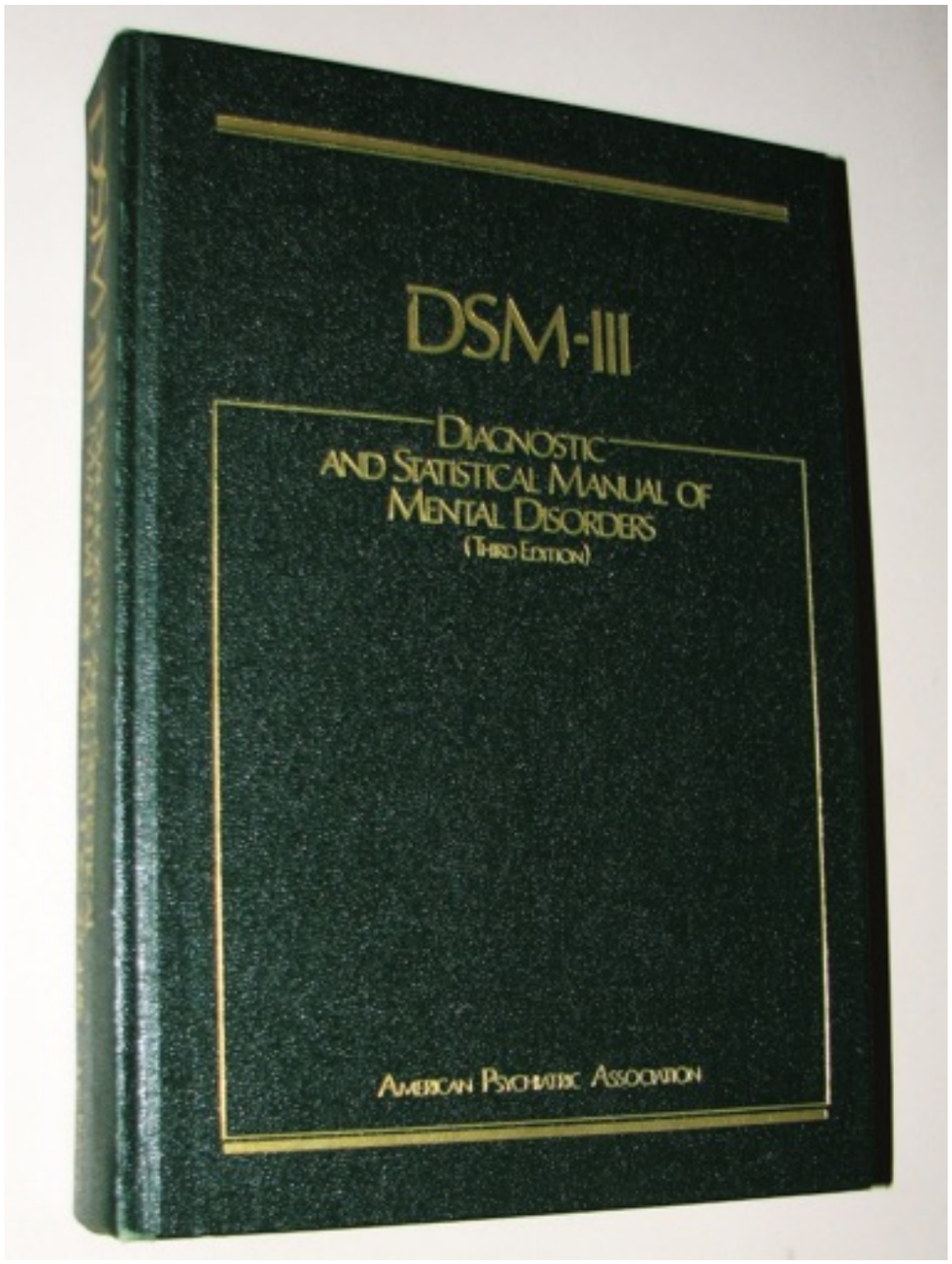
Narratives in Psychiatry and Medical Expertise: Confessions of a Trespasser

Robert Whitaker
November 2016



DSM III was the "book that changed everything."

—Jeffrey Lieberman
American Psychiatric Association President

The Narrative Told to the Public in the DSM III Era

- Major mental disorders are biological illnesses (diseases of the brain.)
- The major disorders, such as depression and schizophrenia, are caused by chemical imbalances in the brain.
- Psychiatric medications fix chemical imbalances in the brain, and thus are like "insulin for diabetes."
- The second-generation drugs (SSRIs and atypical antipsychotics) are safe and effective, and lead to markedly improved outcomes.

The DSM III Narrative Is Presented to the American Public

"The major psychiatric illnesses are diseases. They should be considered medical illnesses, just as diabetes, heart disease, and cancer are." The thought was that 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*
The Broken Brain, 1984

The Low-Serotonin Narrative in the America Media

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 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.

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.

2005: The APA reports that “75% of consumers believe that mental illnesses are usually caused by a chemical imbalance in the brain.” -- APA press release.

2014: “Antidepressant medications work to restore proper chemical balance in the brain.” -- Balanced Mind Parent Network

2014: “Depression is caused by a chemical imbalance in the brain.” -- The Depression and Bipolar Support Alliance.

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

The Low-Serotonin Narrative in the Scientific Literature

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

--NIMH, 1984.

The Low Serotonin Theory of Depression Collapses

APA's *Textbook of Psychiatry,* 1999

"The monoamine hypothesis, which was first proposed in 1965, holds that monamines such as norepinephrine and 5-HT (serotonin) are deficient in depression and that the action of antidepressants depends on increasing the synaptic availability of these monoamines. The monoamine hypothesis was based on observations that antidepressants block reuptake inhibition on norepinephrine, 5-HT, and/or dopamine. However, inferring neurotransmitter pathophysiology from an observed action of a class of medications on neurotransmitter availability is similar to concluding that because aspirin causes gastrointestinal bleeding, headaches are caused by too much blood loss and the therapeutic action of aspiring in headaches involves blood loss. Additional experience has not confirmed the monoamine depletion hypothesis."

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

--Stephen Stahl, *Essential Psychopharmacology*, 2000

"After more than a decade of PET studies, monamine depletion studies, and genetic association analyses examining polymorphisms in monaminergic genes, there is little evidence to implicate true deficits in serotonergic, noradrenergic, or dopaminergic neurotransmission in the pathophysiology of depression. This is not surprising, as there is no a priori reason that the mechanism of action of a treatment is the opposite of disease pathophysiology."

Eric Nestler, "Linking Molecules to Mood," 2010.

The Dopamine Hypothesis of Schizophrenia

There is "no good evidence for the perturbation of the dopamine function in schizophrenia."

--John Kane, Long Island Jewish Medical Center, 1994

"There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia."

--Stephen Hyman, *Molecular Psychiatry*, 2002

"Vigorous search for abnormalities in the dopamine system in schizophrenia so far has yielded inconclusive results. The increasing understanding of the behavioral complexity of schizophrenia suggests that it is unlikely that a single neurotransmitter system can explain such diverse symptoms, for example, inattention and hallucinations. Thus, any simple, exclusive pathology of the dopamine system was and is doubtful."

--Aurelija Jucaite and Svante Nyberg, *Emerging Therapies for Schizophrenia*, 2012

Rest in Peace: The Chemical Imbalance Theory of Mental Disorders

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

--Kenneth Kendler, *Psychological Medicine*, 2005.

