

# The Case for Psychiatric Drug Withdrawal

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October 2016

# The Problem With Psychiatric Drugs

- The drugs create abnormalities in brain function. They do not fix chemical imbalances, but instead create them.
- Over the long-term, psychiatric drugs increase the chronicity of psychiatric disorders, and impair functioning. They lower long-term recovery rates.

# 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*.

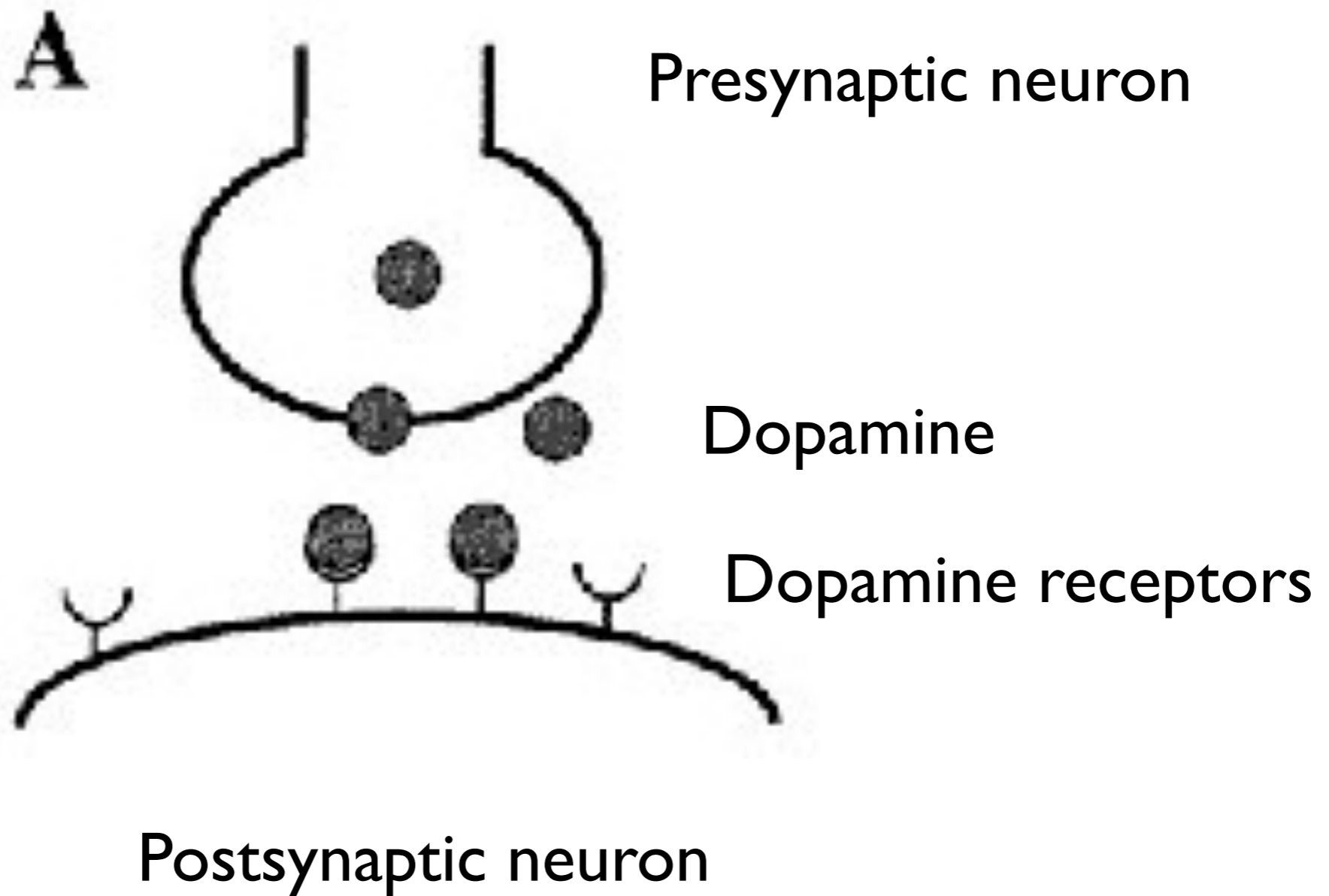
# A Paradigm for Understanding Psychotropic Drugs

**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.”

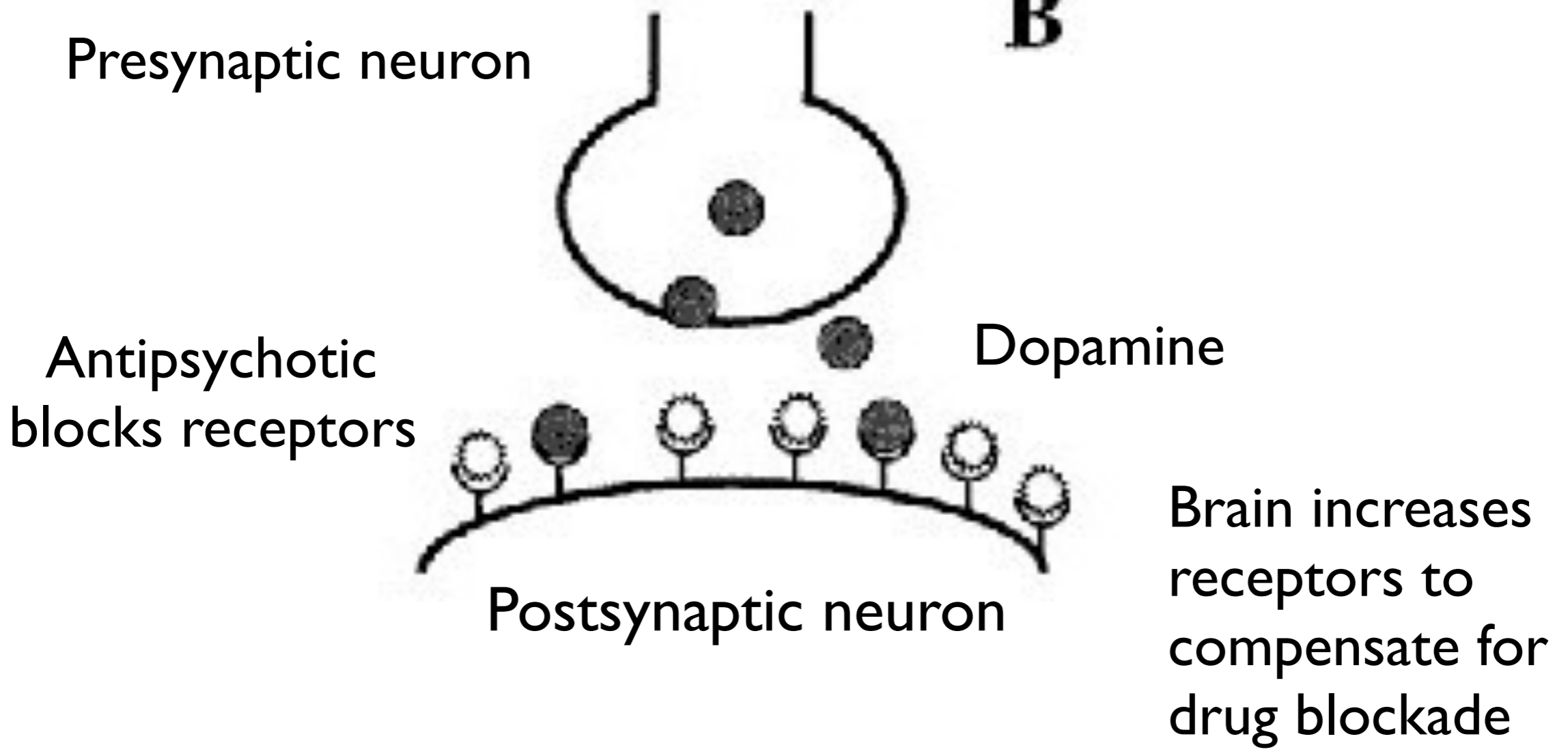
Source: Hyman, S. “Initiation and adaptation: A paradigm for understanding psychotropic drug action.” *Am J Psychiatry* 153 (1996):151-61.

