

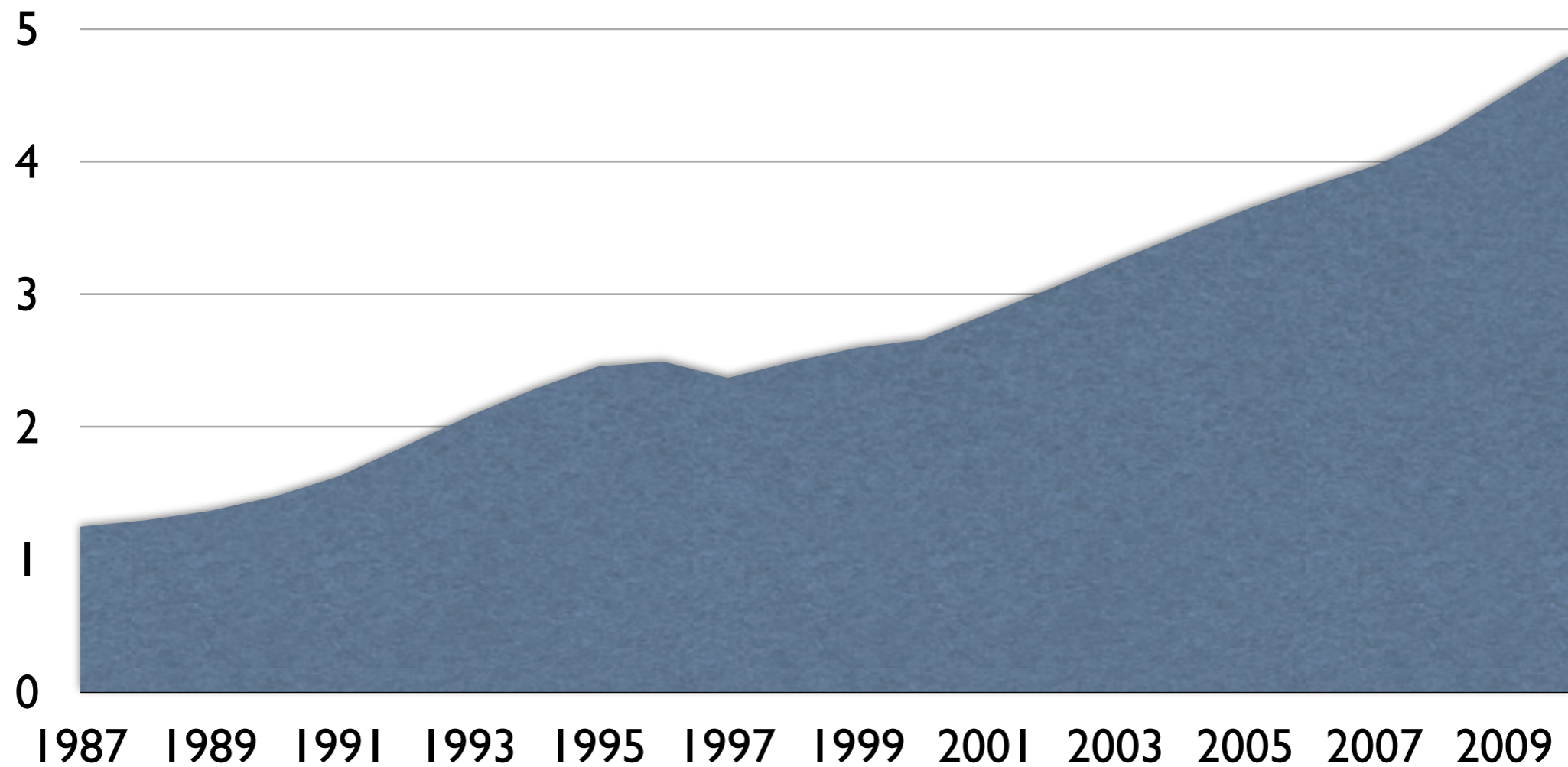
The Evidence Is In

Our Drug-Based Paradigm of
Care Has Failed--Finding Ways
to Humanistic Approaches