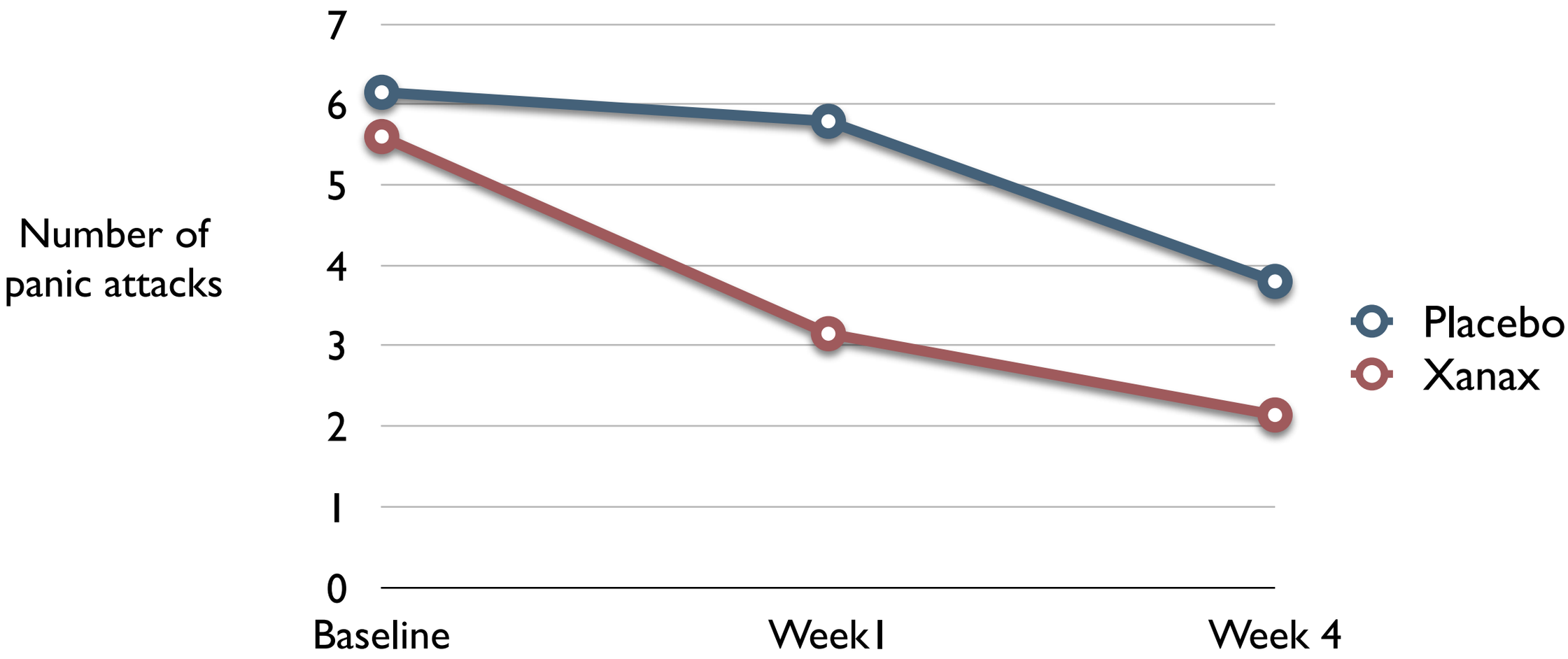
The Rewriting of the Past

"I am not one who easily loses his temper, but I confess to experiencing markedly increased limbic activity whenever I hear someone proclaim, 'Psychiatrists think all mental disorders are due to a chemical imbalance!' In the past 30 years, I don't believe I have ever heard a knowledgeable, well-trained psychiatrist make such a preposterous claim, except perhaps to mock it. On the other hand, the 'chemical imbalance' trope has been tossed around a great deal by opponents of psychiatry, who mendaciously attribute the phrase to psychiatrists themselves. And, yes—the 'chemical imbalance' image has been vigorously promoted by some pharmaceutical companies, often to the detriment of our patients' understanding. 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*

The Xanax Reports

This was the story emphasized in the medical literature



Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22.

The Conclusion That Was Drawn

"Alprazolam (Xanax) was found to be effective and well-tolerated."

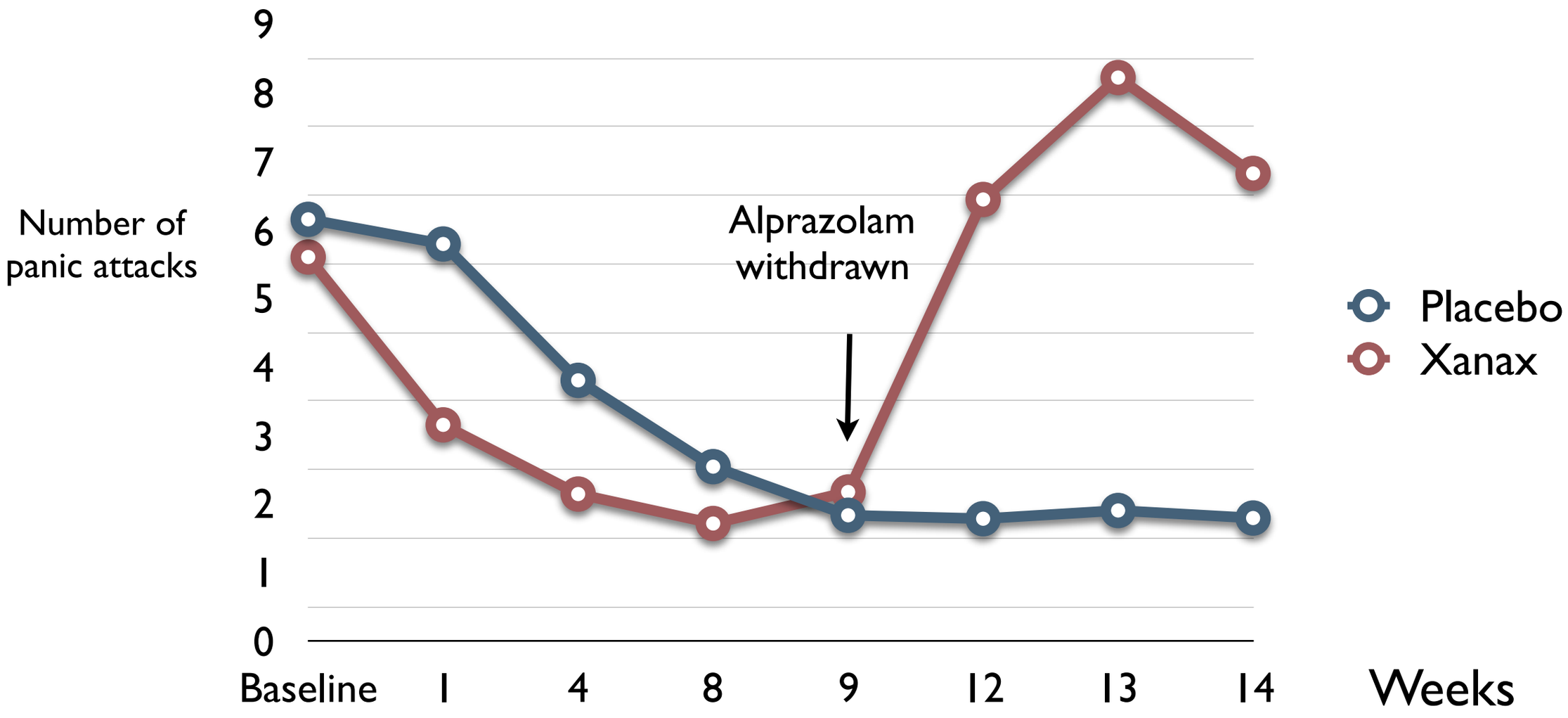
Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22.

Which Led to These Media Reports

This new treatment helps "70 to 90 percent" of those with panic disorder." —*St. Louis Post Dispatch*, "In a Panic? Help is on the Way." October 7, 1990.

"A biochemical malfunctioning in the brain is believed to be one of the causes of pain attacks. Xanax can block the attacks by interacting with several different systems in the brain." — Associated Press, Nov 19, 1990.

Now For the Rest of The Story



In Upjohn's study, patients were treated with the drug or placebo for eight weeks. Then this treatment was slowly withdrawn (weeks 9 through 12), and during the last two weeks patients did not receive any treatment. Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988): 413-22. Also, C. Pecknold. "Alprazolam in panic disorder and agoraphobia." *Archives of General Psychiatry* 45 (1988):429-36.

Prozac: The Medical Literature Tells of a Modest Advance

- Fluoxetine "provides effective antidepressant activity with fewer and less troublesome side effects than imipramine . . . None of the adverse events reported by fluoxetine patients were considered to be drug related."—*J Clin Psychiatry,* 1984

- Fluoxetine is equal in efficacy to imipramine, and "no serious side effects were observed." —*J Clin Psychiatry,* 1985

- "Fluoxetine is better tolerated than imipramine."—*J Clin Psychiatry,* 1985

- Fluoxetine produced greater improvement than placebo on all major efficacy parameters."—*J Clin Psychiatry,* 1985

Behind Closed Doors: The FDA Was Not Impressed

- In four of eight placebo-controlled trials, the fluoxetine patients had fared no better than the placebo group, and in the others, fluoxetine was only slightly better than placebo.
- In general, "imipramine was clearly more effective than placebo, whereas fluoxetine was less consistently better than placebo."
- At least 39 patients treated with fluoxetine had gone psychotic, and slightly more than one percent had become manic or hypomanic.
- Other side effects included insomnia, nervousness, tremors, and impaired coordination.
- Eli Lilly had engaged in "large-scale underreporting" of the harm that fluoxetine could cause.

Fluoxetine, concluded FDA reviewer Richard Kapit, "may negatively affect patients with depression."

The NIMH Informs the Public of a Very Effective Drug

NIMH's DART Campaign upon Prozac's Release

- The campaign was mounted to "change public attitudes so that there is greater acceptance of depression as a disorder rather than a weakness."

- Depression regularly went "underdiagnosed and underrated," and it could "be a fatal disease if left untreated."

