

# Causation, Not Just Correlation: Increased Disability in the Age of Prozac

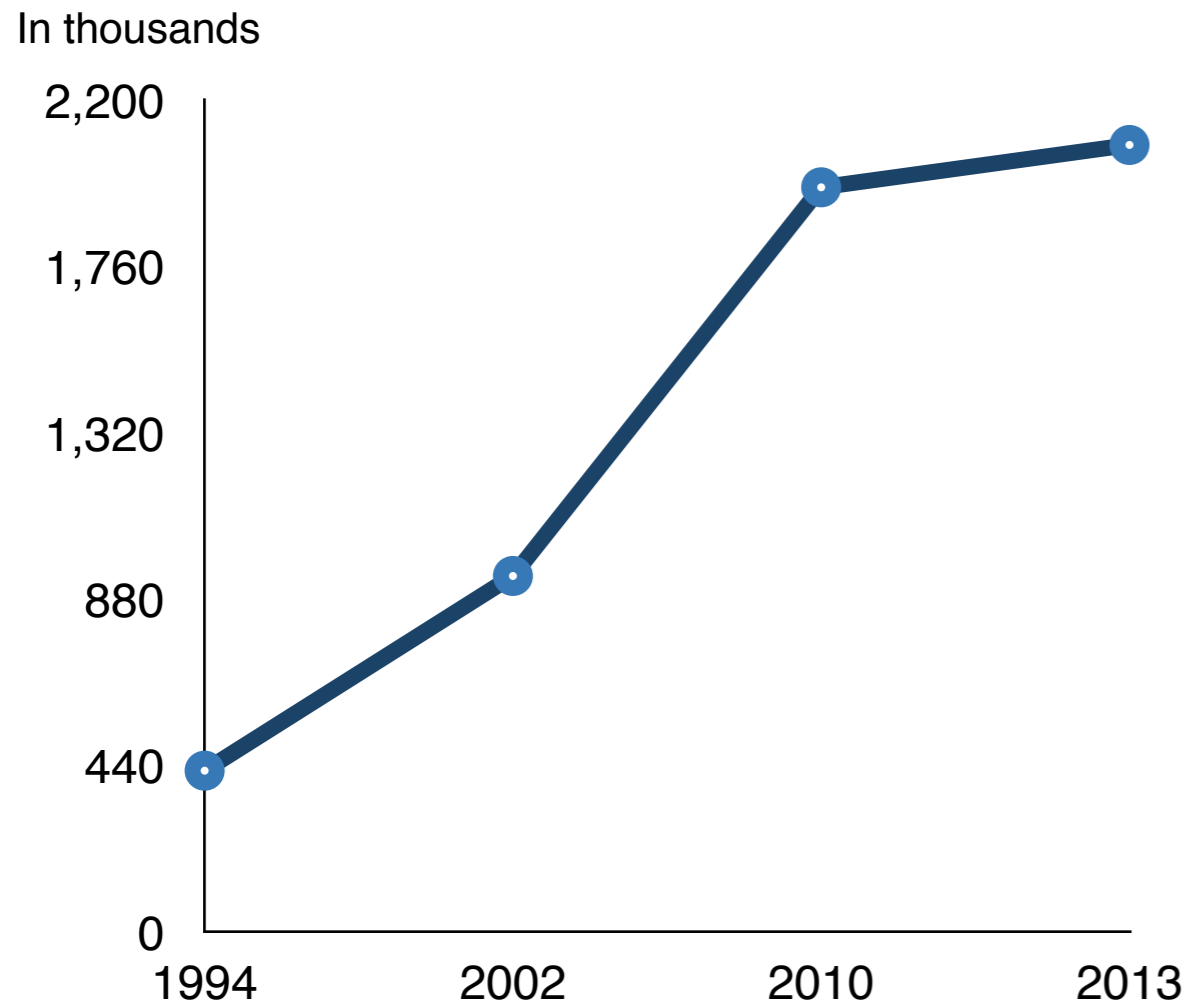
Robert Whitaker  
May 2016

# The Case for Causation

- As prescriptions for antidepressants and other psychiatric drugs have risen, the number of people disabled by mental disorders, in country after country, has risen in lockstep (the correlative data).
- Psychiatric drugs are causative agents. They are expected to affect psychiatric and functional outcomes.
- Research studies reveal that antidepressants increase the risk that: (1) depression will run a chronic course; (2) a unipolar patient will convert to bipolar disorder; (3) a patient will become impaired and go on government disability.
- Studies have shown that benzodiazepines impair functioning in multiple domains when taken over the long-term.
- Research studies have found that antipsychotics appear to worsen functional outcomes over the long term.

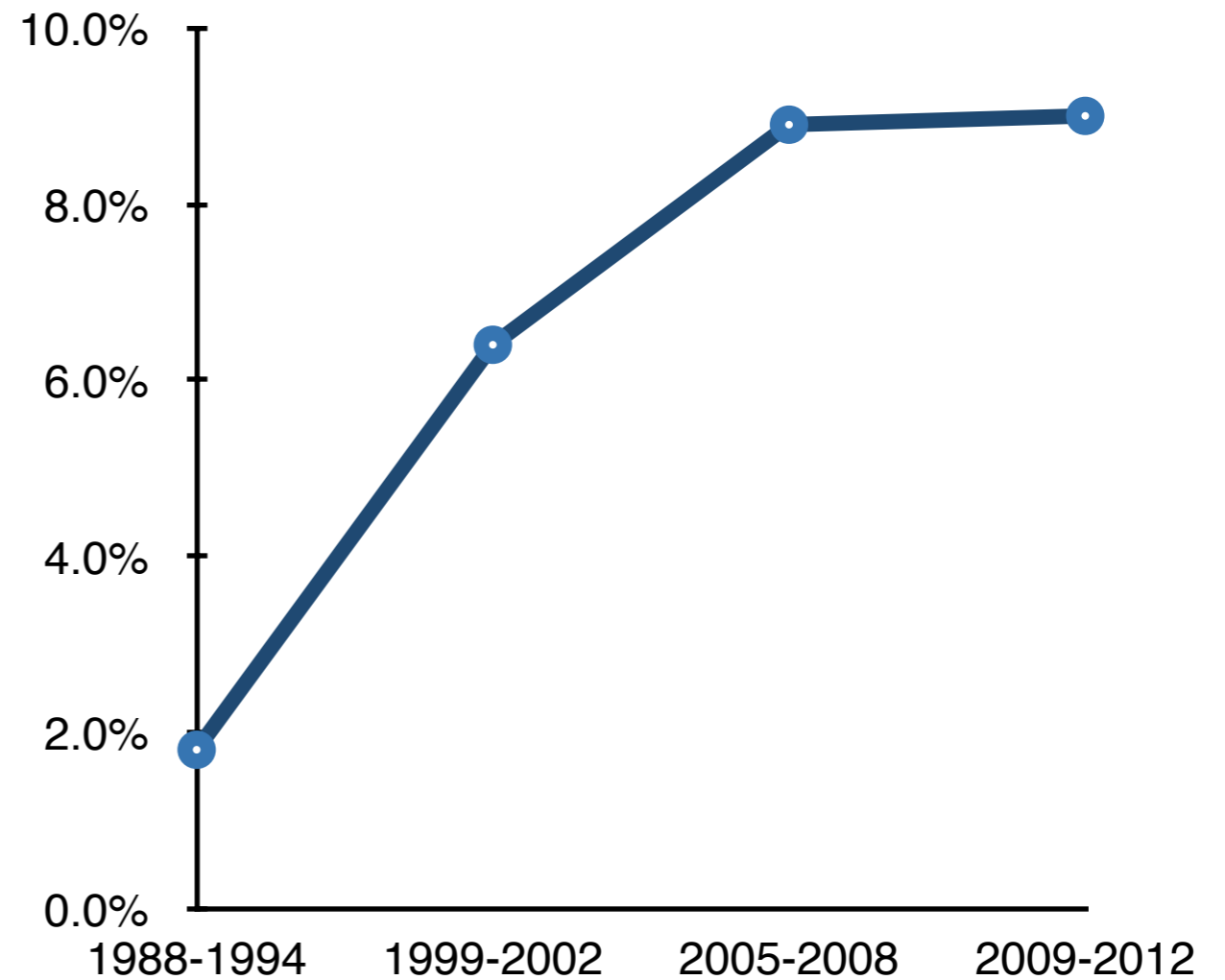
# United States, 1988-2013

## Number on government disability due to mood disorders



Source: R. Rosenheck. "The growth of psychopharmacology in the 1990s." *Int J of Law and Psychiatry* 28 (2005):467-83. U.S. Social Security Administration, Annual Statistical Report on the Social Security Disability Insurance Program, and SSI Annual Statistical Report, 2010-2013.

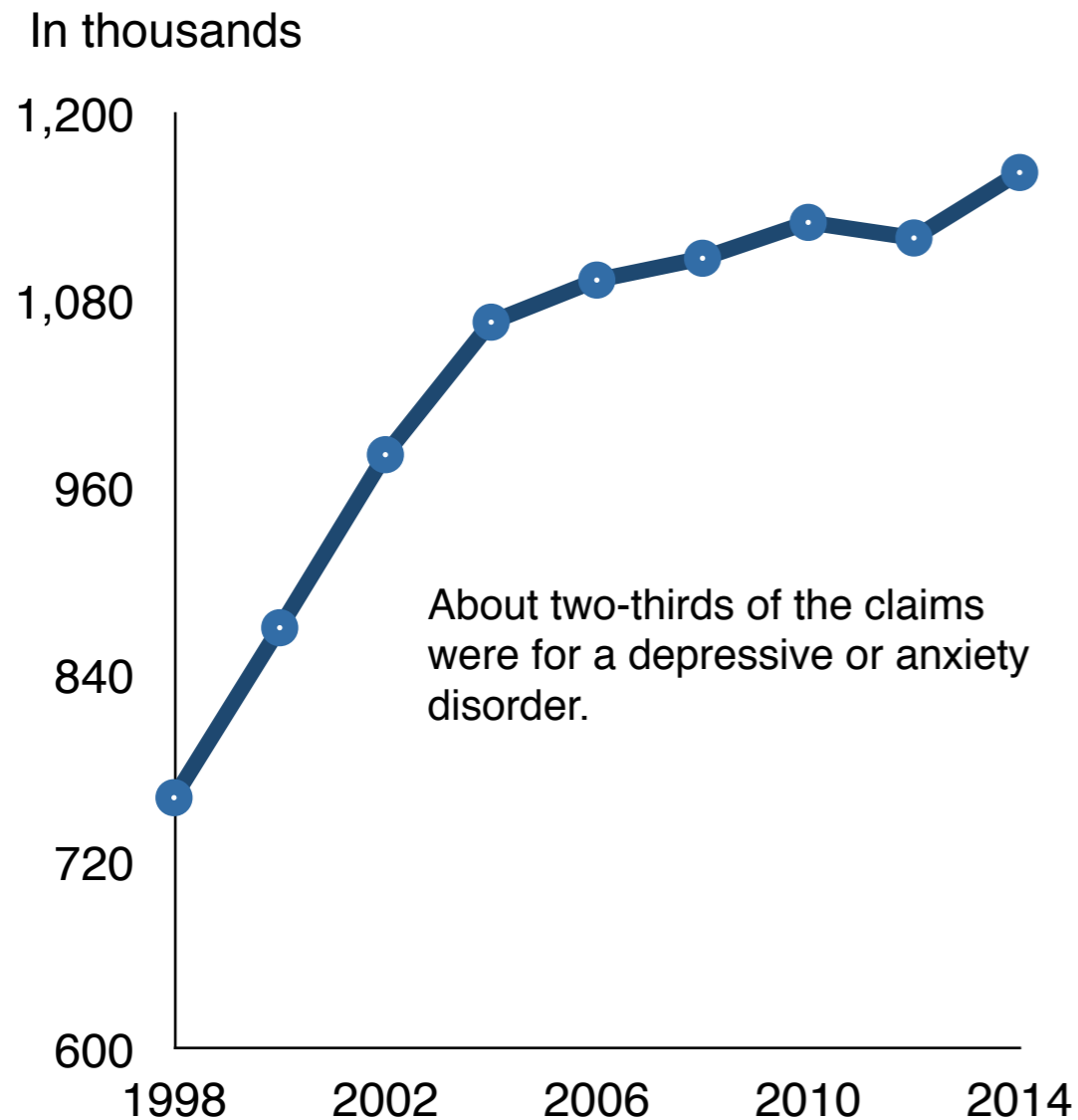
## Percent of population who used antidepressants in past month



Source: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention. "Health, United States, 2014."