Robert Whitaker/Jaakko Seikkula
August 2014

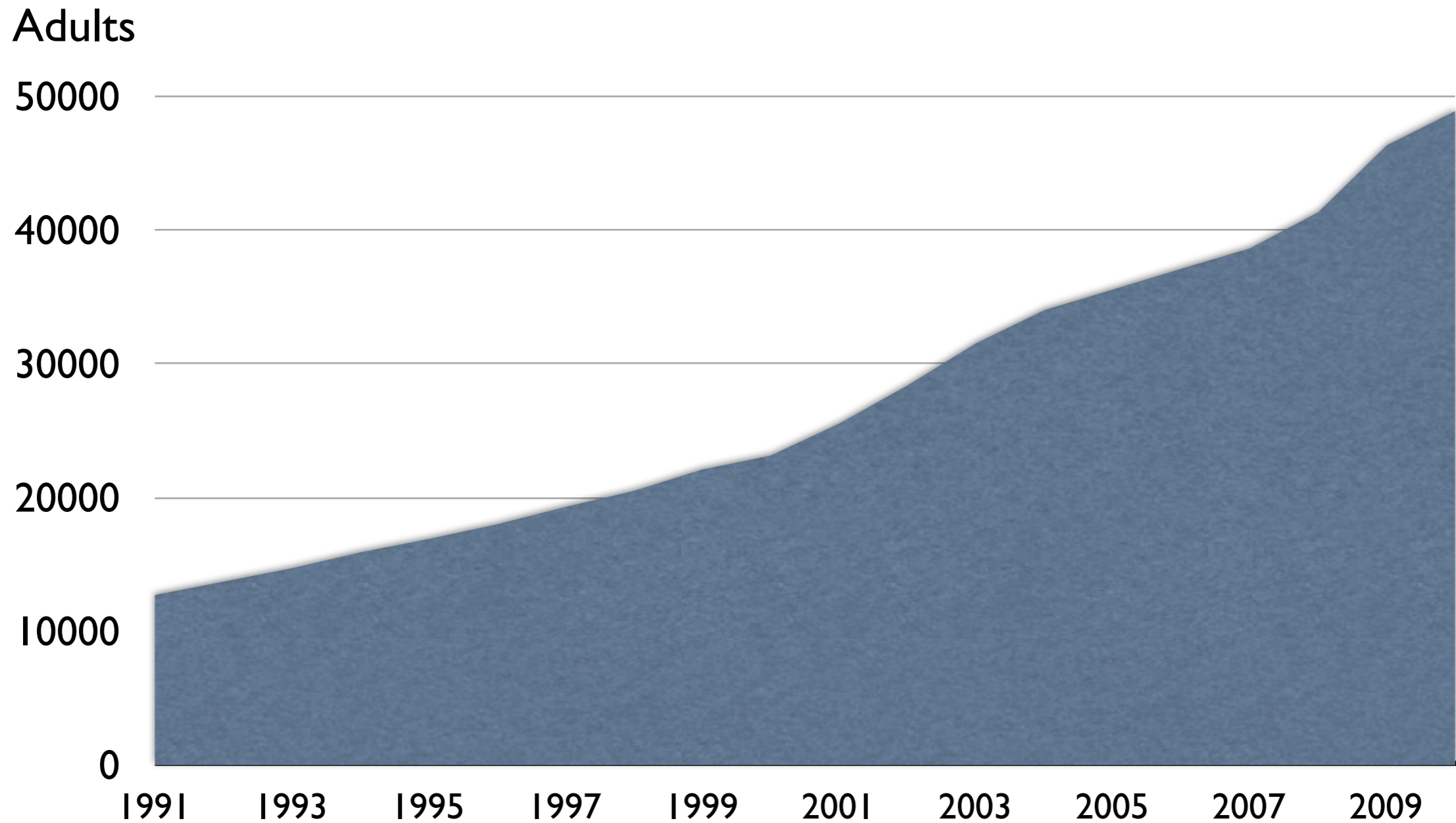
U.S. Disability in the Prozac Era

Millions of adults, 18 to 66 years old



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

Adults

250000

200000

150000

100000

50000

1990

1992

1994

1996

1998

2000

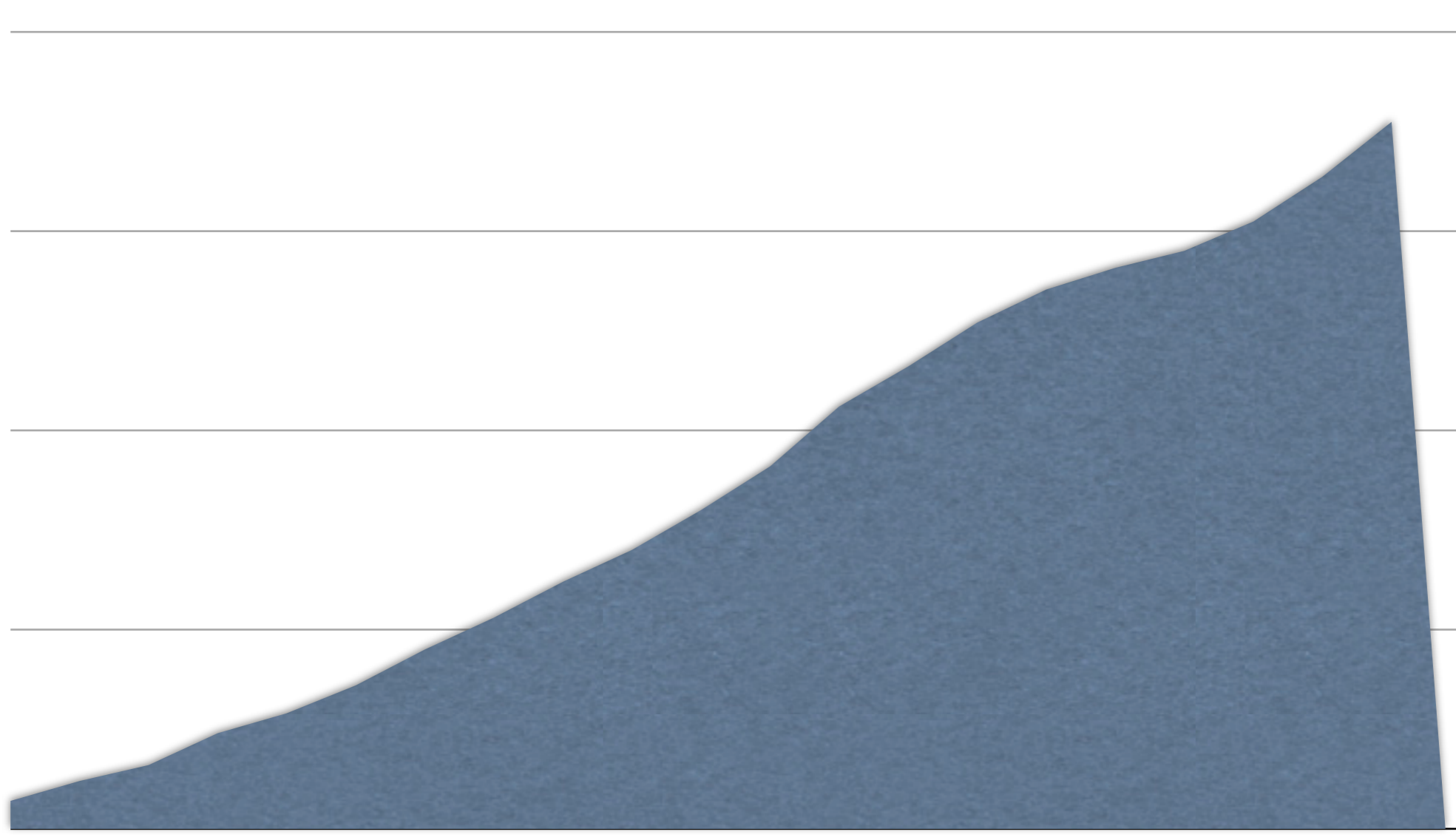
2002

2004

2006

2008

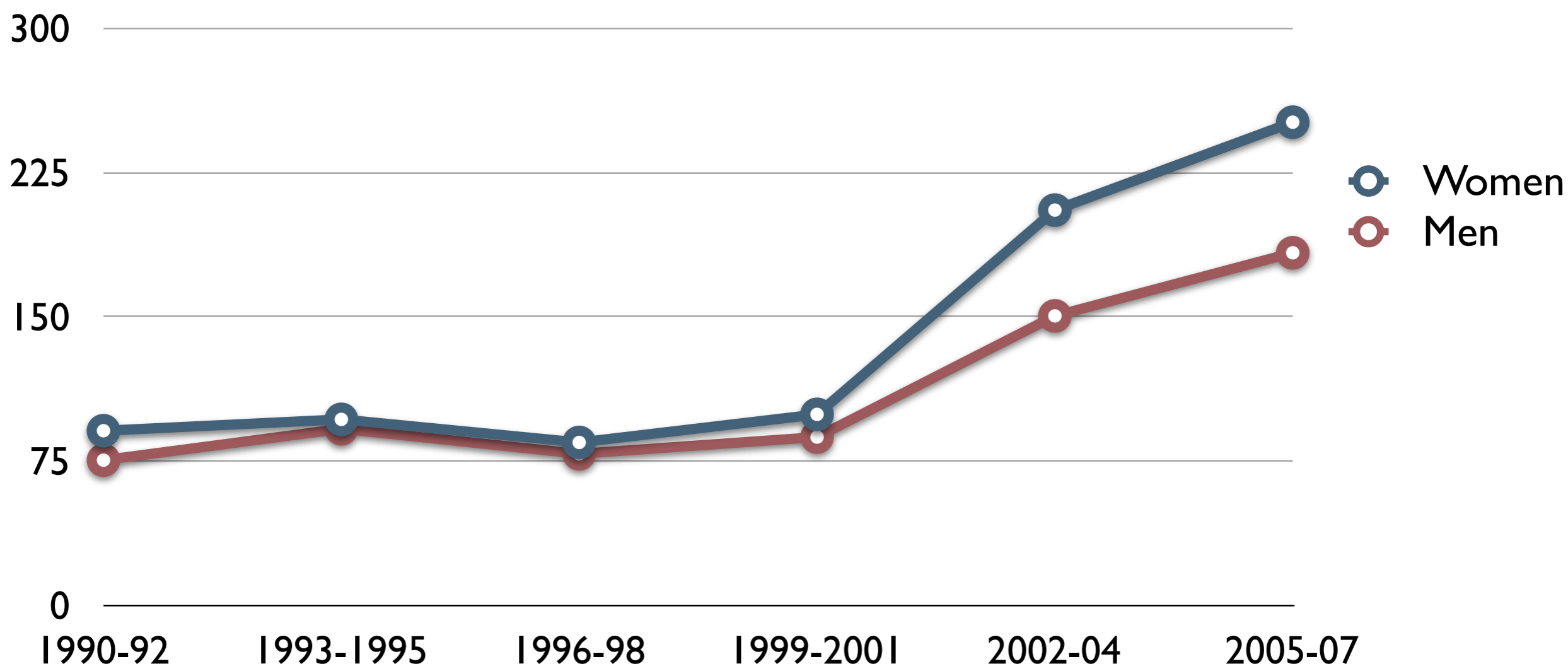
2010



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