# Dopamine function before exposure to antipsychotics



# Dopamine function after exposure to antipsychotics

**B**





# 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” With All Psychiatric Drugs

“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

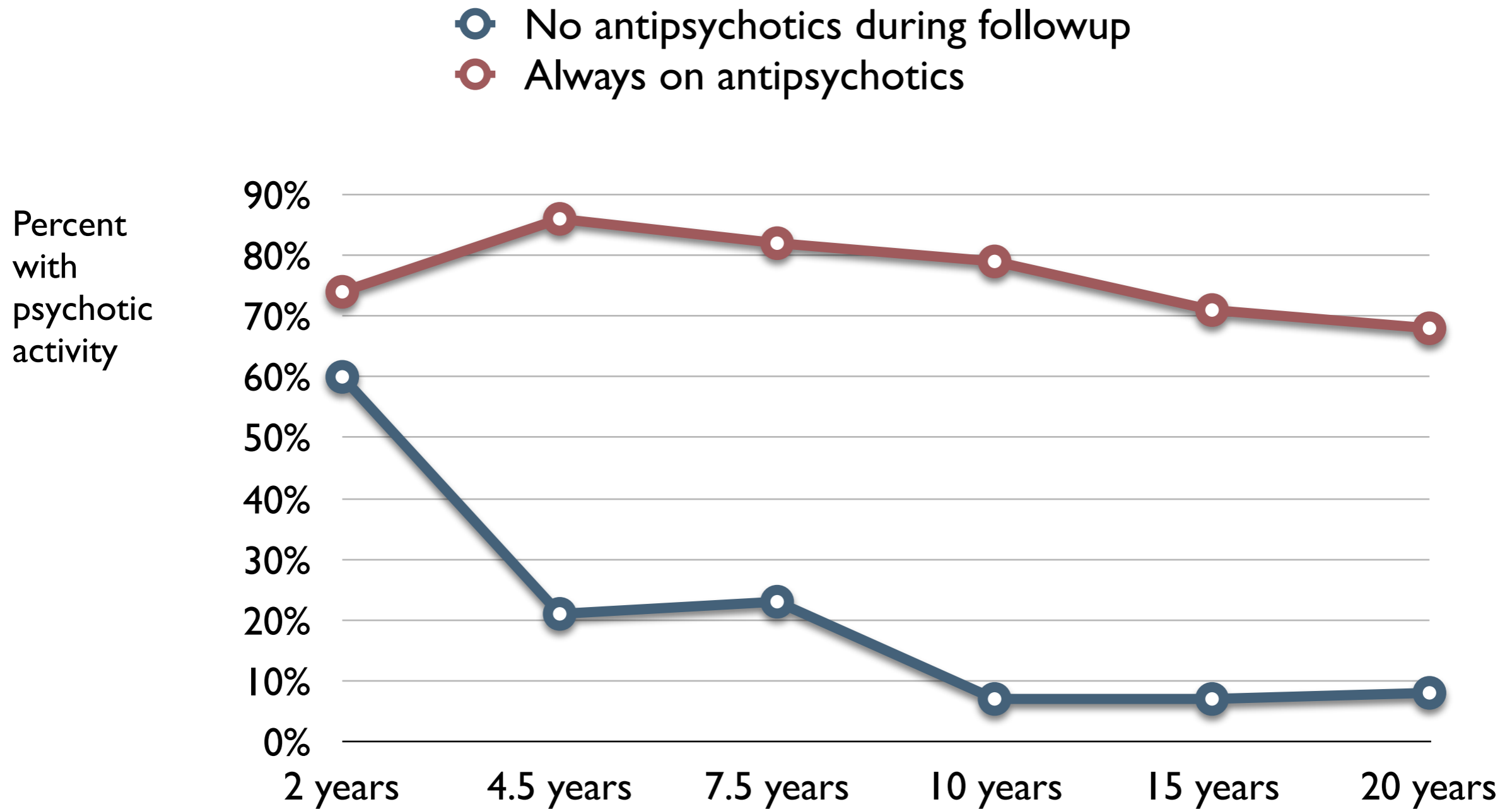
Source: El-Mallakh, R. “Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression.” *Medical Hypotheses* 76 (2011): 769-773.