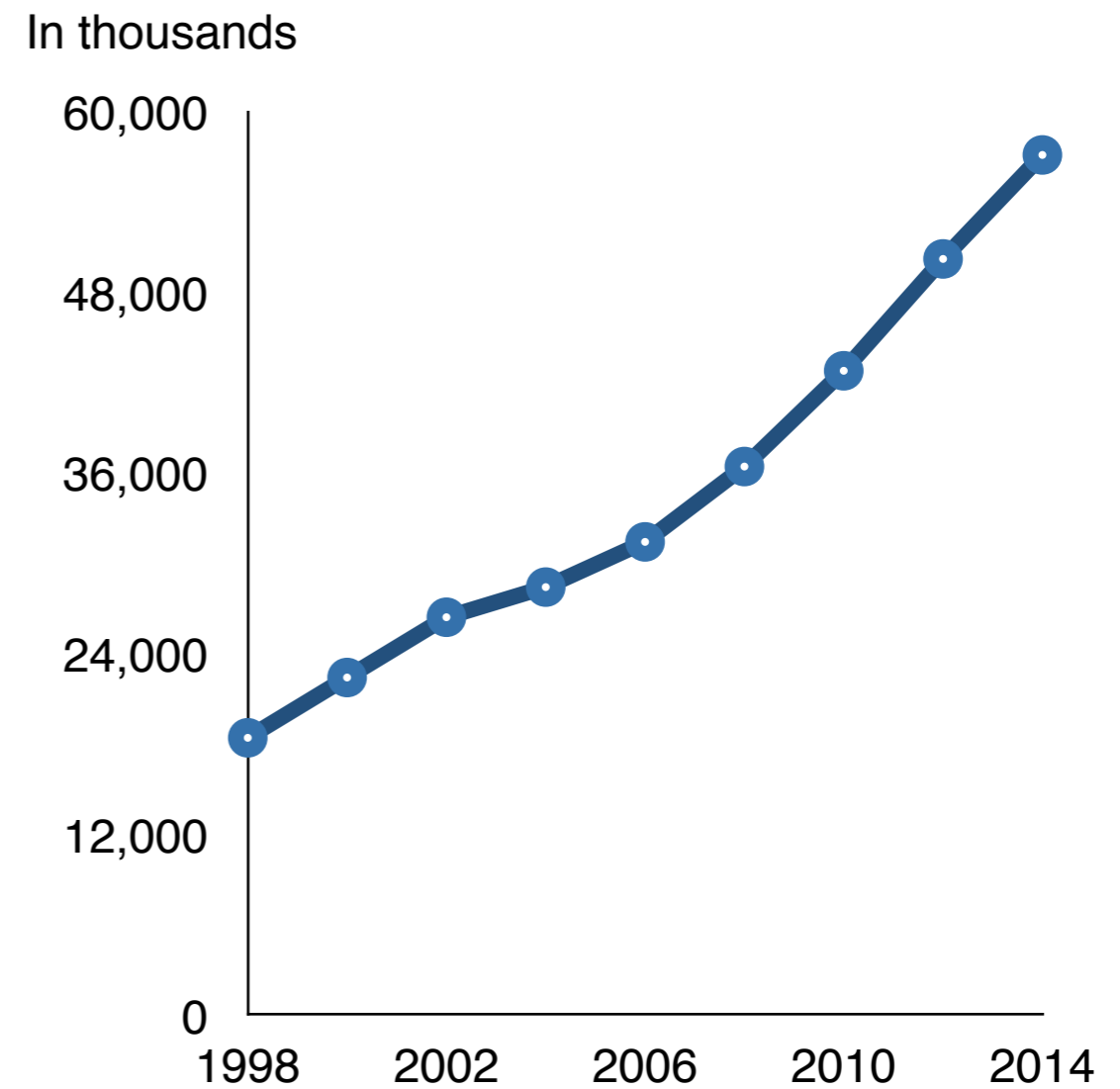
# United Kingdom, 1998-2014

## Claims for sickness and disability benefits owing to mental illness in UK



Source: S. Viola, J. Moncrieff. "Claims for sickness and disability benefits owing to mental disorders in the UK: trends from 1995 to 2014." *BJPsych Open* 2 (2016):18-24

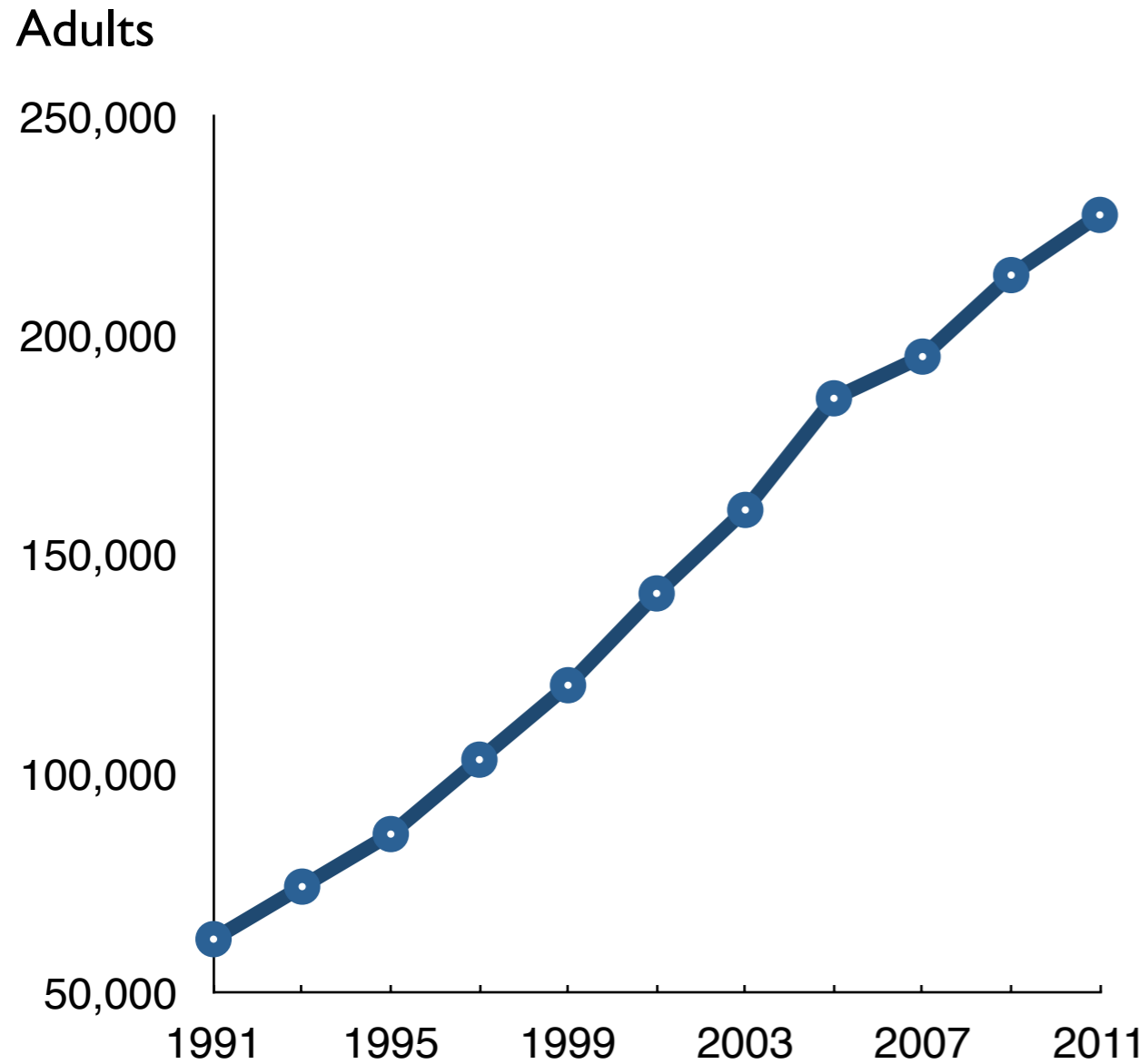
## Prescriptions for antidepressants in England



Source: S. Viola, J. Moncrieff. "Trends in prescriptions and costs of drugs for mental disorders in England, 1998-2010." *Brit J of Psychiatry* 200 (2012):393-398. Also, UK Health and Social Care Information Centre (2011-2014)...

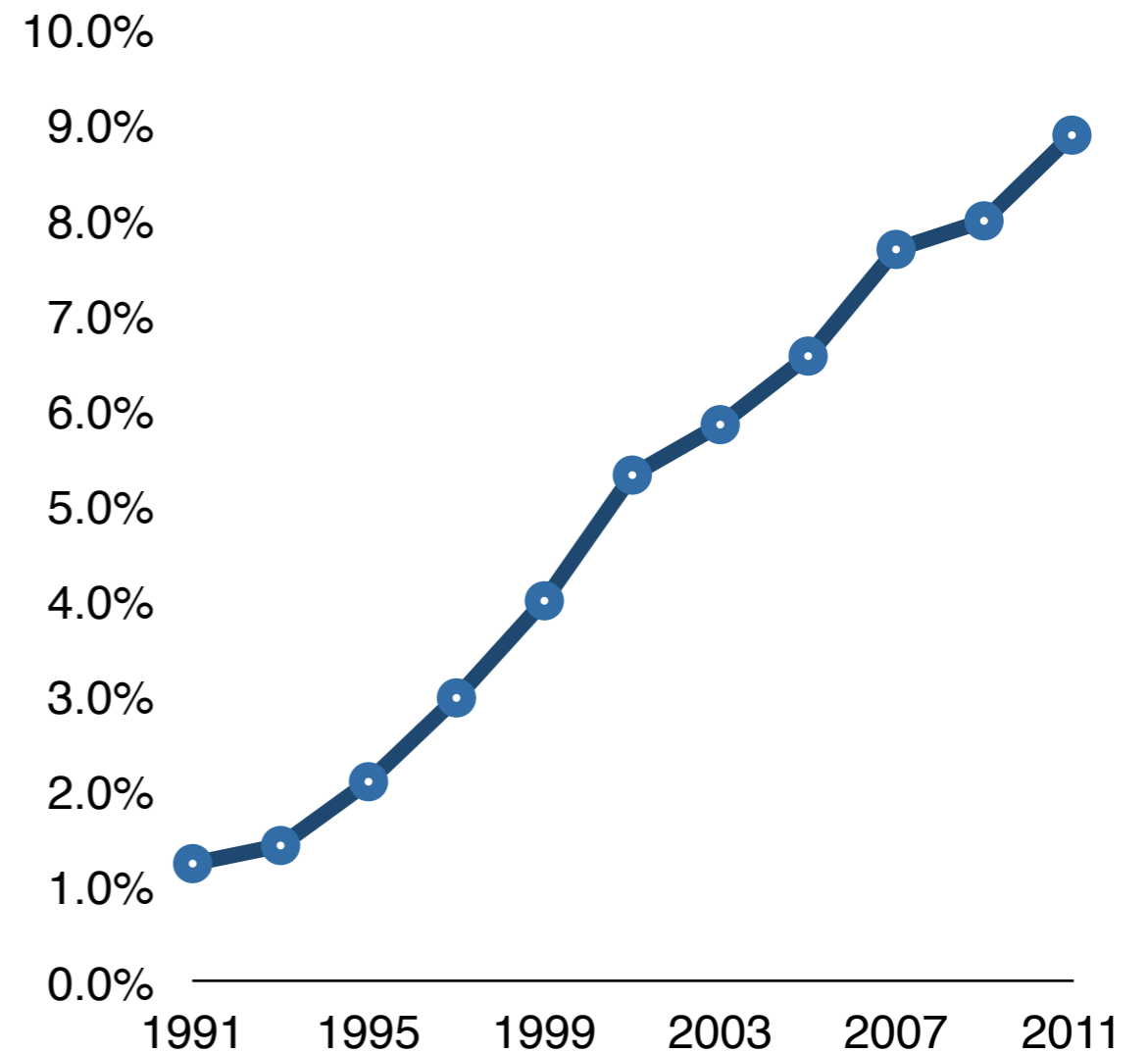
# Australia, 1990-2011

## Number on disability due to mental illness



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

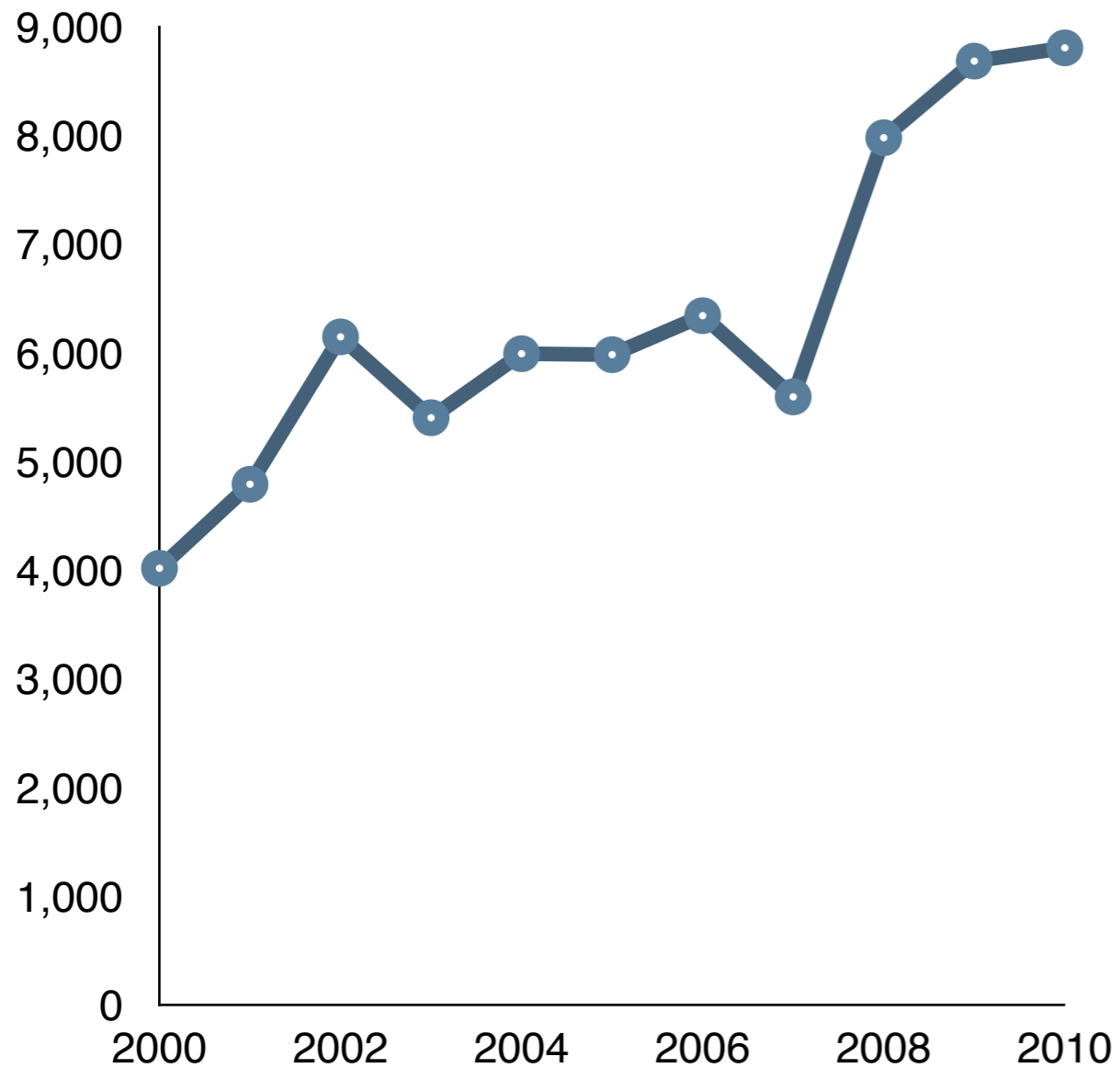
## Percent of population that used antidepressants



Source: "Antidepressants: Global Trends." *The Guardian*, Nov. 20, 2013.

