Rethinking Psychiatric Care:

History, Science, and the Long-term Effects of Psychiatric Drugs

Robert Whitaker
May 2013

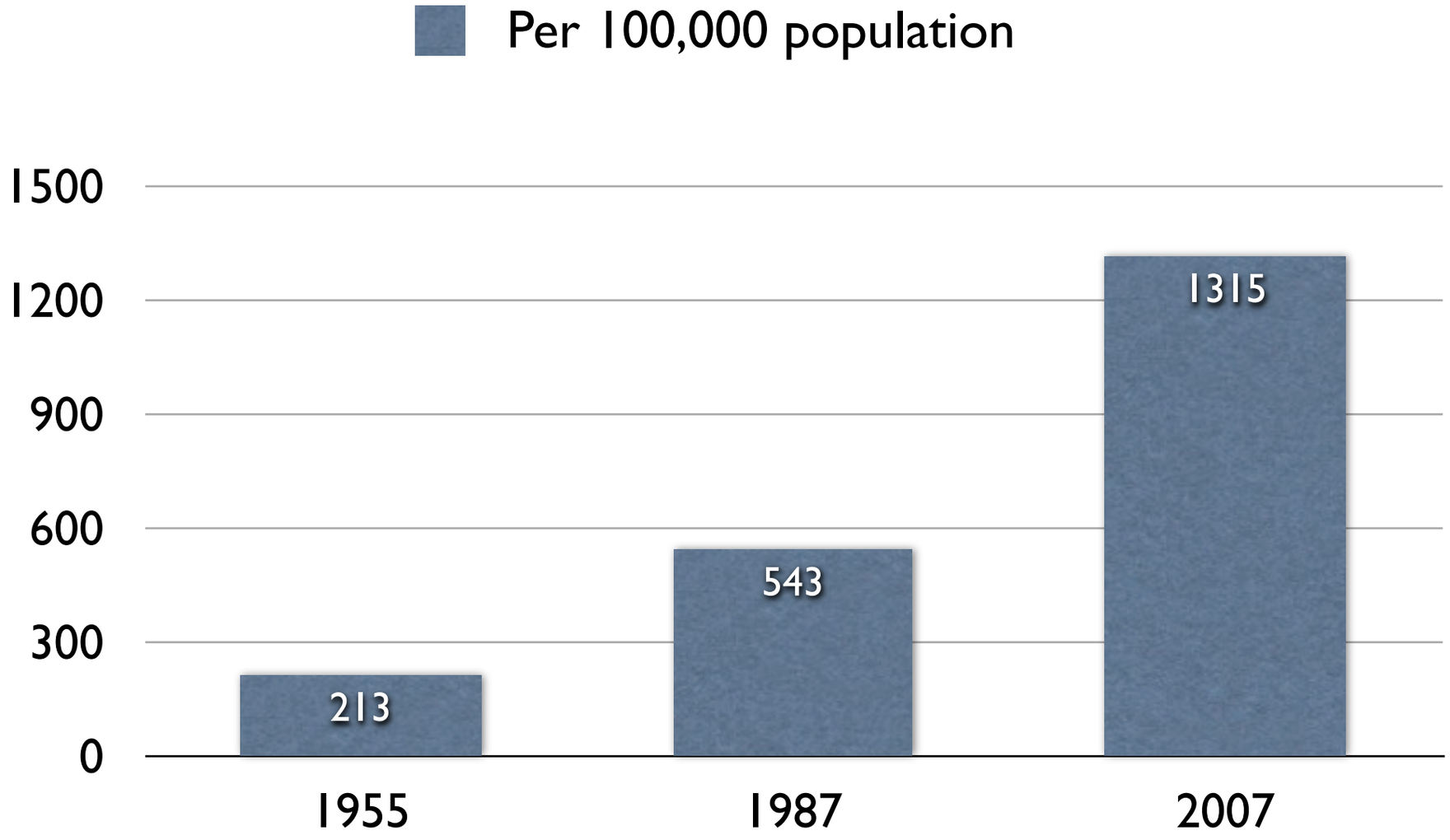
The Common Wisdom

The introduction of chlorpromazine into asylum medicine in 1955 "initiated a revolution in psychiatry, comparable to the introduction of penicillin in general medicine."

