

Rethinking the Use of Psychiatric Drugs

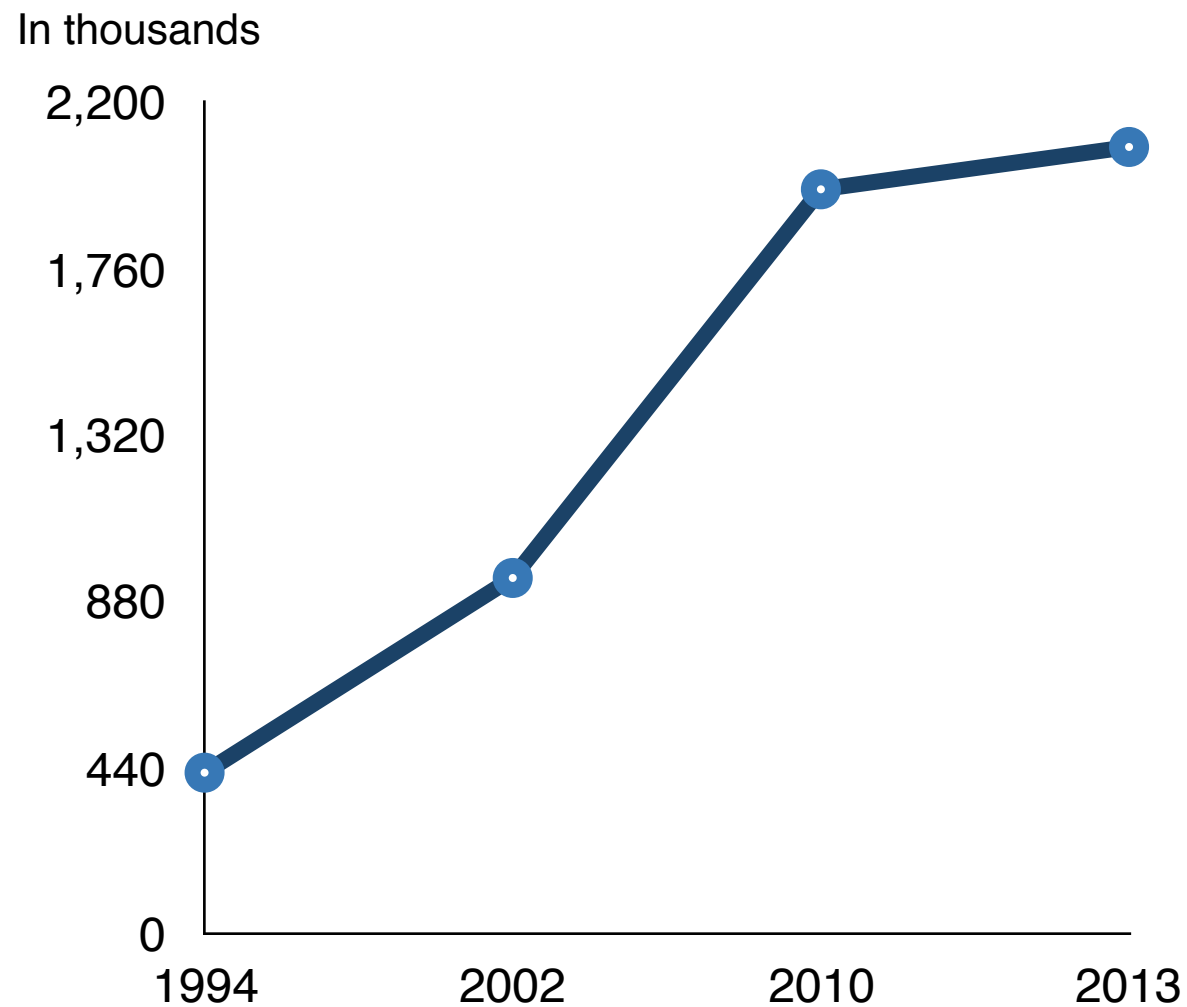
Robert Whitaker
November 2016

The Problem With Psychiatric Drugs

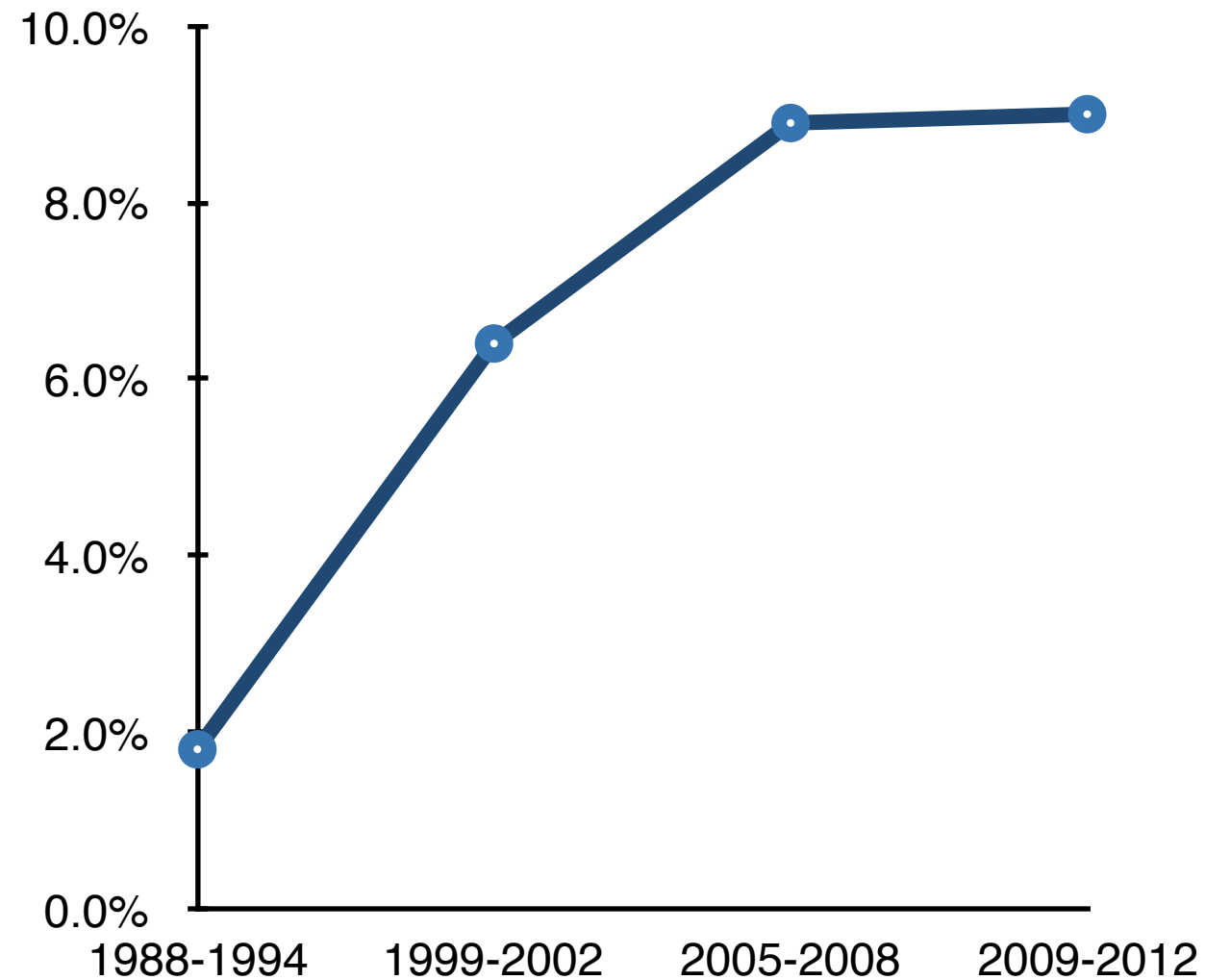
- As prescriptions for antidepressants and other psychiatric drugs have risen, the number of people disabled by mental disorders, in country after country, has risen in lockstep.
- Psychiatric drugs do not normalize brain chemistry; they create abnormalities in the functioning of neurotransmitter systems.
- 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.
- Research studies have found that antipsychotics worsen functional outcomes over the long term.

United States, 1988-2013

Number on government disability due to mood disorders



Percent of population who used antidepressants in past month

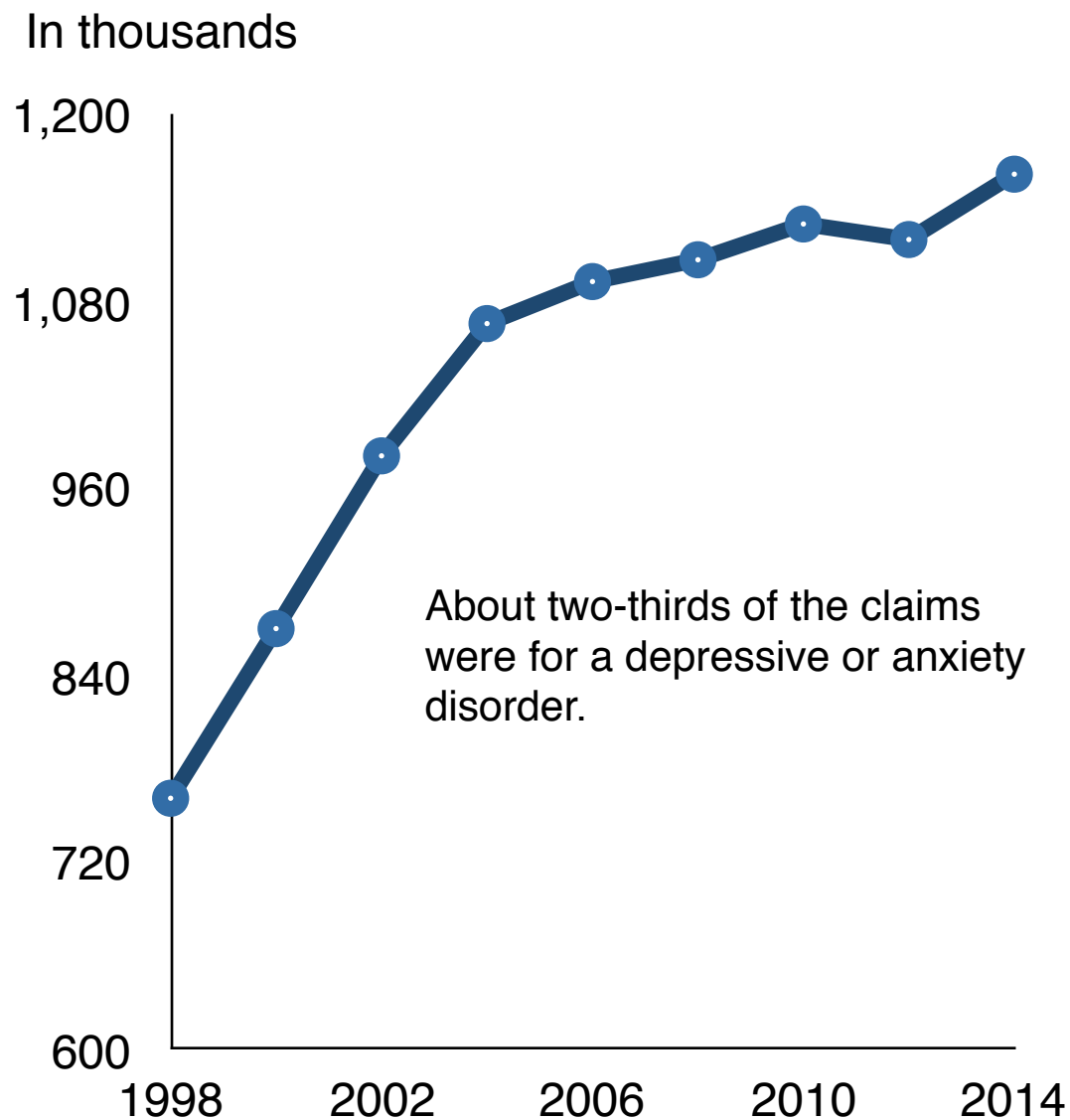


Source: R. Rosenheck. "The growth of psychopharmacology in the 1990s." *Int J of Law and Psychiatry* 28 (2005):467-83. U.S. Social Security Administration, Annual Statistical Report on the Social Security Disability Insurance Program, and SSI Annual Statistical Report, 2010-2013.