# Martin Harrow's Long-Term Study of Psychotic Patients

## Patient Enrollment

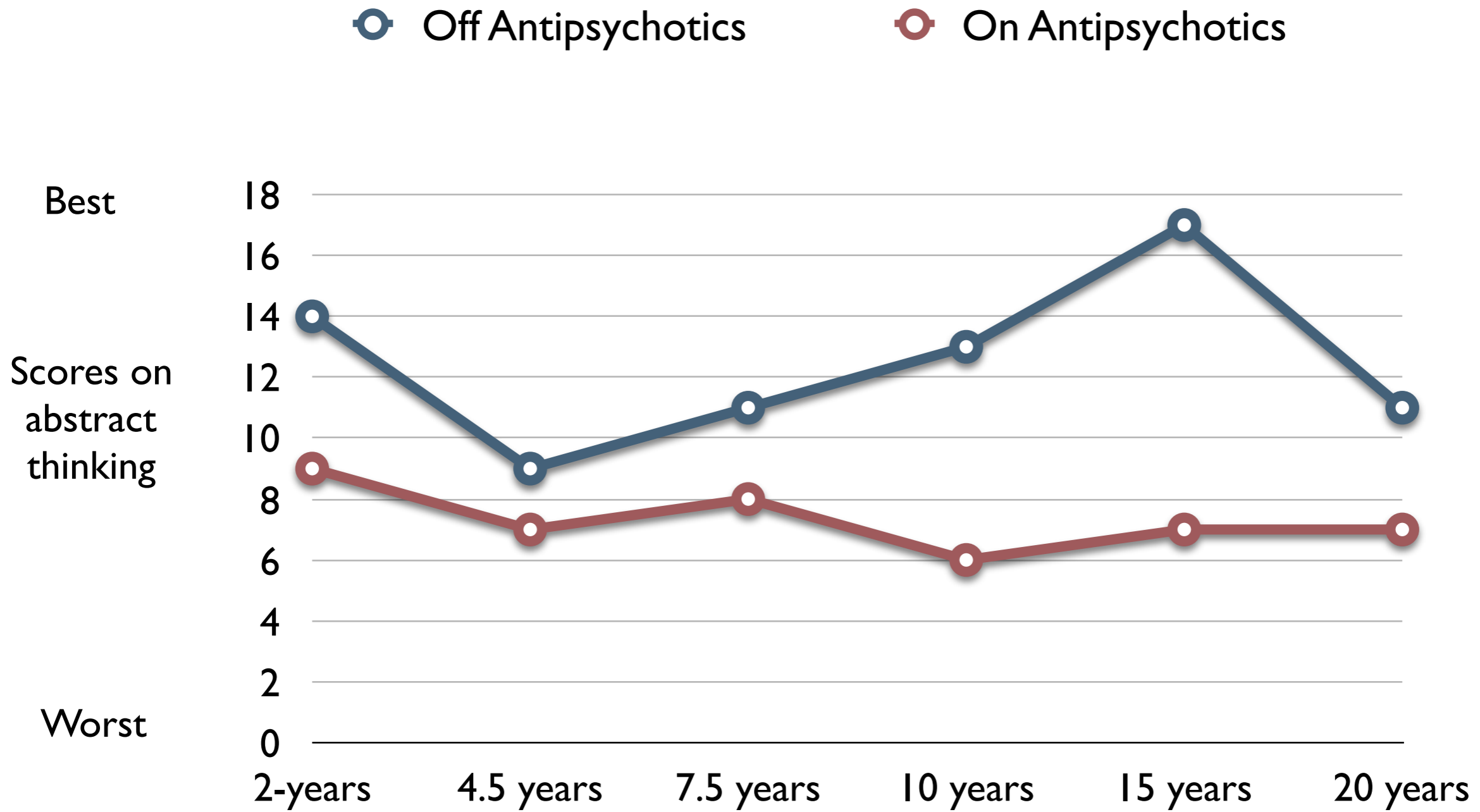
- 64 schizophrenia patients
- 81 patients with other psychotic disorders
  - 37 psychotic bipolar patients
  - 28 unipolar psychotic patients
  - 16 other milder psychotic disorders
- Median age of 22.9 years at index hospitalization
- Previous hospitalization
  - 46% first hospitalization
  - 21% one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

# Psychotic Symptoms of Schizophrenia Patients



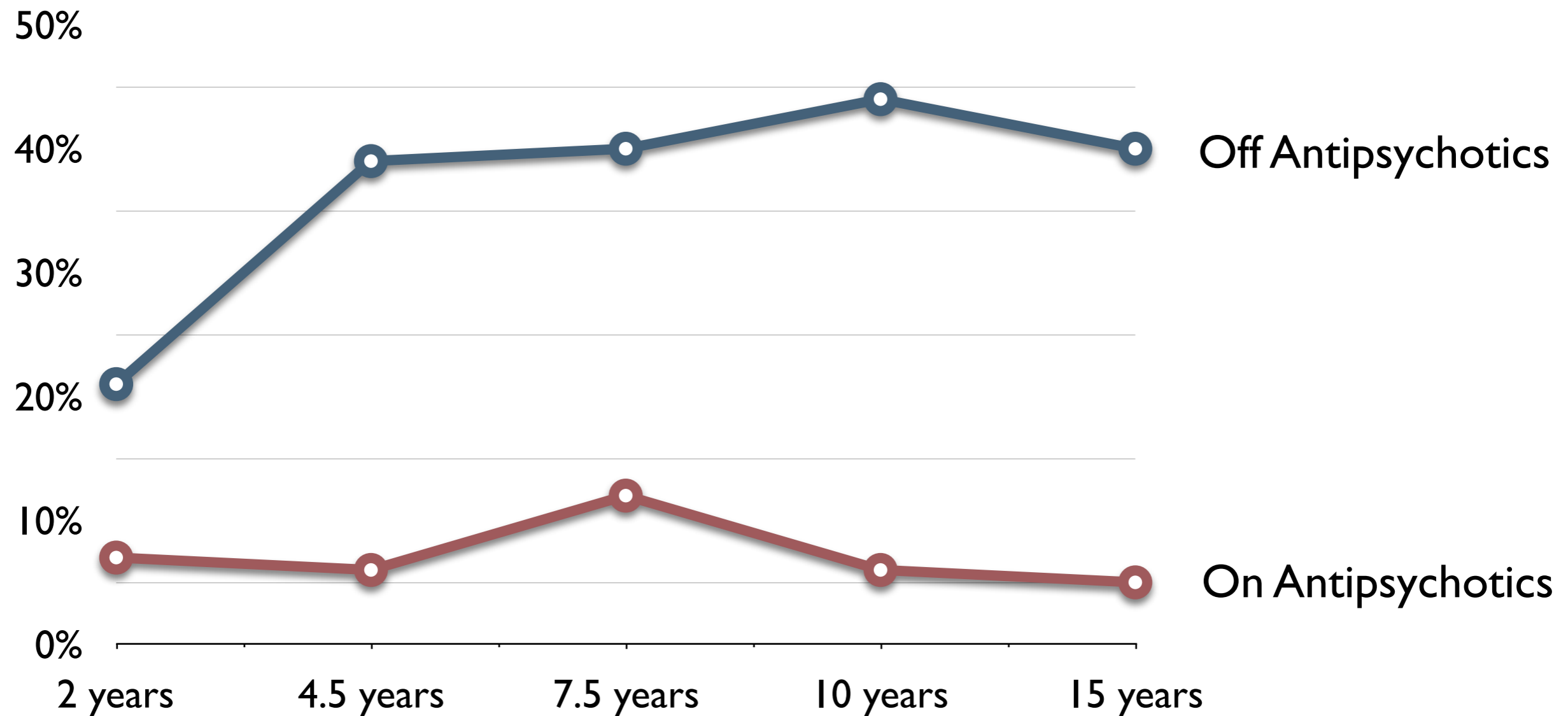
Source: Harrow M. "Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis?" *Psychological Medicine*, (2014):doi:10.1017/S0033291714000610