- Antidepressants produced recovery rates of "70% to 80%" in comparison with "20% to 40% for placebo."

Media Reports Tell of a Wonder Drug

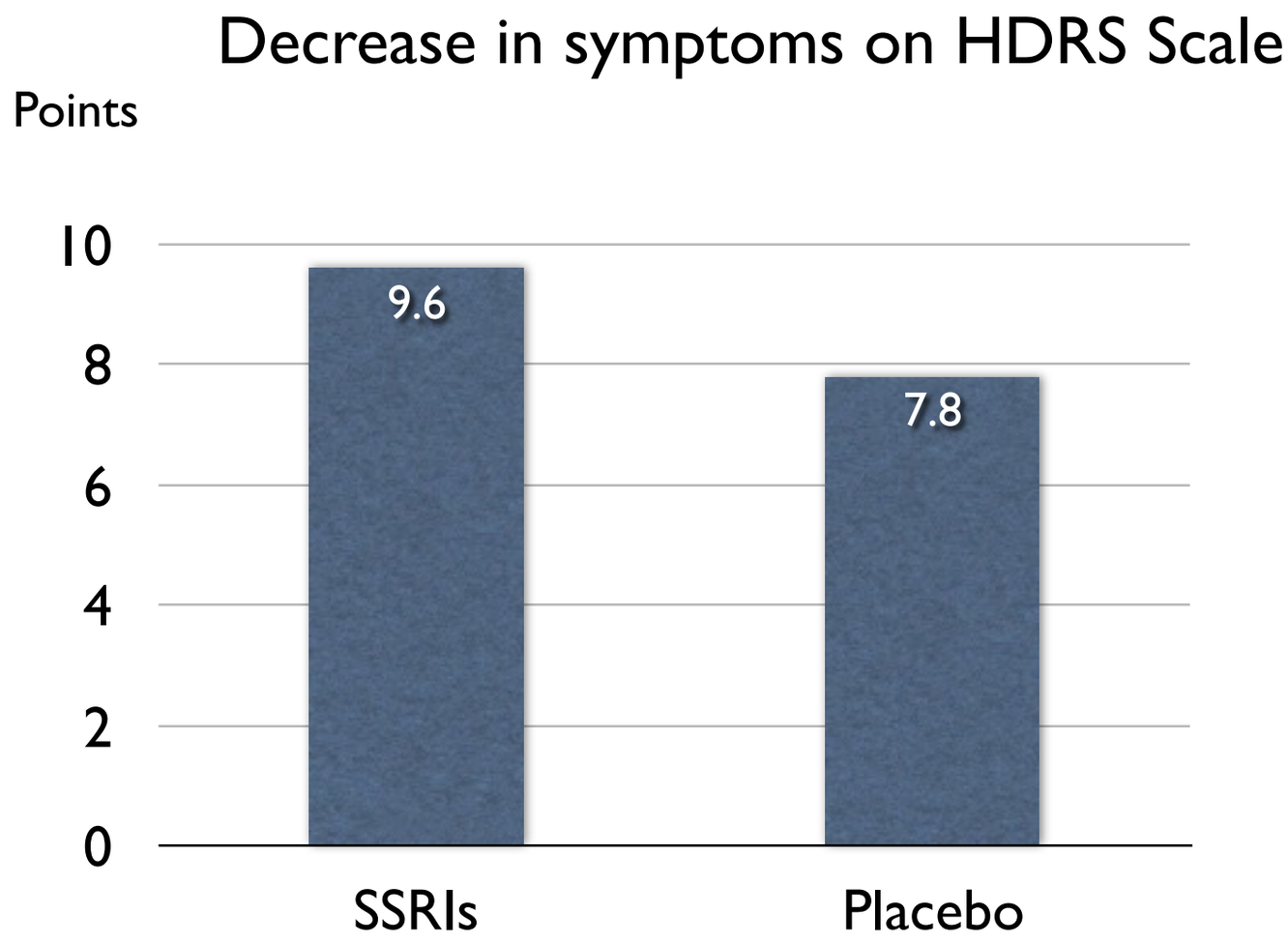
- "Bye, Bye Blues: A New Wonder Drug for Depression." *New York* magazine cover story, December 18, 1989.

- "Prozac: A Break-Through Drug for Depression." *Newsweek* cover, March 26, 1990.

- Prozac works "by restoring the balance of neurotransmitter activity in the brain, correcting an abnormal excess or inhibition of the electrochemical signals that control mood, thoughts, appetite, pain and other sensations." *New York Times, M*arch 29, 1990.

- "Most doctors believe that chronic depression . . . is caused by a chemical imbalance. To correct it, the doctor prescribed Prozac." *Sixty Minutes*

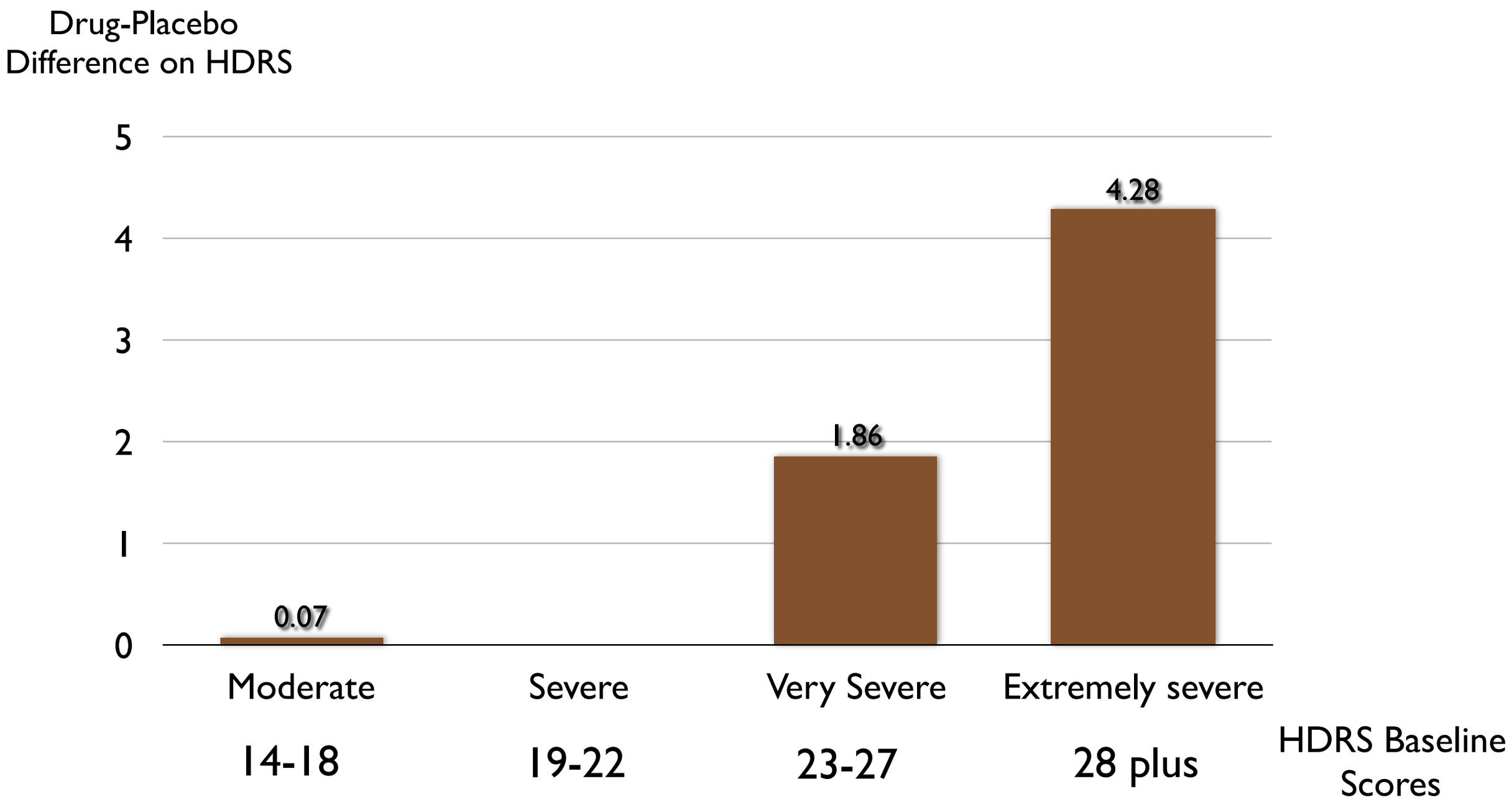
A Review of the FDA Data: Efficacy of Four SSRIs In Clinical Trials



The National Institute of Clinical Excellence in Britain determined that a three-point difference was needed on the Hamilton scale to demonstrate a "clinically significant benefit." Difference here is 1.8 points.

Source: I. Kirsch, "Initial severity and antidepressant benefits," *PLoS Medicine* 5 (2008):260-68.