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

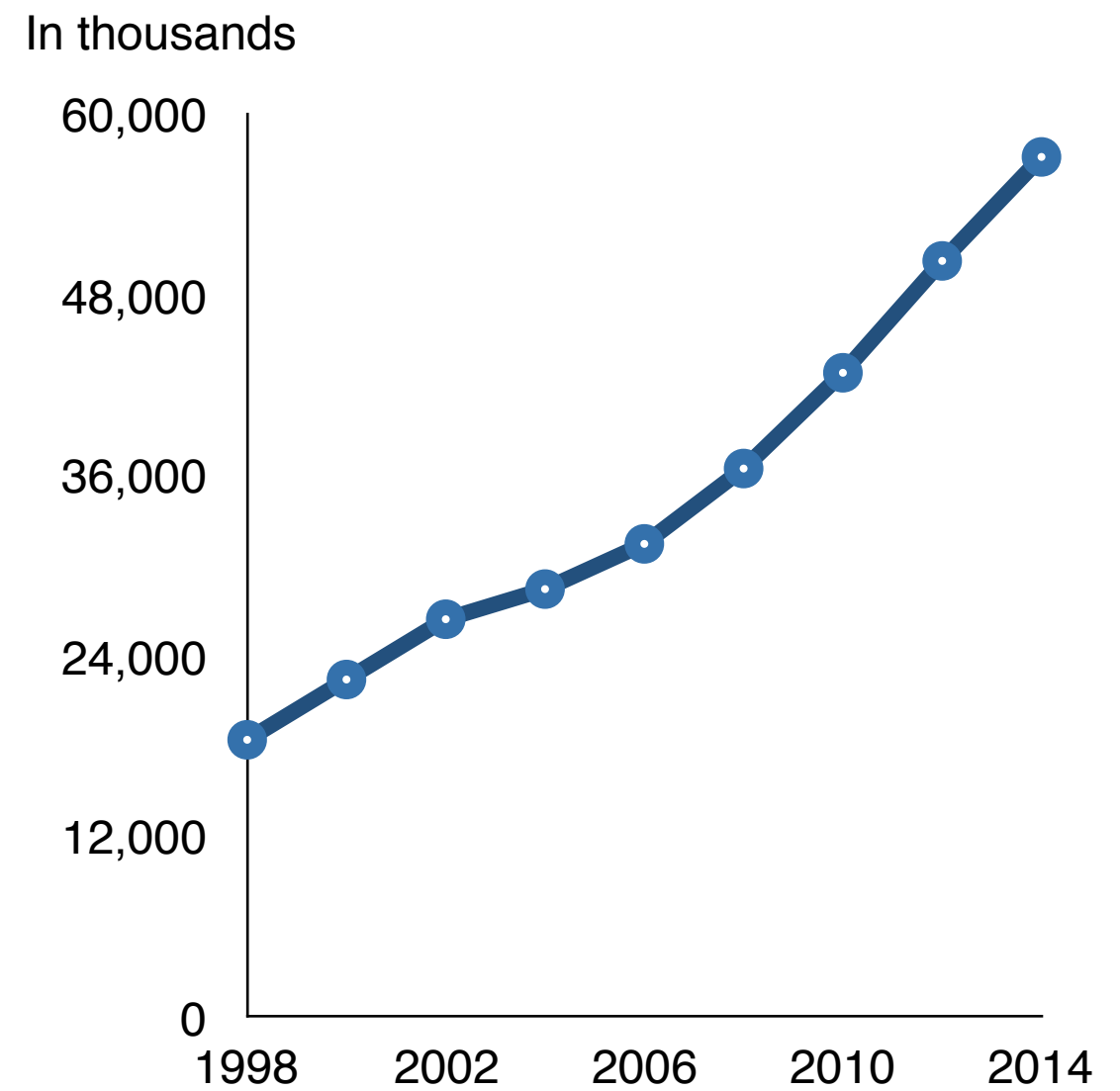
United Kingdom, 1998-2014

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

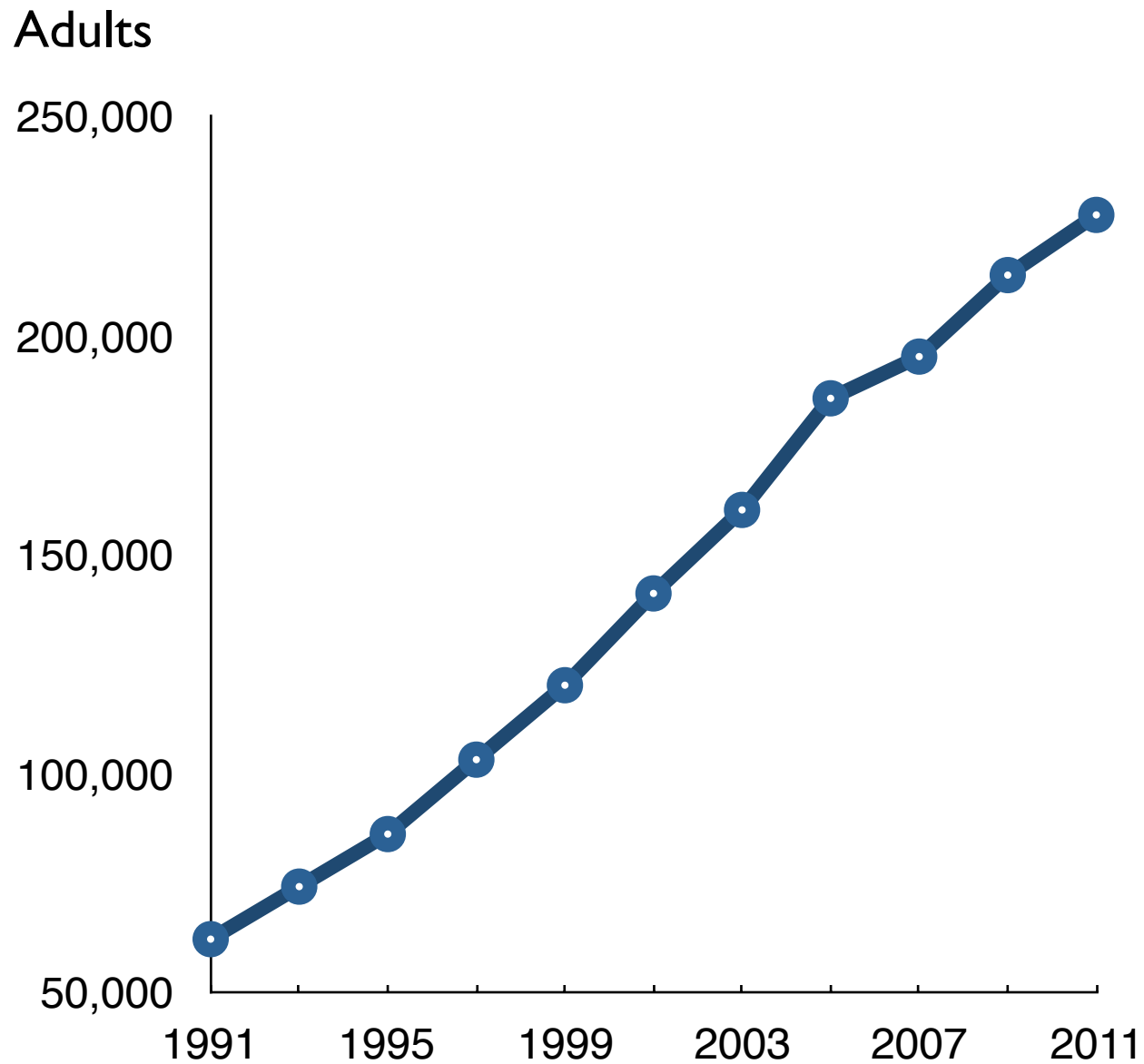
Prescriptions for antidepressants in England



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)...

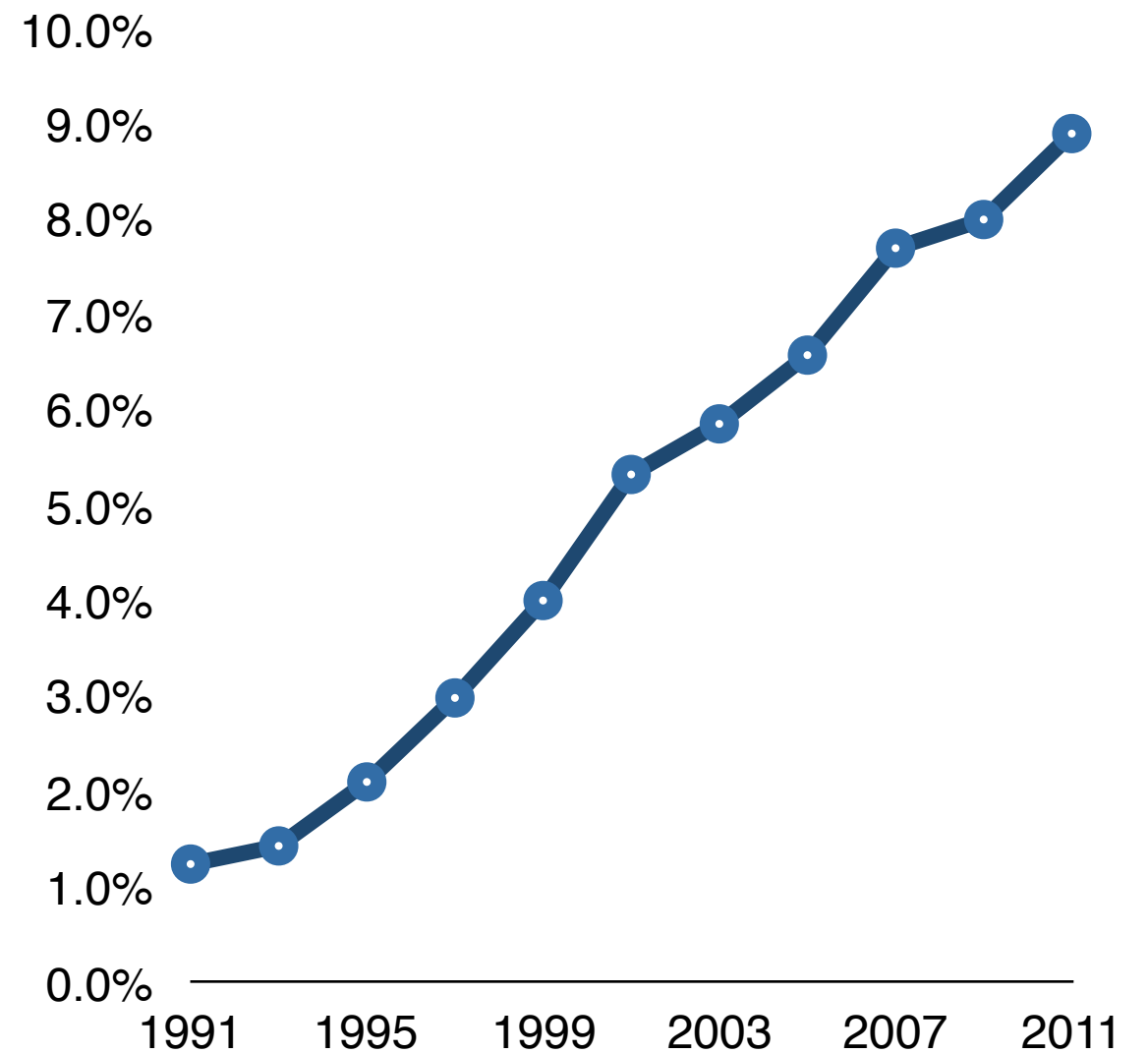
Australia, 1990-2011

Number on disability due to mental illness



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

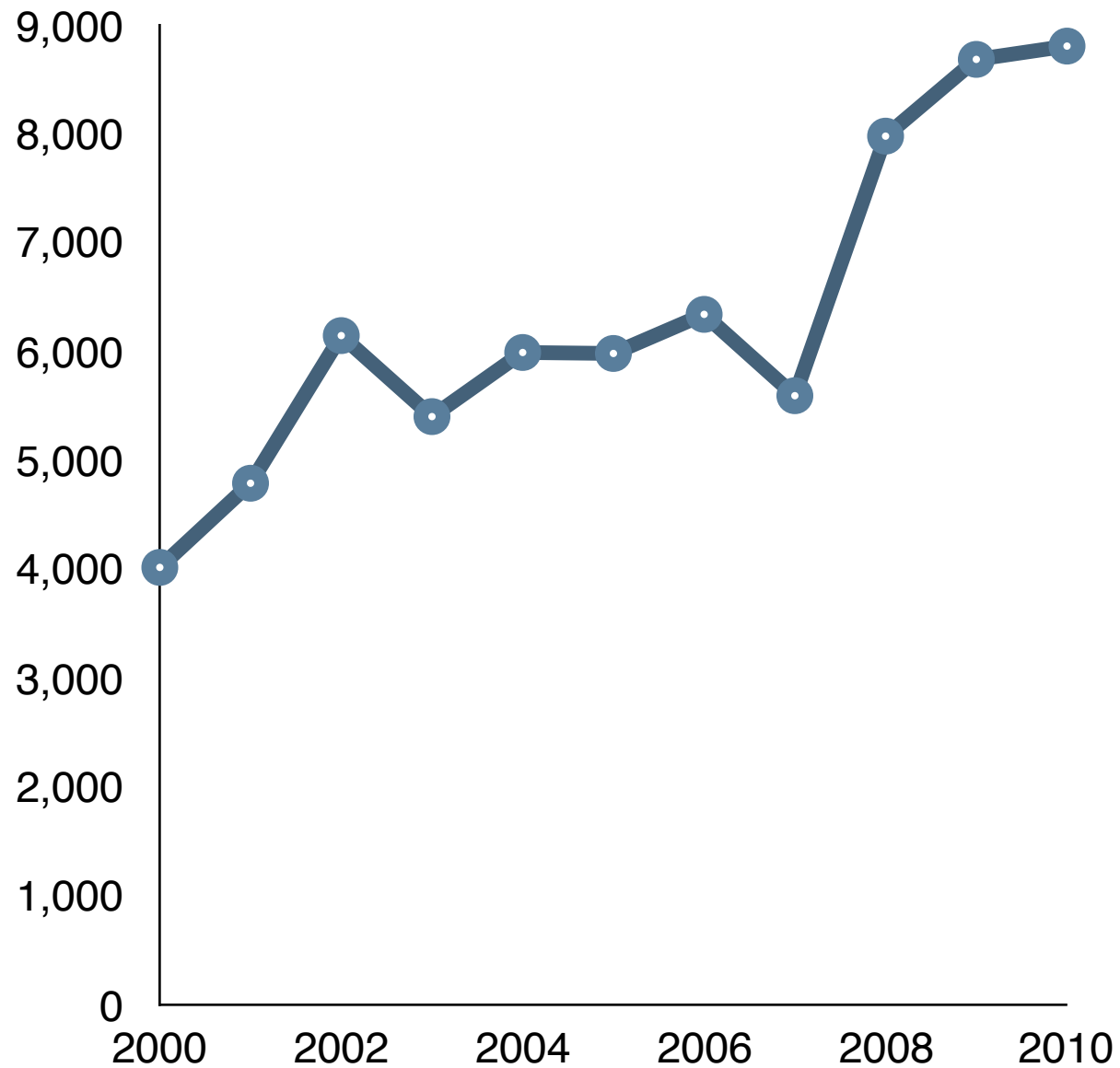
Percent of population that used antidepressants



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

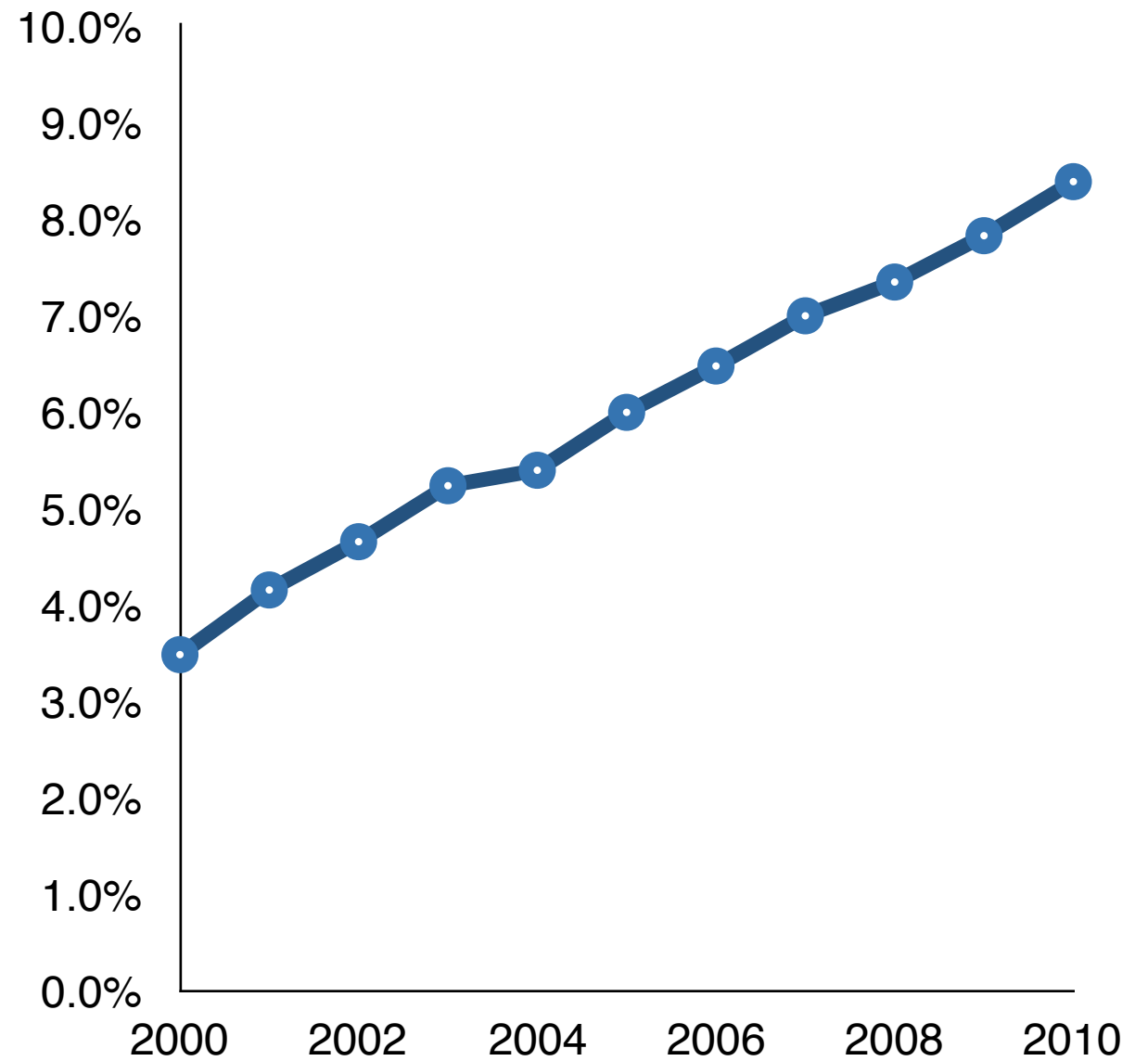
Denmark, 2000-2010

New cases of disability due to mental illness



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

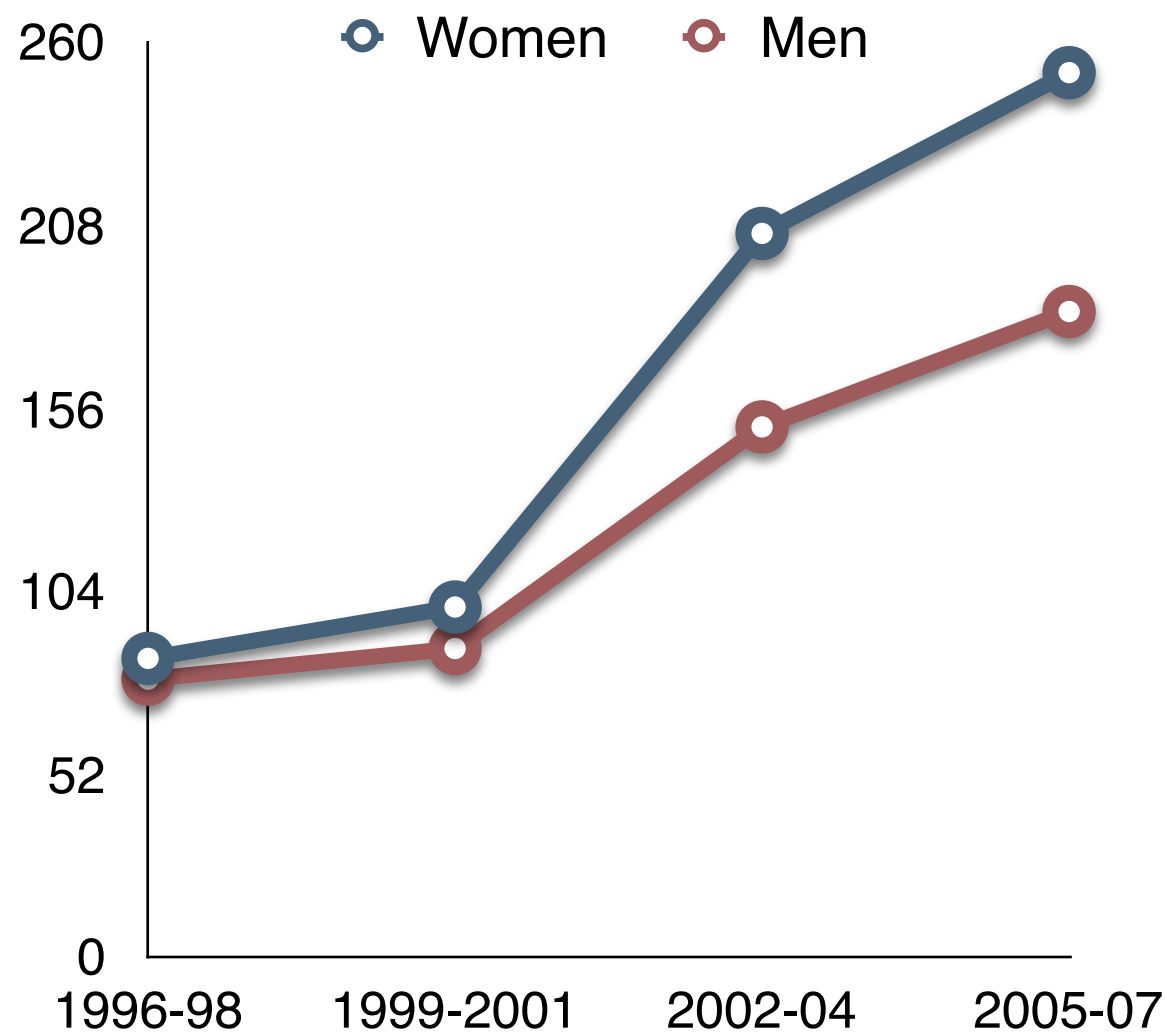
Percent of population that used antidepressants