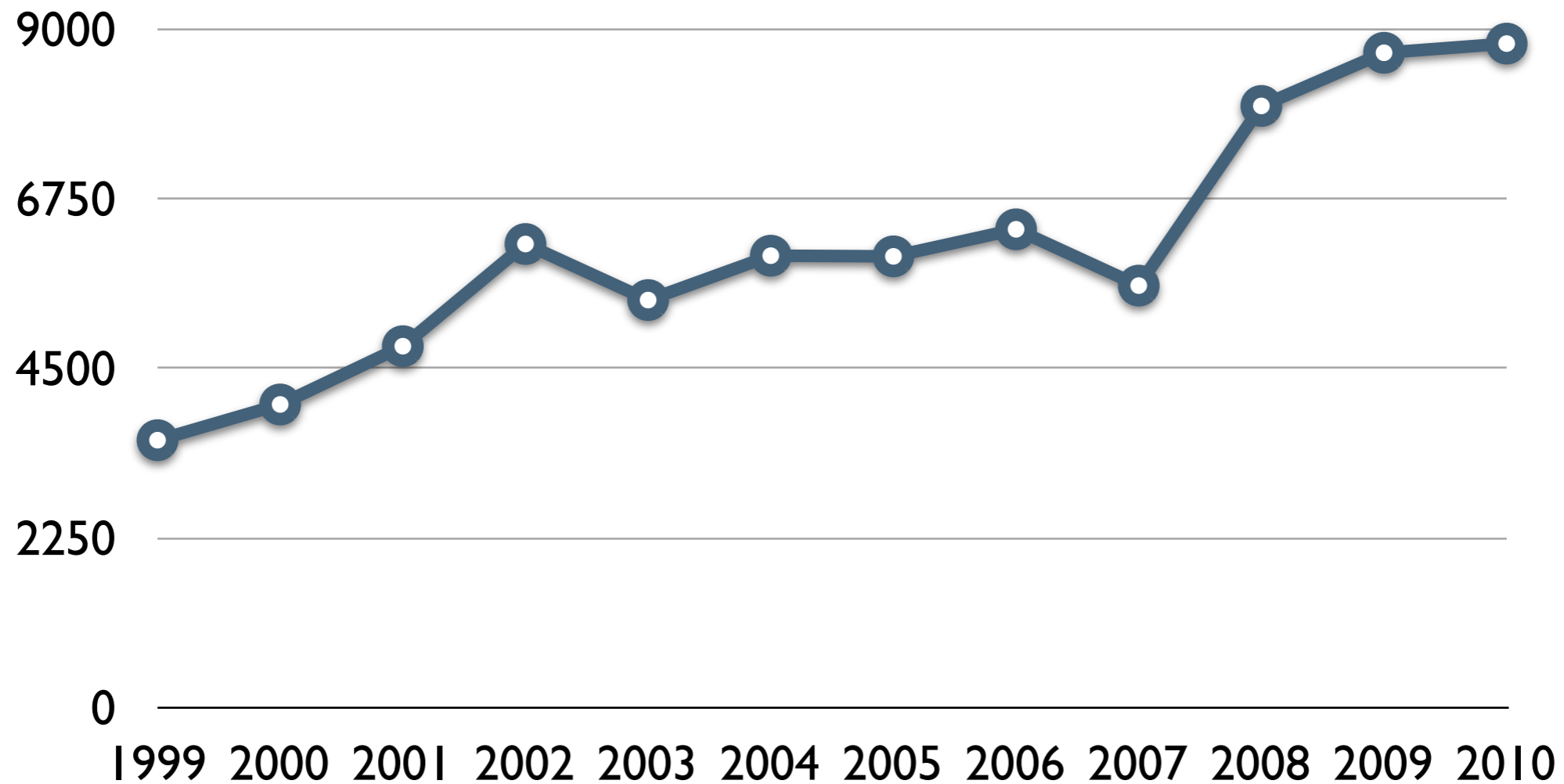
Disability Due to Mental and Behavioural Disorders in Iceland, 1990-2007

Number of New Cases Annually per 100,000 Population



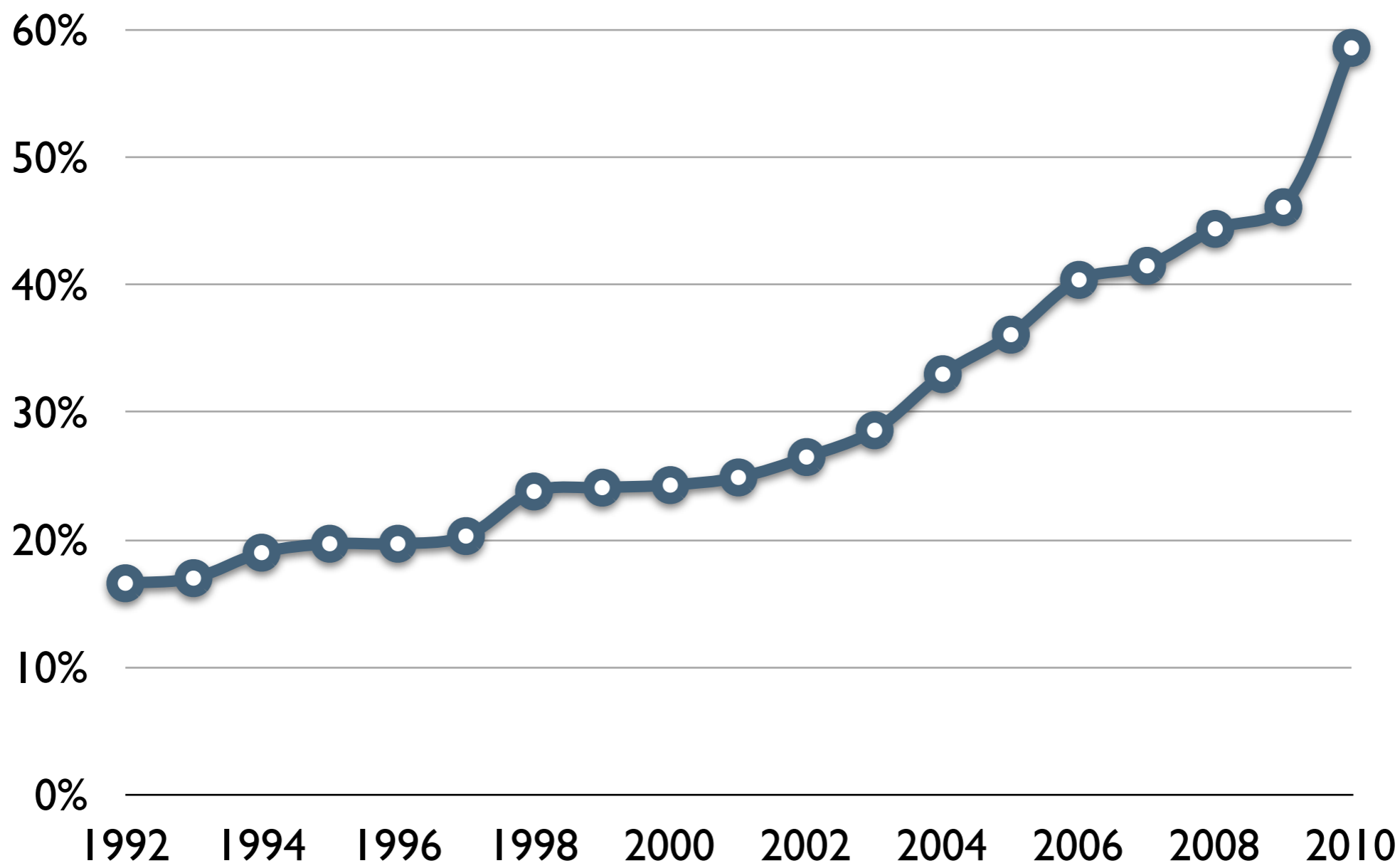
Source: Thoriacius, S. "Increased incidence of disability due to mental and behavioural disorders in Iceland, 1990-2007." *J Ment Health* (2010) 19: 176-83.

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.