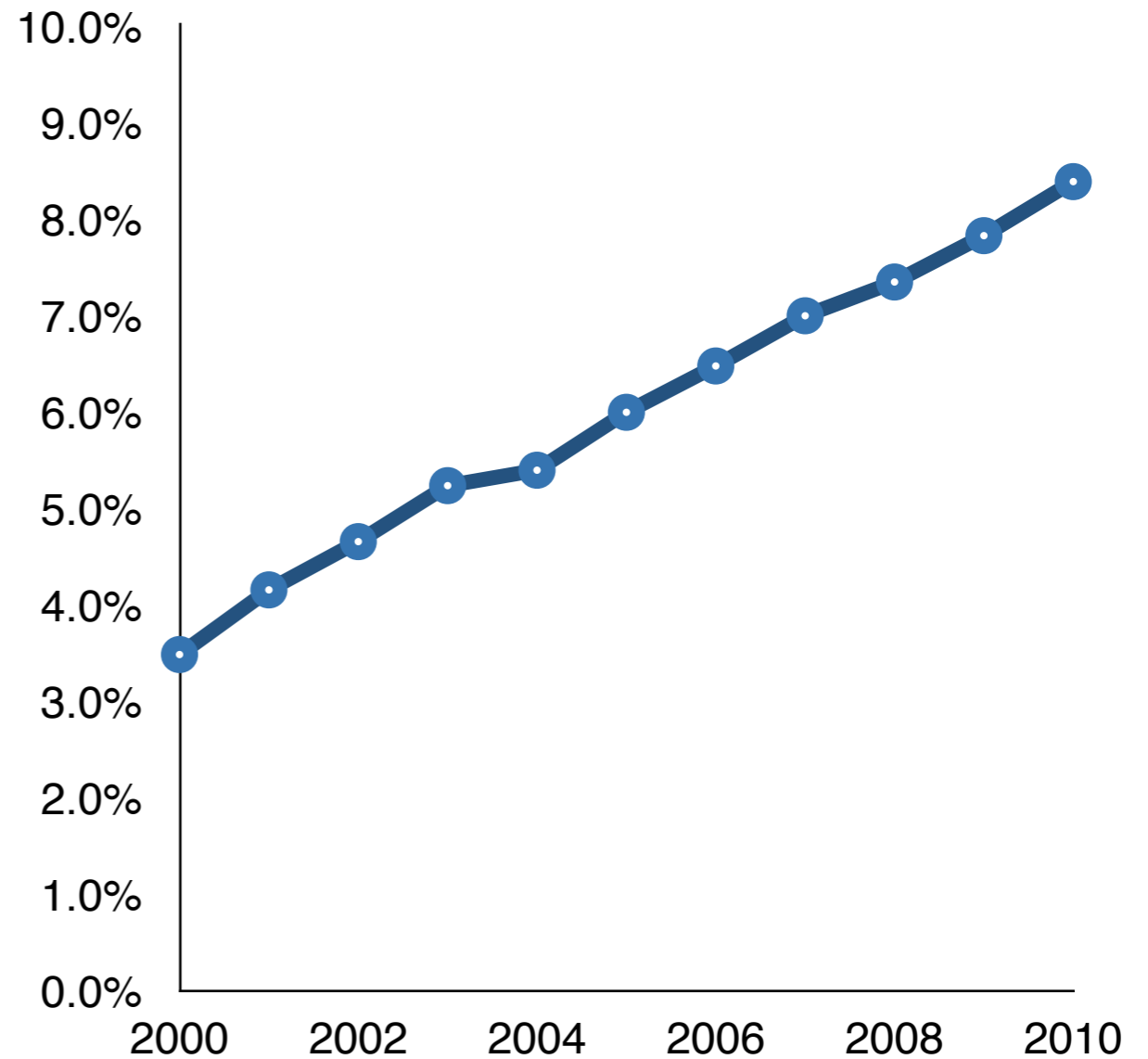
# Denmark, 2000-2010

## New cases of disability due to mental illness



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

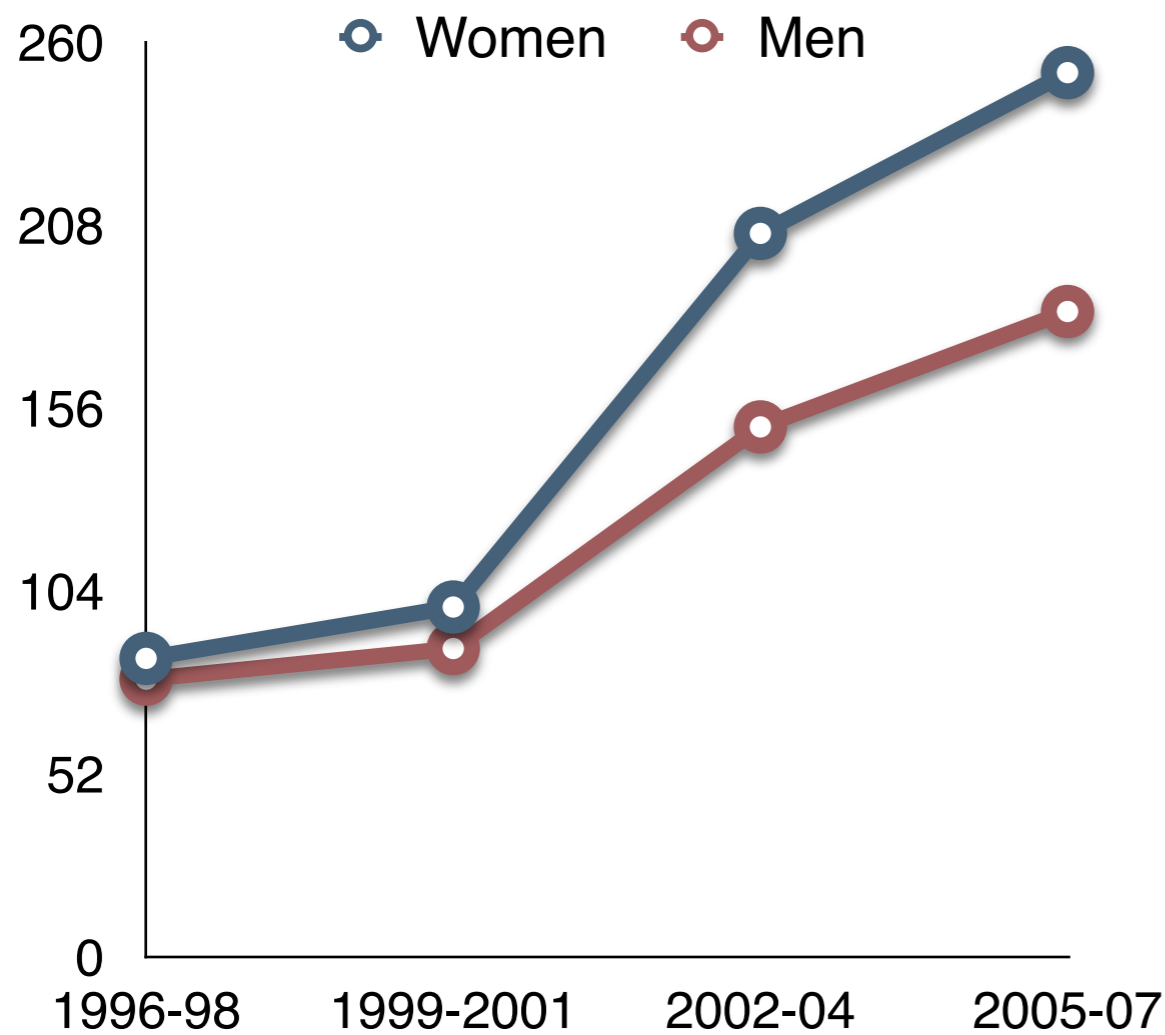
## Percent of population that used antidepressants



Source: "Antidepressants: Global Trends." *The Guardian*, Nov. 20, 2013.

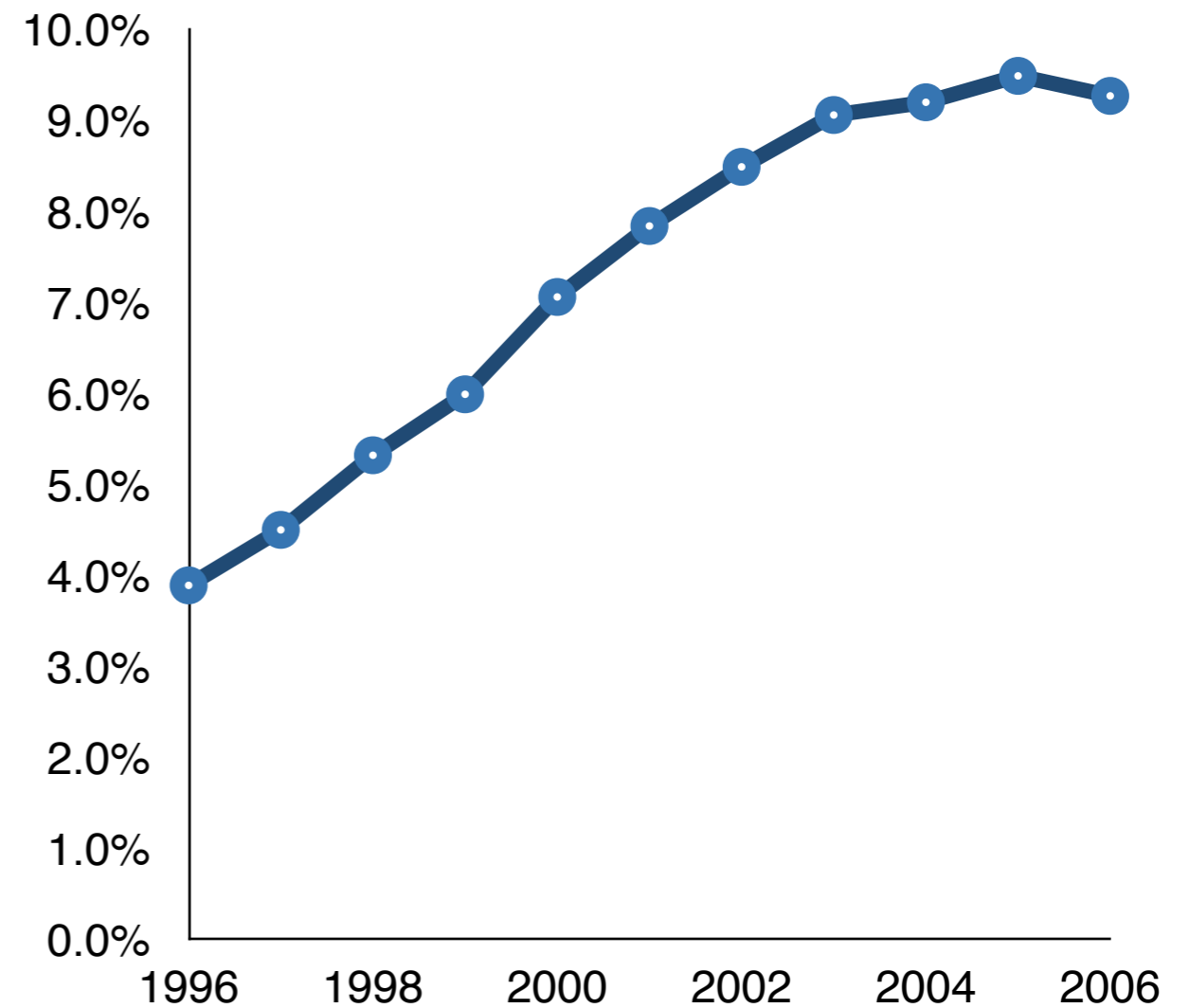
# Iceland, 1996-2006

New cases of disability annually per 100,000 population



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

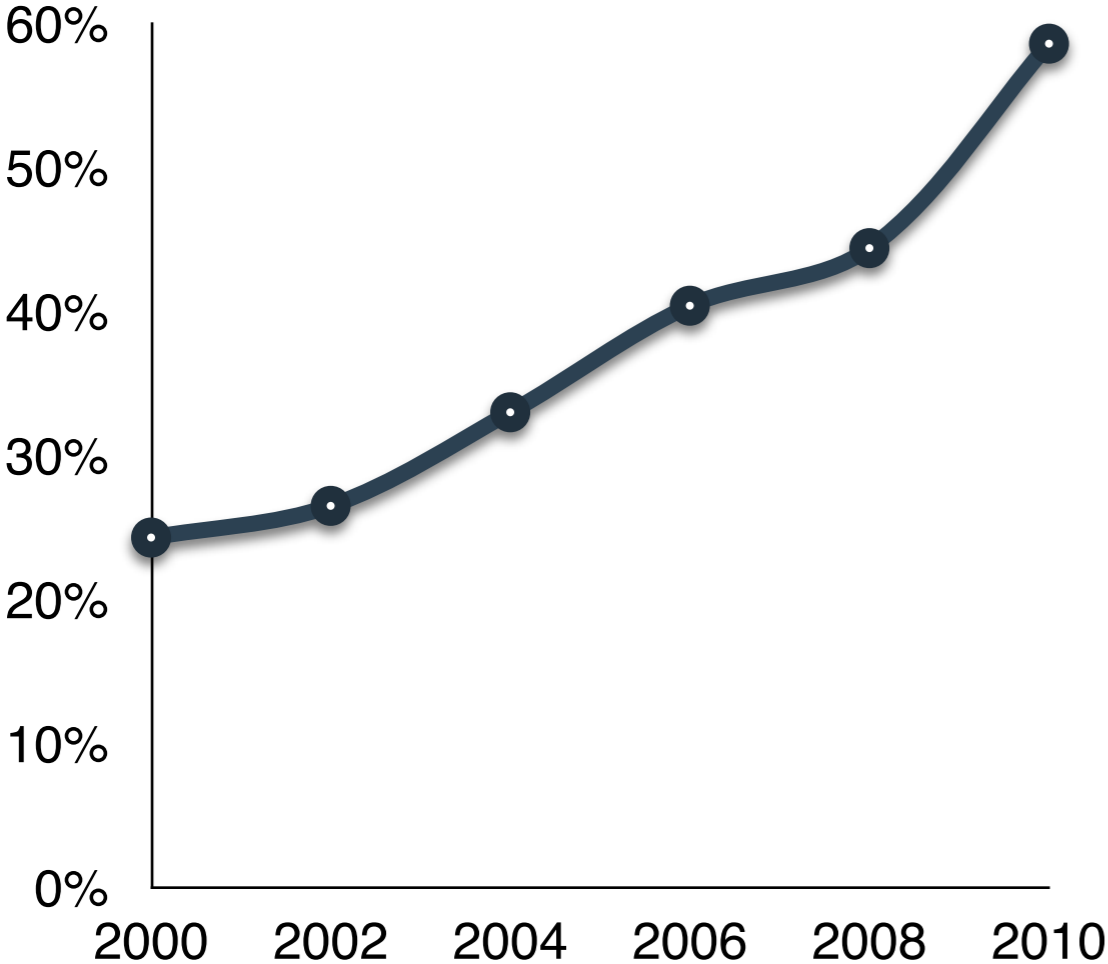
Percent of population that used antidepressants