--Edward Shorter, *A History of Psychiatry*

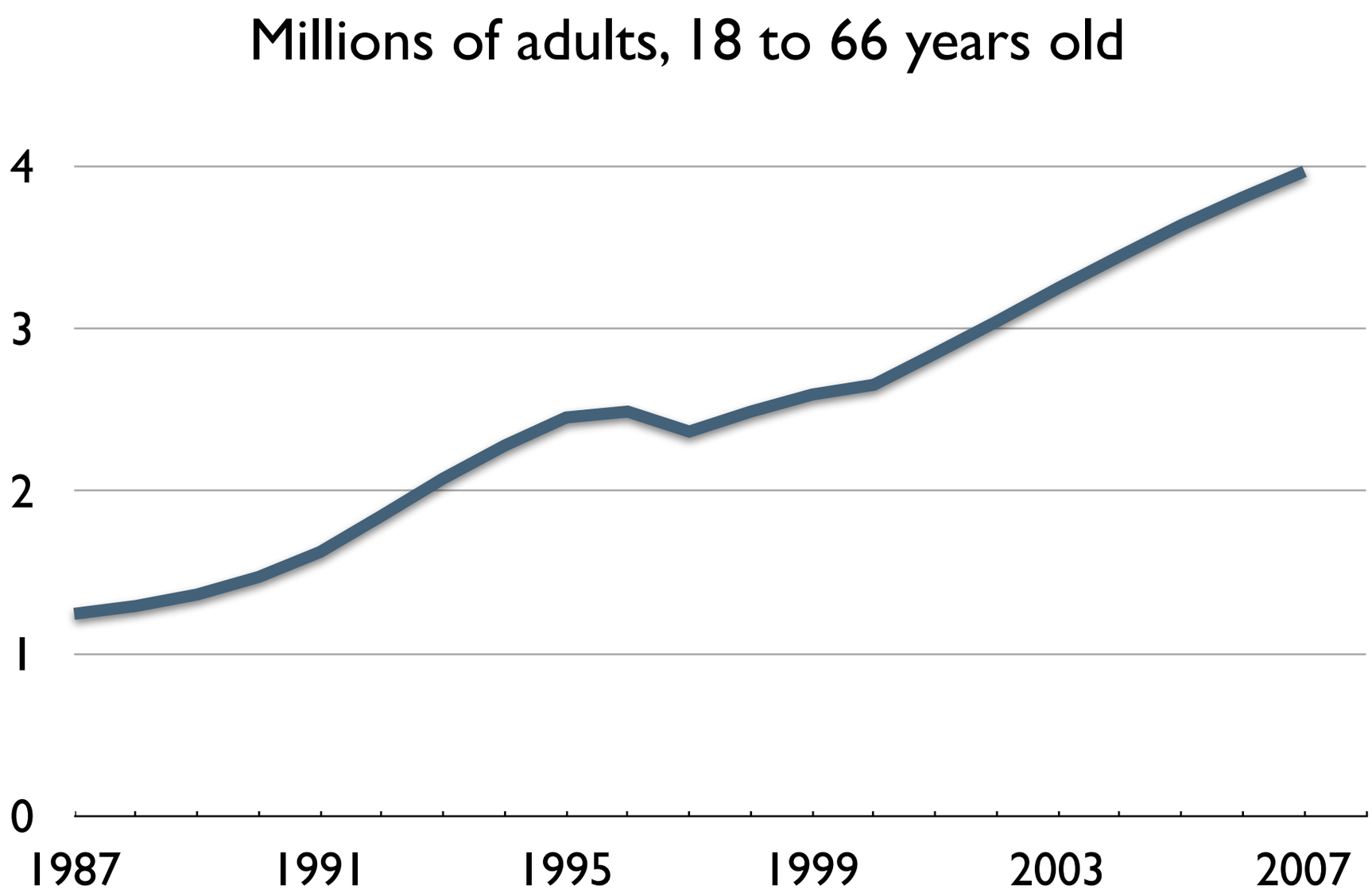
The Disabled Mentally Ill in the United States, 1955-2007