How Do Psychiatric Medications Act on the Brain?

The Problem of Oppositional Tolerance

The Chemical Imbalance Theory of Mental Disorders

- Arose from understanding of how drugs act on brain (1960s-1970s)
- Investigations of dopamine theory of schizophrenia and serotonin theory of depression started in 1970s

Findings re the Chemical Imbalance Theory of Mental Disorders

A. Serotonin Theory of Depression

“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 monoamine deficiency accounts for depression; that is, there is no real monoamine deficit.”--Stephen Stahl, *Essential Psychopharmacology*, 2000

B. Dopamine Theory of Schizophrenia

“There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia.” Stephen Hyman, *Molecular Psychiatry*, 2002

C. Chemical Imbalance Theory of Mental Disorders (in general)

“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*.

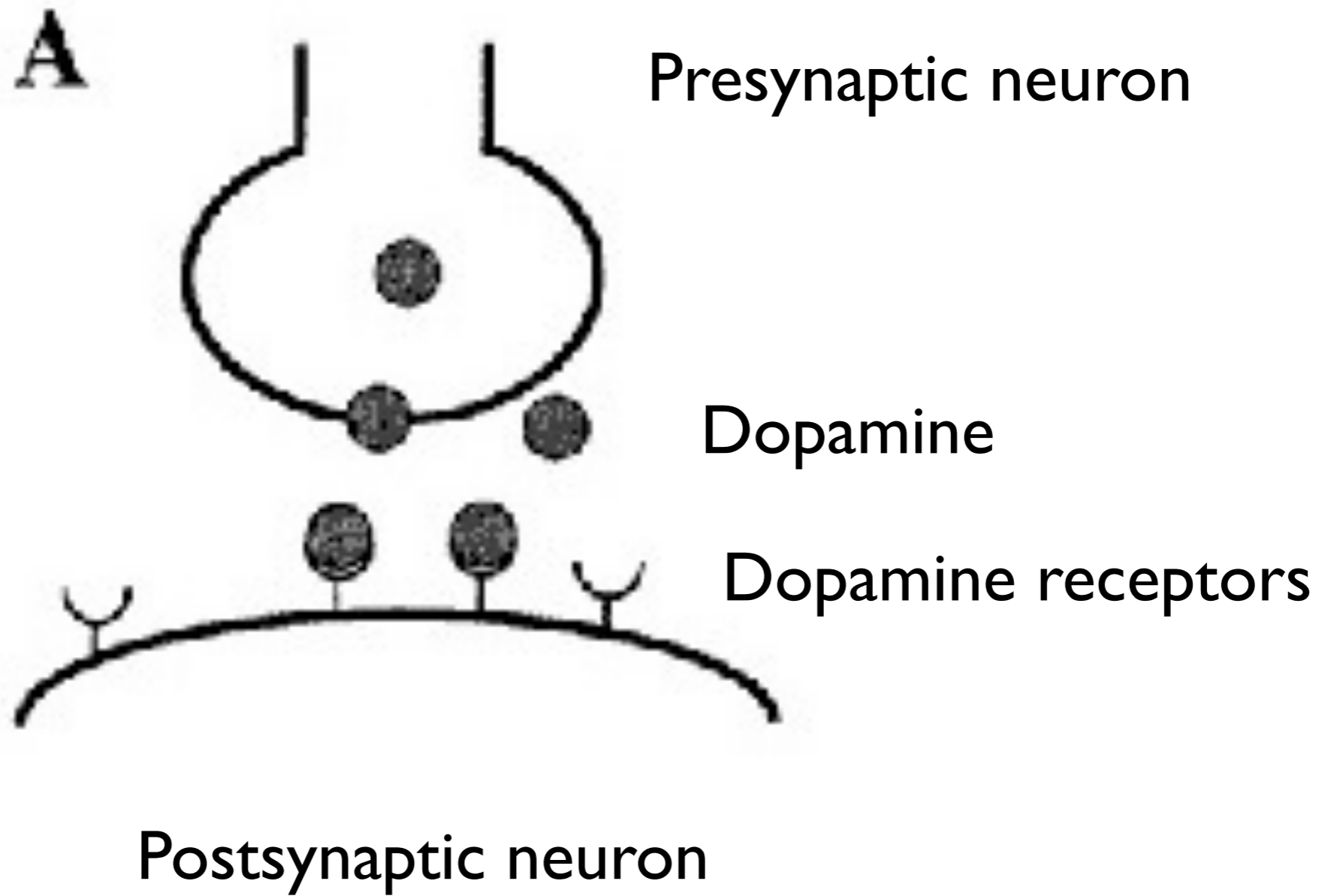
A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

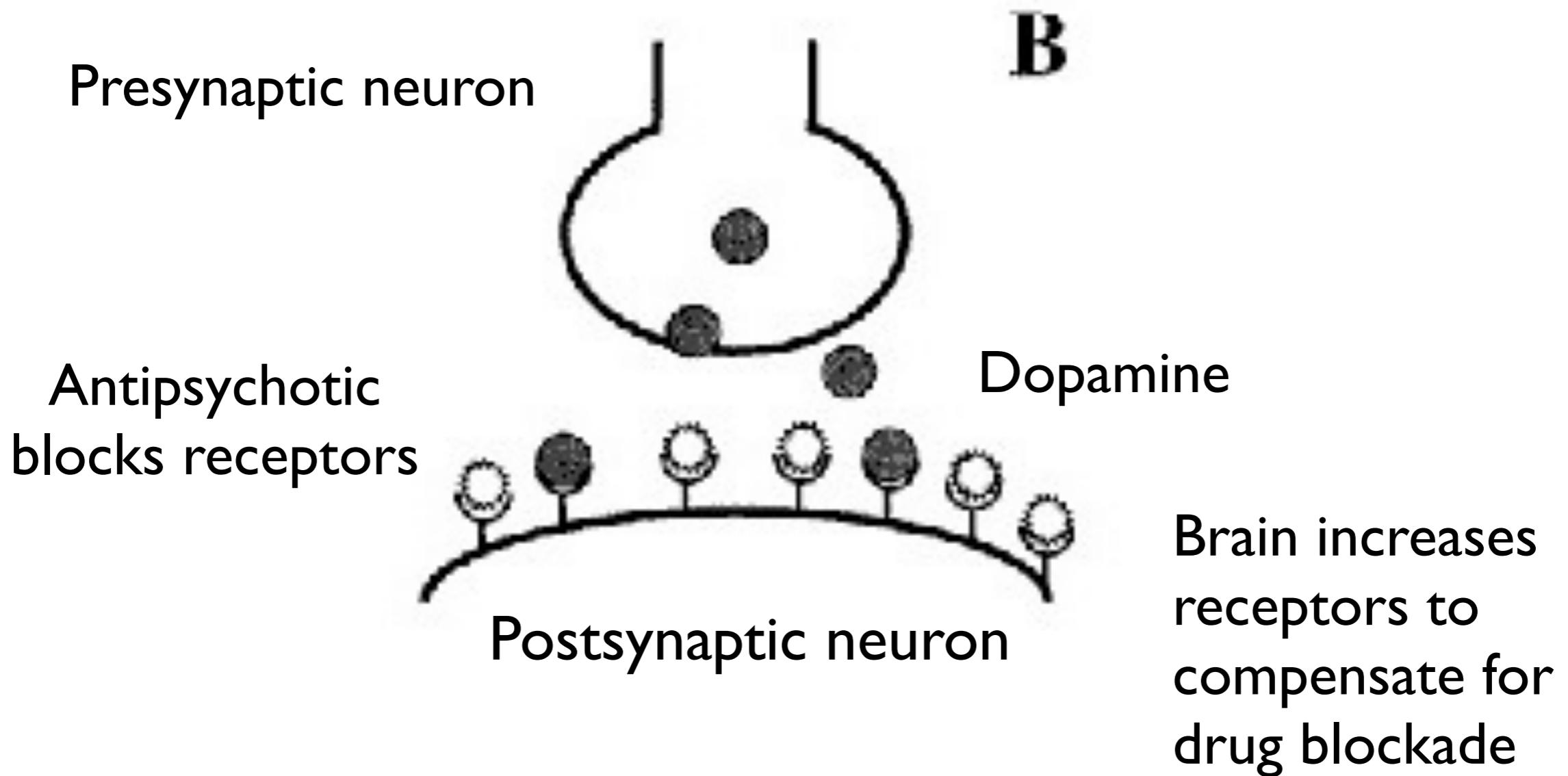
- Psychiatric medications “create perturbations in neurotransmitter functions.”
- In response, the brain goes through a series of compensatory adaptations in order “to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu.”
- The “chronic administration” of the drugs then cause “substantial and long-lasting alterations in neural function.”
- After a few weeks, the person’s brain is now functioning in a manner that is “qualitatively as well as quantitatively different from the normal state.”