Efficacy of Four SSRIs According to Severity of Illness



Source: I. Kirsch, "Initial severity and antidepressant benefits," *PLoS Medicine* 5 (2008):260-68.

One-Year Remission Rates in NIMH Study of Medicated Depression in "Real-World" Patients

•126 patients were treated with antidepressants and given emotional and clinical support "specifically designed to maximize clinical outcomes."

• Only 26% responded to antidepressants (50% reduction in symptoms).

• Only half of those who responded stayed better for a significant period of time

• Only 6% remitted and then remained in remission at the end of one year.

Source: J. Rush. "One-year clinical outcomes of depressed public sector outpatients," *Biological Psychiatry* 56 (2004):46-53.

Risperidone: The Medical Literature Tells of a Significant Advance

More than 20 articles in psychiatric journals report that in clinical trials risperidone is equal or superior to haloperidol in reducing psychotic symptoms and superior to haloperidol in improving negative symptoms of schizophrenia. The articles report that risperidone reduced hospital stays, improved the patient's ability to function socially, and reduced hostility.

"Risperidone has important advantages compared with haloperidol. When administered in an effective dose range, risperidone produced greater improvements on all five dimensions of schizophrenia." — *J of Clinical Psychiatry,* 1997.

The Media Tells of a Breakthrough Drug

New York Times: "No major side effects" had appeared in the two-thousand-plus patients treated with risperidone in the clinical trials. The drug was thought to "relieve schizophrenia symptoms by blocking excessive flows of serotonin or dopamine, or both."—January 15, 1992

Washington Post: Risperidone"represents a glimmer of hope for a disease that until recently had been considered hopeless." Risperidone did not "cause sedation, blurred vision, impaired memory or muscle stiffness, side effects commonly associated with an earlier generation of antipsychotic drugs."— February 16, 1993

The FDA's View of the Clinical Trials of Risperidone

- In the trials, Janssen compared multiple doses of risperidone to a high dose of haloperidol, which biased the trials by design. As a result, the trials were "incapable" of making any meaningful comparison between the two drugs.

- As for its safety, eighty-four patients treated with risperidone in the clinical trials had suffered a "serious adverse event," which the FDA defined as a life-threatening event or one that required hospitalization.

Letter of approval by Robert Temple, director of the FDA's Office of Drug Evaluation, to Janssen, December 29,1993:

"We would consider any advertisement or promotion labeling for RISPERDAL false, misleading, or lacking fair balance under section 502 (a) and 502 (n) of the ACT if there is presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness."

The Understanding Twenty Years Later

Government-funded trials of risperidone and other atypicals, conducted in the United States and the United Kingdom, found that there were no significant differences in efficacy between the newer drugs and the older drugs, and no significant differences in their safety profiles. One British study concluded that, if anything, patients had a "better of quality of life" on one of the first-generation antipsychotics.

The Lancet, 2009

"What was seen as an advance 20 years ago—when a new generation of antipsychotic drugs with additional benefits and fewer adverse effects was introduced—is now, and only now, seen as a chimera that has passed spectacularly before our eyes before disappearing and leaving puzzlement and many questions in its wake . . . As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective. The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed. But how is it that for nearly two decades we have, as some have put it, been beguiled into thinking they were superior?"

P. Tyrer. "The spurious advance of antipsychotic drug therapy." *Lancet* 373, (2009): 4-5.

Assessment of Long-term Effects of Stimulants for ADHD, 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

In the abstract:

"By thirty-six months, the earlier advantage of having had fourteen months of the medication algorithm was no longer apparent, possibly due to age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medication altogether, or other factors not yet evaluated."

Source: Jensen, "A 3-year follow-up of the NIMH MTA study," *J Amer Academy of Child & Adolescent Psychiatry* 46 (2007):989-1002.

Three-Year Results from NIMH's MTA Study

In the paper, if you read carefully:

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.

Six-Year Results from MTA Study

In the abstract:

There were no significant differences between the medicated youth and the unmedicated youth at the end of six and eight years.

Source: Molina, "MTA at 8 years," *J Amer Academy of Child & Adolescent Psychiatry 48 (2009):*484-500.

Six-Year Results from MTA Study

In the discussion and a review of the data, if this part of the study is carefully read:

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.

What the Public in the United States 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*

The NIMH's STAR*D Trial

- The largest antidepressant trial ever conducted (4,041 patients)

- Funded by the NIMH at a cost of $35 million, and took six years to conduct.

- As it was conducted to study "real-world" strategies for helping people recover and stay well, with a one-year followup, it was expected to produce results that would have "substantial public health and scientific significance."

- If patients didn't respond to a first antidepressant, they were were switched to a second drug, and so on, through four treatment steps.

Announced Results

NIMH: "Over the course of all four treatment levels, almost 70% of those who did not withdraw from the study became symptom free."

Current Psychiatry Reports: "With all steps included, almost 70% of participants who remained in the study experienced remission. Patients and clinicians are encouraged not to give up."

Source: NIMH press release. "Questions and answers about the NIMH sequenced treatment alternatives to relieve depression (STAR*D) study--all medication levels." November 2006. D. Warden, "The STAR*D Project Results." *Current Psychiatry Reports* 9 (2007):449-459.

Deconstructing STAR*D: How the 70% Success Rate Was Calculated

- **Study Dropouts Counted as Responders:** The 70% figure was a theoretical remission rate, based on the premise that if all of the all study dropouts had stayed in trial through all four treatment steps, they would have remitted at same rate as those who remained in the trial.

- **Rating Scales Were Switched:** According to the protocol, the Hamilton Rating Scale was to be used to measure symptoms. The researchers were also testing a second scale, the QIDS-SR, in order to validate that scale. The protocol stated it would not be used to report results. However, in their published articles, when they calculated the 70% remission rate, the investigators used the QIDs data, which added 200 patients to the remitted group.

- **Ineligible Patients Were Enrolled:** The investigators enrolled 607 patients who had a baseline Hamilton score less than 14, and thus, according to the protocol, weren't depressed enough to be in the trial. Yet these ineligible patients were included when calculating the remission rate.

- **A "Tag, You're Cured" Design Was Used:** Patients' symptoms were assessed every two weeks during the 14 weeks of acute care treatment, and if at any time their symptoms dropped below seven on the Hamilton scale (which means some symptoms may still be present), they were declared remitted and whisked to the long-term followup study. Thus, patients were given multiple chances to remit, and if patients had even one good evaluation day, they were declared "symptom-free."

Re-Calculating Remission Rates

Even with this "tag, you're cured" design, only 1,192 of the 3,110 patients who began the study with a Hamilton score greater than 14 remitted (38%). The remaining 62% either failed to remit or dropped out.

Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

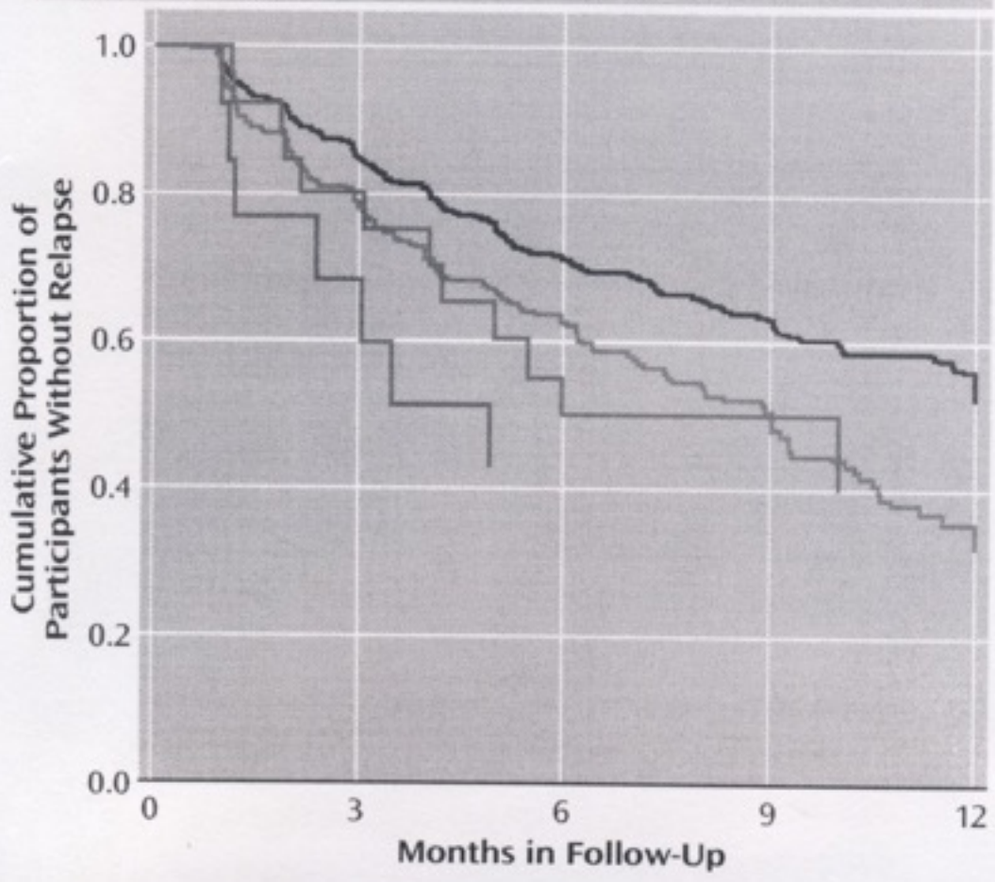
STAR*D Long-Term Results

How many patients remitted and then stayed well during the followup?