(under government care)



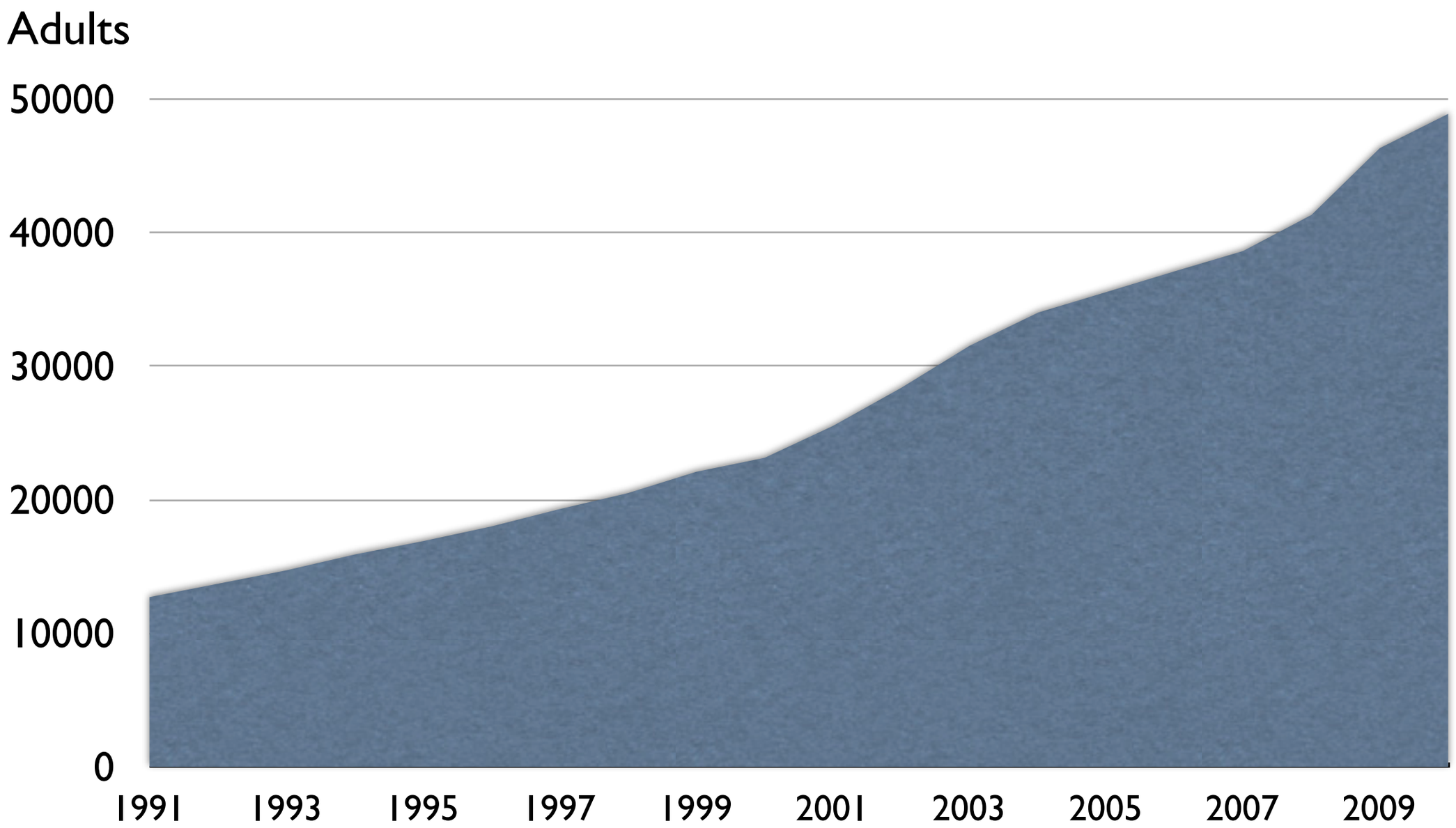
Source: Silverman, C. *The Epidemiology of Depression* (1968): 139. U.S. Social Security Administration Reports, 1987-2007.