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

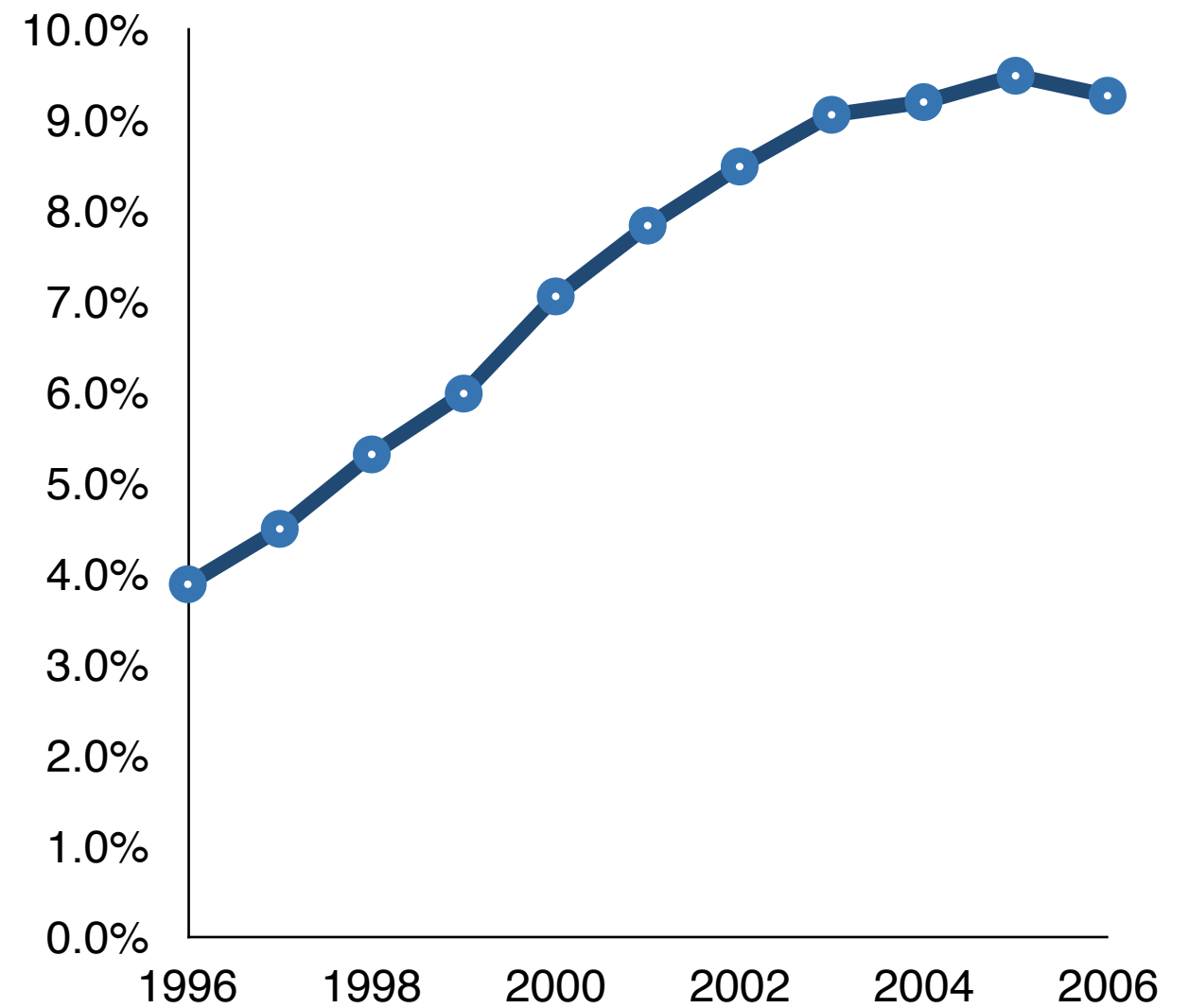
Iceland, 1996-2006

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.

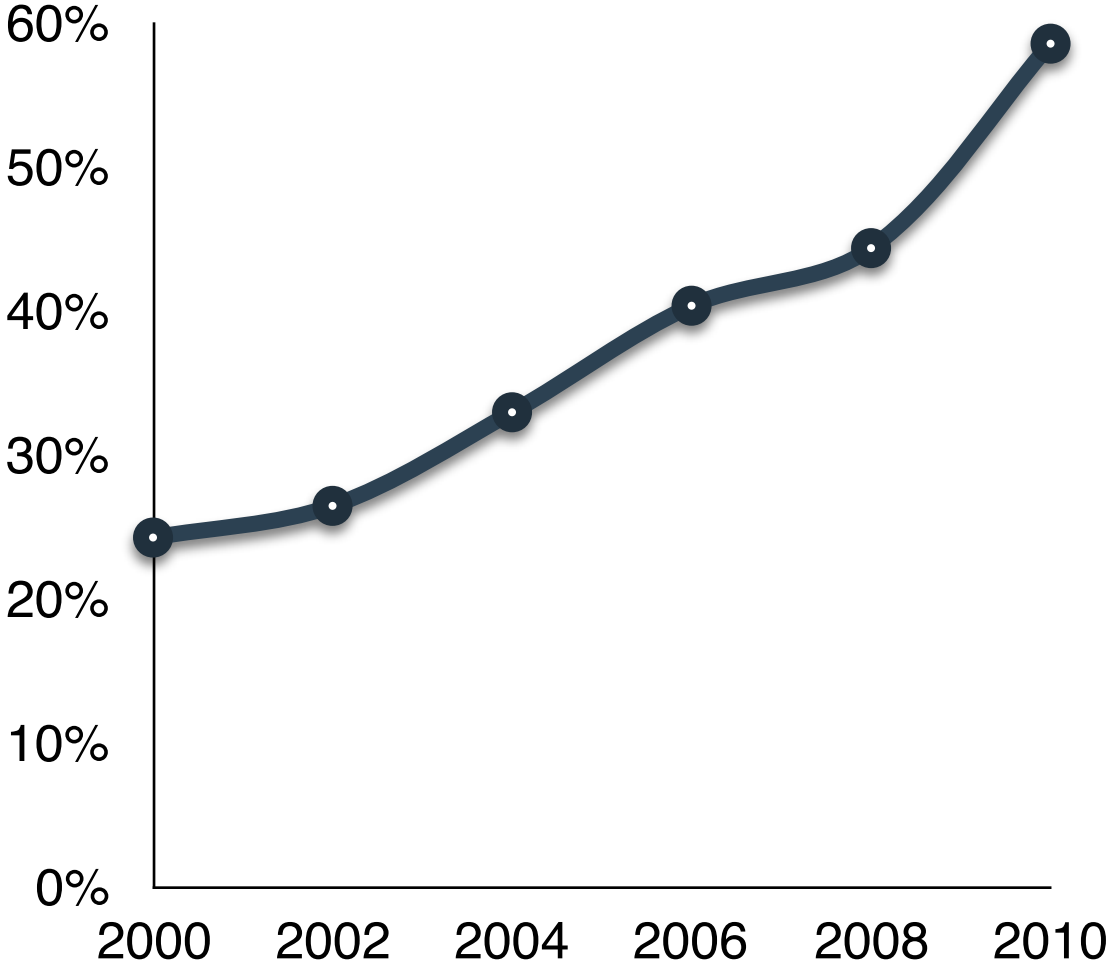
Percent of population that used antidepressants



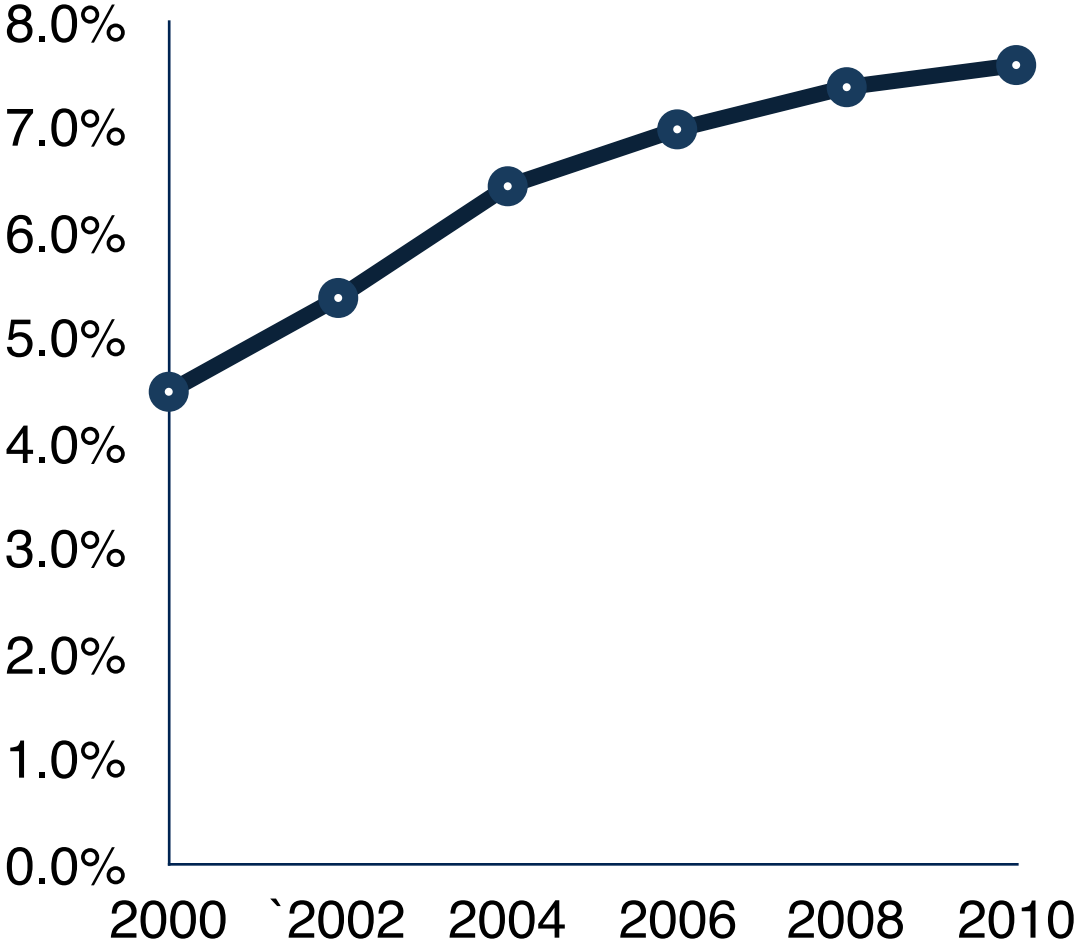
Source: "Antidepressants: Global Trends." *The Guardian*, Nov. 20, 2013.

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.

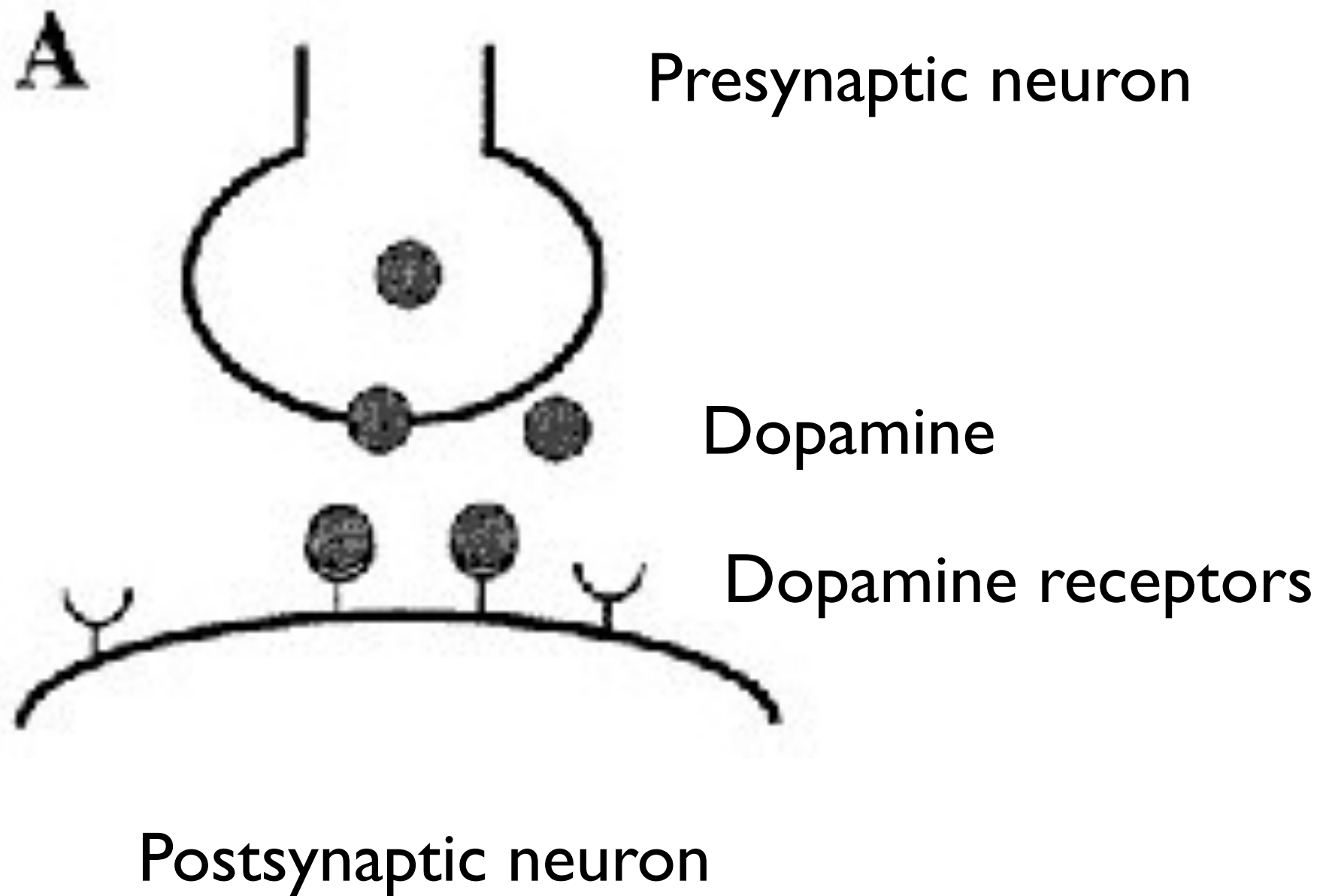
Psychotropic Drugs Create Abnormalities in Brain Function

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.”