(This chart includes those who weren't depressed enough to be enrolled in the study.)

FIGURE 3. Relapse During Follow-Up Phase by Number of Acute Treatment Steps for STAR*D Participants Who Entered Follow-Up Phase in Remission[a]

Step 1 N=1,085	628	431	290	84
Step 2 N= 383	199	133	79	20
Step 3 N= 35	16	11	8	2
Step 4 N= 15	8	5	5	2
Total N=1,518	851	580	382	108



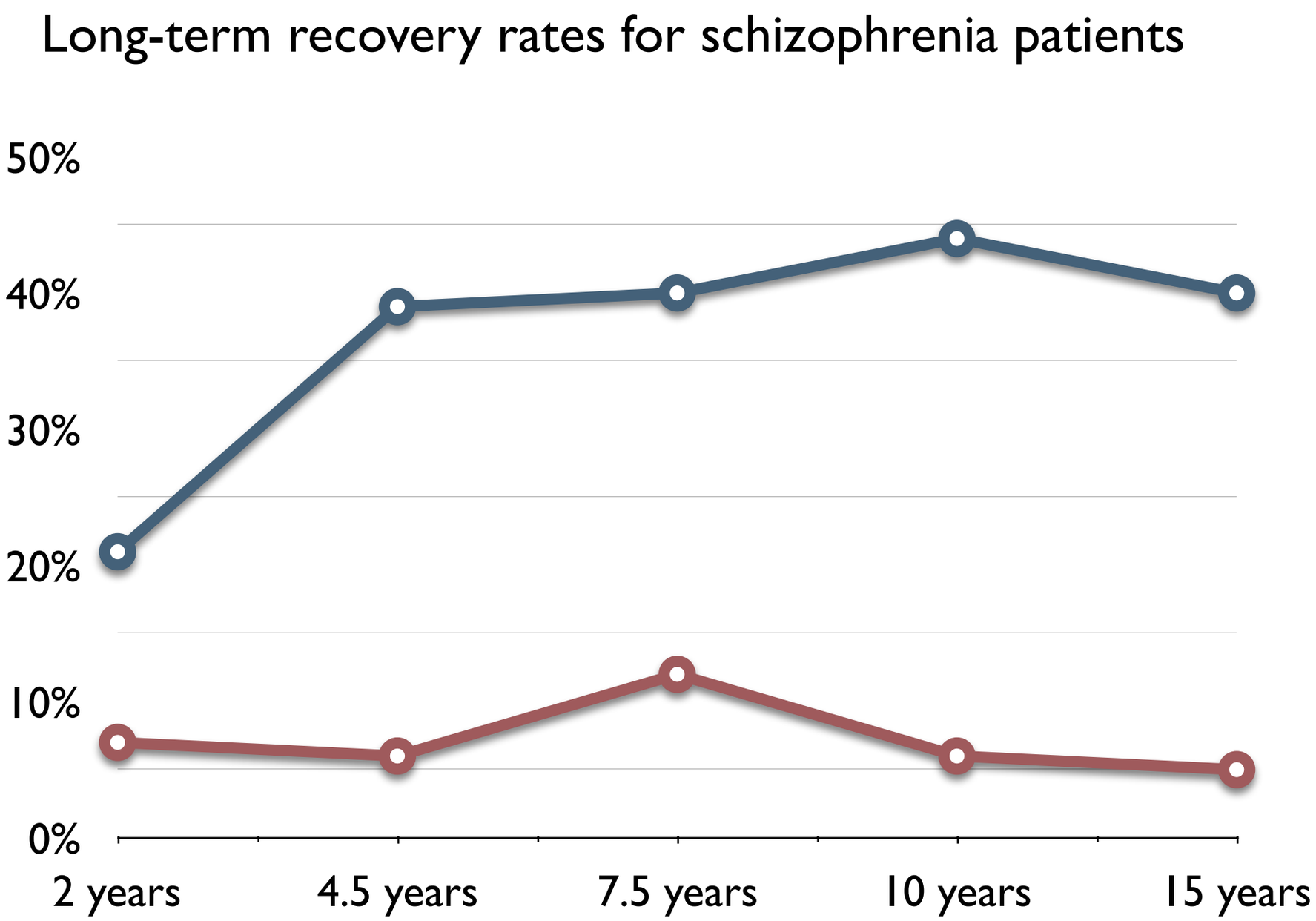
[a] Significant overall difference among steps (χ^2=23, df=3, p<0.0001). Significant post-hoc comparisons with Bonferroni corrections revealed significant differences between steps 1 and 2.

The Actual Bottom-line Results

Of the 4,041 patients who entered the trial, 108 remitted and then stayed well and in the trial throughout the one-year followup. That is a documented stay well-rate of 3%; yet the common belief remains that STAR*D showed that with multiple tries of an antidepressant, two-thirds were relieved of their depression (and presumably stayed well.)

Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

Have you heard about this NIMH study?

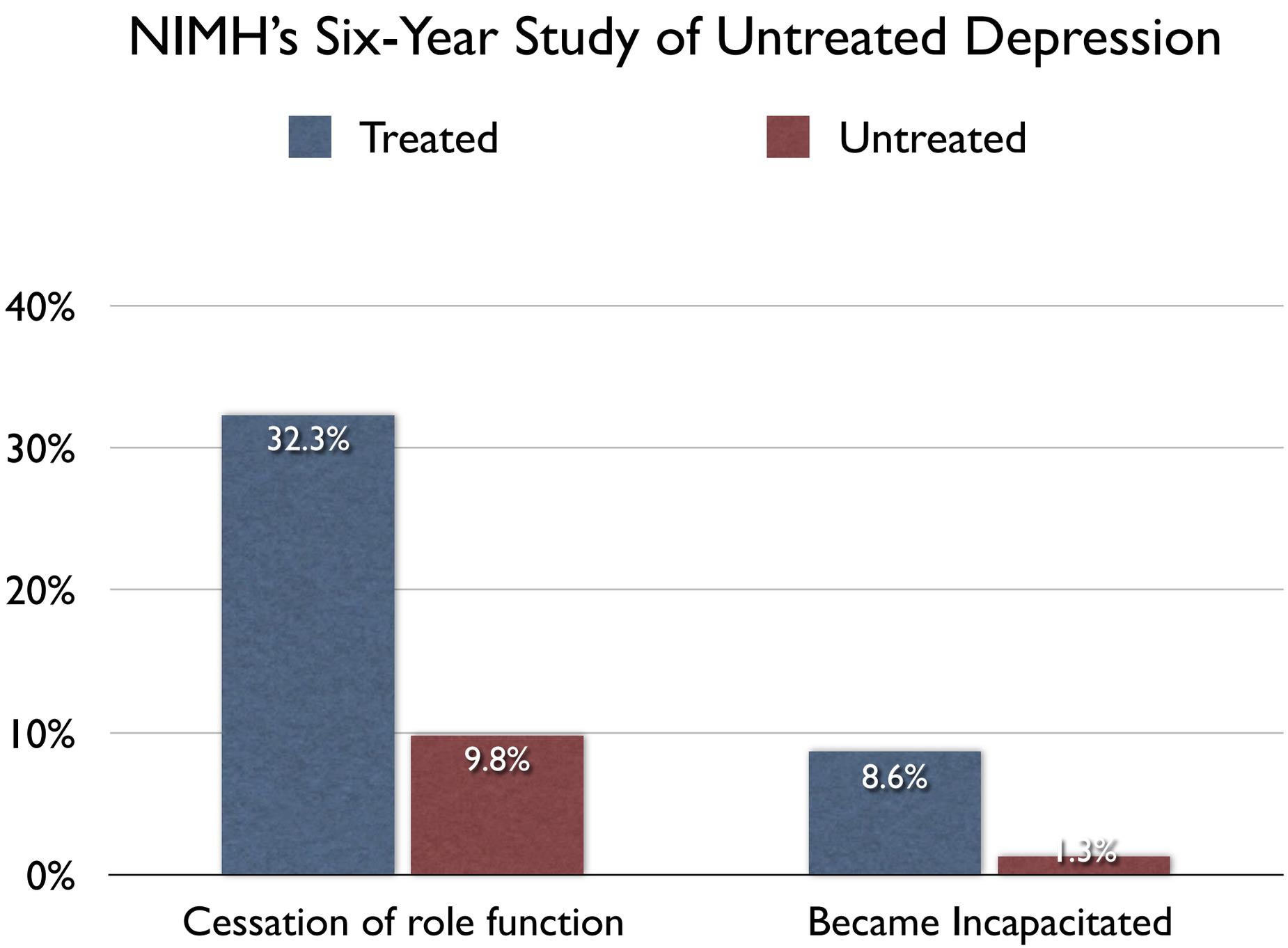


Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

"I conclude that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics."