# 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

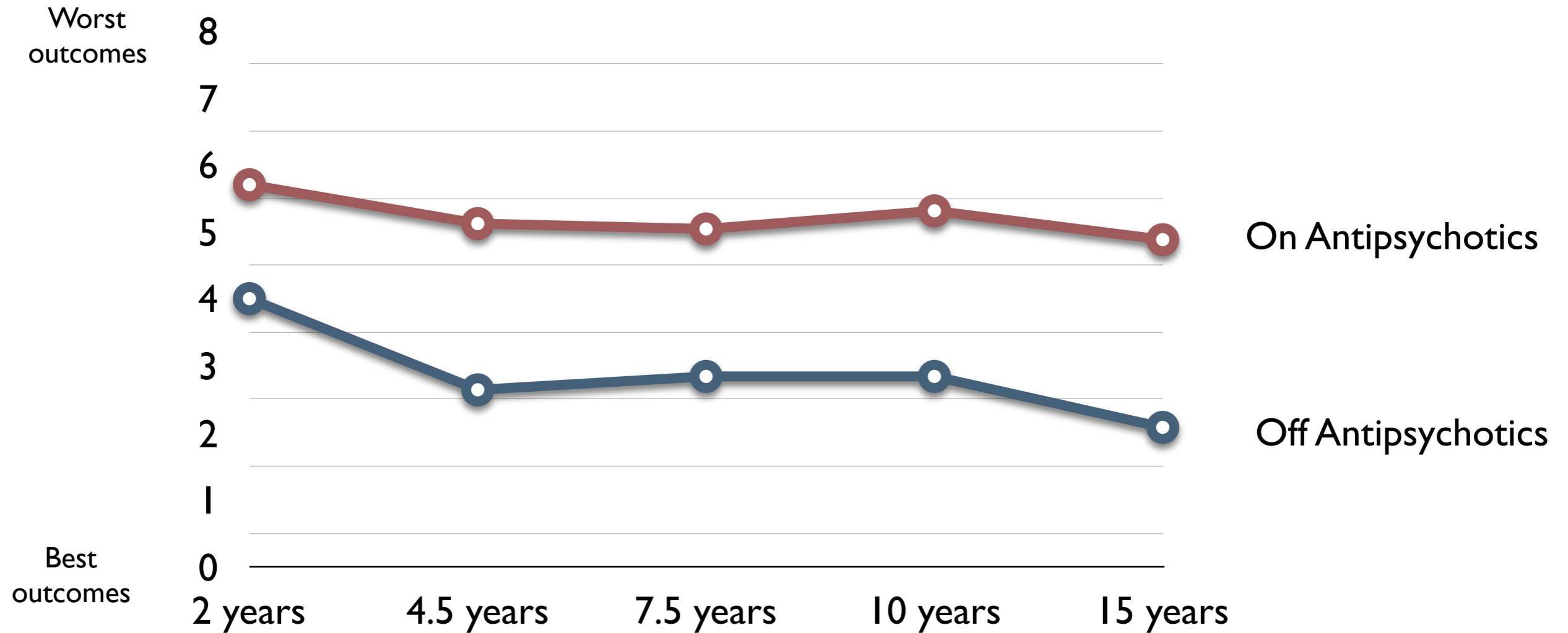


Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

“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

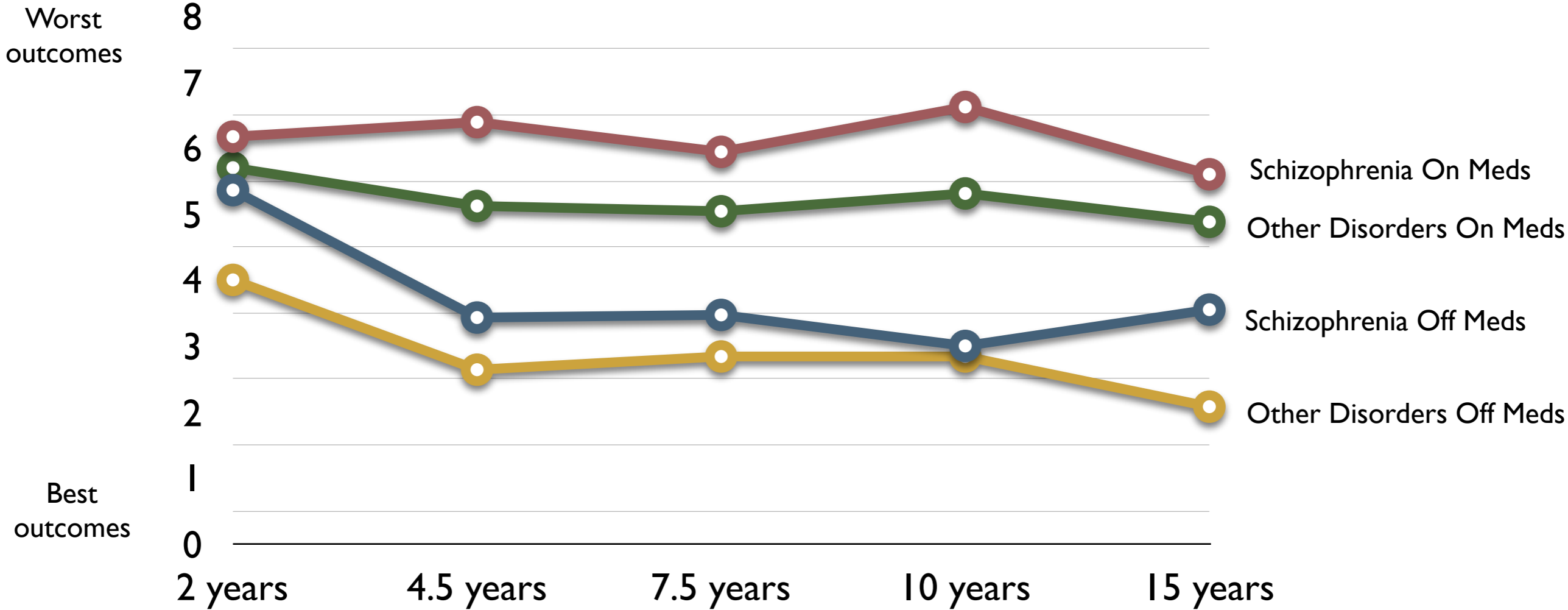
# Global Adjustment of “Other Psychotic” Patients



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.”