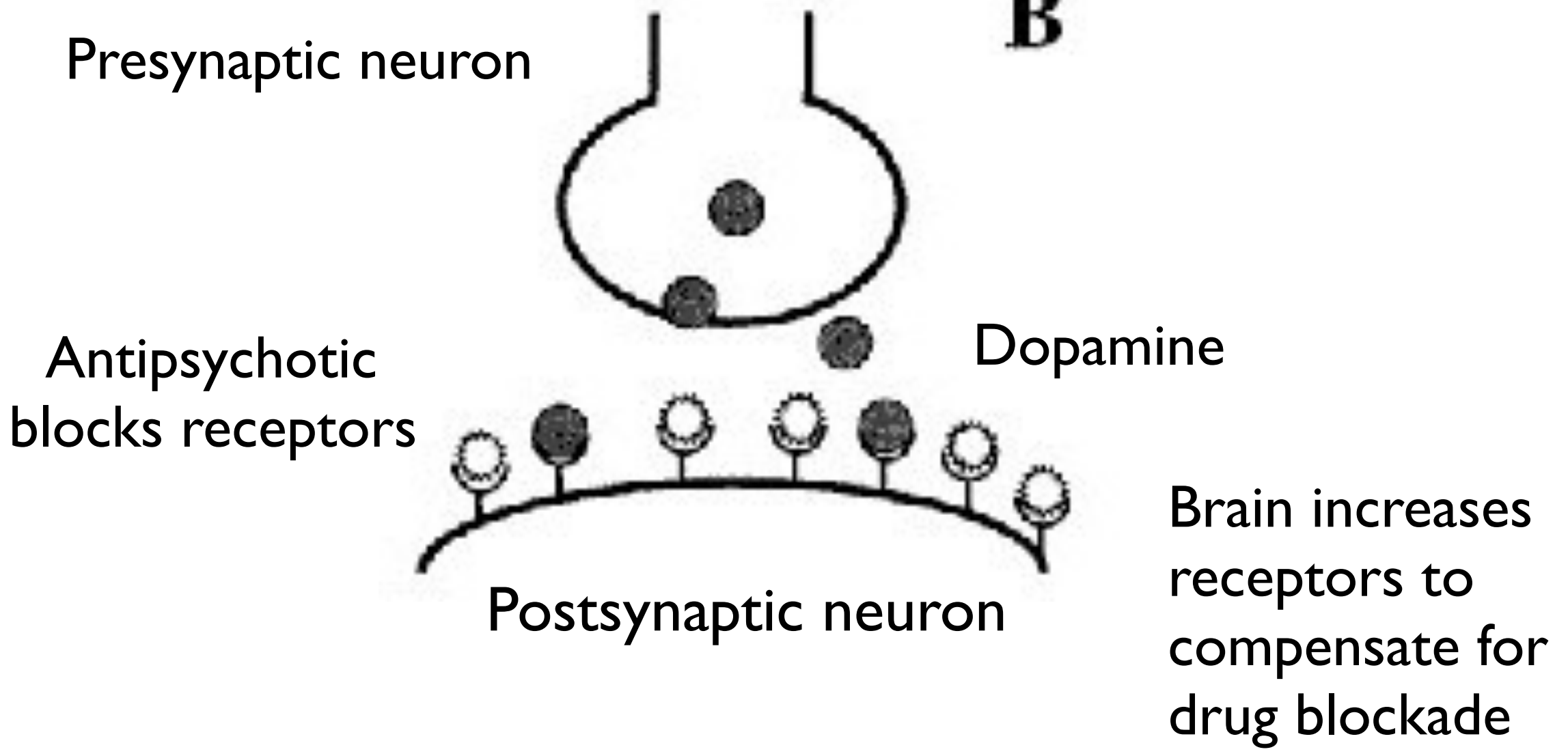
Source: Hyman, S. “Initiation and adaptation: A paradigm for understanding psychotropic drug action.” *Am J Psychiatry* 153 (1996):151-61.

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

B



Assessing Long-term Outcomes

- What is the natural course of the disorder? What are the spectrum of outcomes for people so diagnosed?
- Does the therapy improve on the “natural” long-term recovery rate?
- What does the scientific literature reveal?

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

“Depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self-limited.” --Jonathan Cole, NIMH, 1964.

“In the treatment of depression, one always has an ally the fact that most depressions terminate in spontaneous remissions. This means that in many cases regardless of what one does the patient eventually will begin to get better.” --Nathan Kline, Journal of the American Medical Association, 1964

Most depressive episodes “will run their course and terminate with virtually complete recovery without specific intervention.” -- Dean Schuyler, head of the depression section at the NIMH, 1974

“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

After Introduction of Antidepressants, Clinicians Worry About Changing Course of Depression

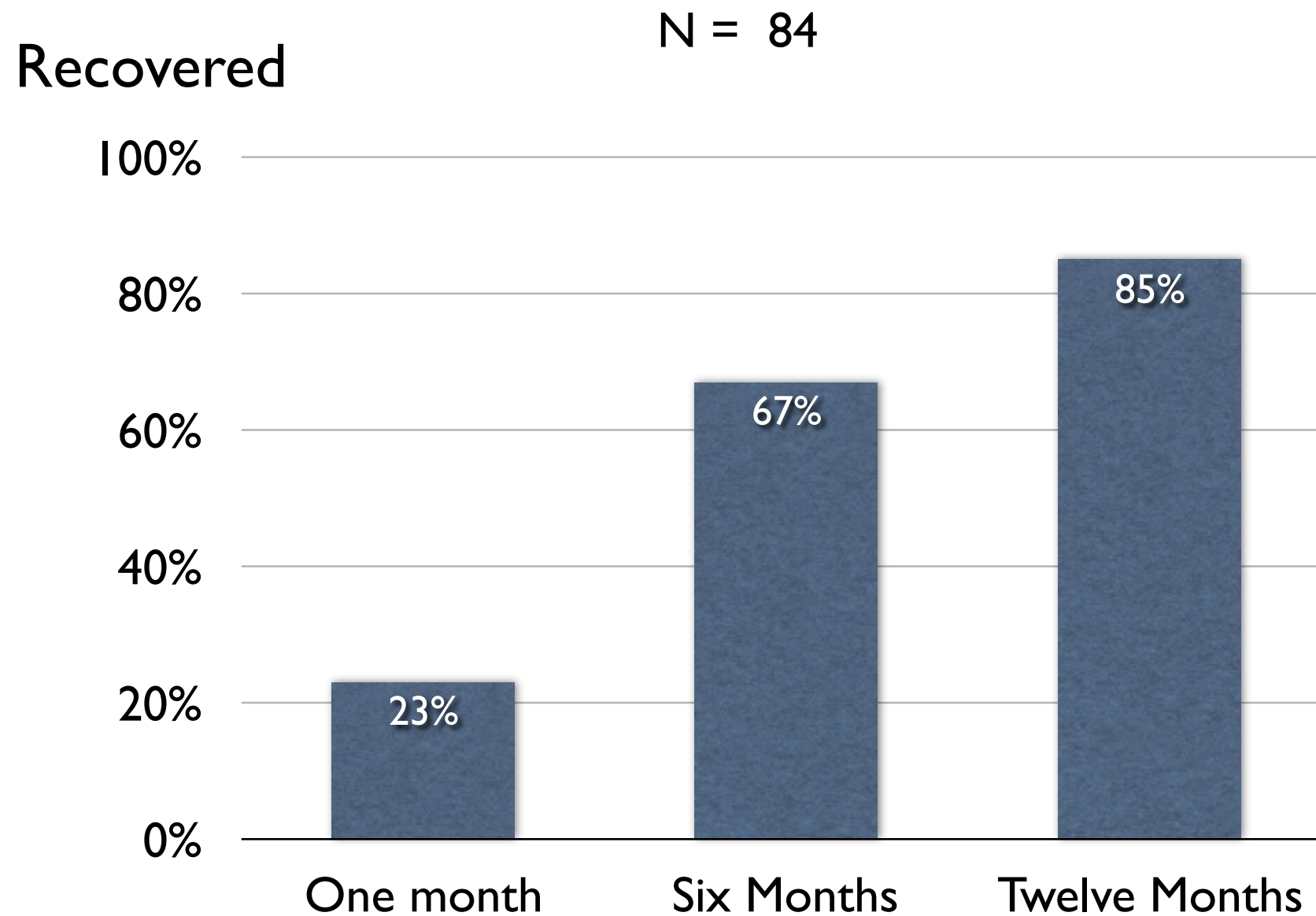
- H.P. Hoheisel, German physician, 1966: Exposure to antidepressants appeared to be “shortening the intervals” between depressive episodes.
- Nikola Schipkowensky, Bulgarian psychiatrist, 1970: The antidepressants were inducing “a change to a more chronic course.”

The APA Acknowledges Change in Course of Depression in Modern Era

American Psychiatric Association's Textbook of Psychiatry, 1999:

It used to be believed that “most patients would eventually recover from a major depressive episode. However, more extensive studies have disproved this assumption.” It was now known that “depression is a highly recurrent and pernicious disorder.”

One-Year Recovery Rates in NIMH Study of Unmedicated Depression in Modern Era



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.”

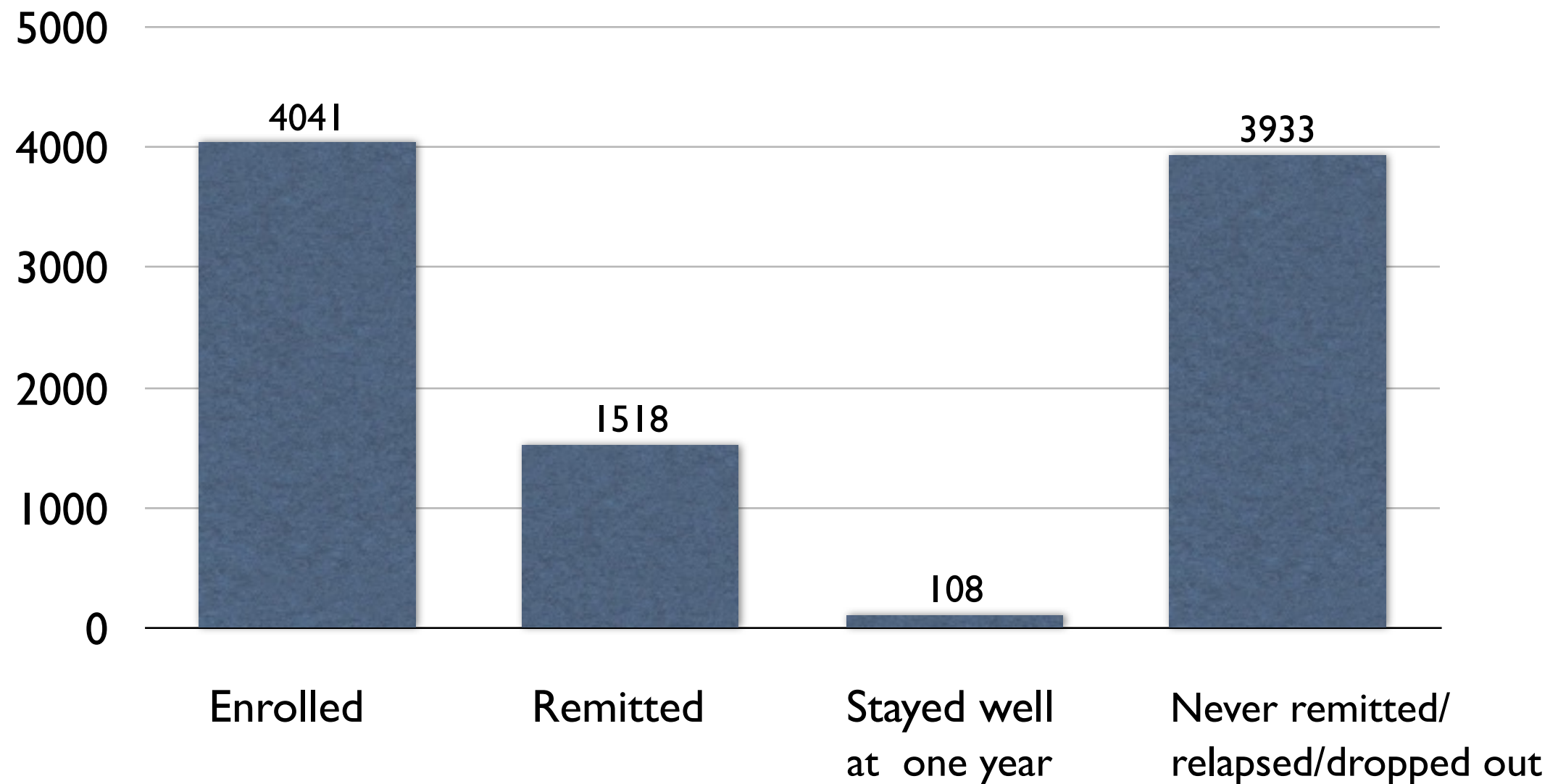
--Michael Posternak

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.

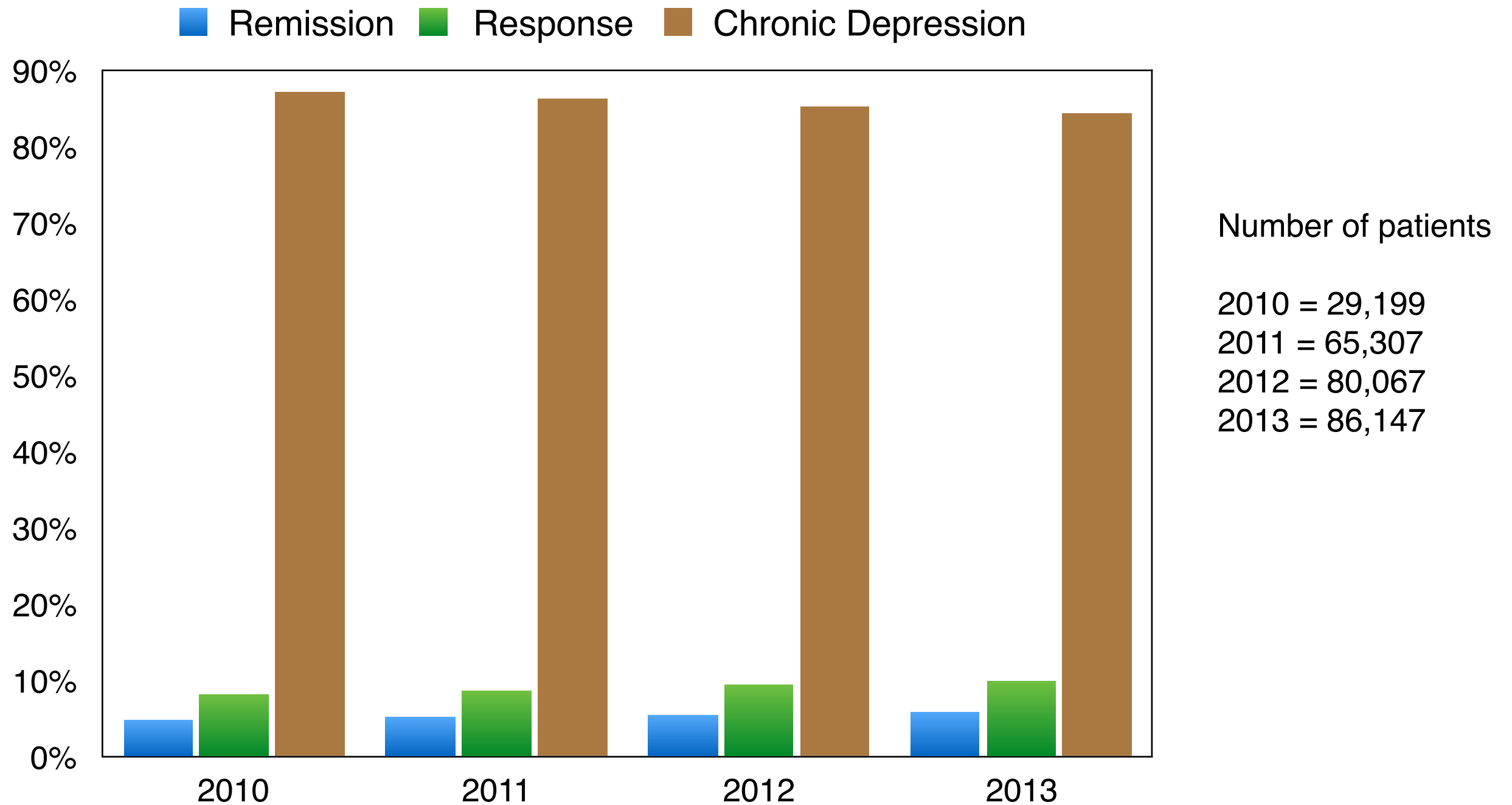
The STAR*D Trial Confirms That Medicated Depression Runs a Chronic Course Today