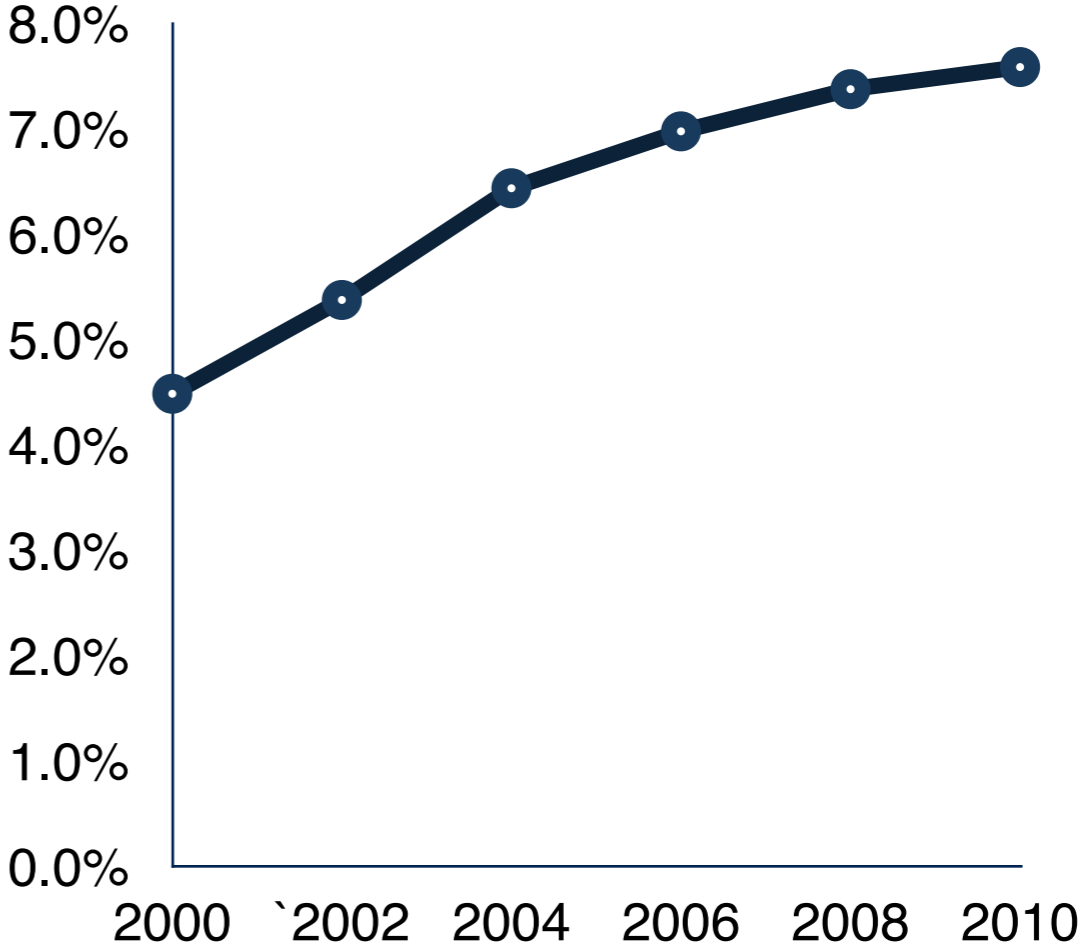
Source: "Antidepressants: Global Trends." *The Guardian*, Nov. 20, 2013.

# Sweden, 2000-2010

Percent of new disability cases due to mental illness



Percent of population that used antidepressants



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

Source: "Antidepressants: Global Trends." *The Guardian*, Nov. 20, 2013.



# Psychotropic Drugs Create Abnormalities in Brain Function

**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.

# Long-term Outcomes for Hospitalized Depressed Patients in the Pre-Antidepressant Era

- Emil Kraepelin, 1921. Sixty percent of 450 patients hospitalized for an initial bout of depression experienced but a single bout of the illness, and only 13% had three or more episodes in their lives.
- Horatio Pollock, New York State, 1931. In a long-term study of 2700 first-episode depressed patients, more than half never had another bout of depression that required hospitalization, and only 13% had three or more episodes.
- Gunnar Lundquist, Sweden, 1945. In an 18-year study of 216 patients, 49% had only a single episode, and another 21% had only one other episode.

Source: A. Zis. "Major affective disorder as a recurrent illness." *Arch Gen Psych* 36 (1979):835-9. G. Winokur. *Manic Depressive Illness* (St. Louis: The C.V. Mosby Company, 1969), 19-20. G. Lundquist. "Prognosis and course in manic-depressive psychoses." *Acta Psychiatrica Scandinavica*, suppl. 35 (1945):7-93.

# Depression Was Understood to Be an Episodic Disorder

“Assurance can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course.”

--George Winokur, Washington University,  
*Manic Depressive Illness*, 1969

# Clinical Perceptions in Early Years of Antidepressant Use

- H.P. Hoheisel, German physician, 1966: Exposure to antidepressants appeared to be “shortening the intervals” between depressive episodes.
- Nikola Schipkowensky, Bulgarian psychiatrist, 1970: The antidepressants were inducing “a change to a more chronic course.”

# The Chronicity Worry is Tested

J.D. Van Scheyen, Dutch psychiatry, 1973:

After conducting a study of 94 depressed patients, he concluded that “long-term antidepressant medication, with or without ECT [electroconvulsive therapy], exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate and a decrease in cycle duration . . . Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?”

# An Episodic Illness Turns Chronic in the Antidepressant Era

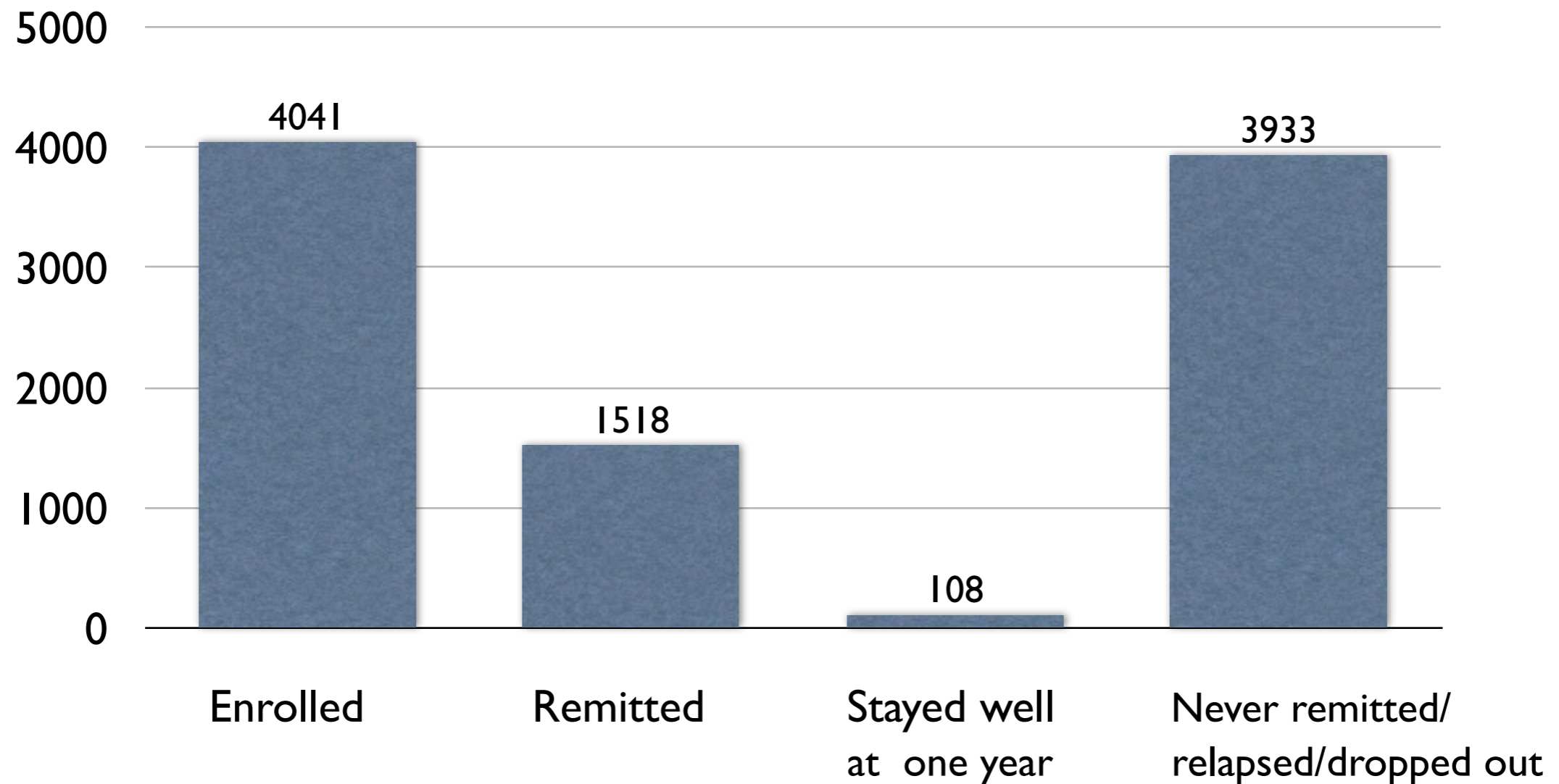
**National Institute of Mental Health Panel on Mood Disorders, 1985:**

“Improved approaches to the description and classification of [mood] disorders and new epidemiologic studies [have] demonstrated the recurrent and chronic nature of these illnesses, and the extent to which they represent a continual source of distress and dysfunction for affected individuals.”

Source: Consensus Development Panel, “Mood disorders,” *Am J Psychiatry* 142 (1985):469-76.

# The STAR\*D Trial Confirms That Medicated Depression Runs a Chronic Course Today

Number of patients



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

# One-Year Remission Rates in NIMH Study of Medicated Depression in “Real-World” Patients

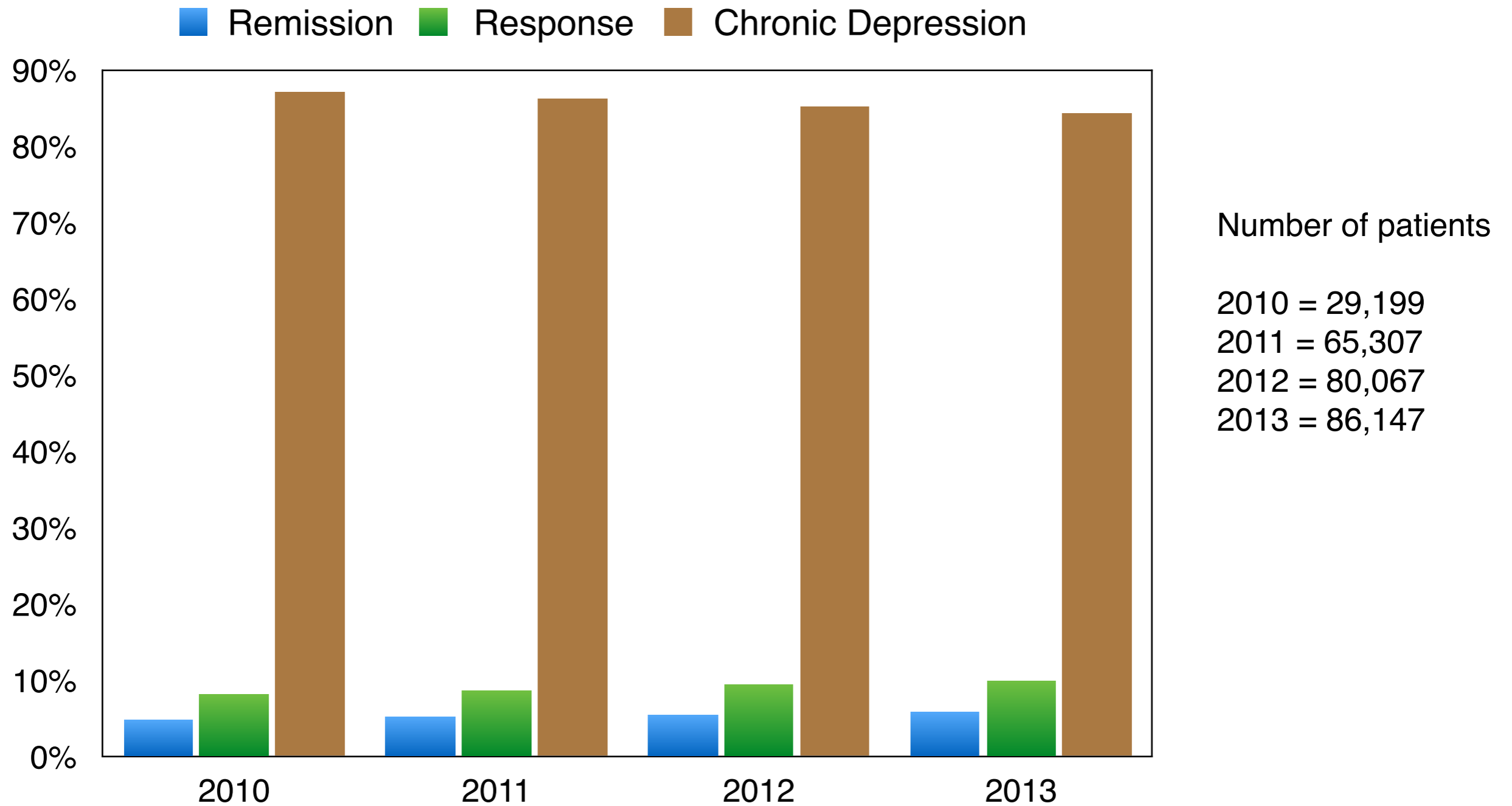
- 126 patients were treated with antidepressants and given emotional and clinical support “specifically designed to maximize clinical outcomes.”
- Only 26% responded to antidepressants (50% reduction in symptoms).
- Only half of those who responded stayed better for a significant period of time
- Only 6% remitted and then remained in remission at the end of one year.



