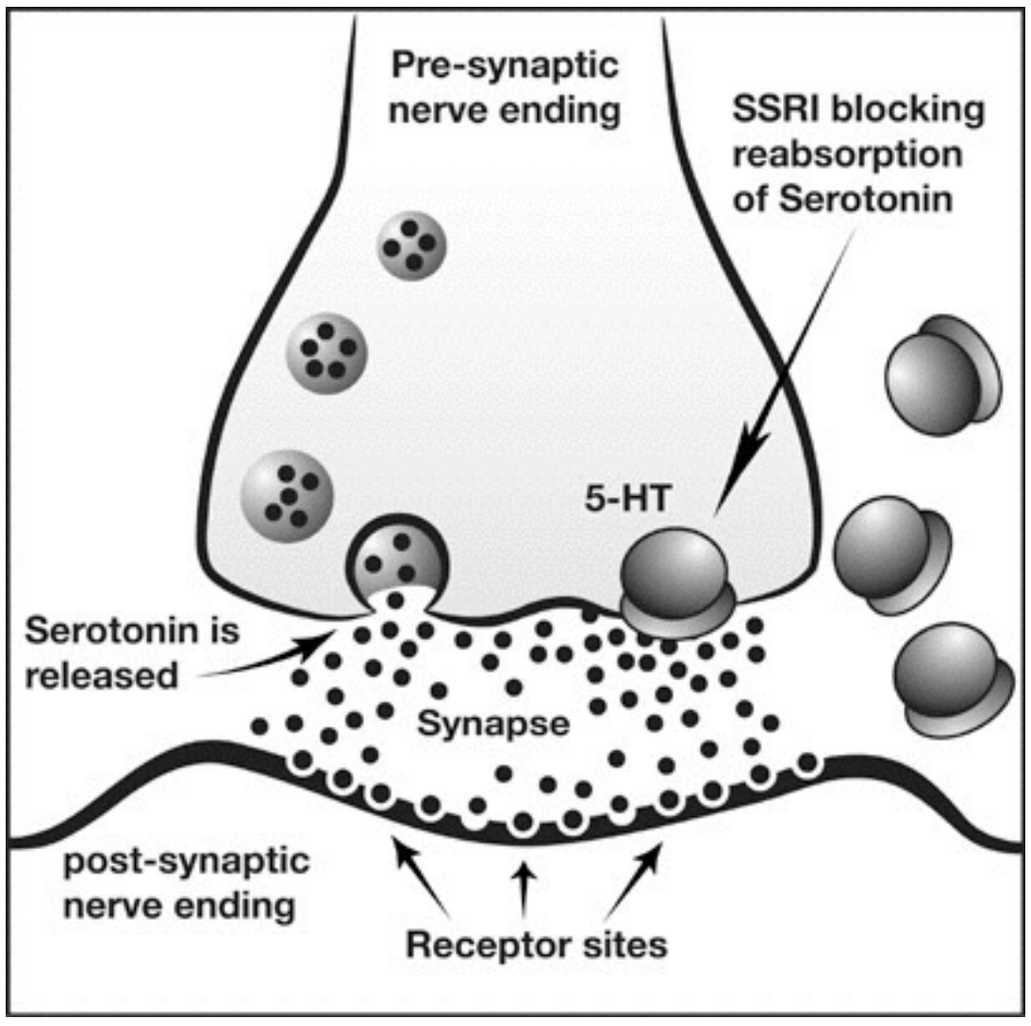
Transmission of neuronal messages



The Scientific Origins of the Theory

The chemical imbalance theory of depression arose in 1965, after researchers discovered that monoamine oxidase inhibitors and tricyclic antidepressants both blocked the normal removal of norepinephrine and serotonin from the synaptic cleft between neurons. This theoretically increased serotonergic levels in the synaptic cleft, and thus researchers hypothesized that perhaps one or more of these neurotransmitters was abnormally low in depressed patients.

How an SSRI Works



But Do People with Depression Have Low Serotonin?

"Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression."

--NIMH, 1984.

"There is no clear and convincing evidence that a monoamine deficiency accounts for depression; that is, there is no real monoamine deficit."

--Stephen Stahl, *Essential Psychopharmacology*, 2000

"I don't think there's any convincing body of data that anybody has ever found that depression is associated, to a significant extent, with loss of serotonin."

--Alan Frazer, University of Texas Health Science Center, 2012

The Scientific Conclusion

"We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them."

--Kenneth Kendler, *Psychological Medicine*, 2005

"In truth, the chemical imbalance notion was always a kind of urban legend, never a theory seriously propounded by well-informed psychiatrists."