Number of patients



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

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



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

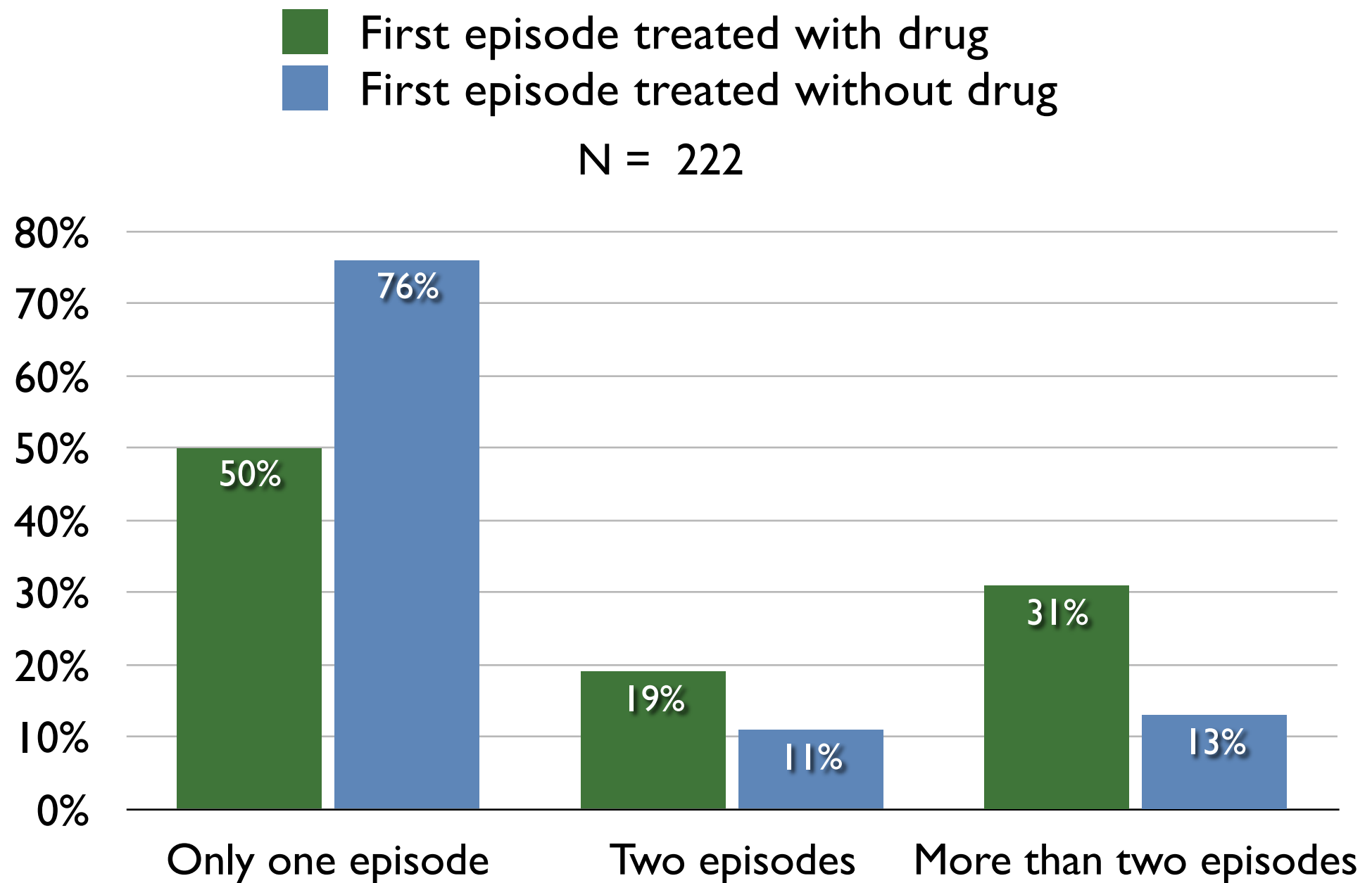
Do Antidepressants Worsen the Long-term Course of Depression?

“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

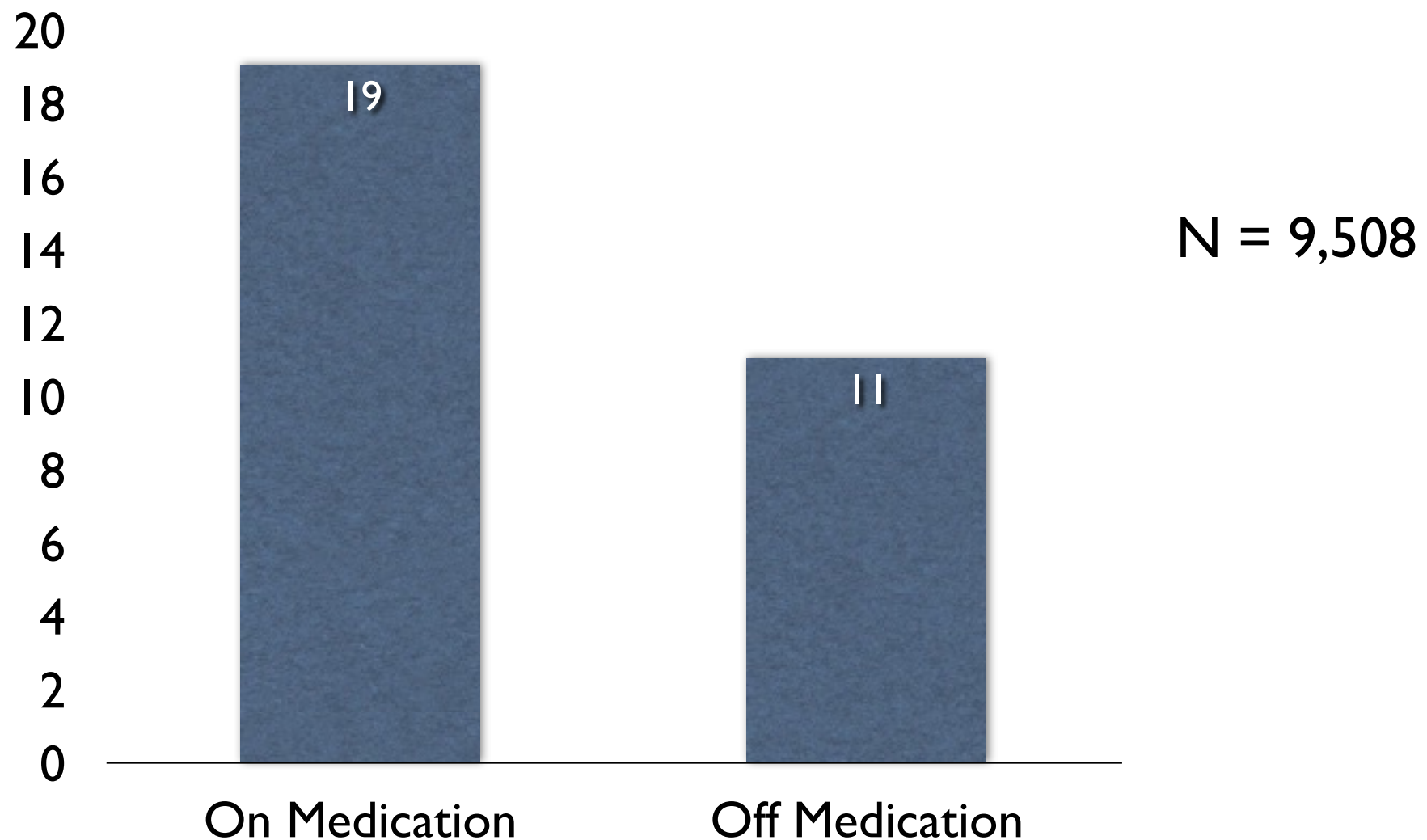
(Over the course of ten years)



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.

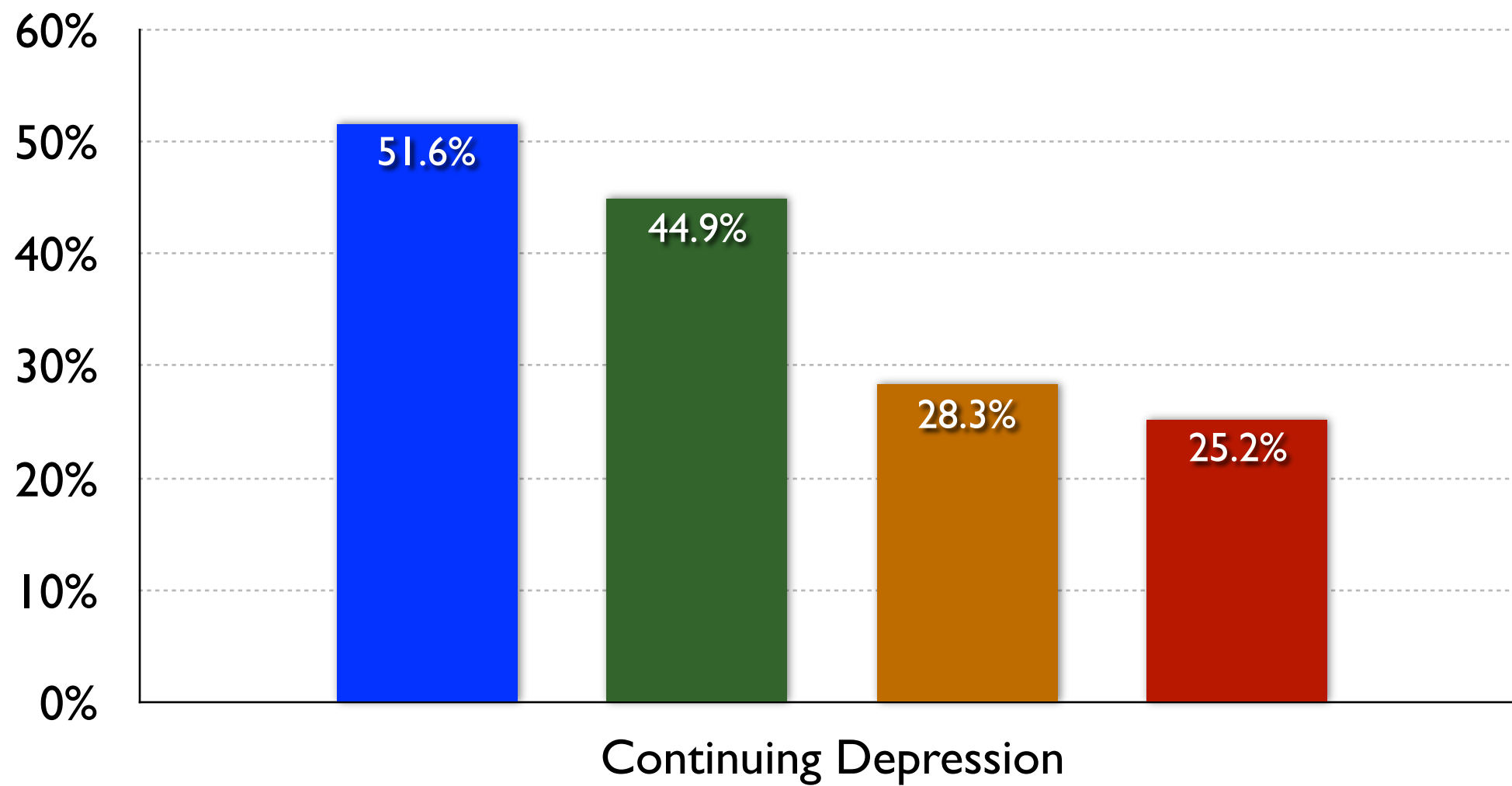
These findings are consistent with Giovanni Fava's hypothesis that "antidepressant treatment may lead to a deterioration in the long-term course of mood disorders."

--Scott Patten

One-Year Outcomes in WHO Screening Study for Depression

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

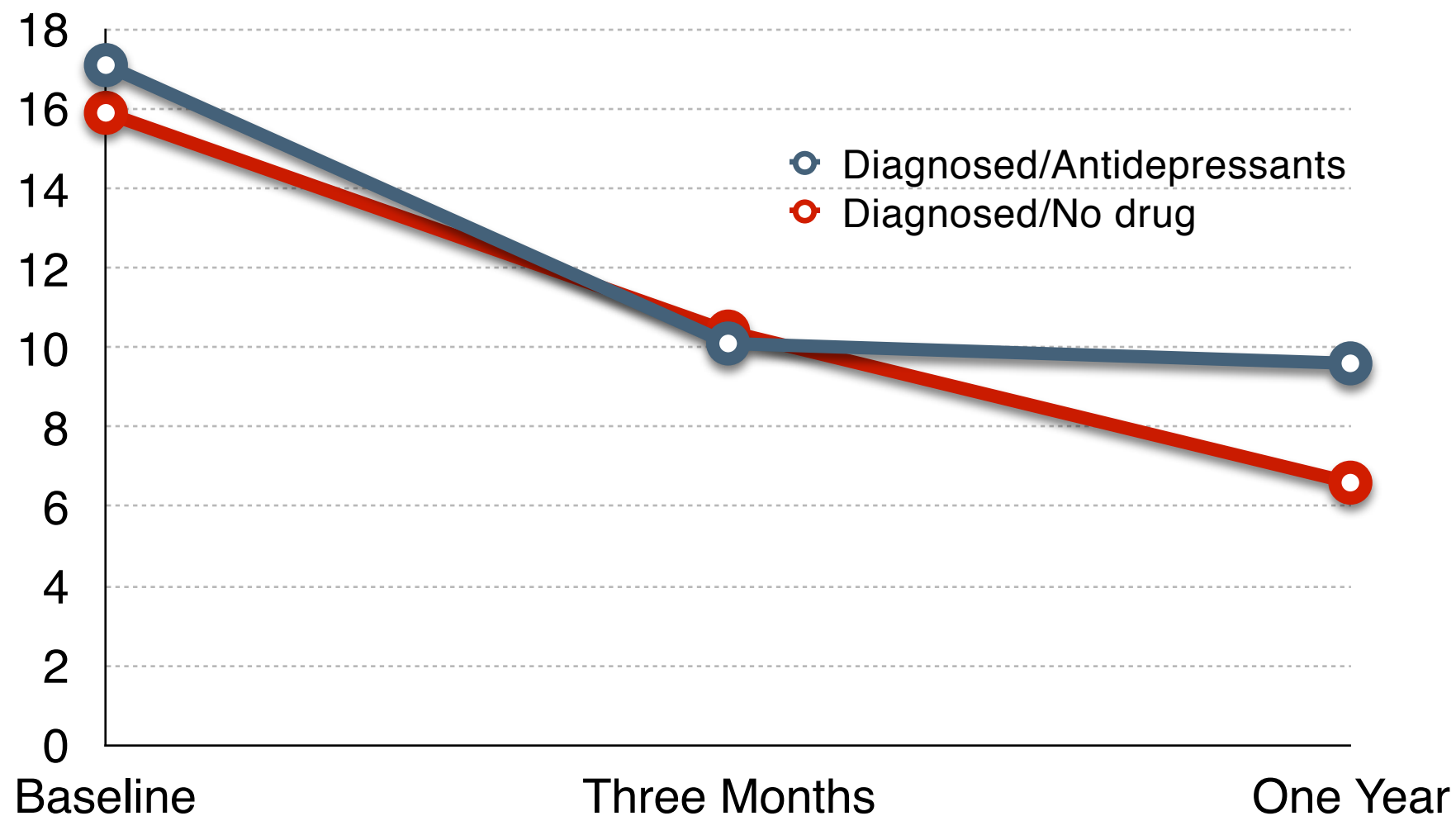
N = 740



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”