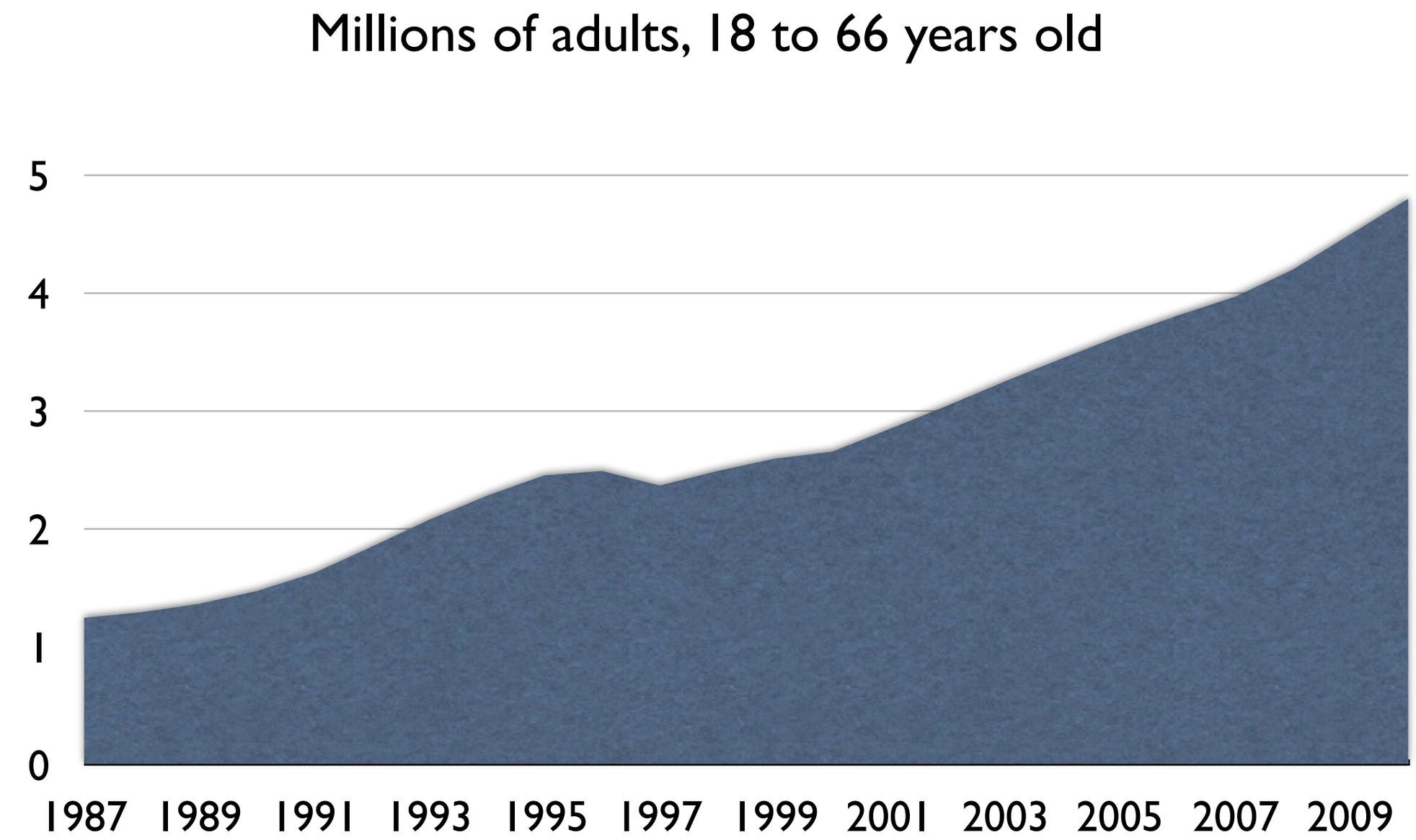
--Martin Harrow, American Psychiatric Association annual meeting, 2008

Or This One?



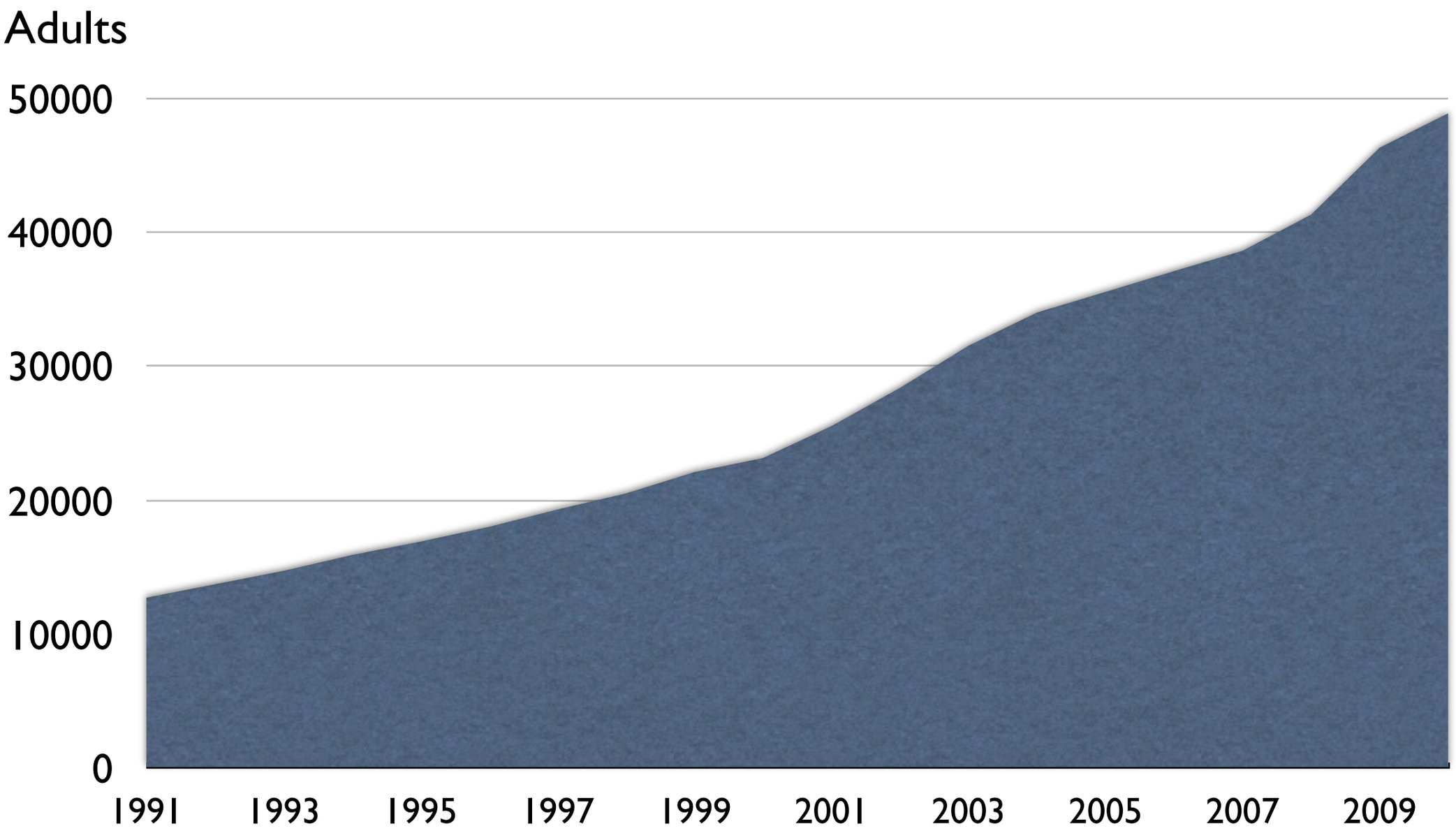
Source: W. Coryell. "Characteristics and significance of untreated major depressive disorder." *American Journal of Psychiatry* 152 (1995):1124-29.