U.S. Disability in the Prozac Era



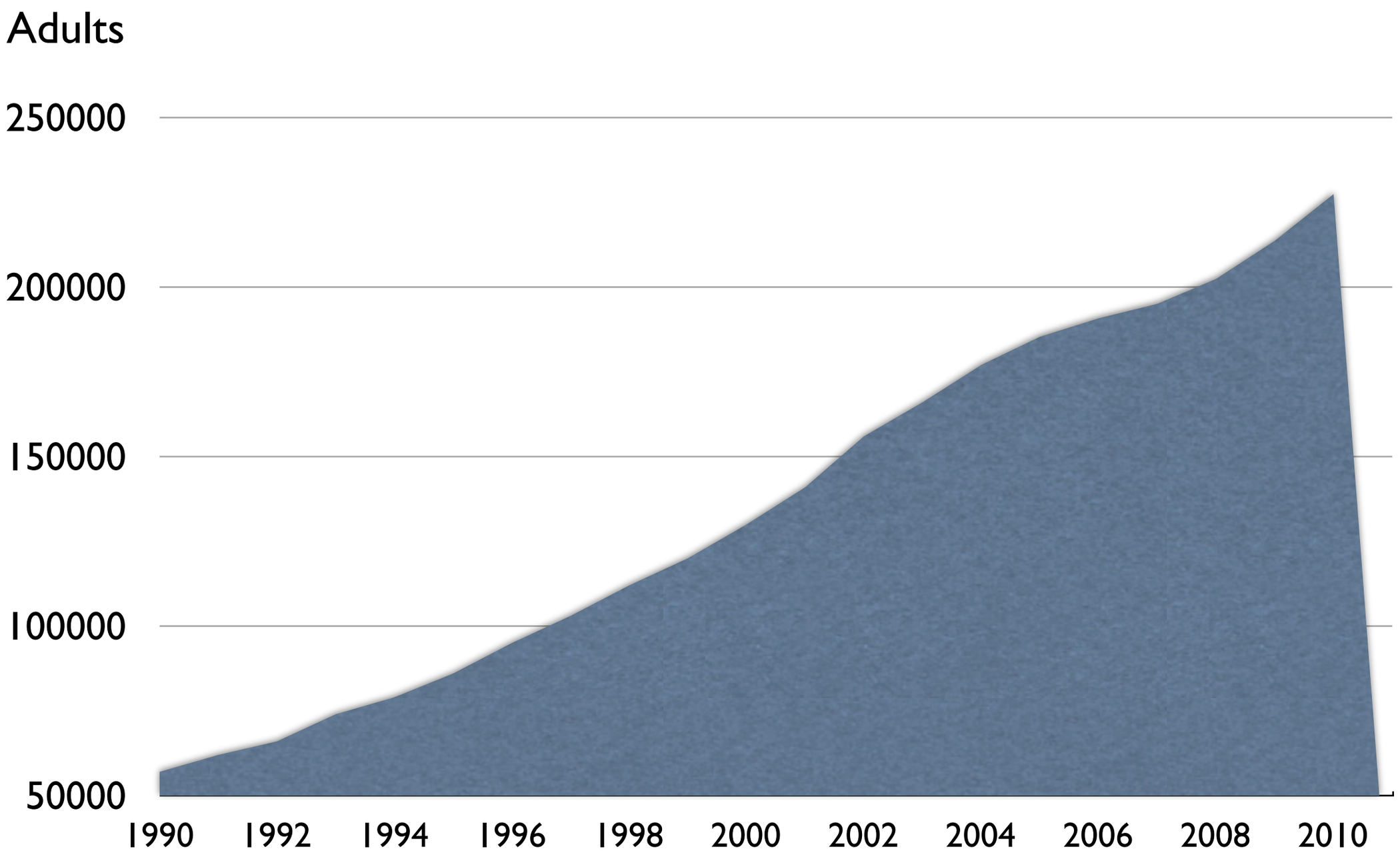
Source: U.S. Social Security Administration Reports, 1987-2007