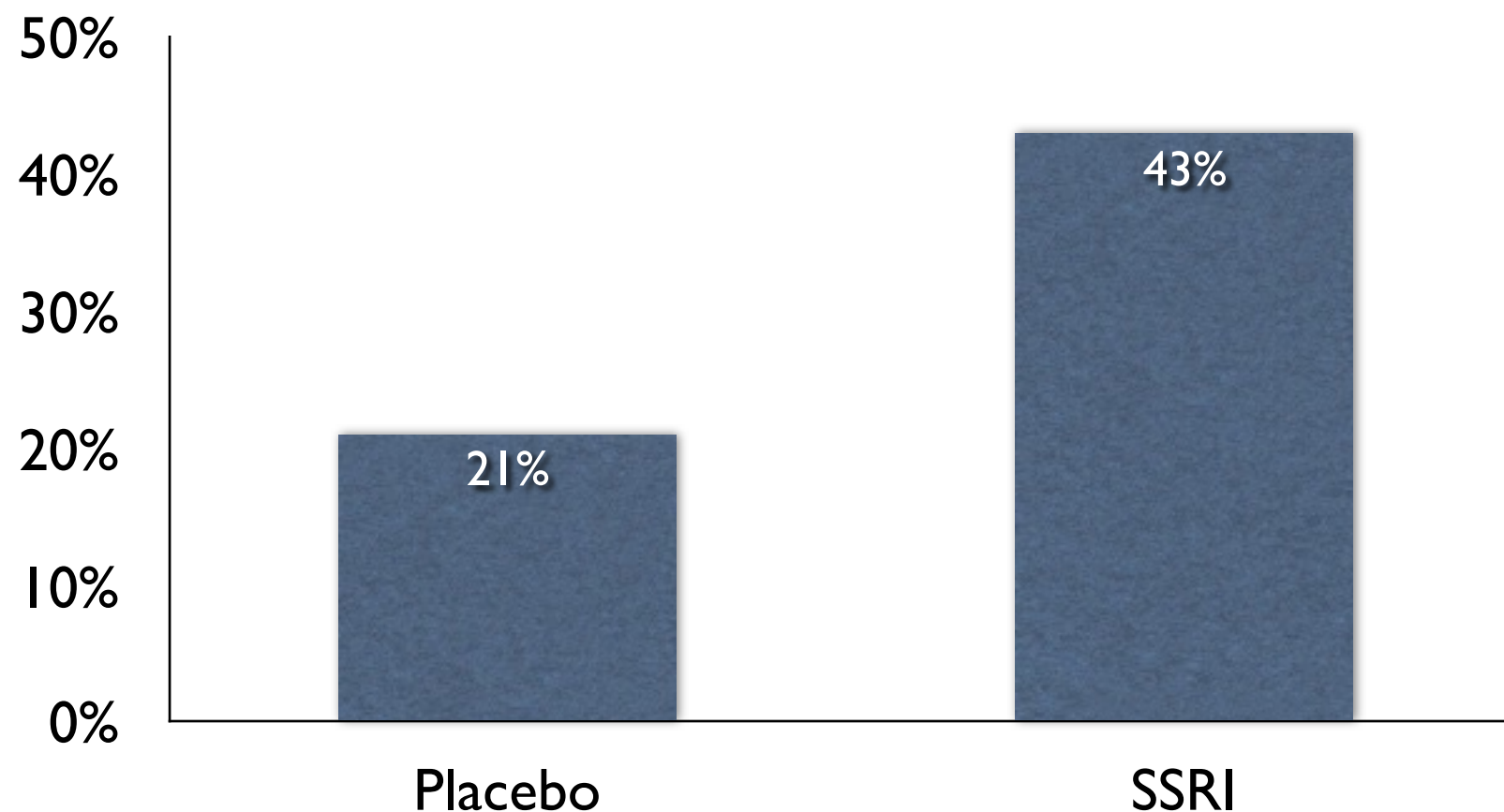
“When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. 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.

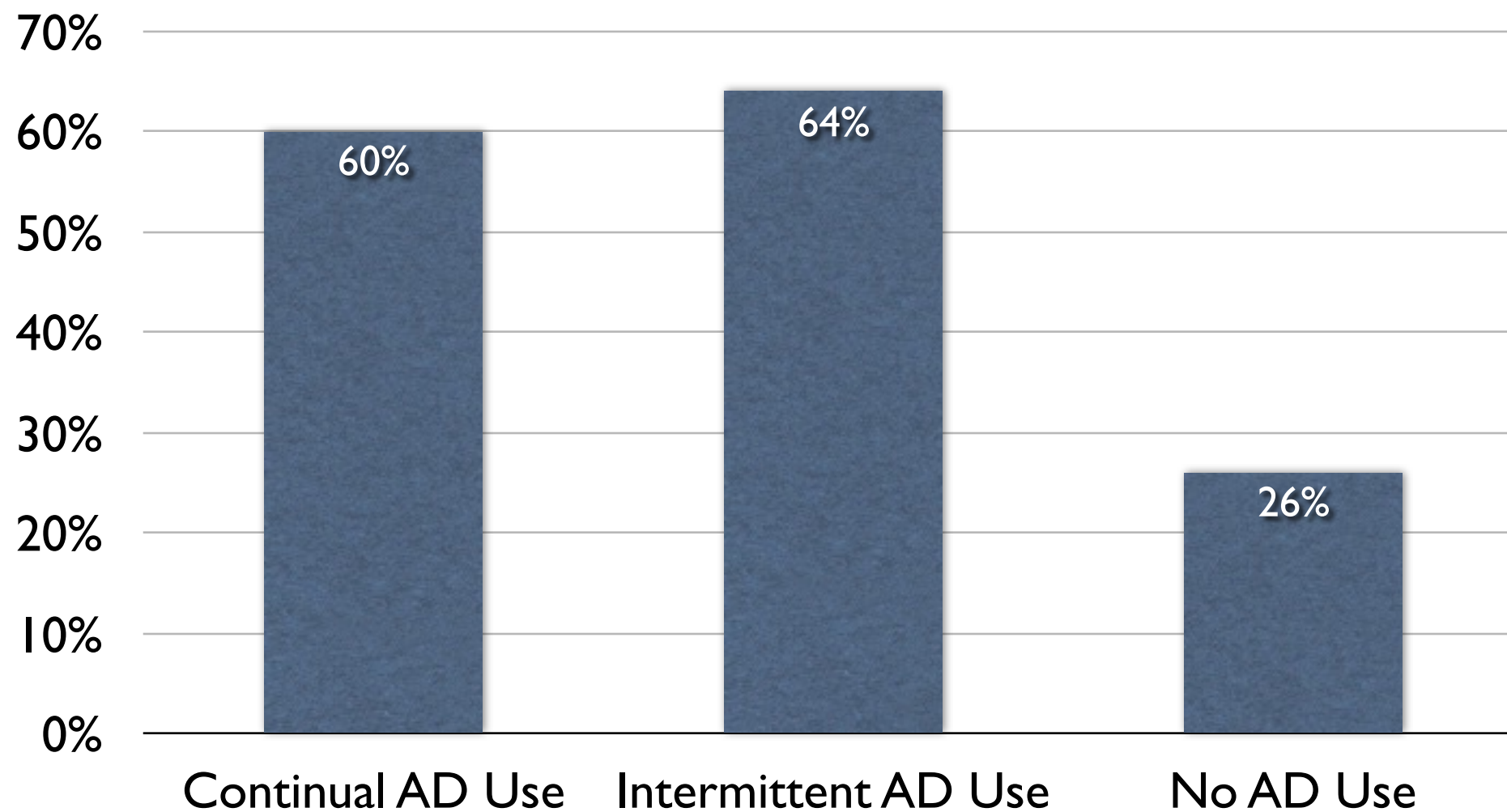
Putting the Hypothesis to the Test

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.

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.

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 Depressed Patient Will Convert to a Bipolar Diagnosis

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
15-29	1421 (4.1%)	2271 (8.3%)	23

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

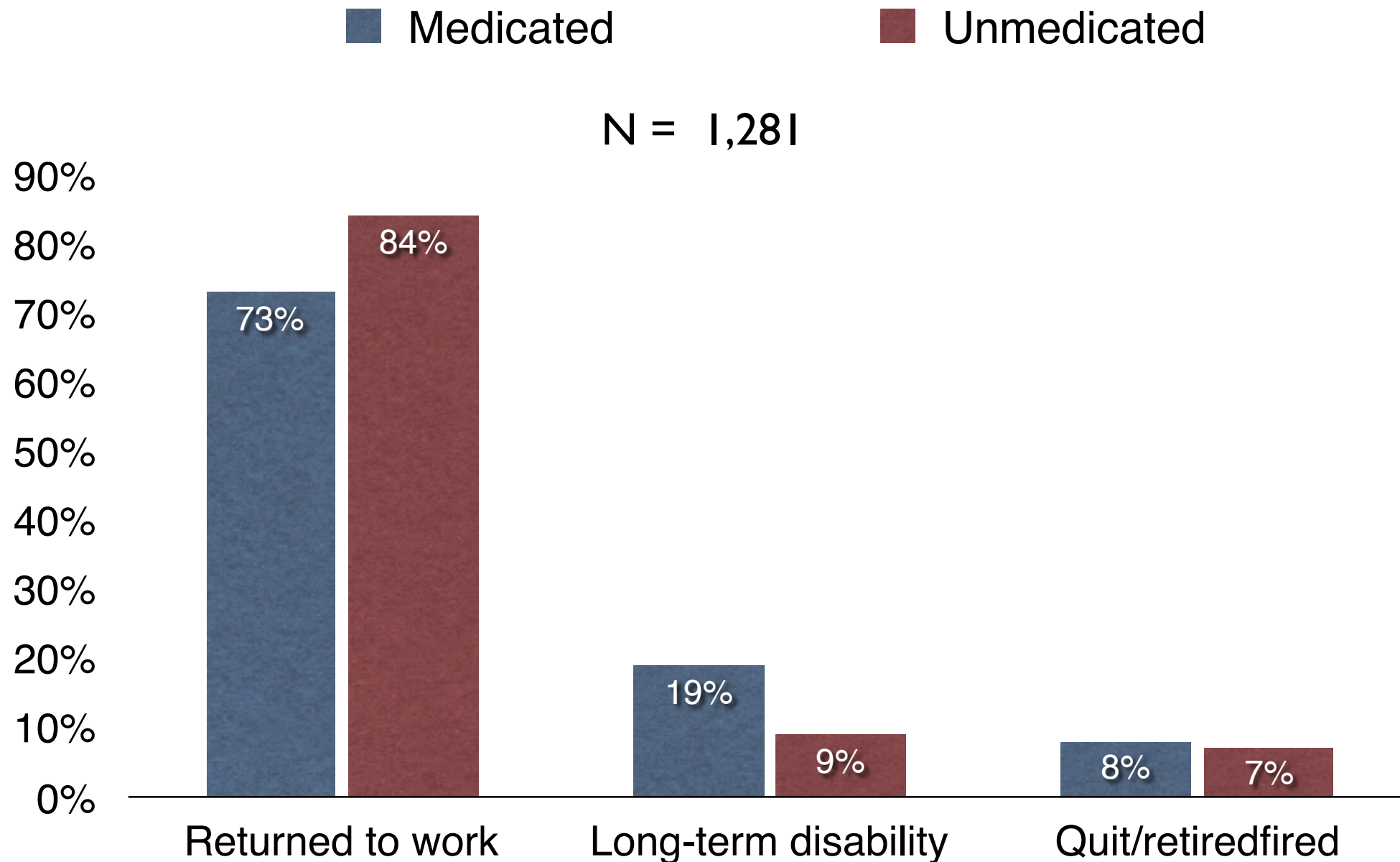
	1994-1995	2002-2003	Increase in rate
Youth (0-19 years)	25 per 100,000	1003 per 100,000	40-fold increase
20 years and older	905 per 100,000	1,679 per 100,000	85% increase

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

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

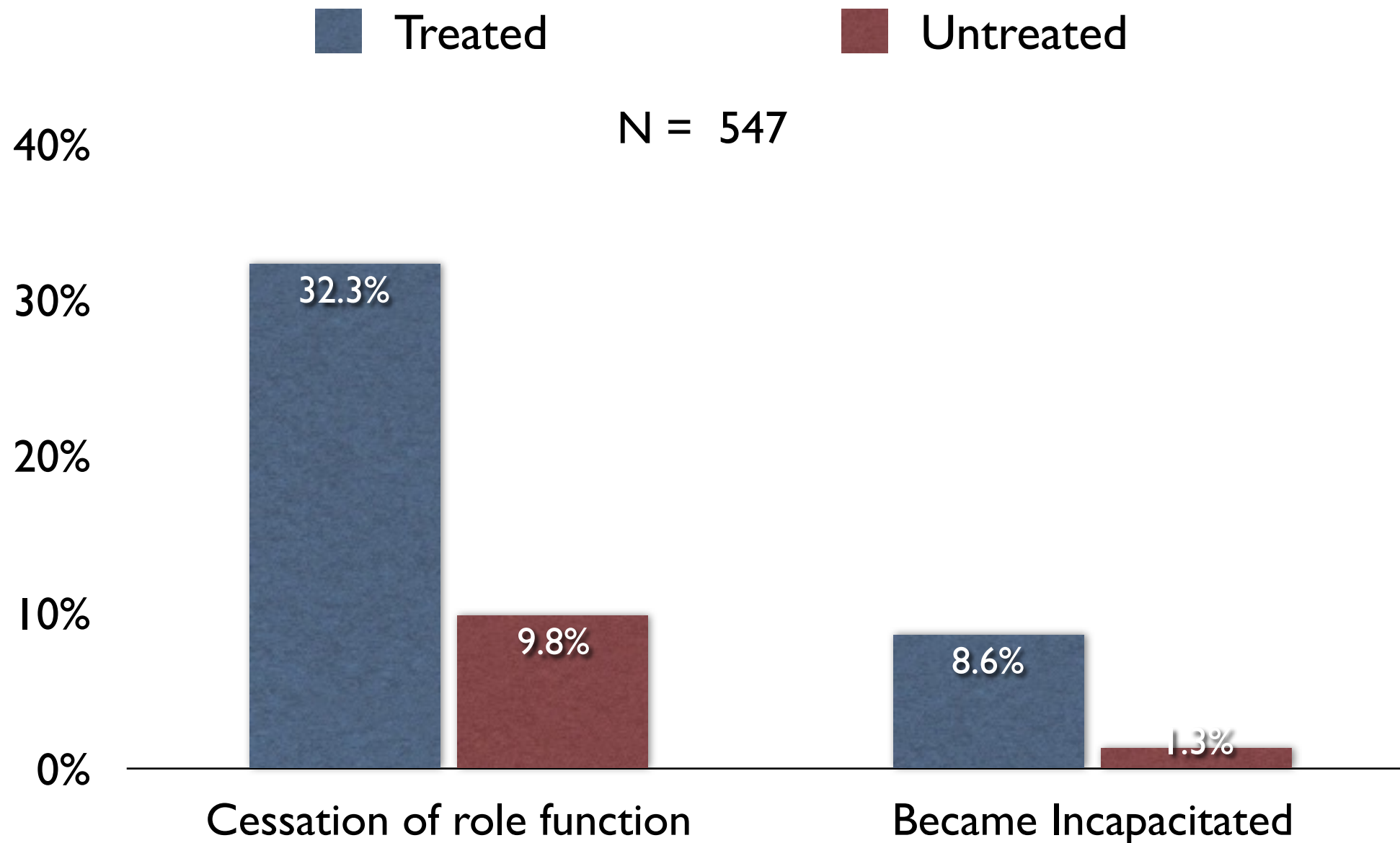
“If you create iatrogenically a bipolar patient, that patient is likely to have recurrences of bipolar illness even if the offending antidepressant is discontinued. The evidence shows that once a patient has had a manic episode, he or she is more likely to have another one, even without the antidepressant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

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.

Schizophrenia Outcomes in the Decade Before Antipsychotics, 1945-1955

- At end of three years following hospitalization, 73% of first-episode patients admitted to Warren State Hospital from 1946 to 1950 were living in the community.
- At the end of six years following hospitalization, 70% of 216 first-episode patients admitted to Delaware State Hospital from 1948 to 1950 were living in the community.
- In studies of schizophrenia patients in England, where the disorder was more narrowly defined, after five years 33% enjoyed a complete recovery, and another 20 percent a social recovery, which meant they could support themselves and live independently.

Source: J Cole, *Psychopharmacology* (1959): 142, 386-7. R. Warner, *Recovery from Schizophrenia* (1985): 74.