U.S. Disability in the DSM III Era



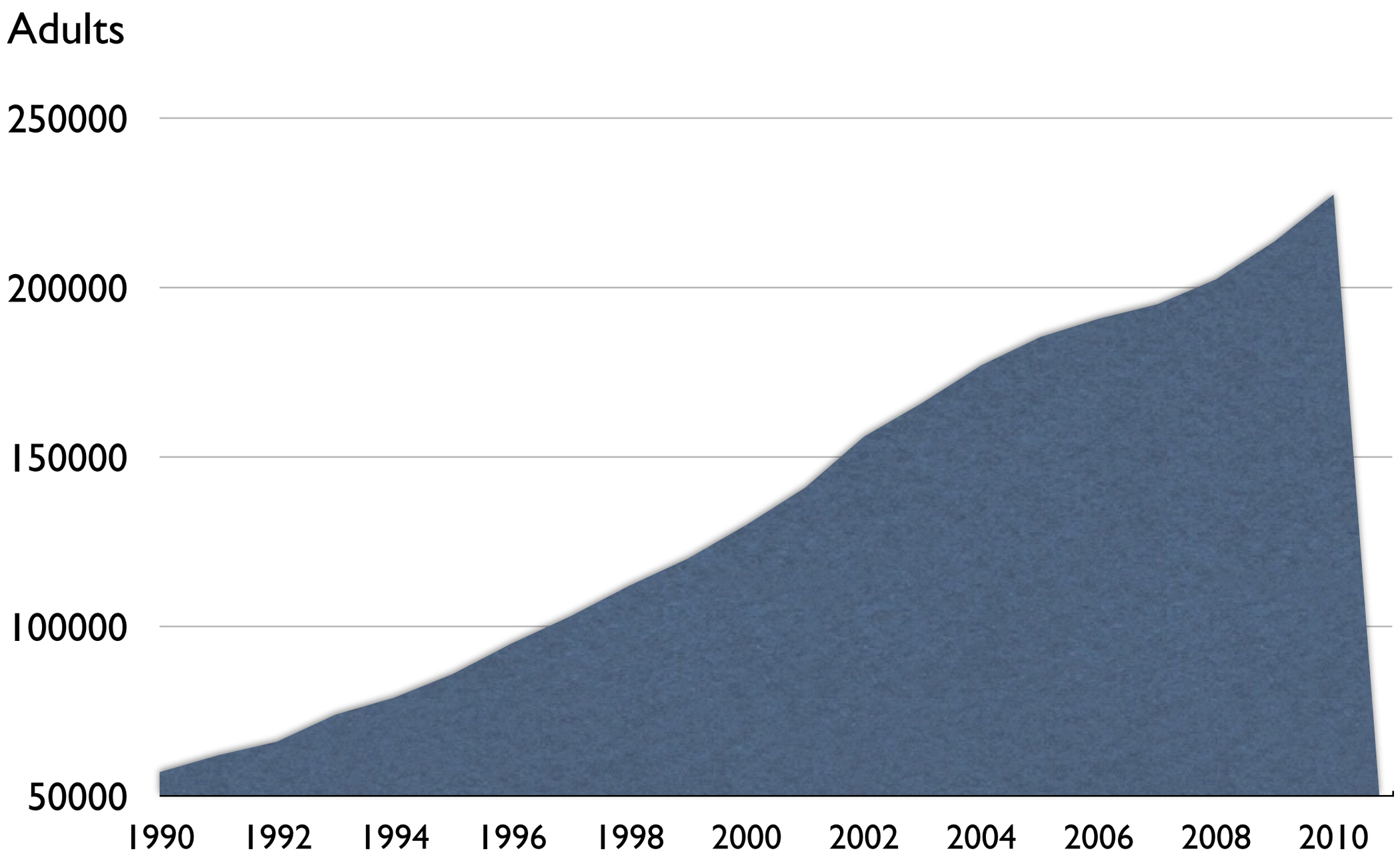
Source: U.S. Social Security Administration Reports, 1987-2010

Disability Due to Psychiatric Disorders in New Zealand, 1991-2010



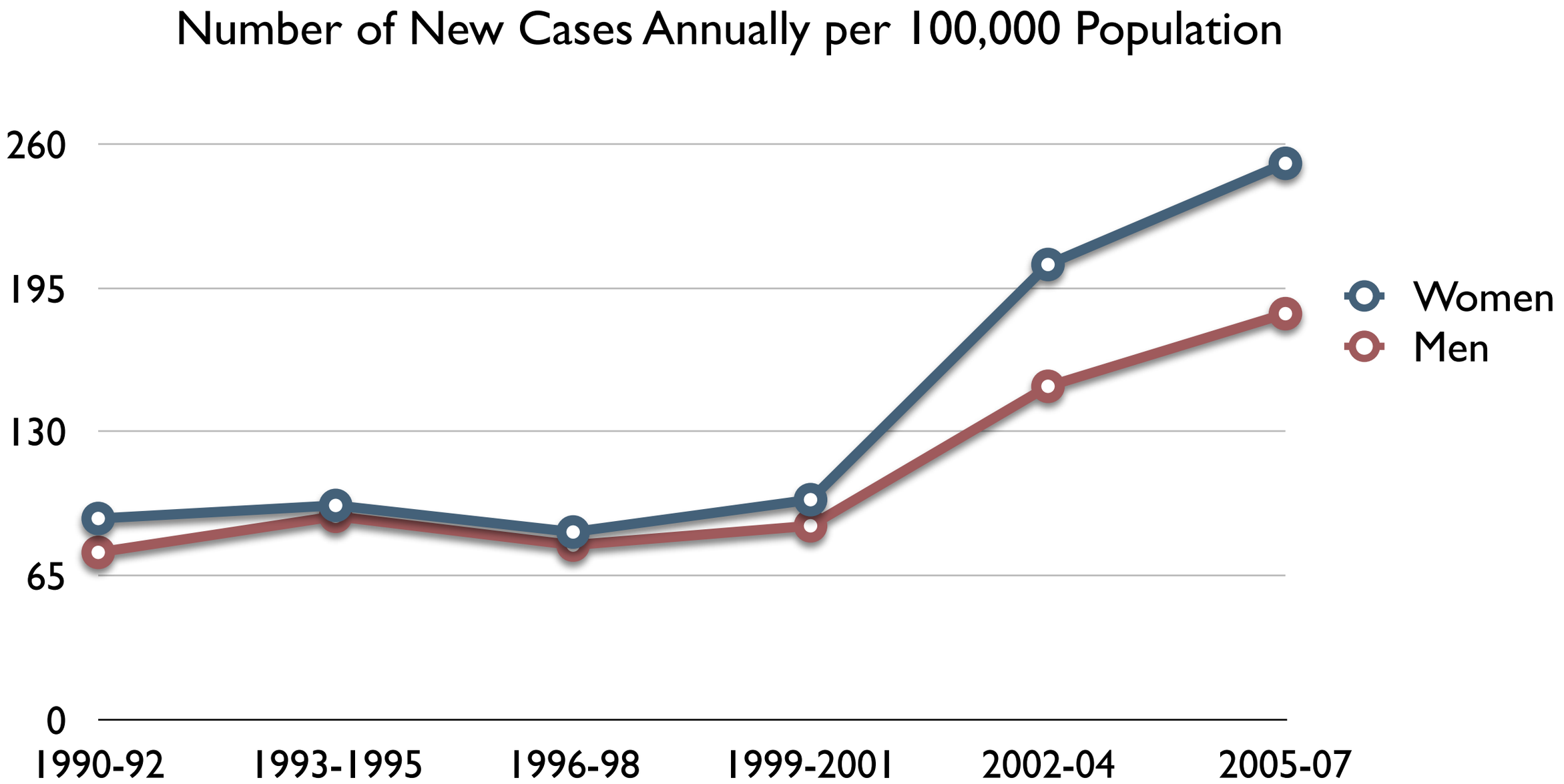
Source: *Statistics New Zealand,* Annual reports, 1999-2010