--Ronald Pies, July 11, 2011 in *Psychiatric Times*

And Yet the Public Believes:

In a 2006 survey:

- 87 percent of Americans said they now knew that schizophrenia was caused by a chemical imbalance.

- 80 percent of Americans said they now knew that depression was caused by a chemical imbalance.

The ADHD Story: A Case Study of Building a Market for Drugs

- Prior to 1980, there was no diagnosis in the APA's diagnostic manual for hyperactive children.

- Attention deficit disorder was first identified as a discrete disorder in 1980. The cardinal symptoms were said to be inattention, impulsivity, and hyperactivity. The disorder was said occur in "as many as 3 percent of prepubertal children."

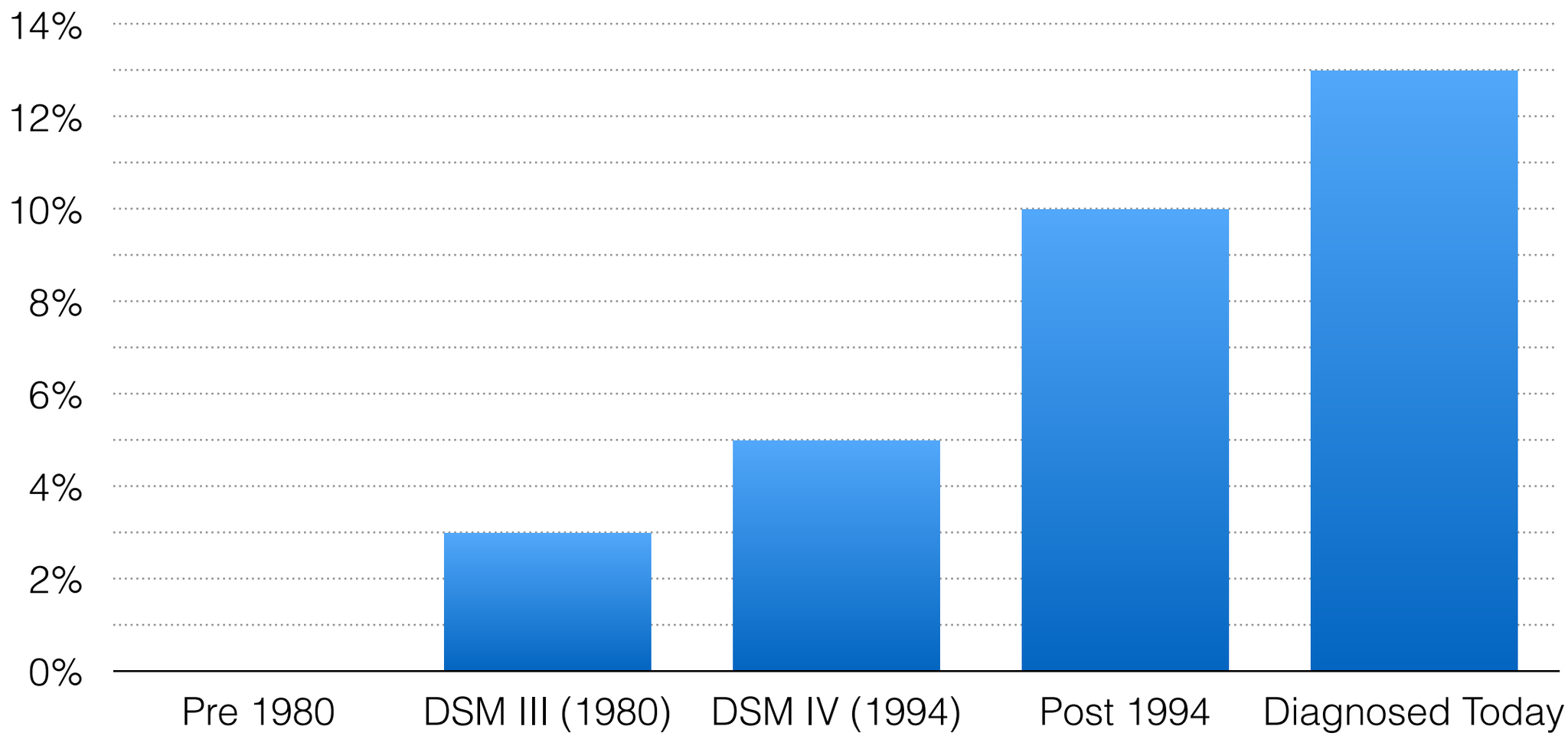
- DSM-IV, published in 1994, stated that the disorder consisted of three subtypes (inattentive only, hyperactive-impulsive only, and those who had both types of symptoms.) The disorder was now said to affect "3 to 5%" of all American children.