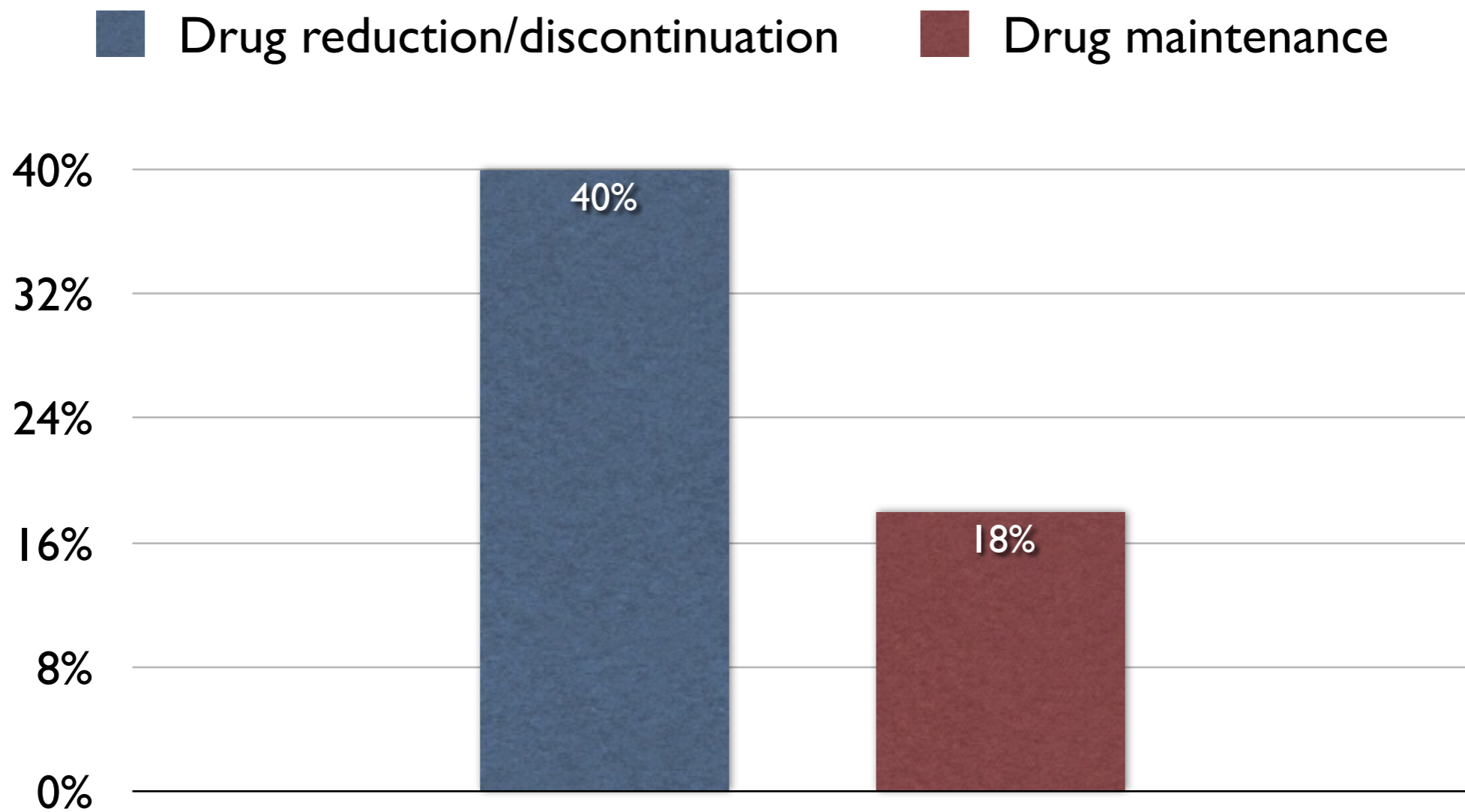
--Martin Harrow, 2013

# Lex Wunderink's Randomized Study of Long-term Outcomes

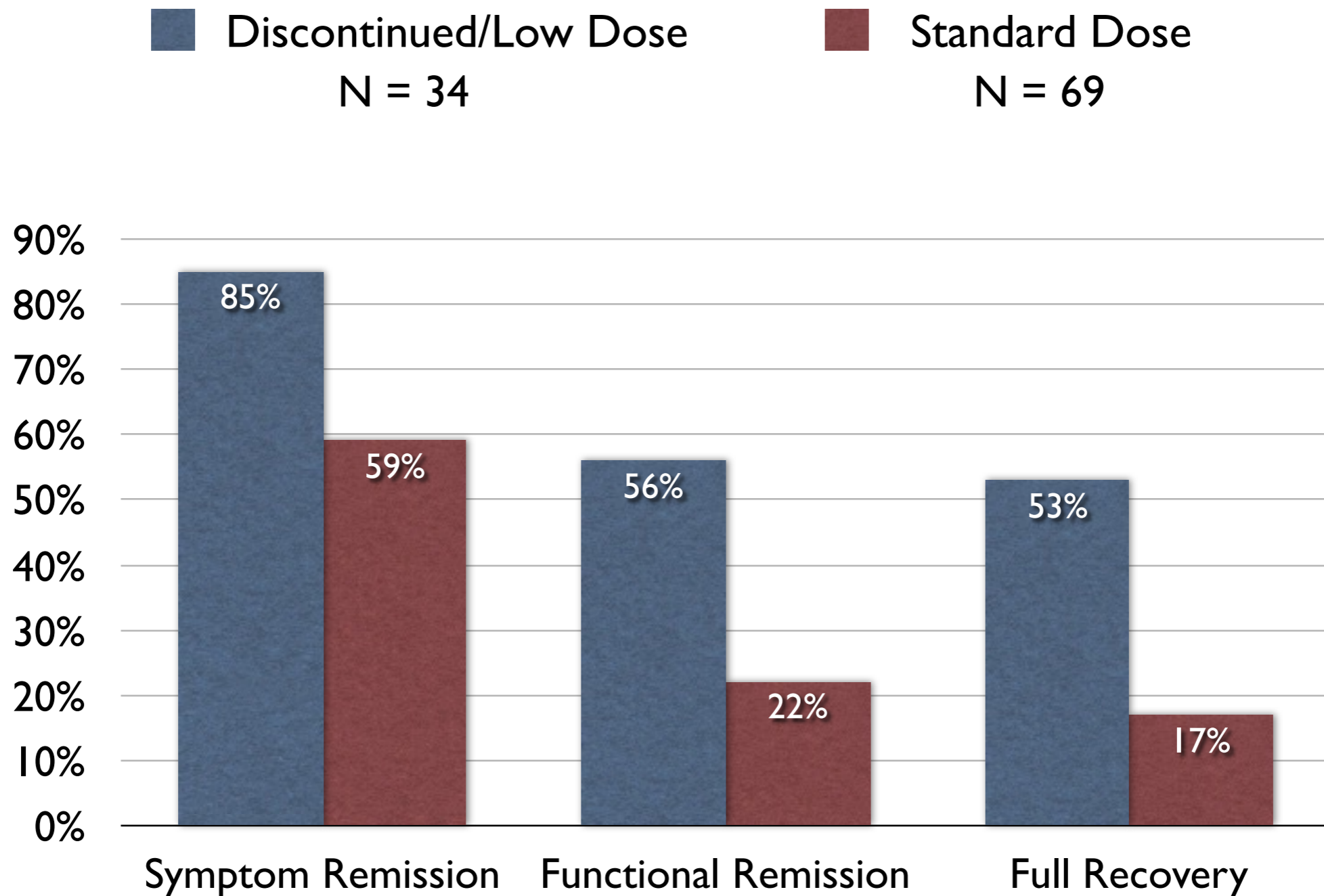
## Study Design

- 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.

# Long-Term Recovery Rates (at 7 Years)



# Outcomes By Antipsychotic Use



# Wunderink's Conclusion

“Antipsychotic postsynaptic blockade of the dopamine signaling system, particularly of the mesocortical and mesolimbic tracts, not only might prevent and redress psychotic derangements but also might compromise important mental functions, such as alertness, curiosity, drive, and activity levels, and aspects of executive functional capacity to some extent.”