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

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics



The “Chemical Imbalance” Paradox

- Investigators have not found that a characteristic “chemical imbalance” is the biological cause of any major mental disorder.
- Investigators have found that psychiatric drugs induce compensatory changes in the brain that create a “chemical imbalance” in the brain, and of the type hypothesized to cause the mental disorder in the first place.

The Possible Consequences of “Oppositional Tolerance”

“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.

What Does the Research Literature Reveal About the Long-term Effects of Psychiatric Medications?

Antipsychotics: A Brief Study

The Evidence for Antipsychotics

Short-term Use

Antipsychotics reduce target symptoms of a disorder better than placebo in six-week trials.

Long-term Use

In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications.

Recognition that the Evidence Base For Long-term Use of Antipsychotics is Lacking

“After fifty years of neuroleptics, are we able to answer the following simple question: Are neuroleptics effective in treating schizophrenia? [There is] no compelling evidence on the matter, when ‘long-term’ is considered.”

And:

“If we wish to base psychiatry on evidence-based medicine, we run a genuine risk in taking a close look at what has long been considered fact.”

--Emmanuel Stip, *European Psychiatry* (2002)

A Paradox Appears (1960s-1970s)

- In the first long-term trial by the National Institute of Mental Health (one-year), the rehospitalization rate was higher for those treated initially in the hospital with an antipsychotic. (1967)
- In a retrospective study by Sanford Bockoven, the five-year outcomes of psychotic patients treated in 1947 (prior to antipsychotics) were markedly better than for a comparable group of patients treated in 1967 with antipsychotics.
- In three longer-term studies funded by the NIMH, psychotic/schizophrenia patients treated with a drug protocol that led to much less use of medication (or no medication at all) had better outcomes at one, two, and three years. (Late 1970s)

The Oppositional Tolerance Question is Raised by NIMH Researchers, in 1977:

“There is no question that, once patients are placed on medication, they are less vulnerable to relapse if maintained on neuroleptics. But what if these patients had never been treated with drugs to begin with? . . . We raise the possibility that antipsychotic medication may make some schizophrenic patients more vulnerable to future relapse than would be the case in the normal course of the illness.”

Source: Carpenter, W. “The treatment of acute schizophrenia without drugs.” *Am J Psychiatry* 134 (1977):14-20.

The Dopamine Supersensitivity Theory

The Mechanism:

Antipsychotics block D2 receptors in the brain. As a compensatory response, the brain then increases the density of its D2 receptors by 30% or more.

The Consequence:

Two Canadian investigators at McGill University, Guy Chouinard and Barry Jones, reasoned that this made the patient more biologically prone to psychosis, and to worse relapses upon drug withdrawal.

“Neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms . . . An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness.”

Source: Chouinard, G. “Neuroleptic-induced supersensitivity psychosis,” *Am J Psychiatry* 135 (1978): 1409-10; and “Neuroleptic-induced supersensitivity psychosis,” *Am J Psychiatry* 137 (1980): 16-20.

Martin Harrow's Long-Term Study of Psychotic Patients

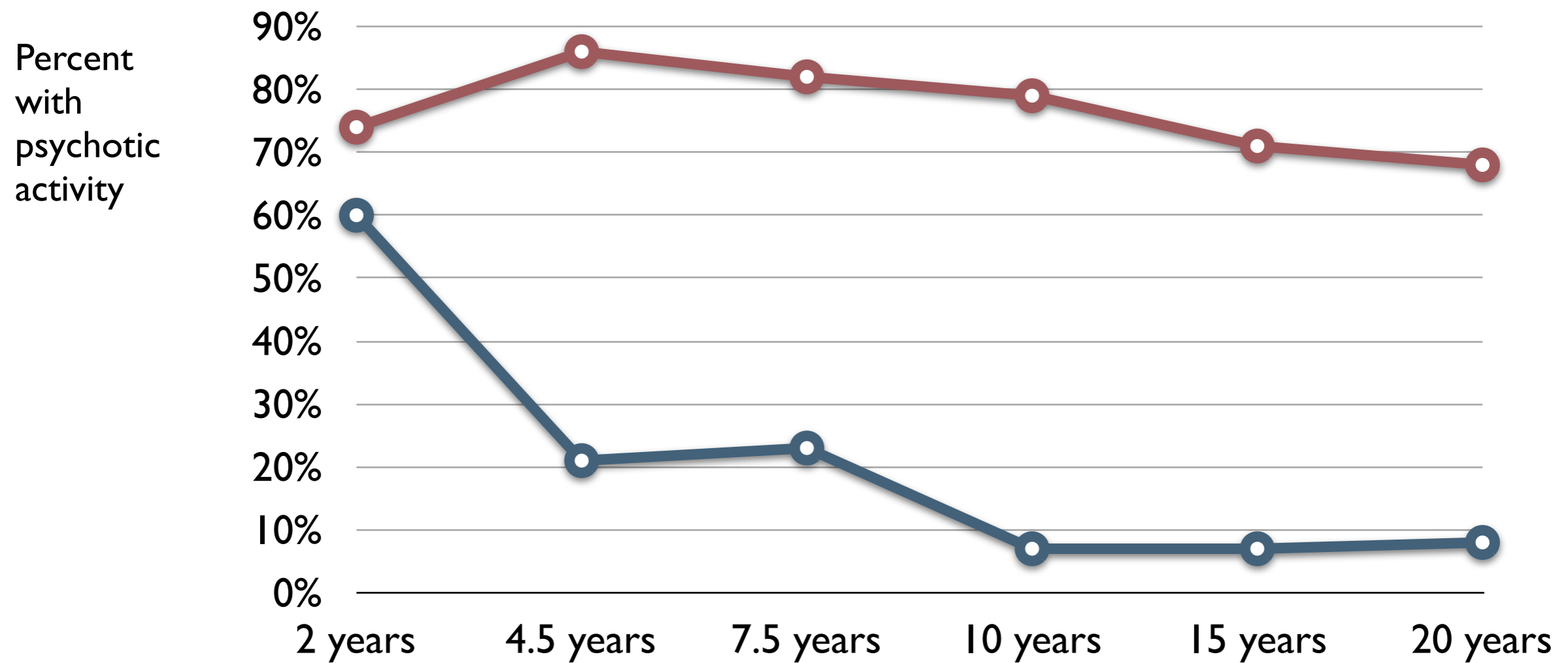
Patient Enrollment

- 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

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.