- Joseph Biederman, who had been a member of the DSM IV work panel for pediatric disorders, now began publishing articles that stated 6 to 9 percent of American schoolchildren had ADHD.

- DSM 5 further loosens the boundaries for diagnosing ADHD.

- Latest survey shows that 13 percent of U.S. youth of school age have been diagnosed with ADHD.

The Growth of ADHD in U.S.



The Payoff to Biederman

From 1996 to 2011, Biederman received speaker's fees, consulting fees and research funding from more than 24 pharmaceutical companies, including Shire, Janssen, and Eli Lilly, which respectively sold Adderall, Concerta, and Strattera, three popular ADHD drugs.

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

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 (2007):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

(By one of PIs)

"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.

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*

Financial Disclosures of MTA Investigators

(Number of ties to pharmaceutical firms)

Investigator	Academic Affiliation	Research Funding	Advisory Board	Consultant	Speaker's Bureau
Peter Jensen, M.D.	Columbia Univ.	1		6	6
L. Eugene Arnold, M.D.	Ohio State Univ.	7		5	4
James Swanson, Ph.D.	U California, Irvine	12	11	14	9
Howard Abikoff, Ph.D.	New York Univ.	4		7	3
Laurence Greenhill, M.D.	Columbia Univ.			14*	
Lily Hechtman, M.D.	McGill Univ.	5	4		4
Glen Elliott, M.D.	Duke Univ.	4		2	3
Jeffrey Epstein, Ph.D.	U California, Irvine	4	1		2
Jeffrey Newcorn, M.D.	Mt. Sinai Medical School	8	16**		7
Timothy Wigal	U California, Irvine	4			2

*Research funding and consulting ties disclosed together. **Advisory board and consulting ties disclosed together.

Source: Disclosure statement in B. Molina, "MTA at 8 Years." *J Am Acad Child Adolesc Psychiatry* 48 (2009):484-500.

The Rise of Prescribing SSRIs for Children

• Prior to DSM III, major depression was seen as mostly a disease of the middle-aged and elderly. Mood problems in children were seen as normative and self-limiting.

• After DSM III, which provided a symptom-based criteria for diagnosing depression, with less inquiry into whether life events might be the source of such symptoms, children were now seen as having major depression if they had such symptoms.

• In addition, irritability was seen as a core symptom of major depression in children, which expanded the percentage of children that could be diagnosed with major depression.

The Prevalence of Childhood Depression

- Based on DSM III and DSM IV criteria, studies of children and adolescents produced one-year depression prevalence rates of 2 to 50 percent.

- The National Comorbidity Survey Replication study, funded by the NIMH, found that based on DSM-IV criteria, nearly 12 percent of teenagers experienced a bout of major depression or dysthymia by age 18.

Source: R. Kessler. "Mood disorders in children and adolescents." *Biol Psychiatry* 49 (2001): 1002–14. K. Merikangas. "Life prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Study-Adolescent Supplement." *J Am Acad Child Adolesc Psychiatry* 49 (2010): 980–9.

The Transformation of a Belief

"Although epidemiological studies of child and adolescent mood disorders have been carried out for many years, progress long was hampered by two misconceptions: that mood disorders are rare before adulthood and that mood disturbance is a normative and self-limiting aspect of child and adolescent development. Research now makes it clear that neither of these beliefs is true."

— Ronald Kessler, 2001

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

Published Trials of SSRIs for Pediatric Depression

- By 2004, there were nine published studies in the research literature that told of the safety and efficacy of Prozac, Paxil, Celexa and Lexapro for treating childhood depression.

- By this time, one in every 40 children of school age in America was taking an antidepressant.

Source: M. Goozner. "SSRI use in children: an industry-biased record." Center for Science in the Publish Interest, February 2004. T. Delate. "Trends in the use of antidepressants in a national sample of commercially insured pediatric patients, 1998 to 2002." *Psychiatr Serv* 55 (2004): 387–91.

Examples of Financial Disclosures to Principal Investigators

Name	Drug	Company	Amount	Time
Martin Keller	Paxil	SmithKline Beecham and Others	Nearly $1 million	1997-98
Karen Wagner	Paxil	GlaxoSmithKline	$160,402	2000-2005
Jeffrey Bostic	Celexa, Lexapro	Forest Laboratories	More than $750,000	1999-2006

FDA's 2004 Report on SSRI Pediatric Trials for Depression

- 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 approved fluoxetine for pediatric use (although critics argued those trials were biased by design.)

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

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.

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.

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.

Financial Conflicts of Interest in TADS Study

- Five of the principal investigators in the TADS study had served on Eli Lilly's speaker's bureau.
- Six more reported other types of financial ties to Eli Lilly: honorariums, research support, and consulting contracts.