# 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 APA Acknowledges Change in Course of Depression in Modern Era

## **American Psychiatric Association's Textbook of Psychiatry, 1999:**

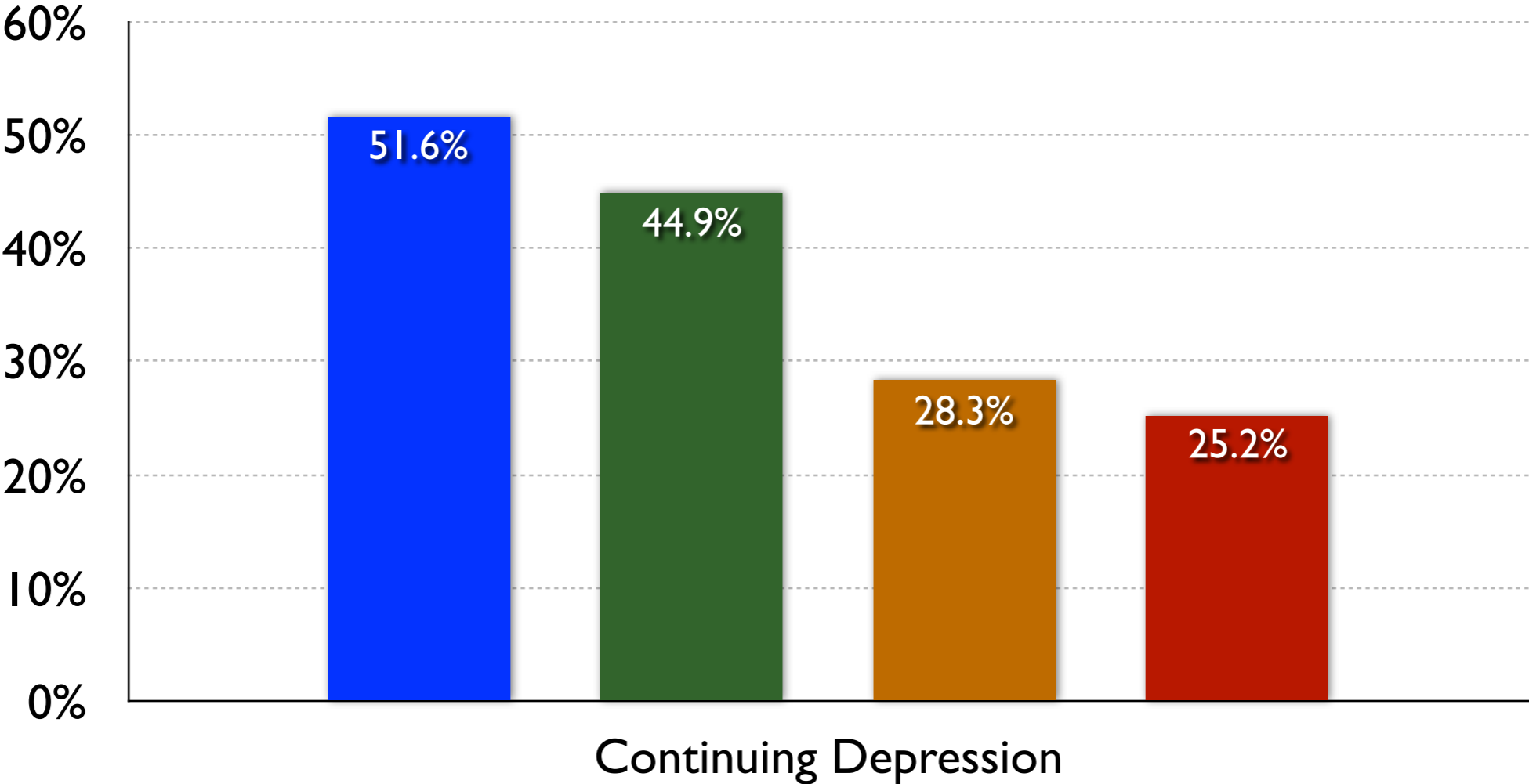
It used to be believed that “most patients would eventually recover from a major depressive episode. However, more extensive studies have disproved this assumption.” It was now known that “depression is a highly recurrent and pernicious disorder.”