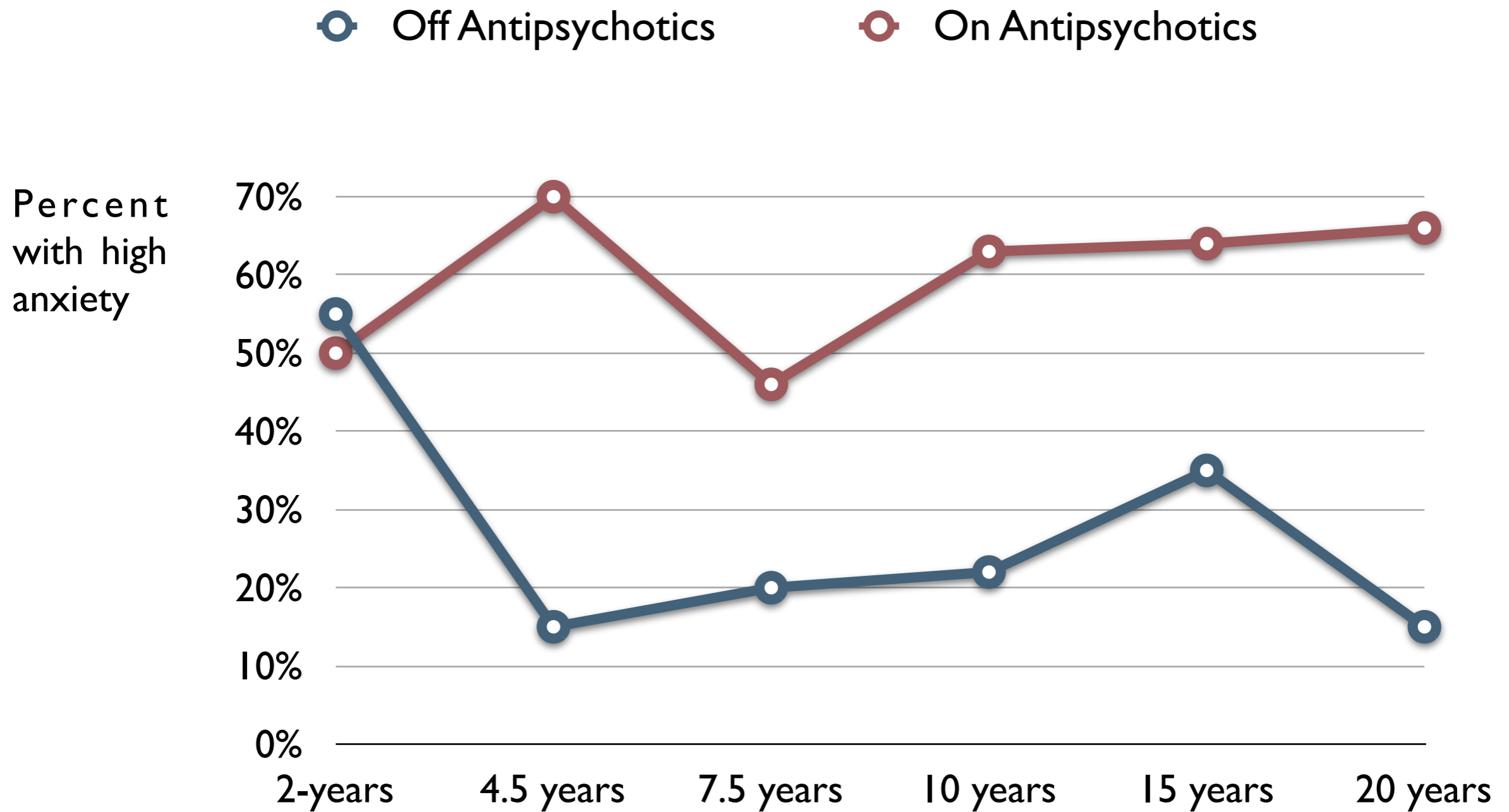
Psychotic Symptoms of Schizophrenia Patients

- No antipsychotics during followup
- Always on antipsychotics



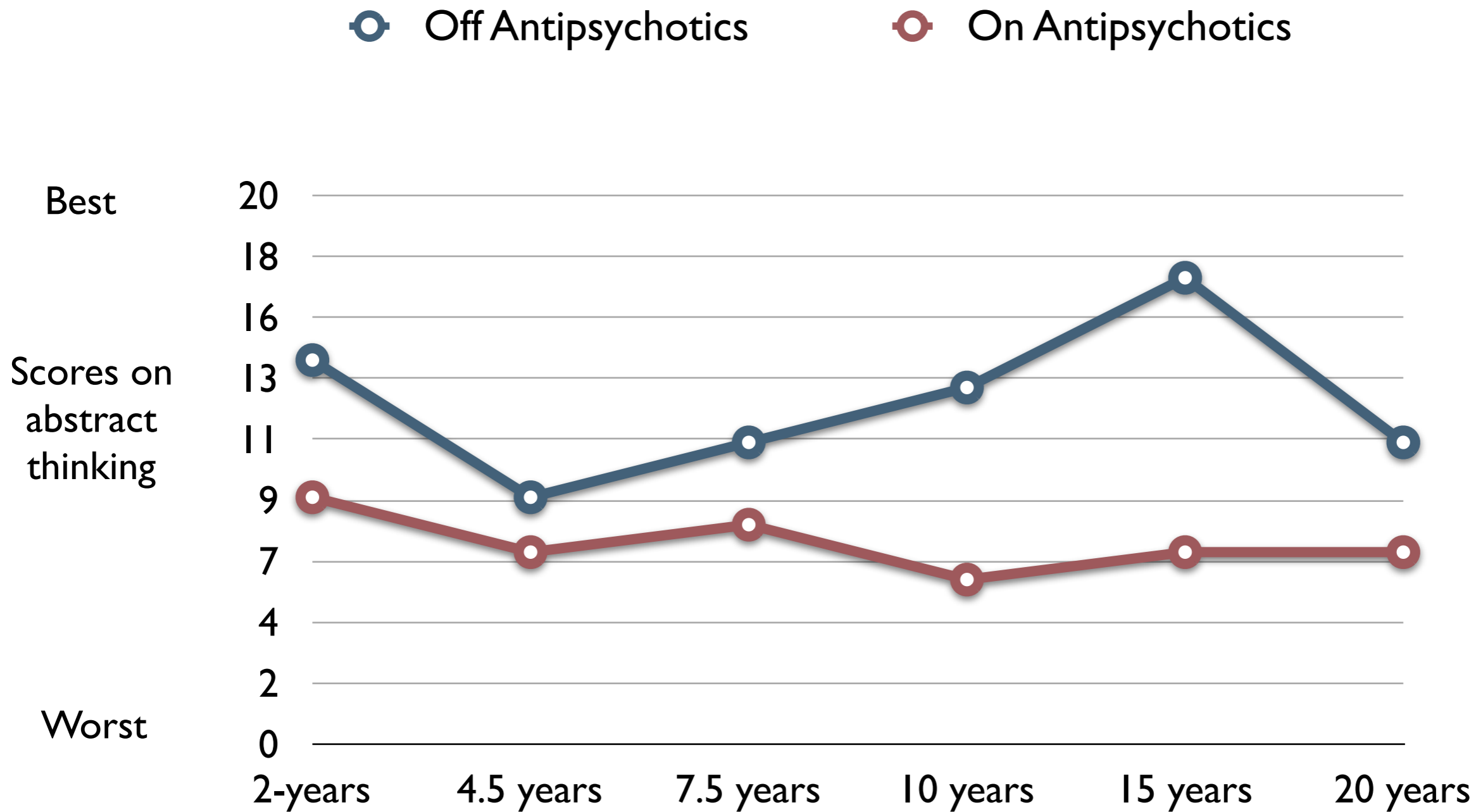
Source: Harrow M. "Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis?" *Psychological Medicine*, (2014):doi:10.1017/S0033291714000610