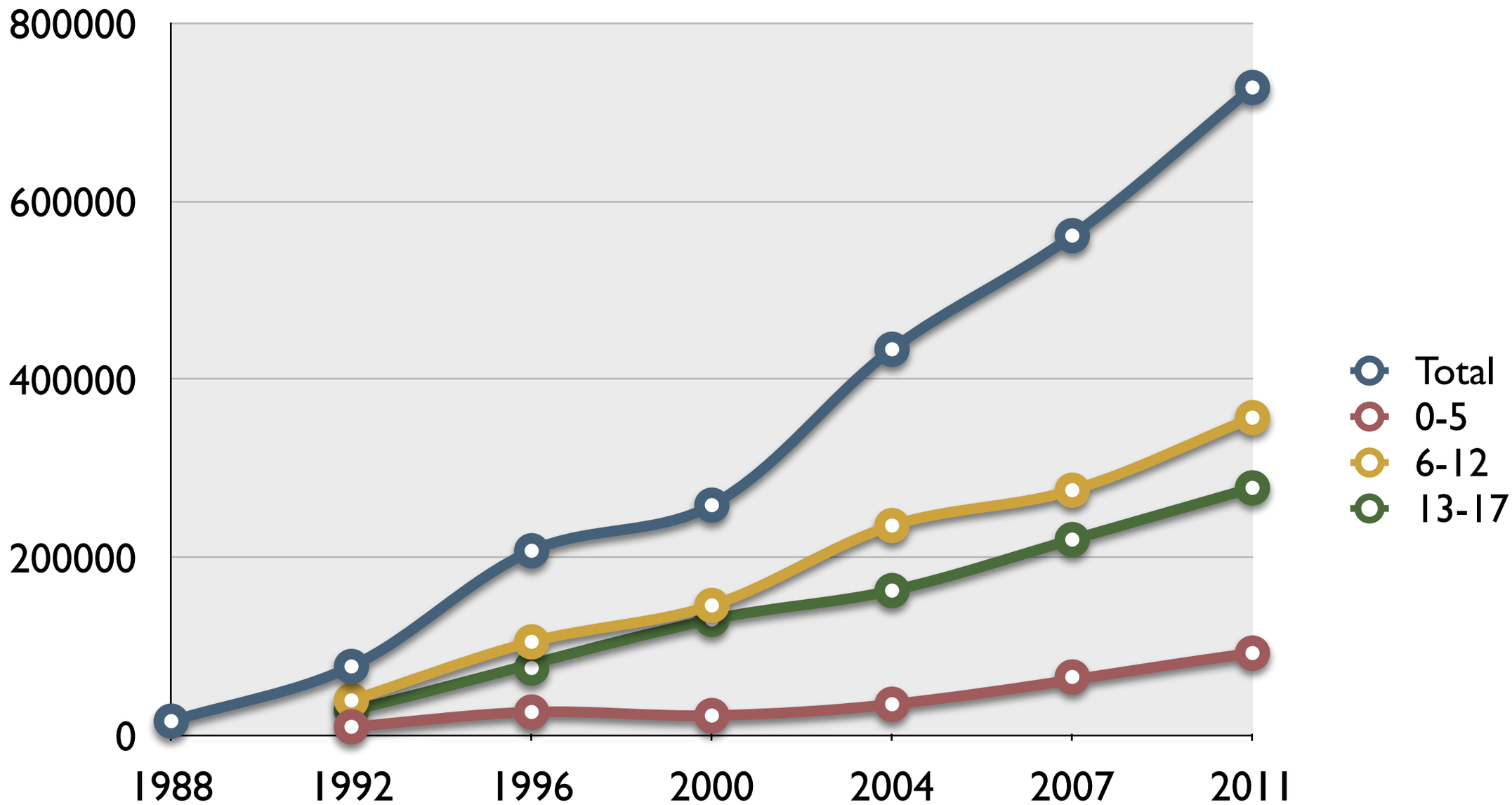
Pediatric Efficacy of SSRIs on Self-Reported Scales and Quality of Life Outcomes

In a 2014 meta-analysis of the literature:

- No significant differences in efficacy of second-generation antidepressants and placebo in *self-reported* depressive symptoms.
- No significant difference in efficacy of second-generation antidepressants over placebo in quality of life, global mental health, self-esteem and autonomy.

Source: G. Spielmans. The Efficacy of Antidepressants on Overall Well-Being and Self-Reported Depression Symptom Severity in Youth: A Meta-Analysis. *Psychother Psychosom* 83 (2014);:158-164

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.