# One-Year Outcomes in WHO Screening Study for Depression

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

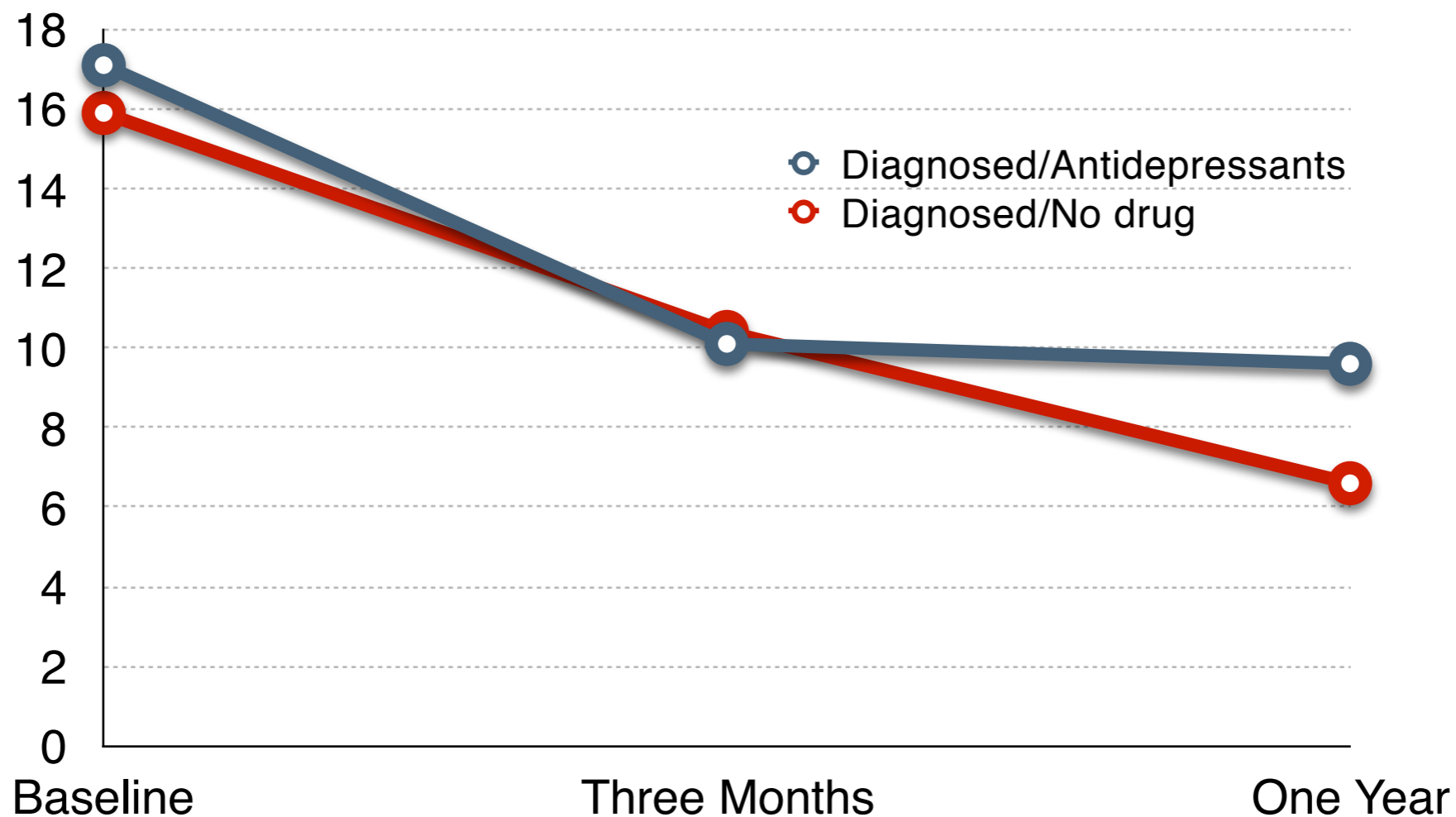
N = 740



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

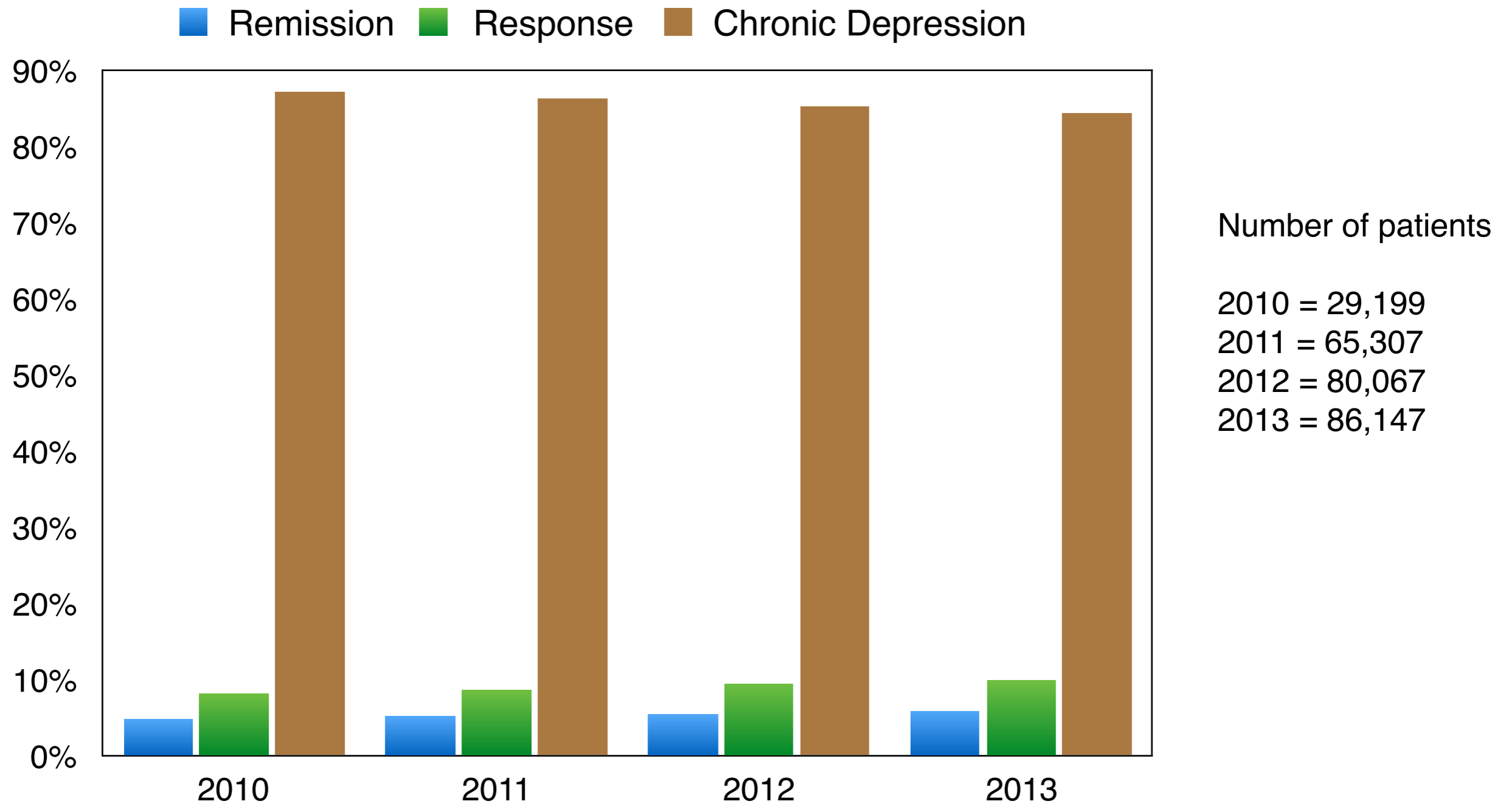
# WHO Study: Medicated Patients Stop Getting Better After Three Months

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.