Anxiety Symptoms of Schizophrenia Patients



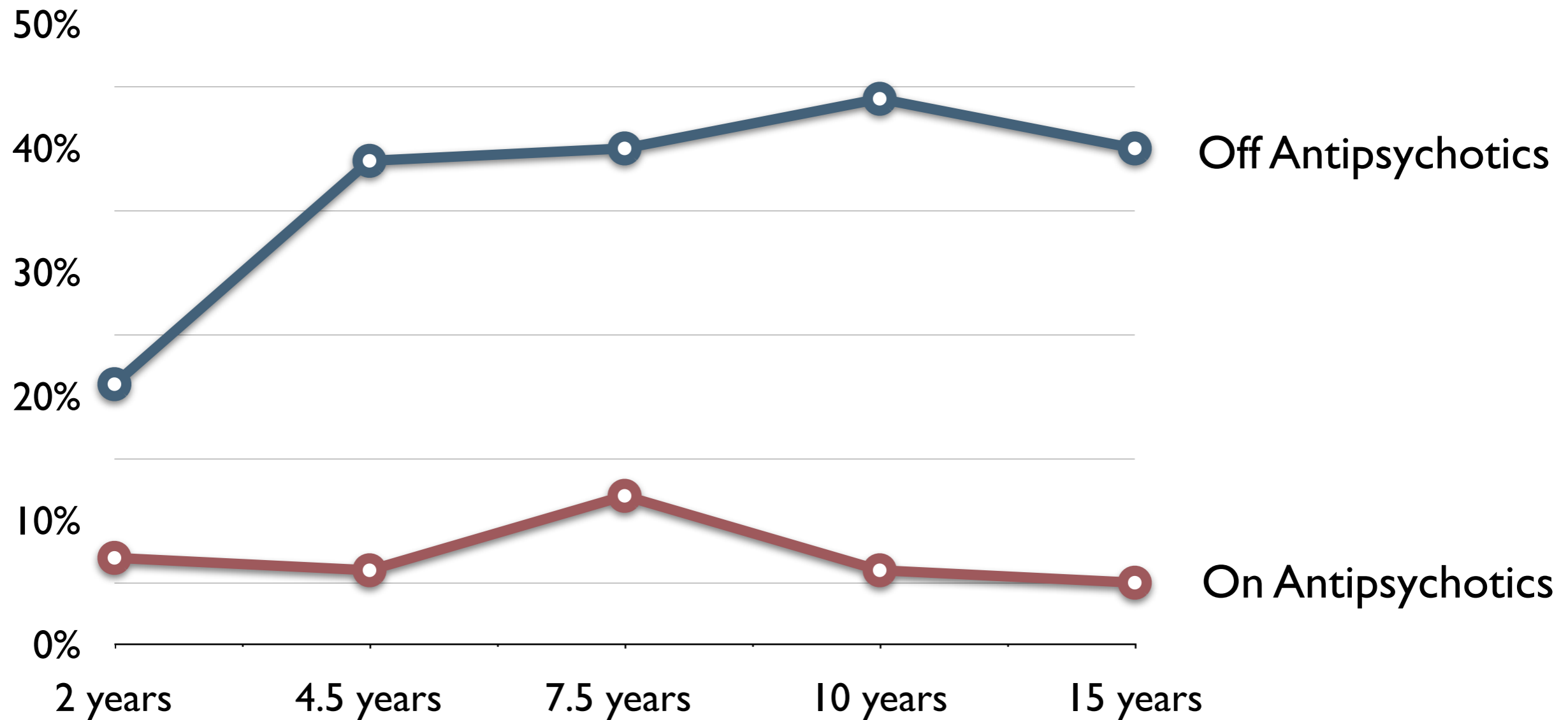
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study." *Psychological Medicine*, (2012):1-11.

Cognitive Function of Schizophrenia Patients



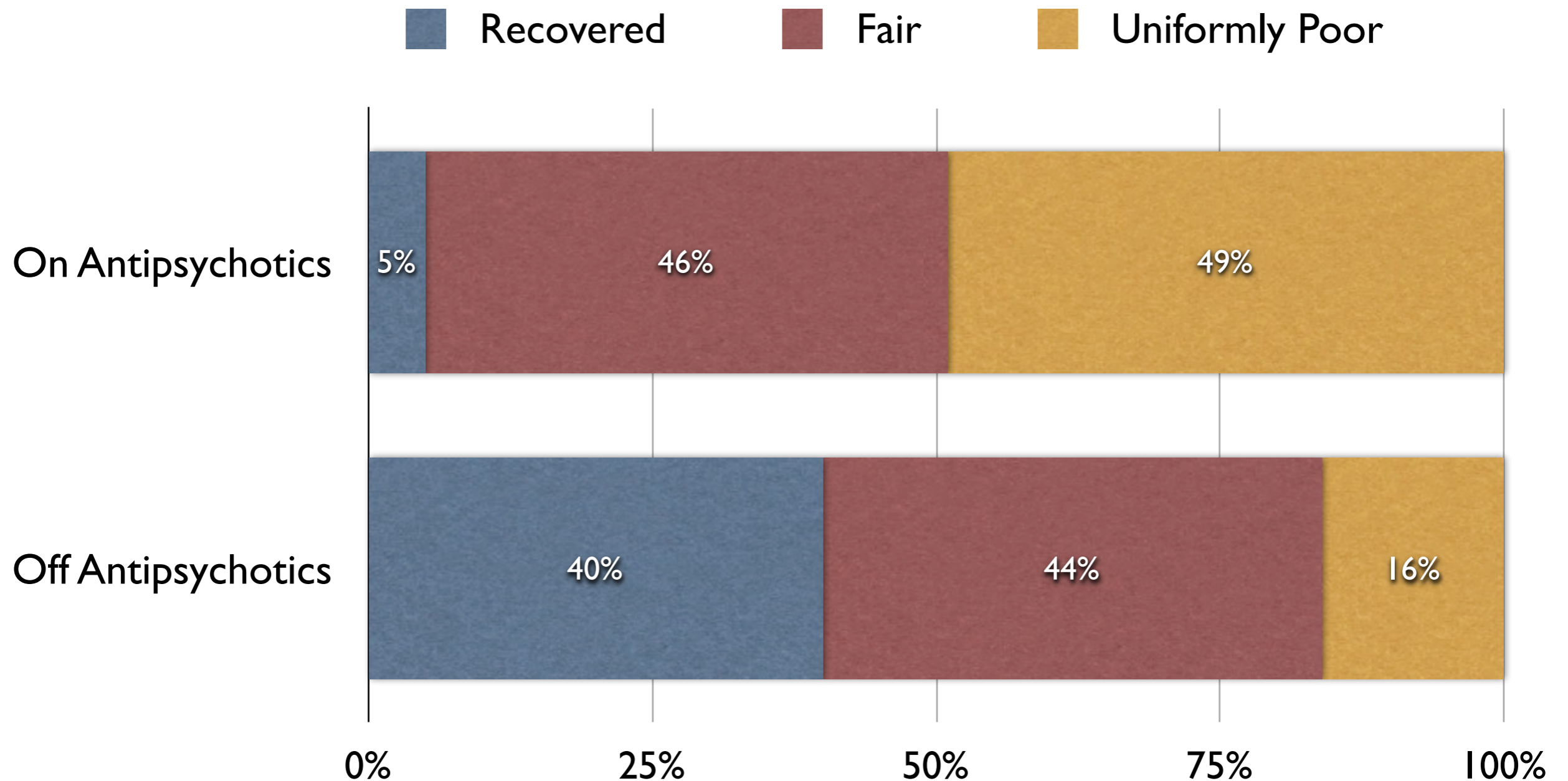
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study." *Psychological Medicine*, (2012):1-11.

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.