A Retrospective Study Finds a Worsening of Functional Outcomes in Modern Drug Era

Relapse Rates Within Five Years of Discharge

1947 cohort: 55%	(n = 100)
1967 cohort: 69%	(n = 100)

Functional Outcomes

1947 cohort: 76% were successfully living in the community at end of five years

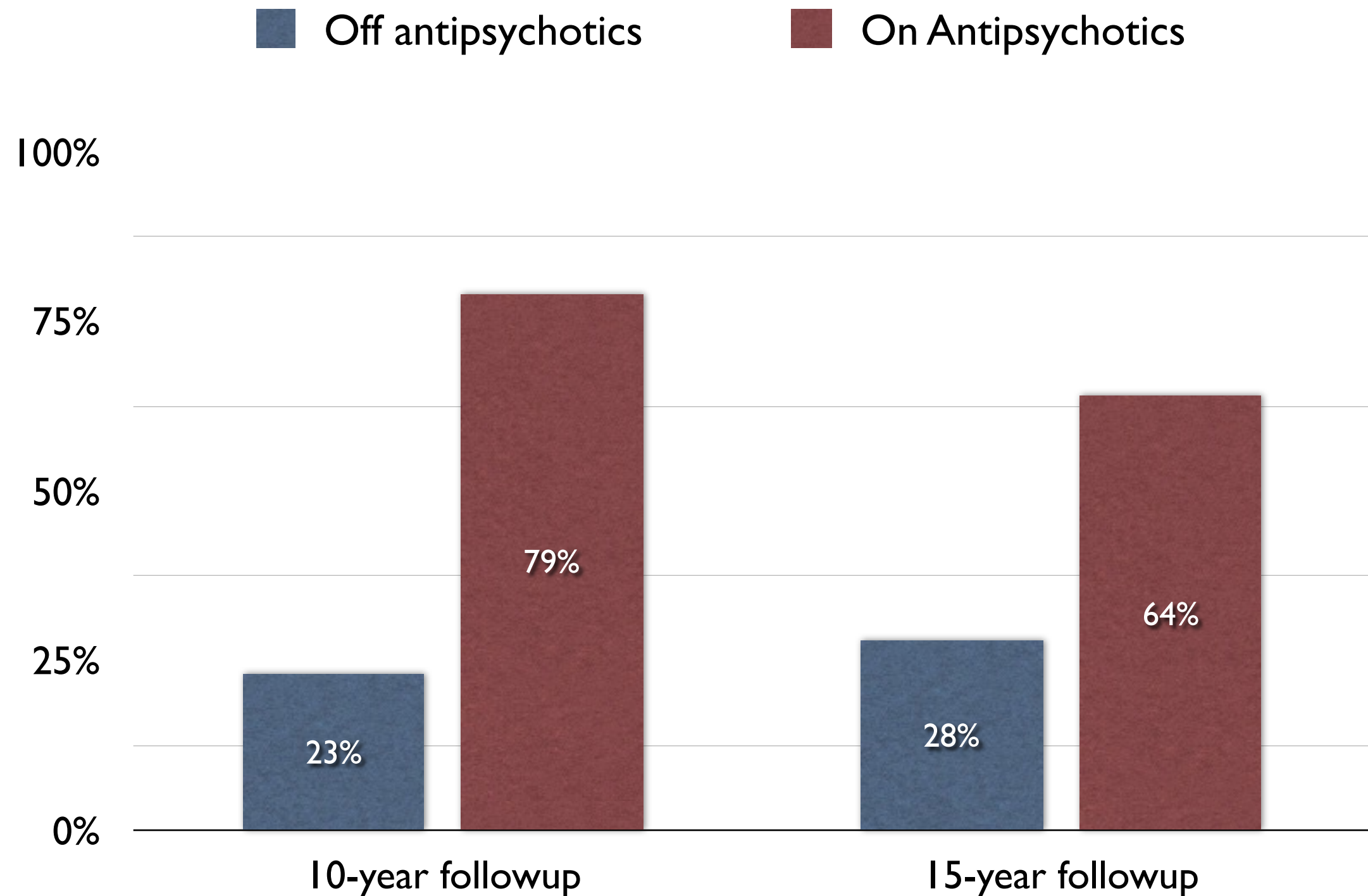
1967 cohort: They were much more “socially dependent”--on welfare and needing other forms of support--than the 1947 cohort.

Martin Harrow's Long-Term Study of Psychotic Patients

Patient Enrollment

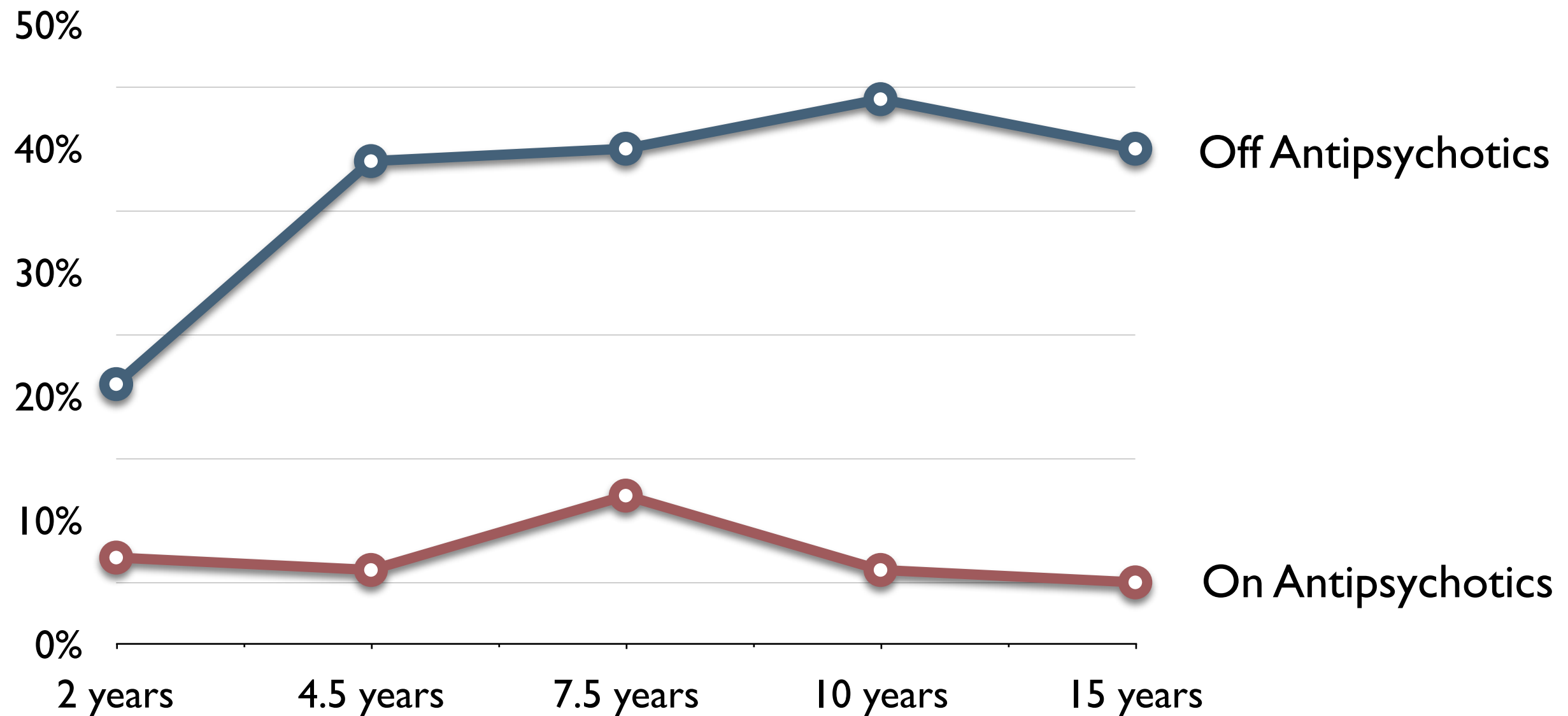
- 64 schizophrenia patients
- 81 patients with other psychotic disorders
 - 37 psychotic bipolar patients
 - 28 unipolar psychotic patients
 - 16 other milder psychotic disorders
- Median age of 22.9 years at index hospitalization
- Previous hospitalization
 - 46% first hospitalization
 - 21% one previous hospitalization
 - 33% two or more previous hospitalizations

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



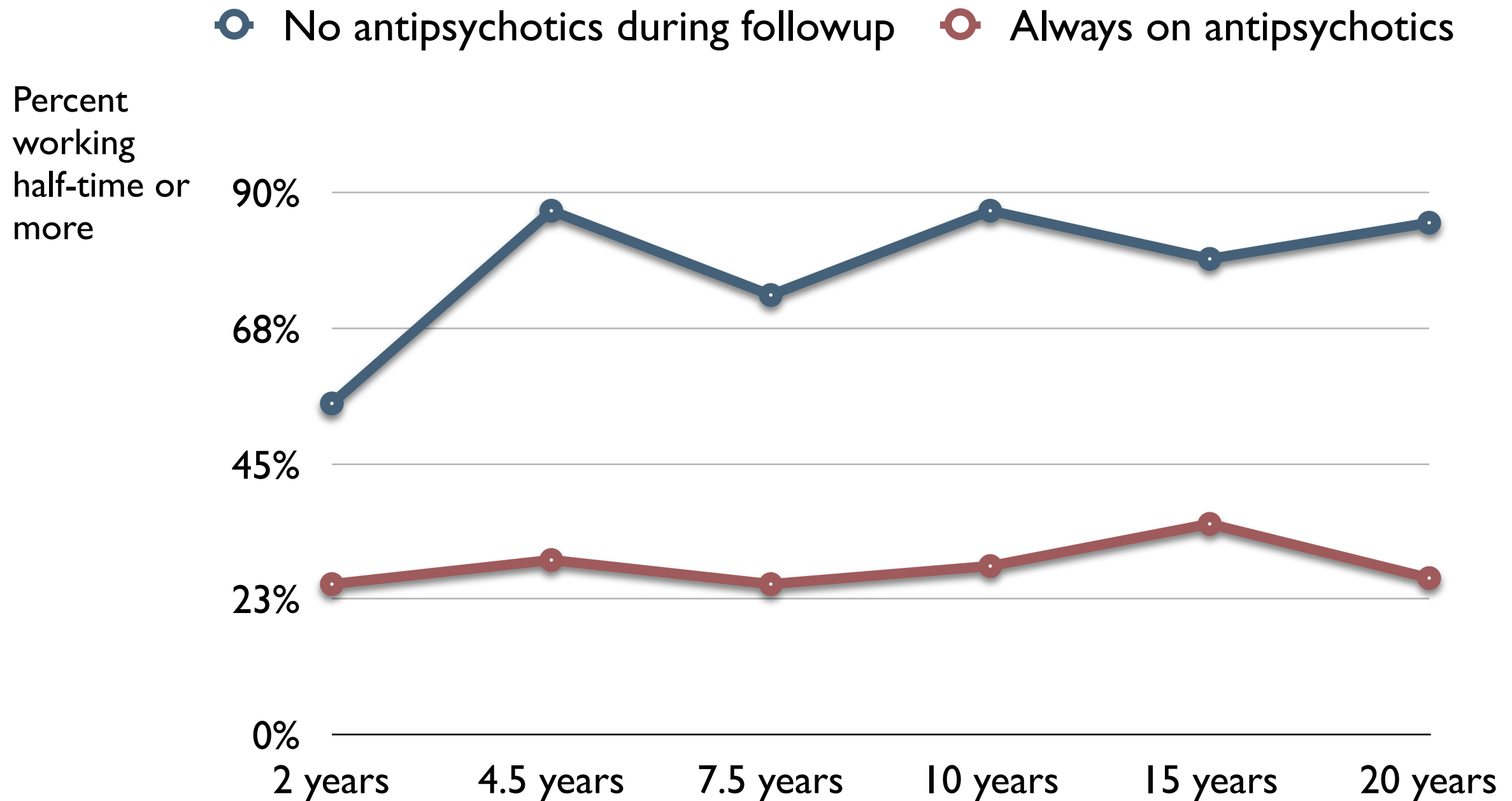
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

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

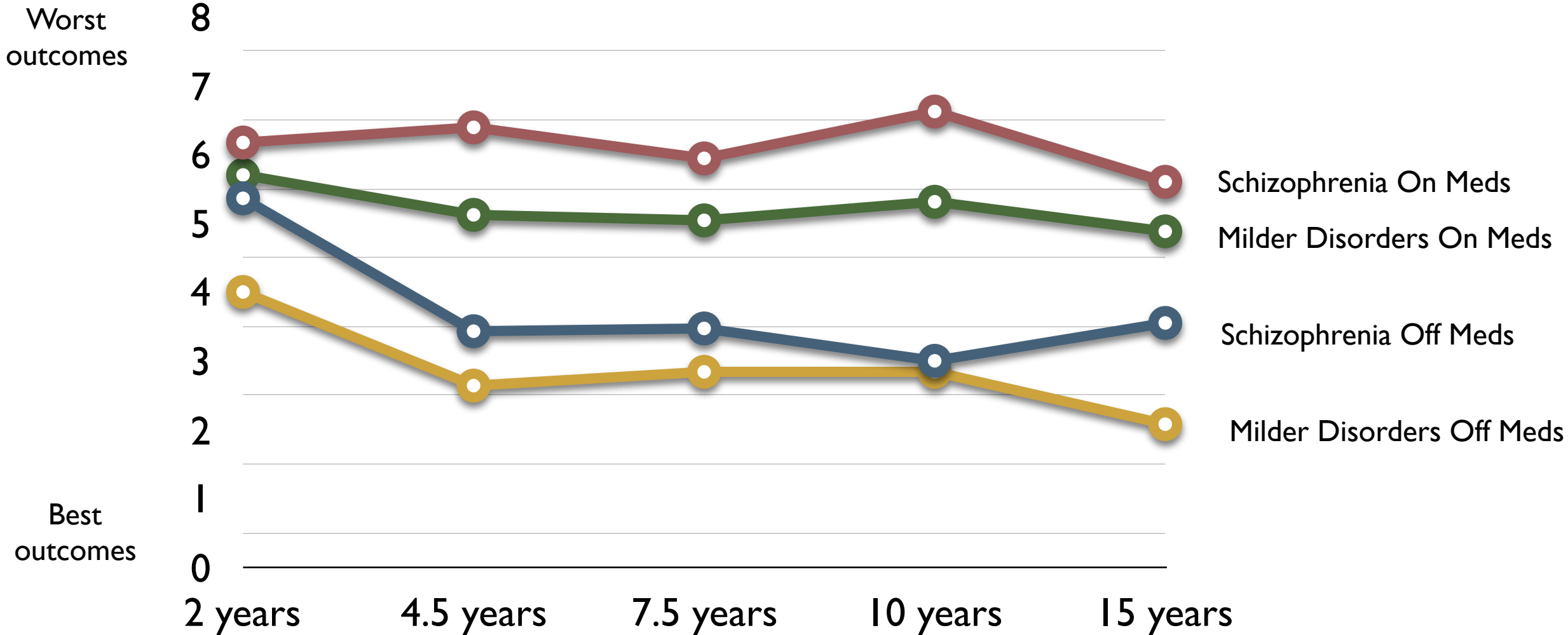


Source: M. Harrow. "Pharmacological Treatment for Psychosis: Emerging Perspectives." Presentation in Syracuse, NY, October 2, 2014.

“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

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.”