**“These findings reveal remarkably low response and remission rates.”**

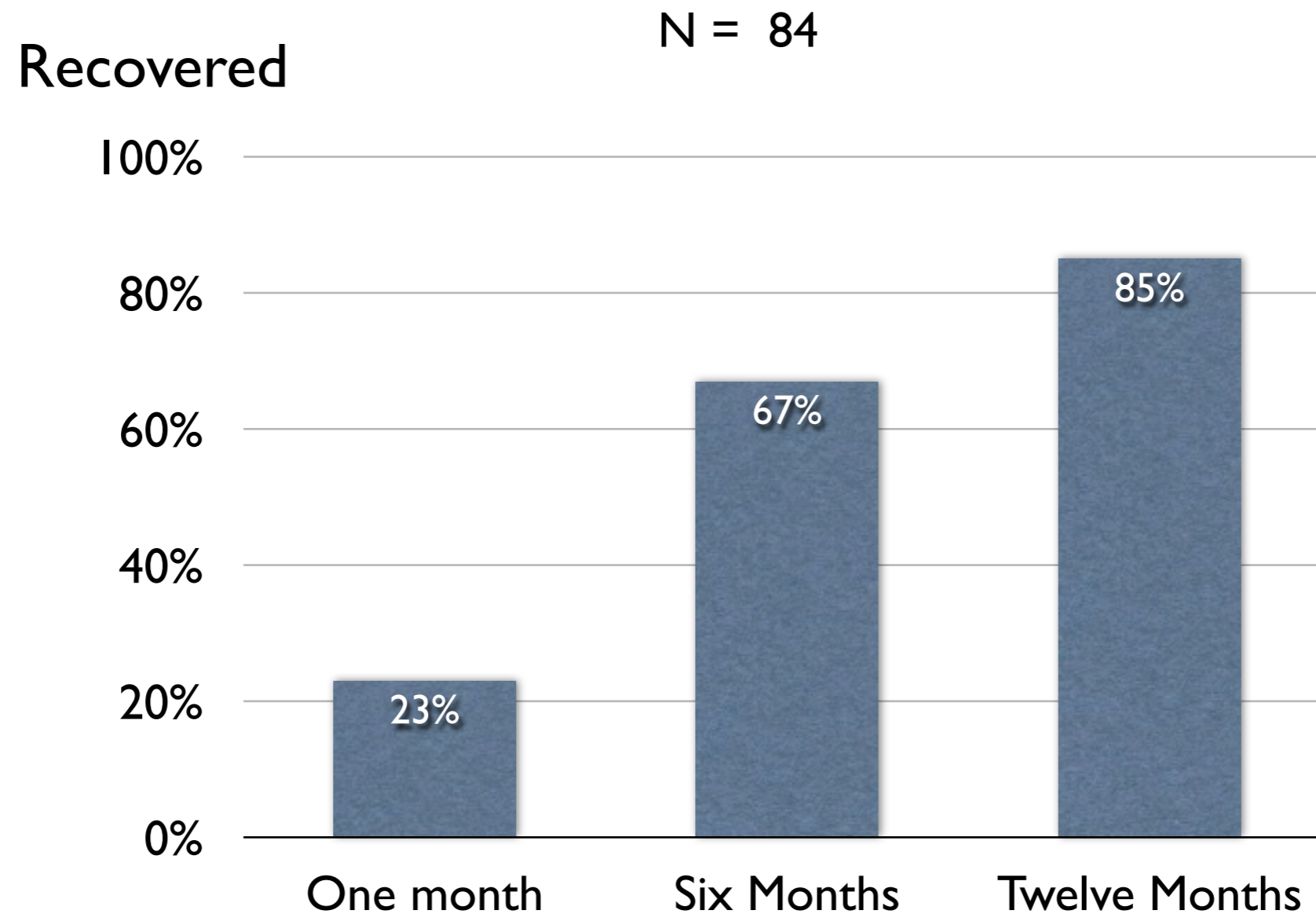
**--John Rush, 2004**

# Real World Outcomes in Minnesota: Few Patients in Recovery At End of Year



Source: MN Community Measures, *Annual Health Care Quality Report (2010-2014)*

# One-Year Recovery Rates in NIMH Study of Unmedicated Depression



Source: M. Posternak, "The naturalistic course of unipolar major depression in the absence of somatic therapy." *Journal of Nervous and Mental Disease* 194 (2006):324-349.

“If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this.”

--Michael Posternak

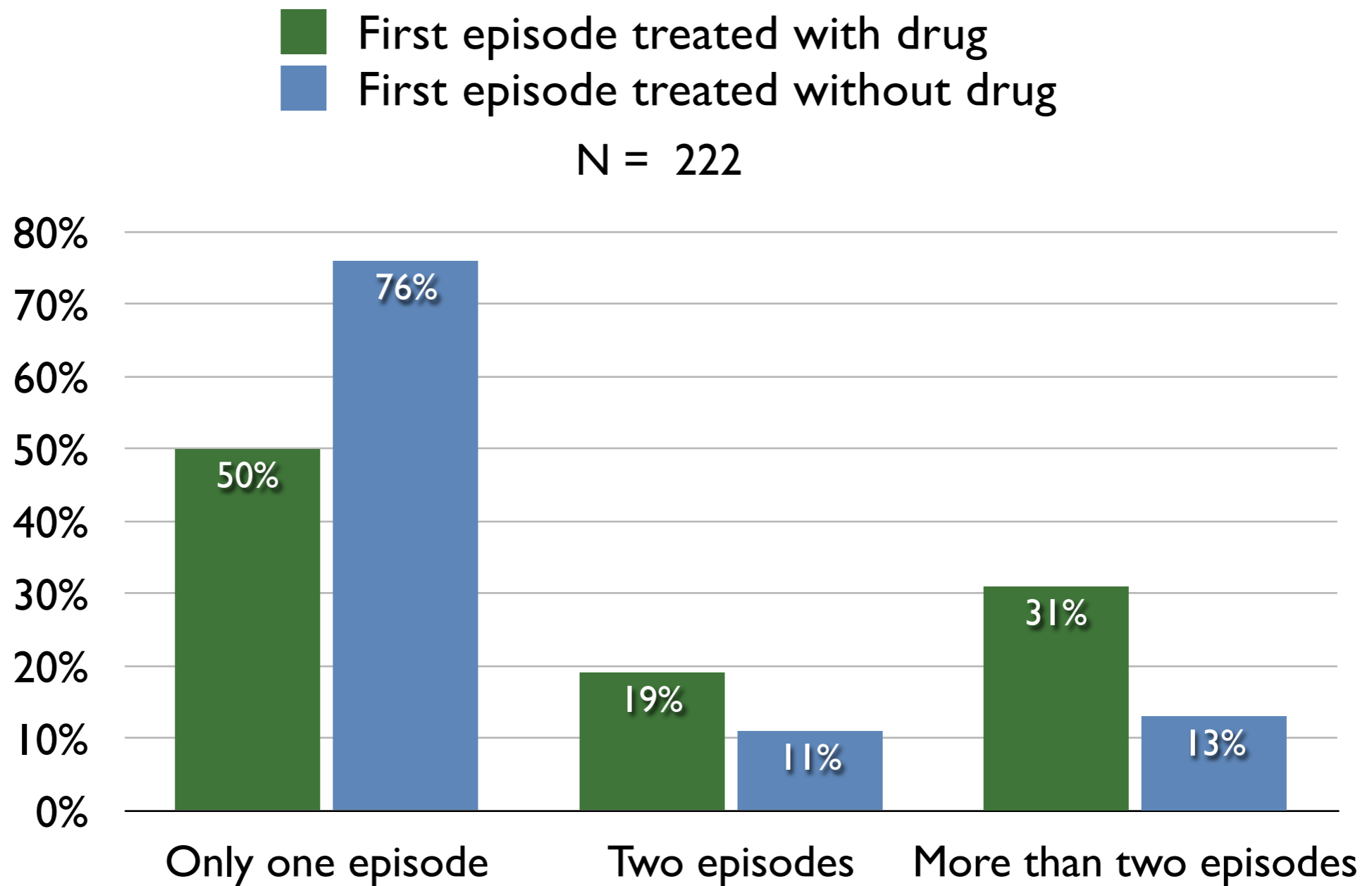
## Do Antidepressants Worsen the Long-term Course of Depression?

“Antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression . . . Use of antidepressant drugs may propel the illness to a more malignant and treatment unresponsive course.”

--Giovanni Fava, *Psychotherapy and Psychosomatics*,  
1995

# Depression in the Netherlands

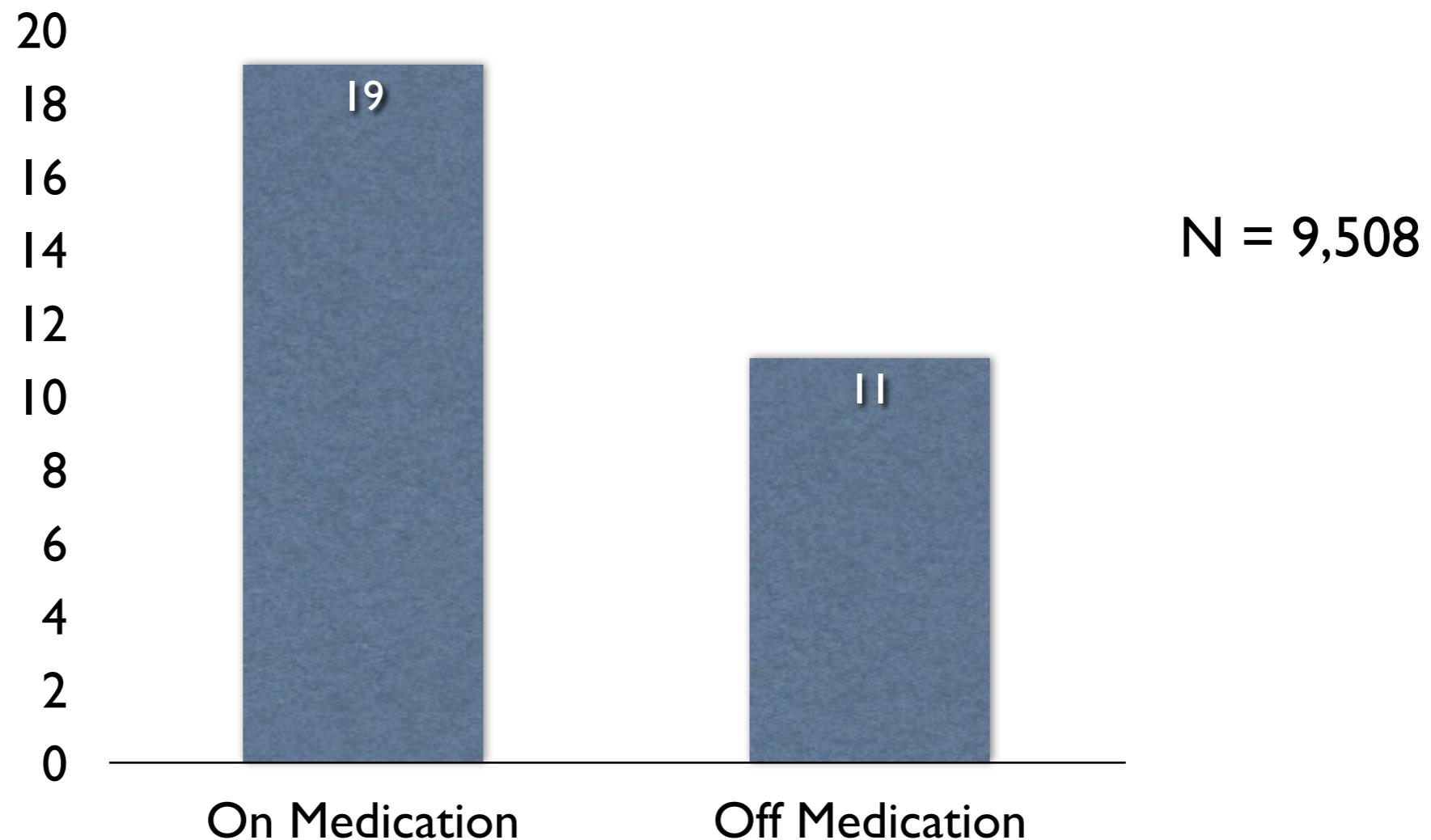
(Over the course of ten years)



Source: E. Weel-Baumgarten, "Treatment of depression related to recurrence," *J Clin Psychiatry & Therapeutics* 25 (2000):61-66.

# Five-Year Outcomes in Canada

Number of Weeks  
Depressed Each Year



Source: S. Patten, "The Impact of antidepressant treatment on population health." *Population Health Metrics* 2 (2004): 9.

These findings are consistent with Giovanni Fava's hypothesis that "antidepressant treatment may lead to a deterioration in the long-term course of mood disorders."