Spectrum of Outcomes in Harrow's Study

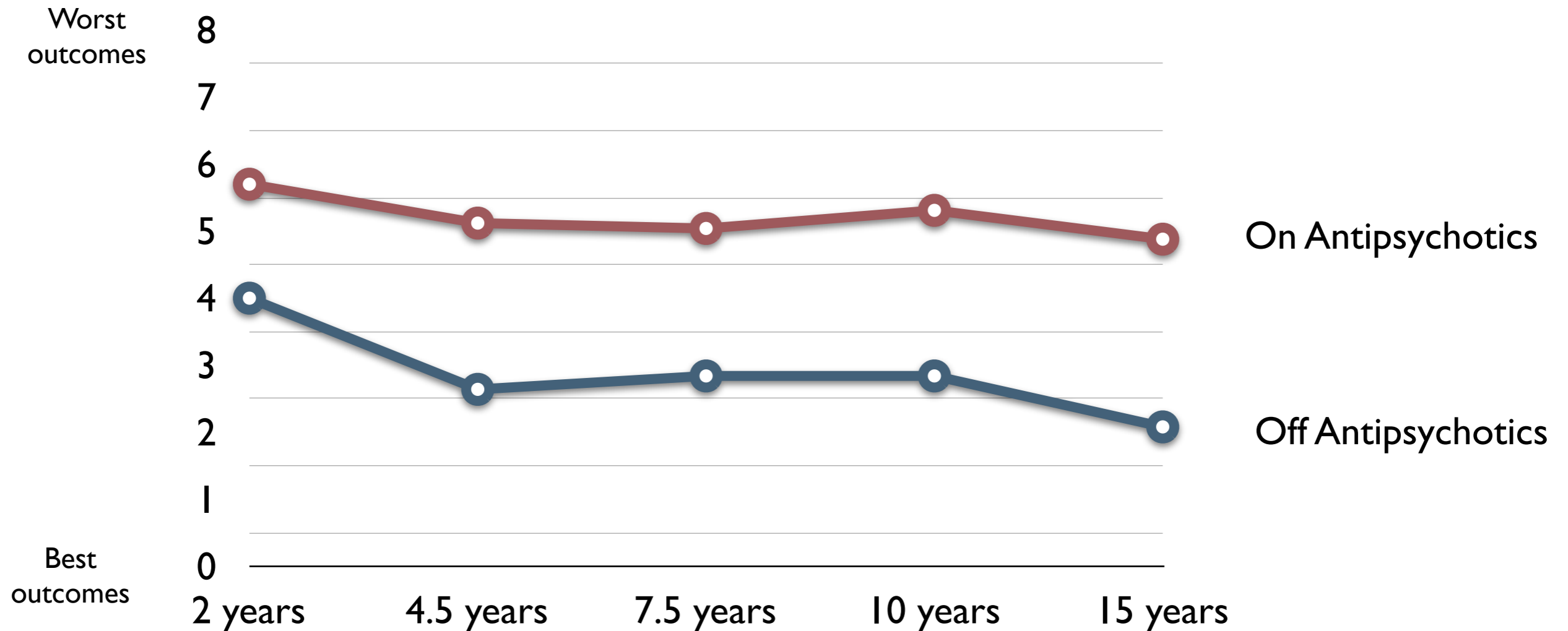


Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

“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.”

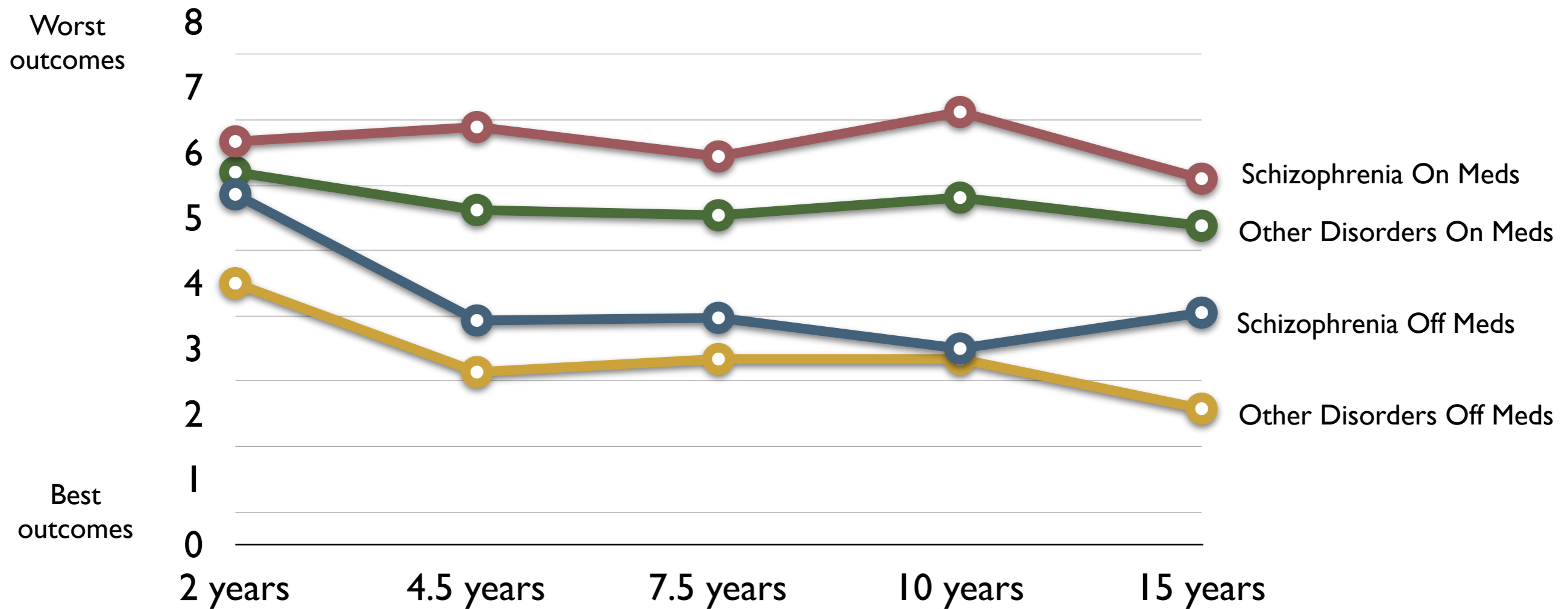
--Martin Harrow, American Psychiatric Association annual meeting, 2008

Global Adjustment of “Other 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.

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

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

Why Are SSRIs Depressogenic Over the Long Term?

“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.

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.

Acknowledgement That Bipolar Outcomes Have Worsened in Modern Era

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.”

Spanish Investigators: Time To Rethink Use of Stimulants

“These drugs are the same stimulants whose harmful consequences are well known in other uses in adults. In this paper we have carried out an exhaustive review of the sources from scientific evidence regarding the short and long term effectiveness of the medication . . . The result is disappointing and should lead to a modification of the CPGs to the use of drugs as tools of last resort, in a small number of cases and limited and short periods of time.”

--Miguel Valverde Eizaquirre

Source: M.Valverde. “Outreach and limitations of the pharmacological treatment of Attention Deficit Disorder with Hyperactivity (ADHD) in children and adolescents and Clinical Practice Guidelines: A literature review.” *Rev Asoc Esp. Neuropsiq* 34 (2014):37-74.

The Problem With Psychiatric Drugs

- The burden of mental illness in the U.S., Europe, and other developed societies has markedly increased in the modern “drug” era.
- The drugs perturb neurotransmitter pathways, and over the long-term, this may produce a compensatory response that is the opposite of what is originally intended (oppositional tolerance.)
- While the medications may be effective over the short-term, the long-term outcomes literature reveals that they increase the chronicity of schizophrenia, depression and bipolar disorder, and worsen long-term functional outcomes.

From the Co-founder of the Cochrane Collaboration:

“I know some excellent psychiatrists who help their patients a lot . . . I also know that some drugs can be helpful sometimes for some patients. And I am not ‘antipsychiatry’ in any way. But my studies in this area lead me to a very uncomfortable conclusion:

Our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good.”

–Peter C. Gøtzsche, 2013

Co-founder of the Cochrane Collaboration

Director of the Nordic Cochrane Center