Disability Due to Psychiatric Disorders in Australia, 1990-2010



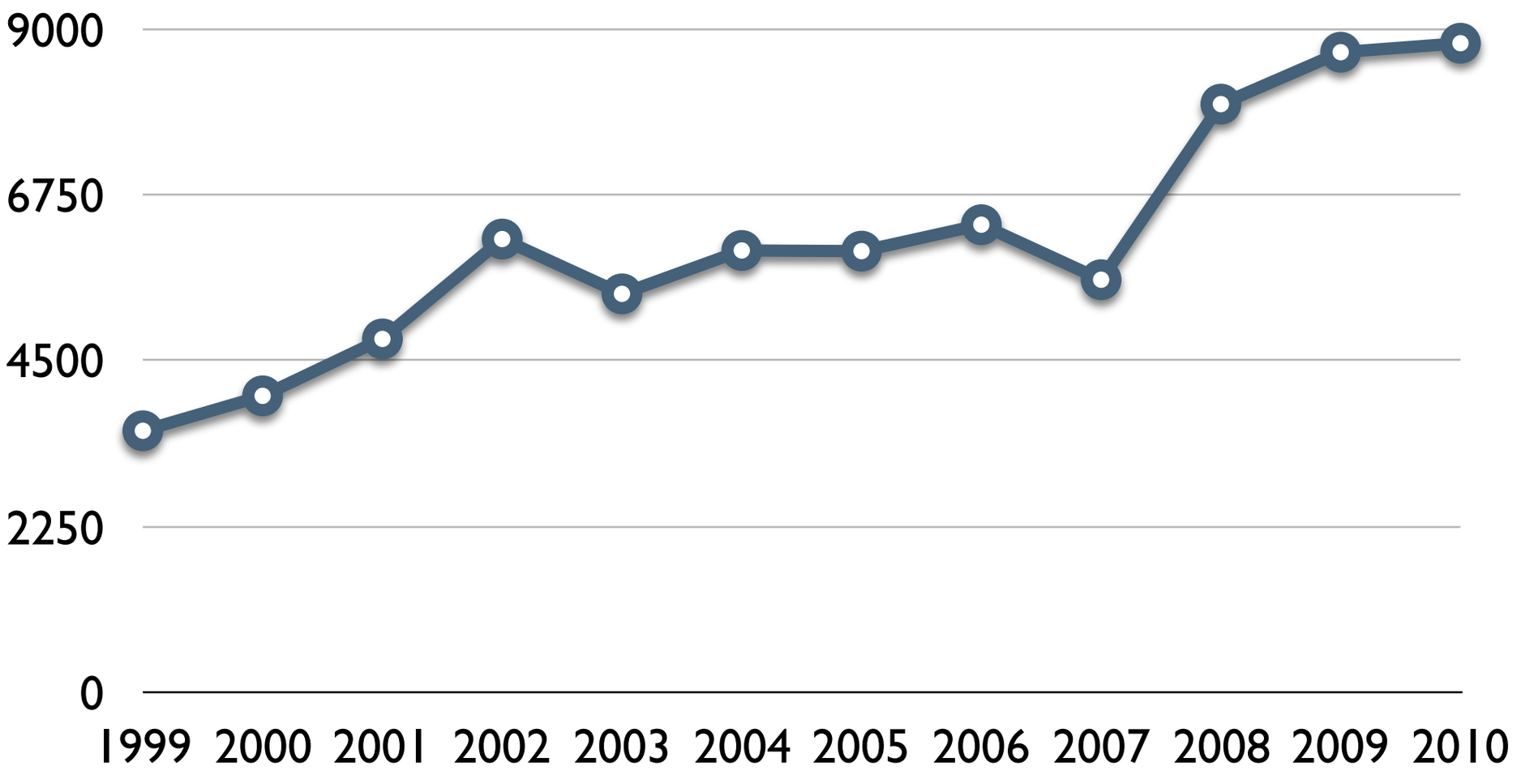
Source: Australian Government, "Characteristics of Disability Support Pension Recipients, June 2011."

Disability Due to Mental and Behavioural Disorders in Iceland, 1990-2007



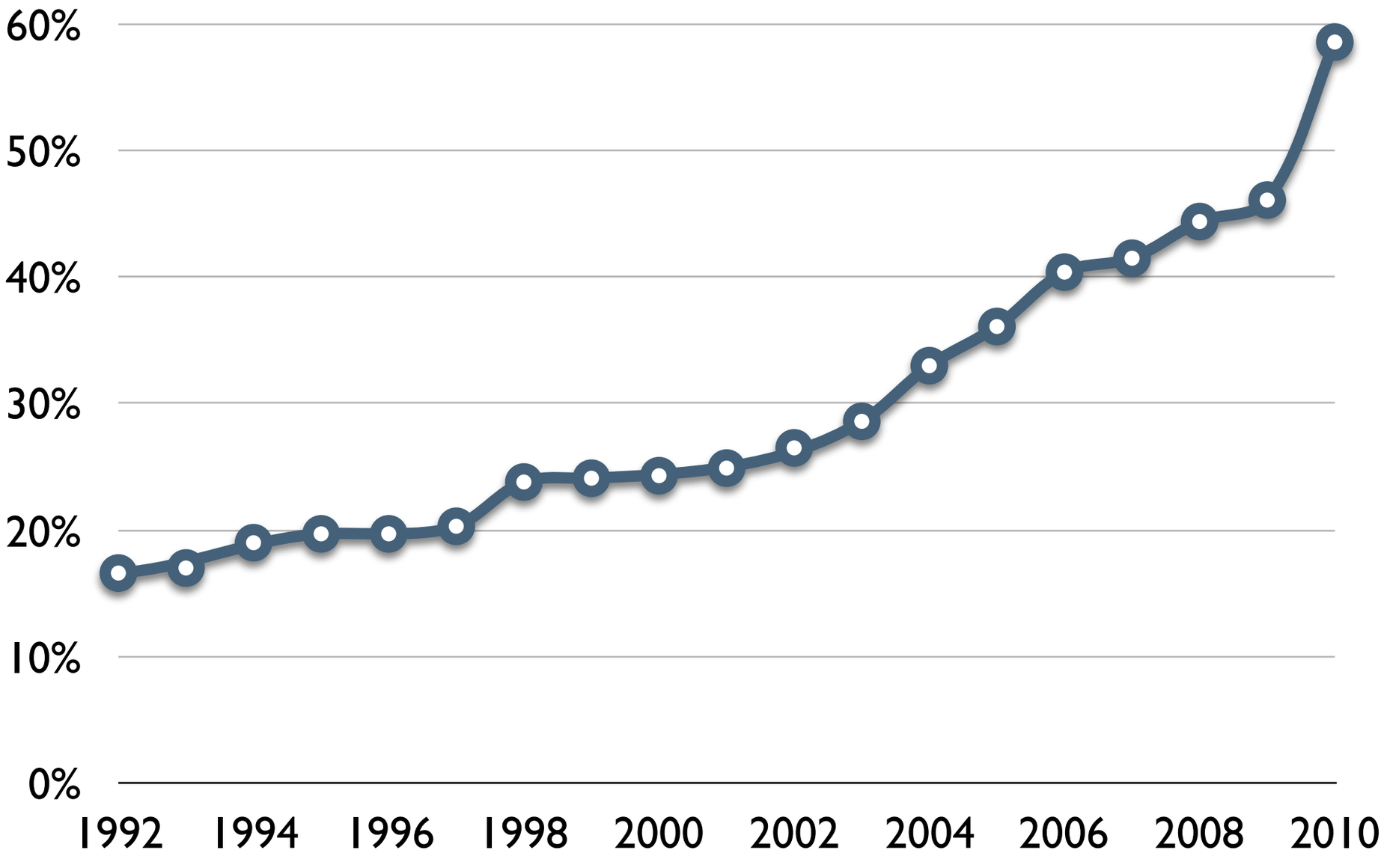
Source: Thoriacius, S. "Increased incidence of disability due to mental and behavioural disorders in Iceland, 1990-2007." *J Ment Health* (2010) 19: 176-83.

New Cases of Disability in Denmark Due to Mental Illness



Source: Danish government, The Appeals Board, Statistics on Early Retirement.

Percentage of All New Disability Cases in Sweden That Are Due to Mental Illness



Source: OECD. Mental Health and Work: Sweden, 2013.

A Battle of Narratives

In the conventional narrative, psychiatry has made great progress in discovering the biology of mental disorders, and the drugs prescribed for those disorders are safe and effective, and improve outcomes.

In the counter-narrative, the chemical imbalance hypothesis failed to pan out, the biology of major mental disorders remains unknown, the second-generation psychiatric drugs are no better than the first-generation drugs, and the increased use of these medications has been associated with a dramatic increase in the burden of mental illness in developed societies. Long-term outcomes for medicated patients are poor.

If the counter-narrative is true, psychiatry, as an institution, has told a false narrative, and societies have organized their psychiatric care around that false narrative.

The Trespasses of a Journalist

"Should we accept the analysis of a journalist who (1) to my knowledge, has not treated a patient or implemented a study and (2) reaches conclusions that run counter to well-established practice guidelines?"

—William Glazer, *Psychiatric Times*, July 31, 2012

"We do not believe that armchair analyses of the literature by non-clinicians will answer the risk/benefit question in a humane and judicious manner. On the contrary, we believe that the working with psychotic patients, and appreciating their often profound suffering, is an essential part of the equation. Critics of psychiatry who have never spent time with patients and families coping with the ravages of schizophrenia simply do not grasp the human tragedy of this illness."

—Ronald Pies, *Psychiatric Times*, Sept. 5, 2016