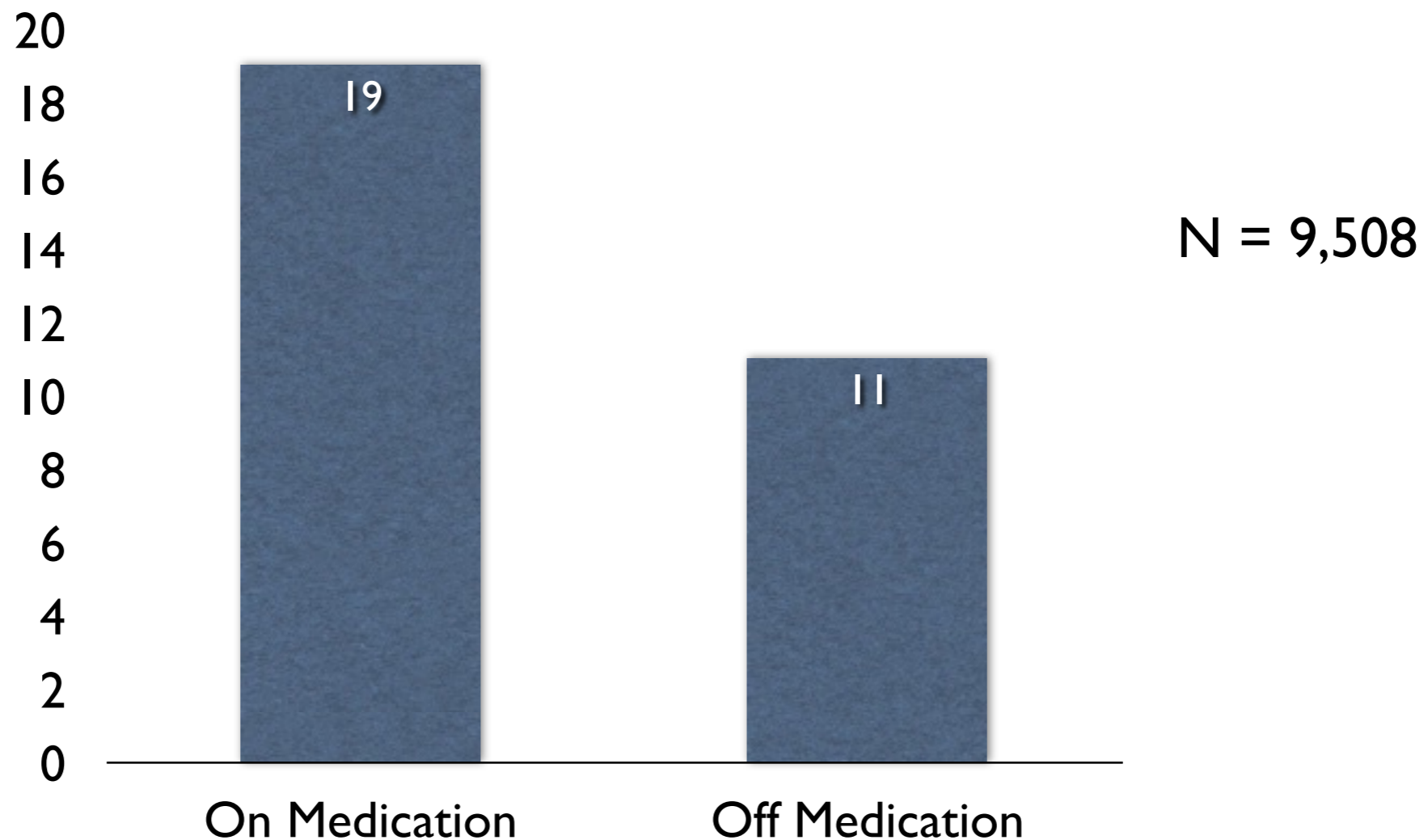
# Real World Outcomes in Minnesota: Few Patients in Recovery At End of Year



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

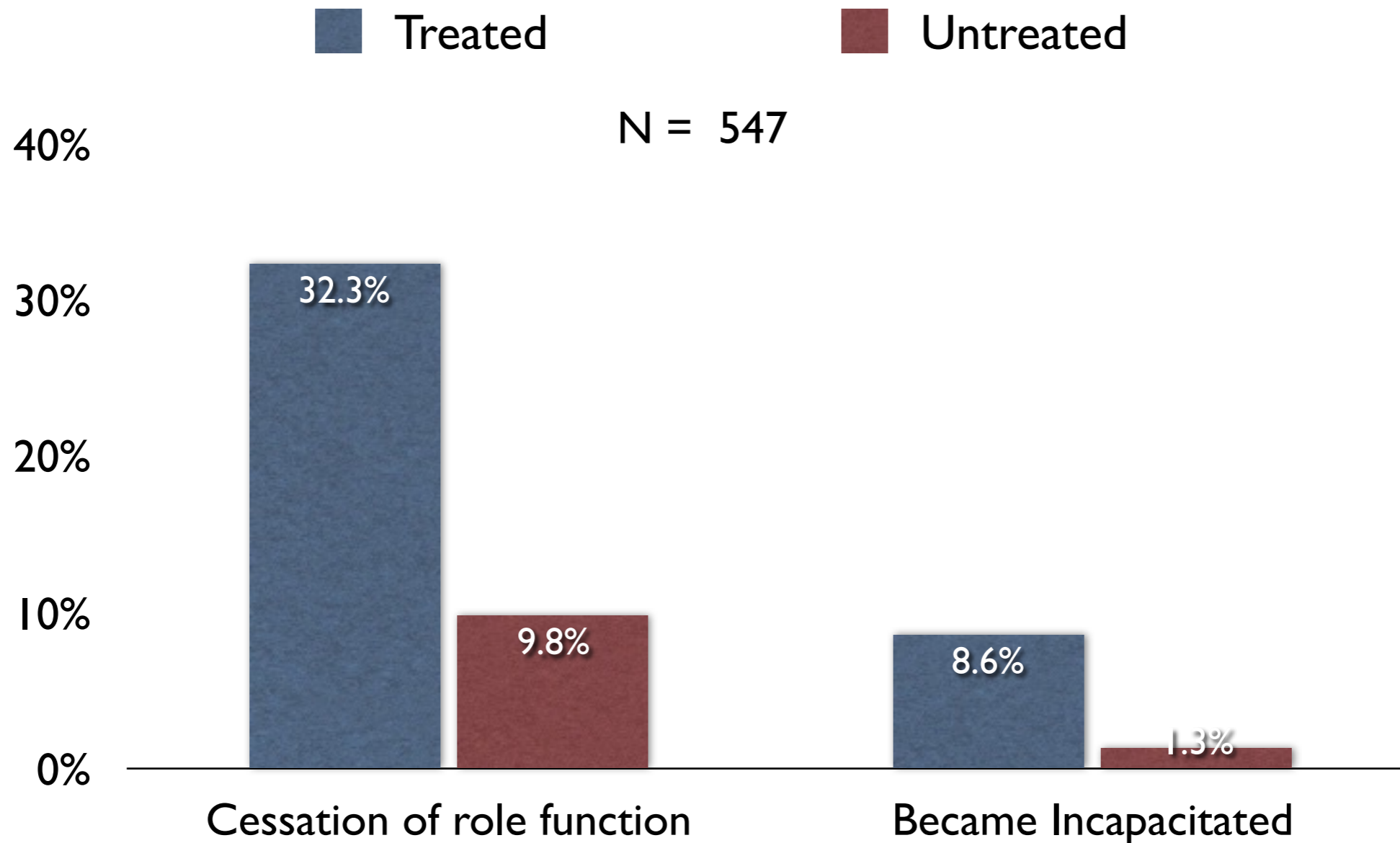
# Five-Year Outcomes in Canada

Number of Weeks  
Depressed Each Year



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

# 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.

## 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

# 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.

# 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.



# 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.

# Research Questions

- Does the brain renormalize upon drug withdrawal? Do presynaptic release of neurotransmitters and post-synaptic receptor densities normalize? If so, how long does this take?
- How often do long-term users of antipsychotics, antidepressants, and benzodiazepines, upon drug withdrawal, exhibit evidence of brain impairments that do not renormalize: tardive dyskinesia, post SSRI sexual dysfunction (PSSD), and protracted withdrawal symptoms?
- Are there drug-tapering protocols that can help renormalization?

- How can withdrawal symptoms be distinguished from “return of the disorder” symptoms?
- What tapering speeds produce the best results? Can tapering protocols be developed? Or must discontinuation efforts be individualized?
- What protocols can be developed for withdrawing from multiple psychiatric drugs?

# A Final Question

Why hasn't the medical community  
addressed this issue before?