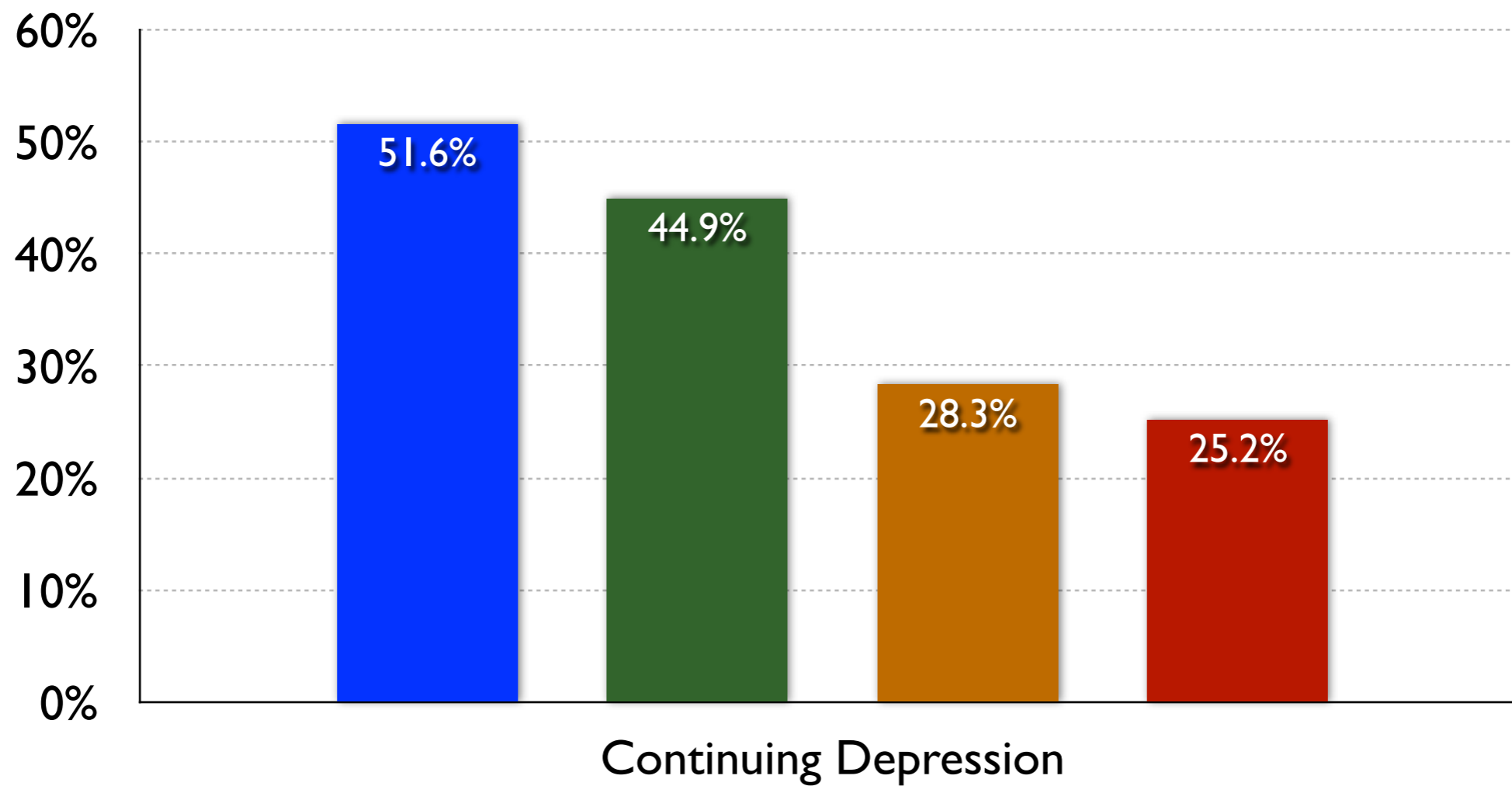
--Scott Patten



# One-Year Outcomes in WHO Screening Study for Depression

Diagnosed/Antidepressants      Diagnosed/Sedatives  
Undiagnosed/no drug      Diagnosed/No drug

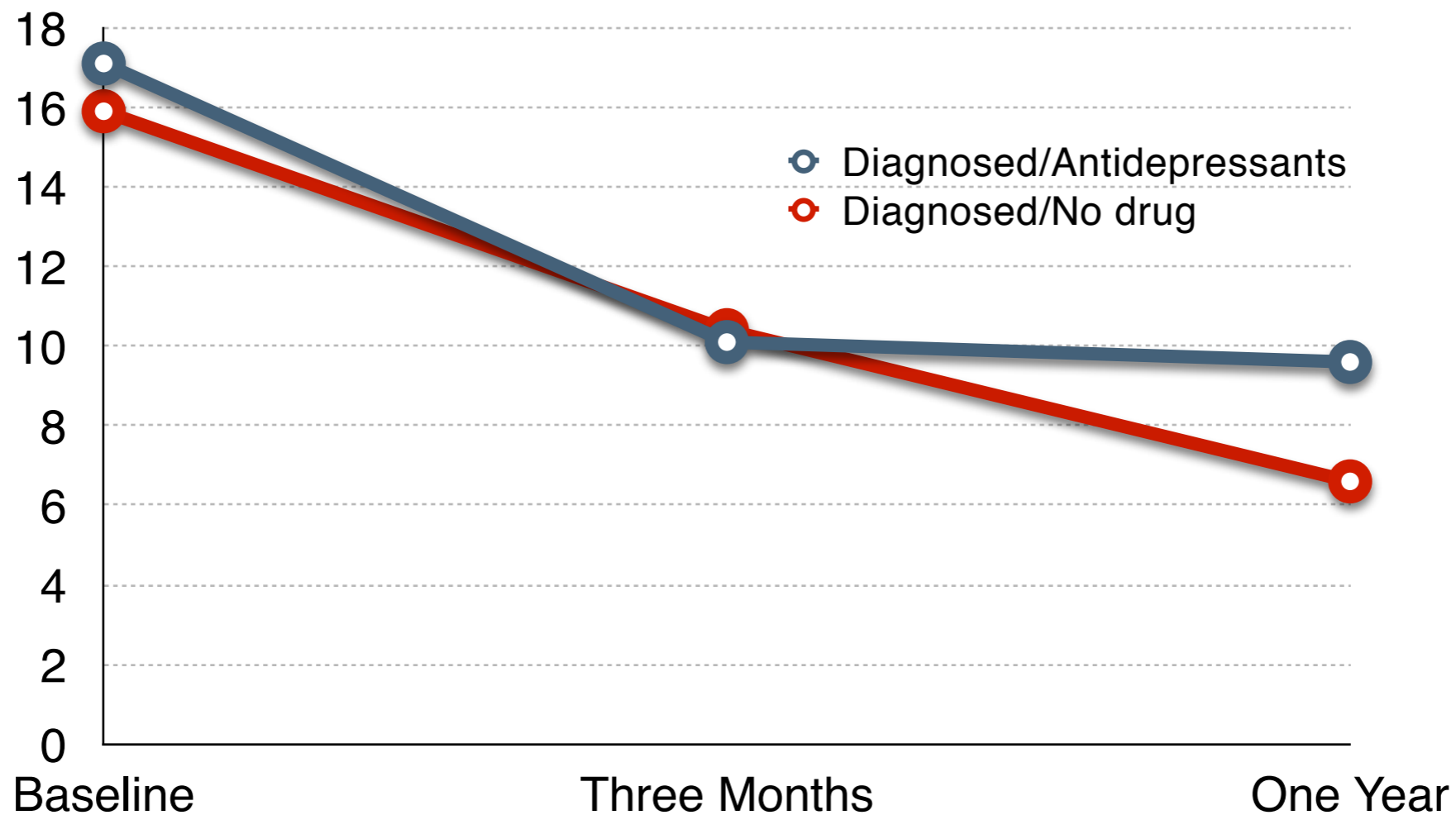
N = 740



Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

# WHO Study: Medicated Patients Stop Getting Better After Three Months

Severity of symptoms  
on GHQ scale



Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

# Antidepressants Lessen the Long-Term Benefits of Exercise

Treatment during first 16 weeks	Percentage of patients in remission at end of 16 weeks	Percentage of patents who relapsed in following six months	Percentage of all patients depressed at end of ten months
Zoloft alone	69%	38%	52%
Zoloft plus exercise	66%	31%	55%
Exercise alone	60%	8%	30%

Source: Babyak, M. "Exercise treatment for major depression." *Psychosomatic Medicine* 62 (2000):633-8.

# The Problem With Antidepressants: Drug-Induced “Oppositional Tolerance”

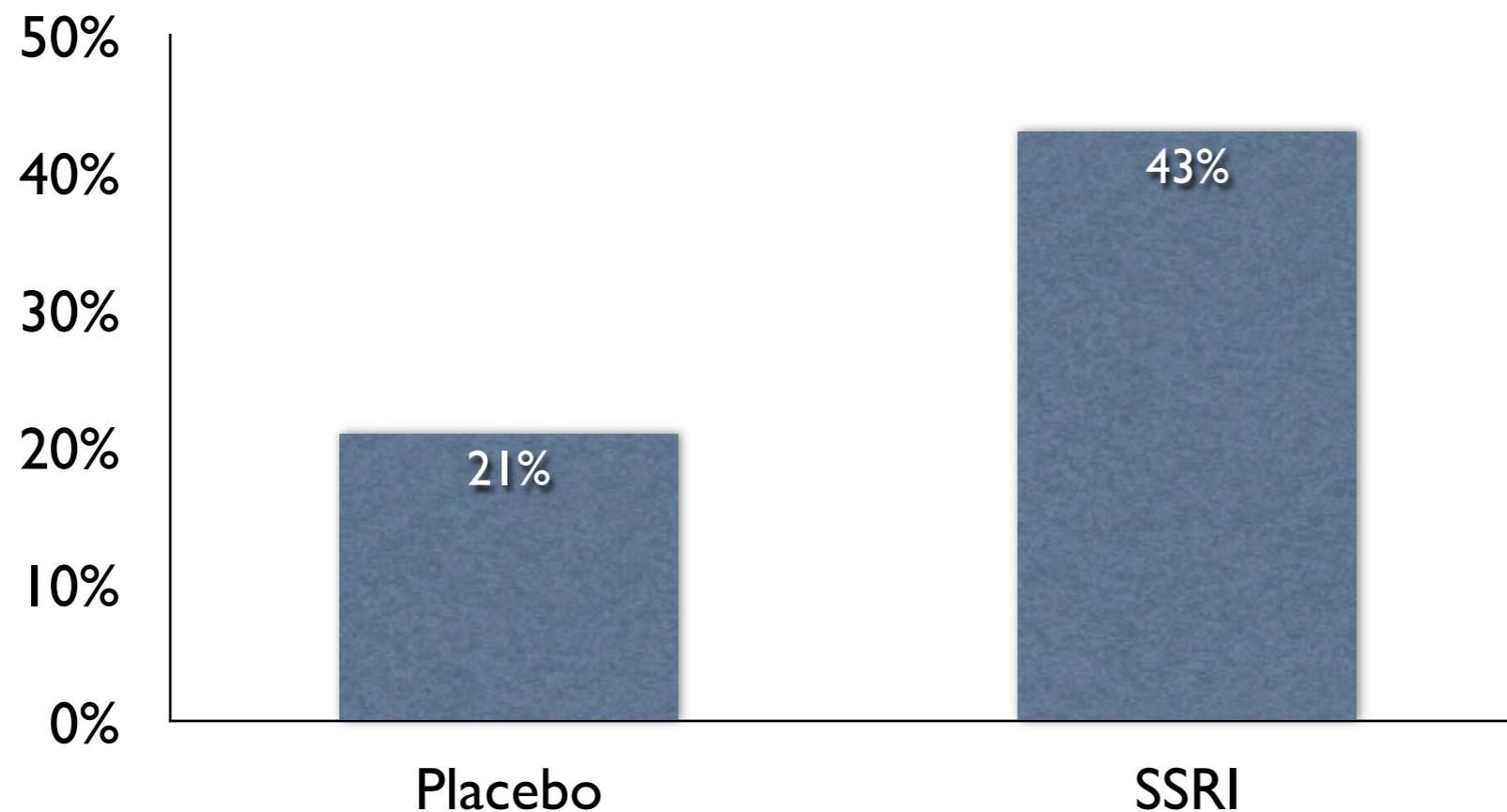
“When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible.”

Giovanni Fava, 2011

Source: G. Fava. “The mechanisms of tolerance in antidepressant action.” *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35 (2011): 1593-1602.

# Putting the Hypothesis to the Test

Three-month relapse rate after initial remission:  
placebo vs. SSRI-withdrawn patients

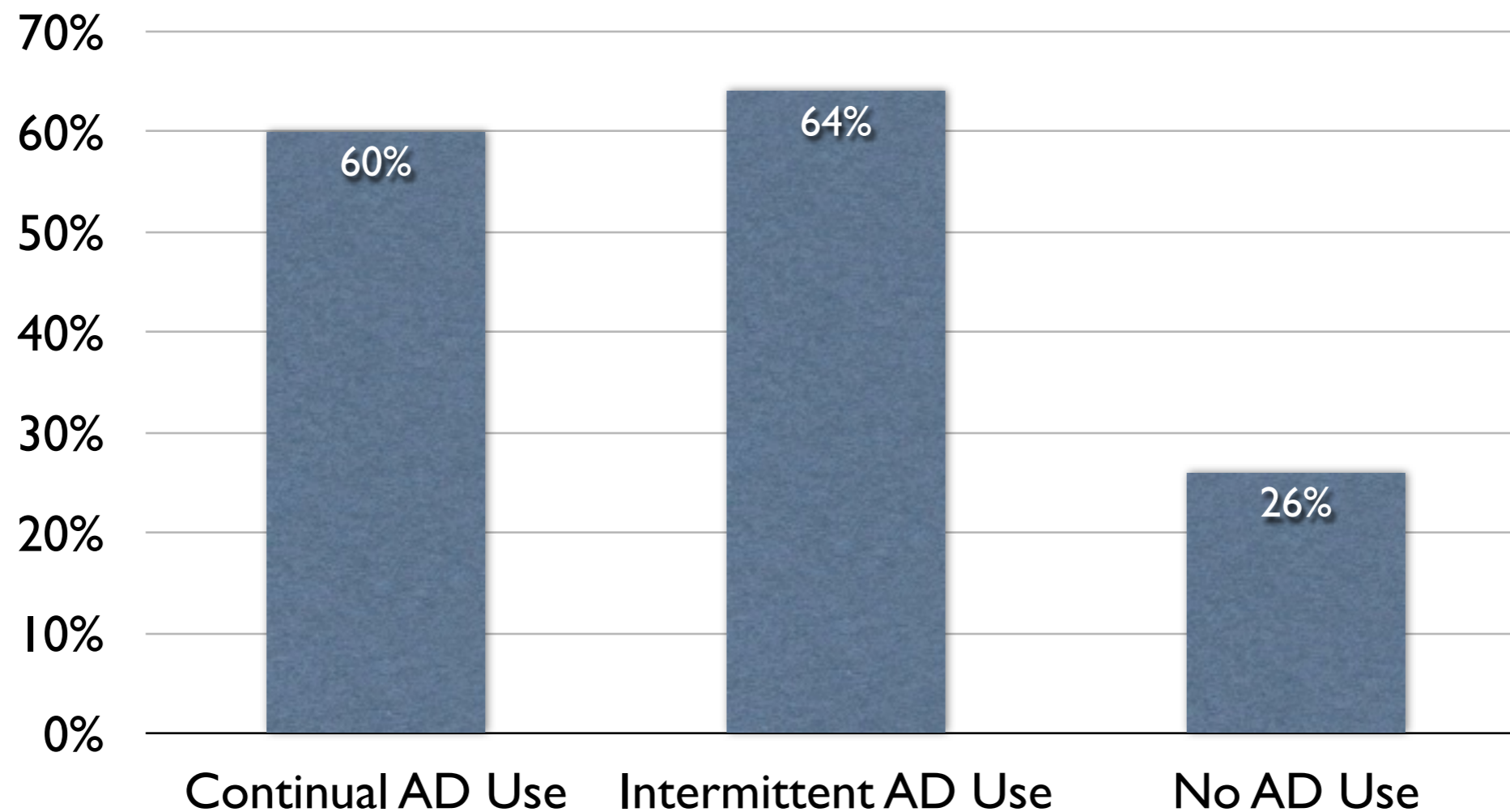


Source: P.Andrews: "Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good." *Frontiers in Psychology* 3 (2012): 1-18.