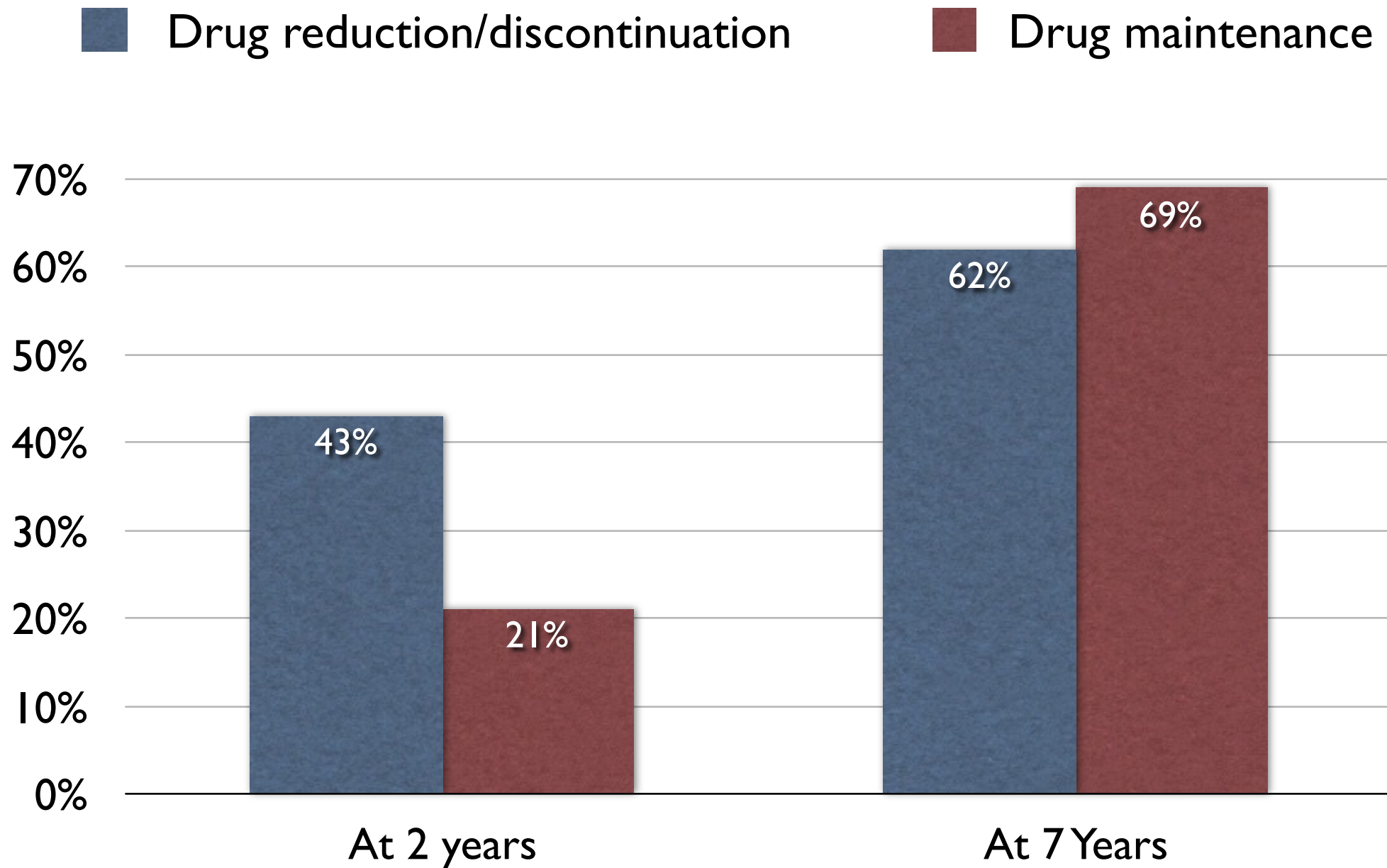
--Martin Harrow, 2013

Lex Wunderink's Randomized Study of Long-term Outcomes

Study Design

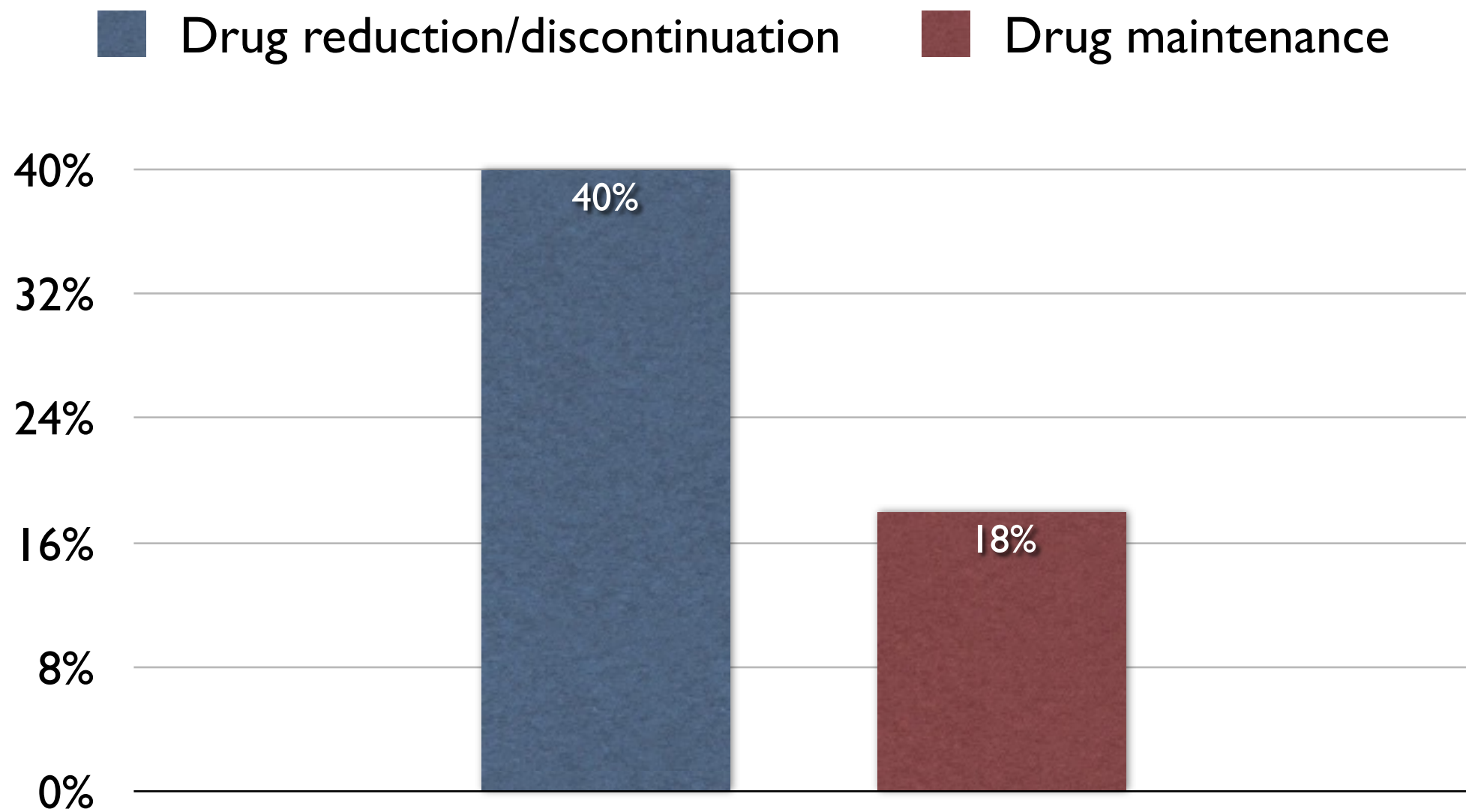
- 128 stabilized first-episode psychotic patients who had been stable for six months on antipsychotics. (103 patients were still in the study at the end of seven years.)
- Randomized either to a dose reduction/discontinuation treatment, or to standard antipsychotic treatment.

Relapse Rates

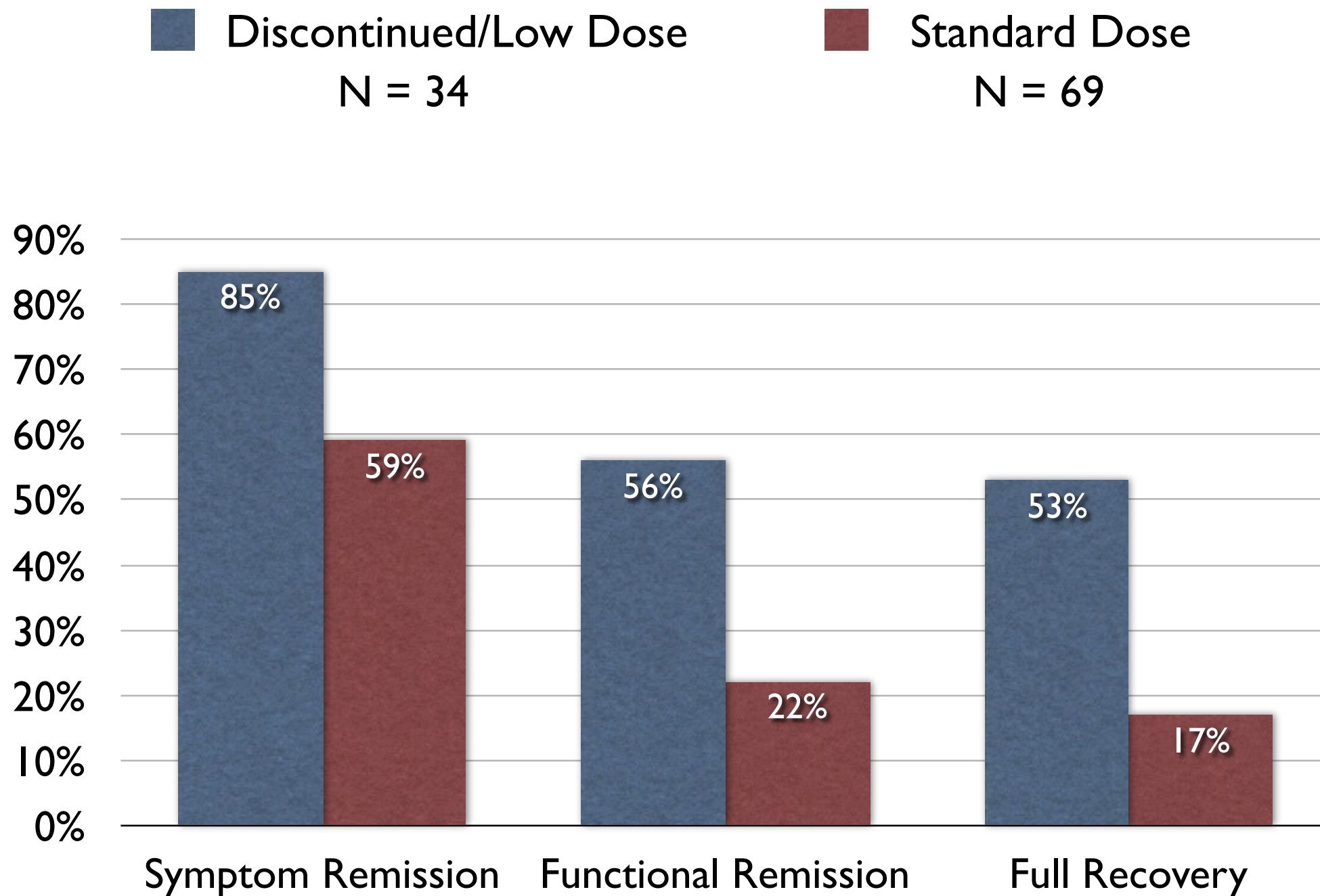


L.Wunderink. "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy." *JAMA Psychiatry*, published online, July 3, 2013.

Long-Term Recovery Rates (at 7 Years)



Outcomes By Antipsychotic Use



L.Wunderink. "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy." *JAMA Psychiatry*, published online, July 3, 2013.

Australian Study of Effects of Medication Compliance on Outcomes

- 81 first episode patients
- 41 randomized to specialized relapse prevention therapy expected to increase medication compliance
- Specialized therapy did increase medication compliance over 30 months
- However, increase in medication adherence associated with “decreases in psychosocial functioning and increases in negative symptoms.”

Conclusion:

“This is consistent with previous research showing an association between better vocational functioning at 2-year followup and placebo treatment compared with antipsychotic medication in a first-episode schizophrenia sample.”

A Call to Rethink Antipsychotics

“It is time to reappraise the assumption that antipsychotics must always be the first line of treatment for people with psychosis. This is not a wild cry from the distant outback, but a considered opinion by influential researchers . . . [there is] an increasing body of evidence that the adverse effects of [antipsychotic] treatment are, to put it simply, not worth the candle.”

--Peter Tyrer, Editor

British Journal of Psychiatry, August 2012

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.

Solutions

The Opportunity:

The research literature is telling us that psychiatric disorders, including more severe ones, may be, in the majority of cases, episodic in nature, rather than chronic illnesses.

The Solution

Treatment protocols that provide psychosocial care and use psychiatric drugs in a selective manner that minimizes initial exposure and their long-term use.

A Model for Selective Use of Antipsychotics

The practice in Western Lapland, Finland (since 1992)

- First-episode patients are not immediately put on antipsychotics. Instead, they are treated with intensive psychosocial care, and benzodiazepines on an as-needed basis, to help people sleep.
- As long as patients are getting better, antipsychotics are not used. If, after several weeks, they are not improving, then low doses of an antipsychotic are prescribed.
- After the medicated patients are stabilized, there is an effort--after six months or so--to gradually withdraw them from the medication.

Outcomes with Selective Use Of Antipsychotics

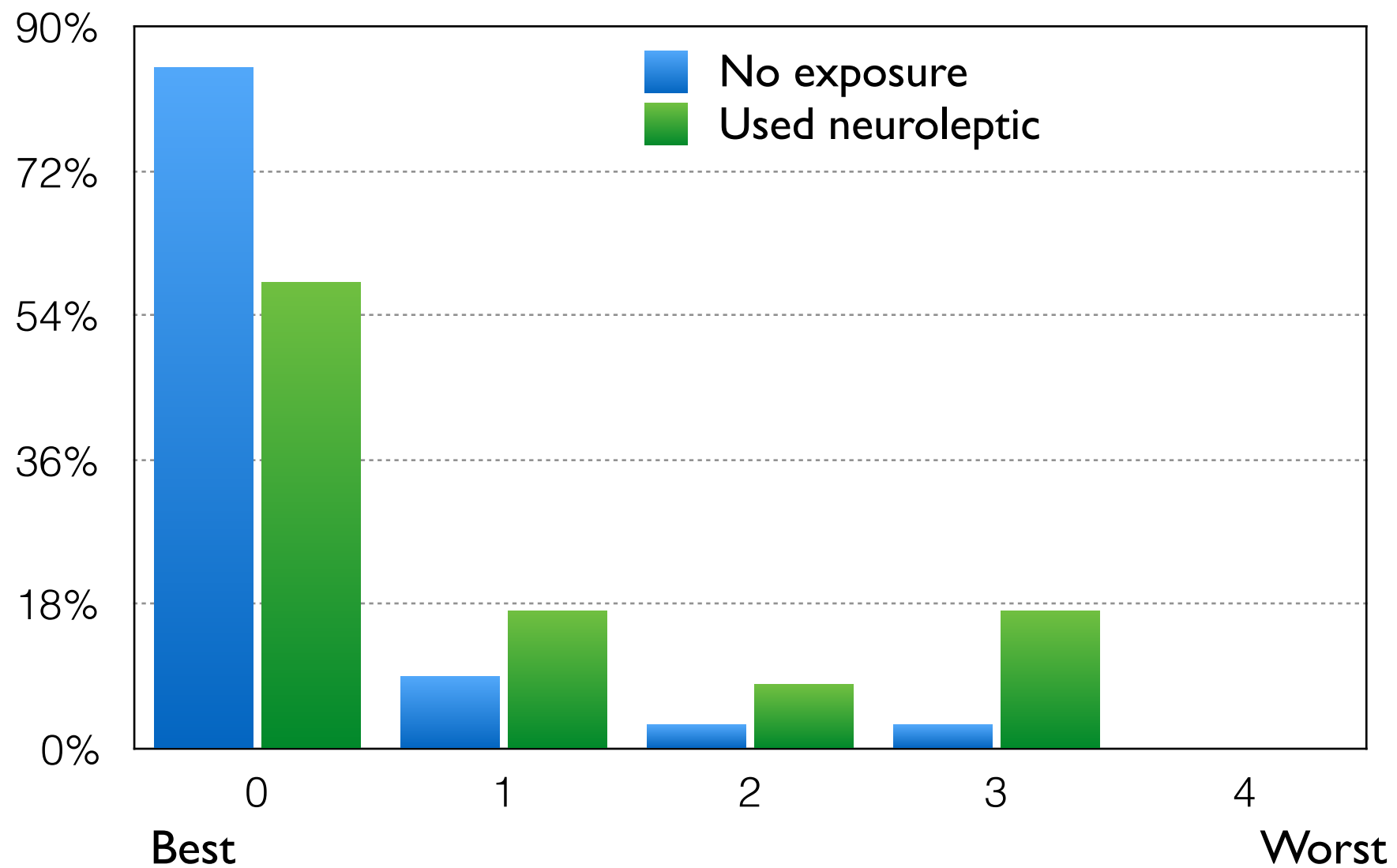
Five-Year Outcomes for First-Episode Psychotic Patients in Finnish Western Lapland Treated with Open-Dialogue Therapy

Patients (N=75)	
Schizophrenia (N=30)	
Other psychotic disorders (N=45)	
Antipsychotic use	
Never exposed to antipsychotics	67%
Occasional use during five years	33%
Ongoing use at end of five years	20%
Psychotic symptoms	
Never relapsed during five years	67%
Asymptomatic at five-year followup	79%
Functional outcomes at five years	
Working or in school	73%
Unemployed	7%
On disability	20%

Source: Seikkula, J. "Five-year experience of first-episode nonaffective psychosis in open-dialogue approach." *Psychotherapy Research* 16 (2006):214-28.

Best Outcomes Are in Never-Exposed Patients

Severity of psychotic symptoms at five years, sorted by neuroleptic exposure during first two years



Presentation by Jaakko Seikkula on "Open Dialogue Research," in Gothenburg, Sweden, Oct. 15, 2016.

On importance of using neuroleptics in a selective fashion:

“I am confident of this idea. There are patients who may be living in a quite peculiar way, and they may have psychotic ideas, but they still can hang on to an active life. But if they are medicated, because of the sedative action of the drugs, they lose this ‘grip on life,’ and that is so important. They become passive, and they no longer take care of themselves.”

--Jaakko Seikkula