“The more antidepressants perturb monoamine levels in the brain, the more the brain appears to push back, which increases the risk of relapse when the drug is discontinued . . . antidepressant use appears to increase [biological] susceptibility to depression.”

--Paul Andrews, 2012

# Two-Year Relapse Rates for Remitted Patients in the Netherlands



Source: C. Bockting. "Continuation and maintenance use of antidepressants in recurrent depression." *Psychotherapy and Psychosomatics* 77 (2008): 17-26.

“Continued antidepressant treatment may oppose the initial acute effects of [the] antidepressant . . . neurobiological mechanism(s) may be involved in increasing vulnerability” to relapse.

--C. Bockting, 2008



# Tardive Dysphoria

“A chronic and treatment-resistant depressive state is proposed to occur in individuals who are exposed to potent antagonists of serotonin reuptake pumps (i.e. SSRIs) for prolonged time periods. Due to the delay in the onset of this chronic depressive state, it is labeled tardive dysphoria. Tardive dysphoria manifests as a chronic dysphoric state that is initially transiently relieved by -- but ultimately becomes unresponsive to -- antidepressant medication. Serotonergic antidepressants may be of particular importance in the development of tardive dysphoria.”

-- Rif El-Mallakh, 2011

Source: El-Mallakh, R. “Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression.” *Medical Hypotheses* 76 (2011): 769-773.

# Summing up the Evidence That Antidepressants Increase the Chronicity of Depression

- Depression has changed from an episodic illness to a chronic one during the antidepressant era.
- In naturalistic studies, unmedicated patients have better long-term outcomes than medicated patients.
- Investigators have proposed a biological explanation for why antidepressants worsen the long-term course of depression.

# Antidepressants Increase the Risk that a Unipolar Patient will Convert to a a Bipolar Diagnosis

1956: First case report of antidepressant-induced mania is published

1985: Swiss investigators tracking change in the patient mix at Burgholzli psychiatric hospital report that the percentage with manic symptoms jumped dramatically following the introduction of antidepressants. “Bipolar disorders increased; more patients were admitted with frequent episodes.”

1993: An American Psychiatric Association guide to depression warns: “All antidepressant treatments, including ECT, may provoke manic or hypomanic episodes.”

# Yale Investigators Quantify the Risk of Conversion to a Bipolar Diagnosis with Antidepressant Use

Study design: Yale Investigators analyzed the records of 87,920 patients, ages 0 to 29, initially diagnosed with an anxiety or non-bipolar mood disorder from 1997-2001. The median follow-up time was 41 weeks. They reported on the number of patients who converted to a bipolar diagnosis according to whether they were “exposed” to an antidepressant.

Converters to a Bipolar Diagnosis

Age	Not Exposed	Exposed	NNH
15-19	698 (4.8%)	1093 (10.9%)	16
20-24	390 (4.3%)	591 (7.6%)	31
25-29	333 (2.7%)	587 (6.2%)	29
<b>15-29</b>	<b>1421 (4.1%)</b>	<b>2271 (8.3%)</b>	<b>23</b>

Source: A. Martin. “Age effects on antidepressant-induced manic conversion,” *Arch of Pediatrics & Adolescent Medicine*(2002) 158: 773-80.

# Increase in Bipolar Diagnoses in United States, 1994 to 2003

Number of office-based visits with a diagnosis of bipolar disorder

	1994-1995	2002-2003	Increase in rate
Youth (0-19 years)	25 per 100,000	1003 per 100,000	40-fold increase
20 years and older	905 per 100,000	1,679 per 100,000	85% increase

Source: Moreno, C. "National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth." *Arch Gen Psychiatry* (2007) 64: 1032-39.

In a survey of members of the Depressive and Manic-Depressive Association, 60 percent of those with a bipolar diagnosis had initially fallen ill with major depression and had turned bipolar after exposure to an antidepressant.

Source: R. El-Mallakh. "Use of antidepressants to treat depression in bipolar disorder." *Psychiatric Services* 53 (2002): 58-84.

Fred Goodwin, former director of the National Institute of Mental Health, 2005:

“If you create iatrogenically a bipolar patient, that patient is likely to have recurrences of bipolar illness even if the offending antidepressant is discontinued. The evidence shows that once a patient has had a manic episode, he or she is more likely to have another one, even without the antidepressant stimulation.”

# Experts Recognize the Decline in Bipolar Outcomes

**Carlos Zarate, head of NIMH Mood Disorders Program, 2000:**

“In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment.”

**Ross Baldessarini, Harvard Medical School, 2007.**

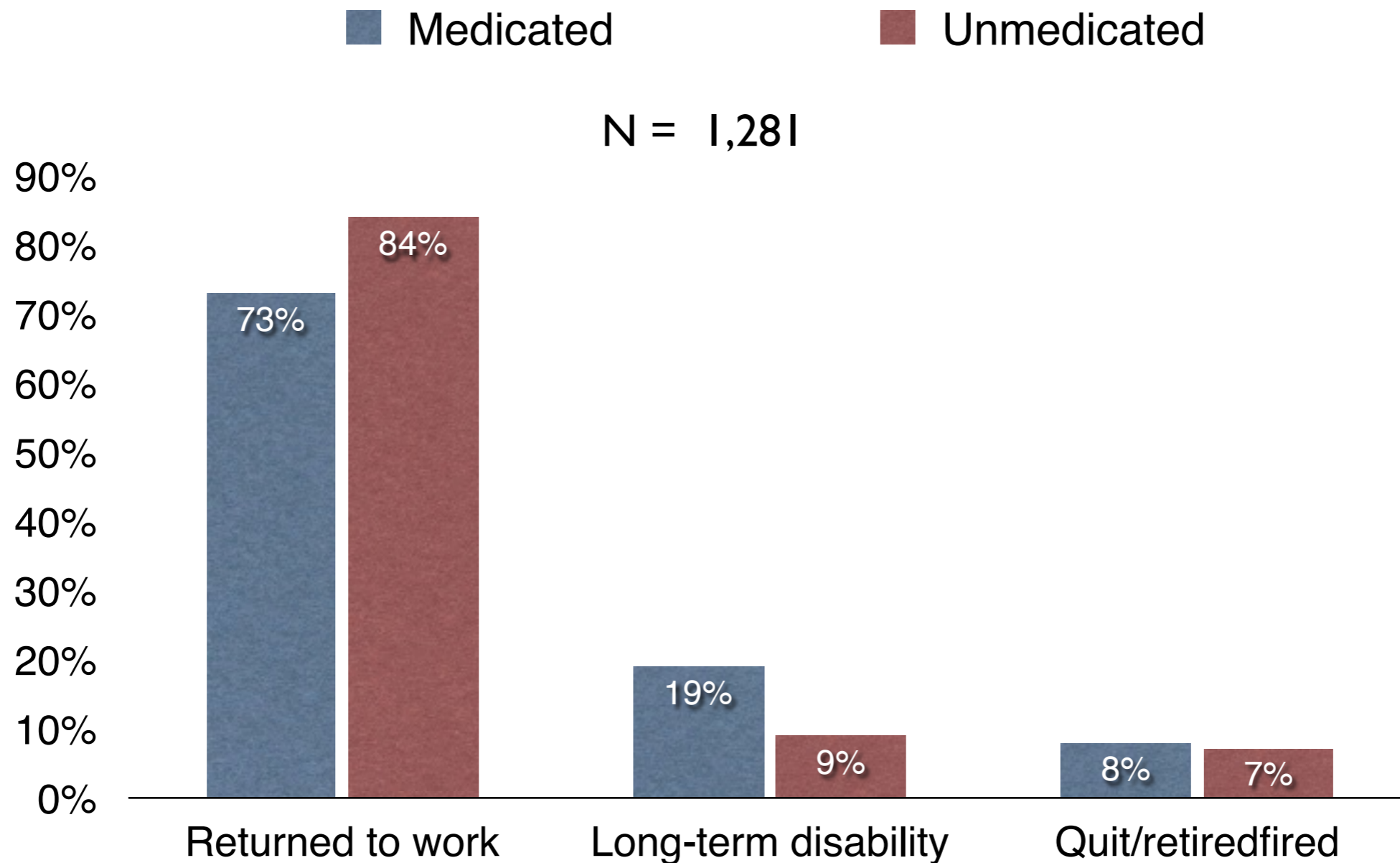
“Prognosis for bipolar disorder was once considered relatively favorable, but contemporary findings suggest that disability and poor outcomes are prevalent, despite major therapeutic advances.”

**Fred Goodwin, 2008**

“The illness has been altered. Today we have a lot more rapid cycling than we described in the first edition [of his book, *Manic Depressive Illness*], a lot more mixed states than we described in the first edition, a lot more lithium resistance, and a lot more lithium treatment failure than we described in the first edition. The illness is not what Kraepelin described any more.”

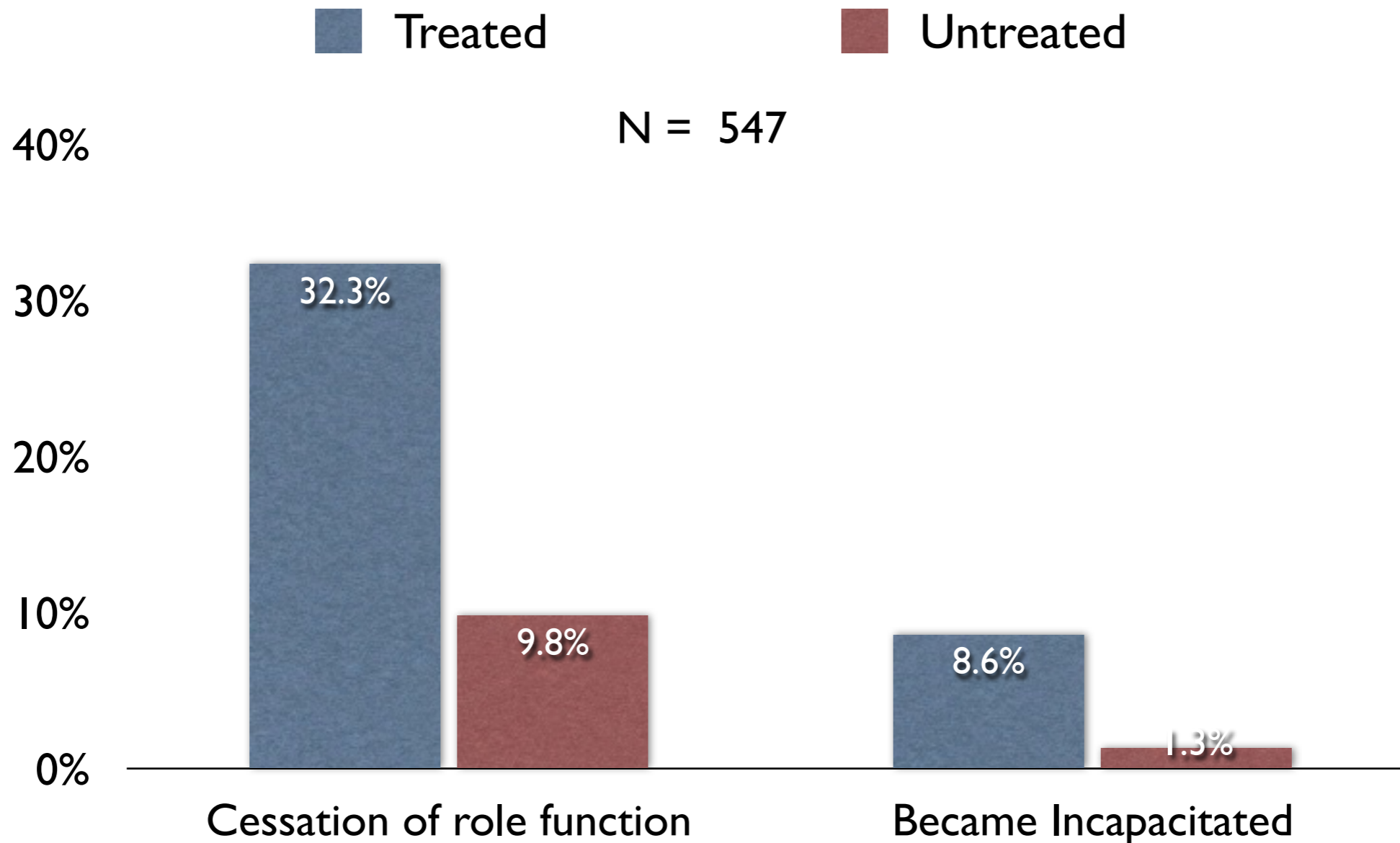


# Canadian Study of Risk of Long-term Disability for Depressed Workers



Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.

# Six-Year Outcomes in NIMH Study of Untreated Depression



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

## Same Prevalence + More Treatment = Soaring Numbers of Adults Disabled by Affective Disorders in U.S.

	<b>1991</b>	<b>2002</b>
U.S. adult population	188 million	214 million
Prevalence of anxiety, mood and substance disorders	29.4%	30.5%
Number with anxiety, mood and substance disorders	55.3 million	65.3 million
Percentage treated for those disorders	20.3%	32.7%
Number treated for those disorders	11.2 million	21.4 million
Number on disability due to affective disorders	292,000	940,000
Percentage with those disorders on disability	1 of 188	1 of 69

Source: Survey on prevalence and treatment of anxiety, mood and substance use disorders in 1991 and 2002; Social Security disability data for 1991 and 1992; estimate of percentage of disabled mentally ill with affective disorders in 1991; report on number of people with affective disorders on disability rolls in 2002.

# The Burden of Bipolar Illness on Society Today

- In 1955, there were 12,750 adults hospitalized with bipolar illness in the United States. Today there are nearly six million adults in the United States with this diagnosis.
- According to the Johns Hopkins School of Public Health, 83 percent of people diagnosed with bipolar are “severely impaired” in some facet of their lives. (5 million adults.)
- Bipolar illness is now said to be the sixth leading cause of medical-related disability in the world.

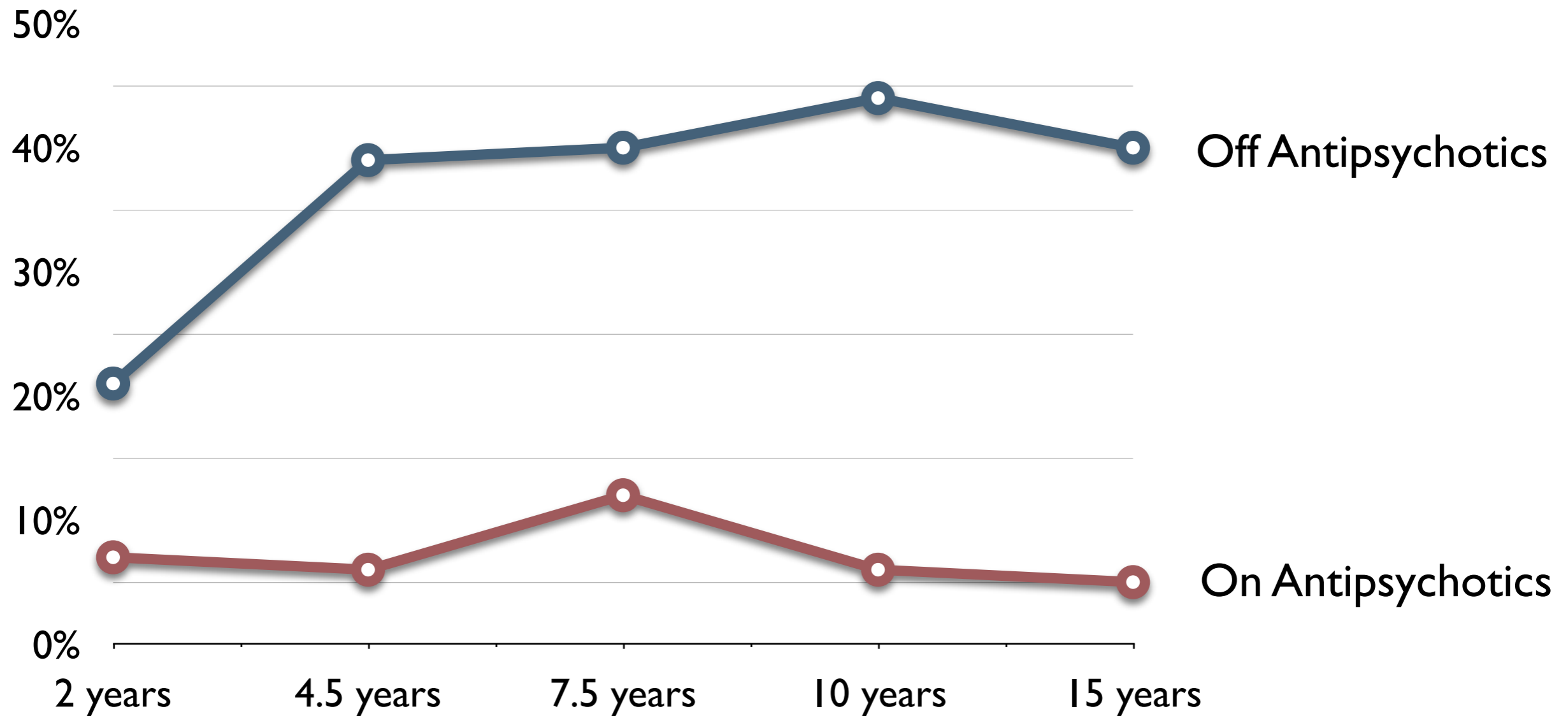
# Adverse Effects of Long-term Benzodiazepine Use

- Cognitive impairment
- Increased depression and anxiety
- Functional impairments
- Physical decline

In a 2007 survey of 4,425 long-term benzodiazepine users, French researchers found that 75% were “markedly ill to extremely ill . . . a great majority of the patients had significant symptomatology, in particular major depressive episodes and generalized anxiety disorder, often with marked severity and disability.”

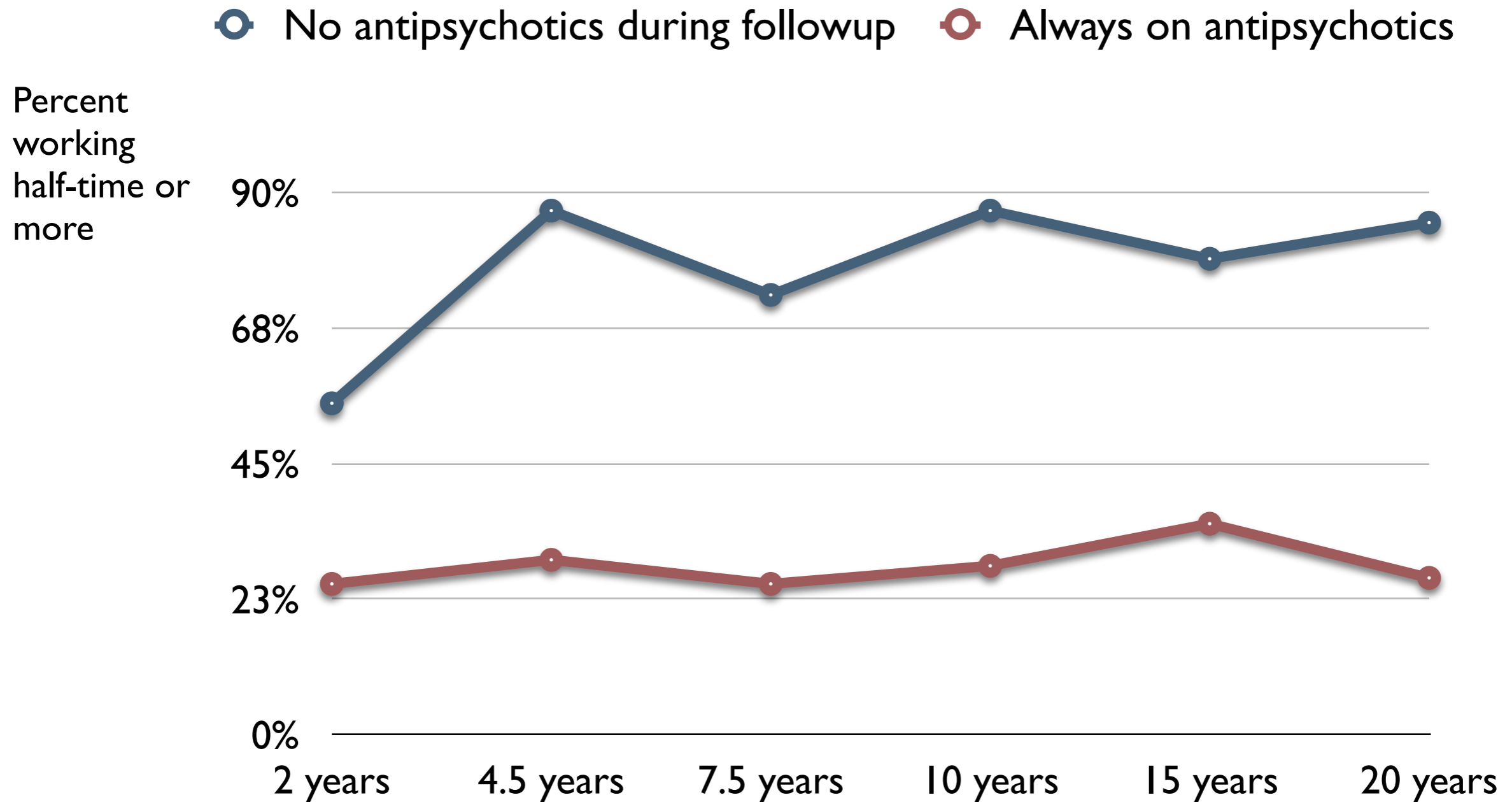
Source: A. Pelissolo. “Anxiety and depressive disorders in 4,425 long term benzodiazepine users in general practice,” *Encephale* 33 (2007):32-38.

# Long-term Recovery Rates for Schizophrenia Patients



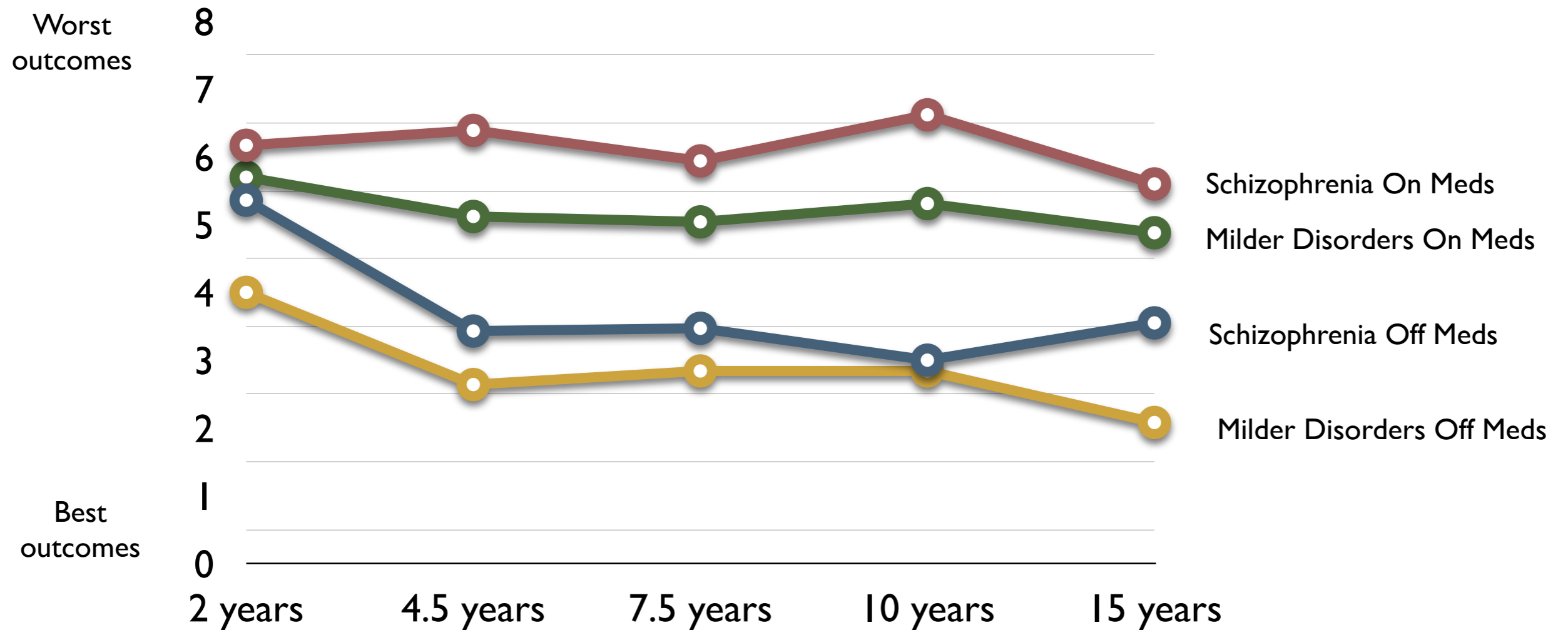
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

# Work History of Schizophrenia Patients



Source: M. Harrow. "Pharmacological Treatment for Psychosis: Emerging Perspectives." Presentation in Syracuse, NY, October 2, 2014.

# Global Adjustment of All Psychotic Patients



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.



“How unique among medical treatments is it that the apparent efficacy of antipsychotics could diminish over time or become ineffective or harmful? There are many examples for other medications of similar long-term effects, with this often occurring as the body readjusts, biologically, to the medications.”

--Martin Harrow, 2013

# Drug-induced Oppositional Tolerance: A Universal Problem?

“Continued drug treatment may induce processes that are the opposite of what the medication originally produced.” This may “cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible.”

-Rif El-Mallakh, University of Louisville, 2011

Source: El-Mallakh, R. “Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression.” *Medical Hypotheses* 76 (2011): 769-773.

# The Evidence All Fits Together

- Correlative data across different cultures
- A robust body of evidence that antidepressants increase the chronicity of depression
- Studies find that patients medicated for depression are more likely to end up disabled by the disorder
- Robust evidence that antidepressants increase the risk that a unipolar patient will switch to bipolar disorder
- Evidence that the prevalence of bipolar disorder has notably increased during the Prozac era, and so too the burden of disability due to bipolar illness
- Evidence that long-term benzodiazepine use leads to impairment in many domains
- Long-term studies of psychotic patients show patients maintained on antipsychotics have much lower recovery rates
- Researchers have proposed a biological explanation for why psychiatric drugs would have these harmful long-term effects