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



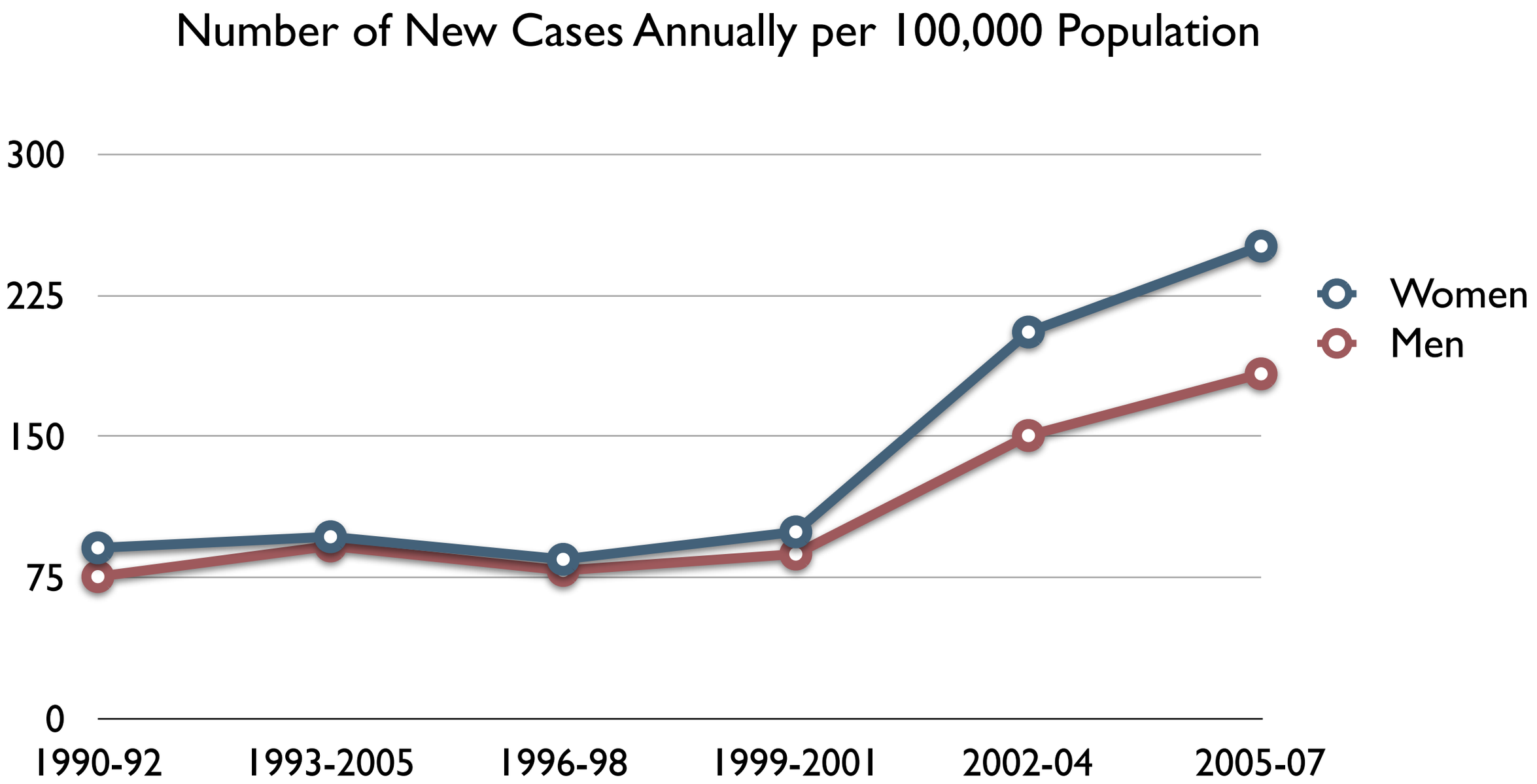
Source: *Statistics New Zealand,* Annual reports, 1999-2010

Disability Due to Psychiatric Disorders in Australia, 1990-2010



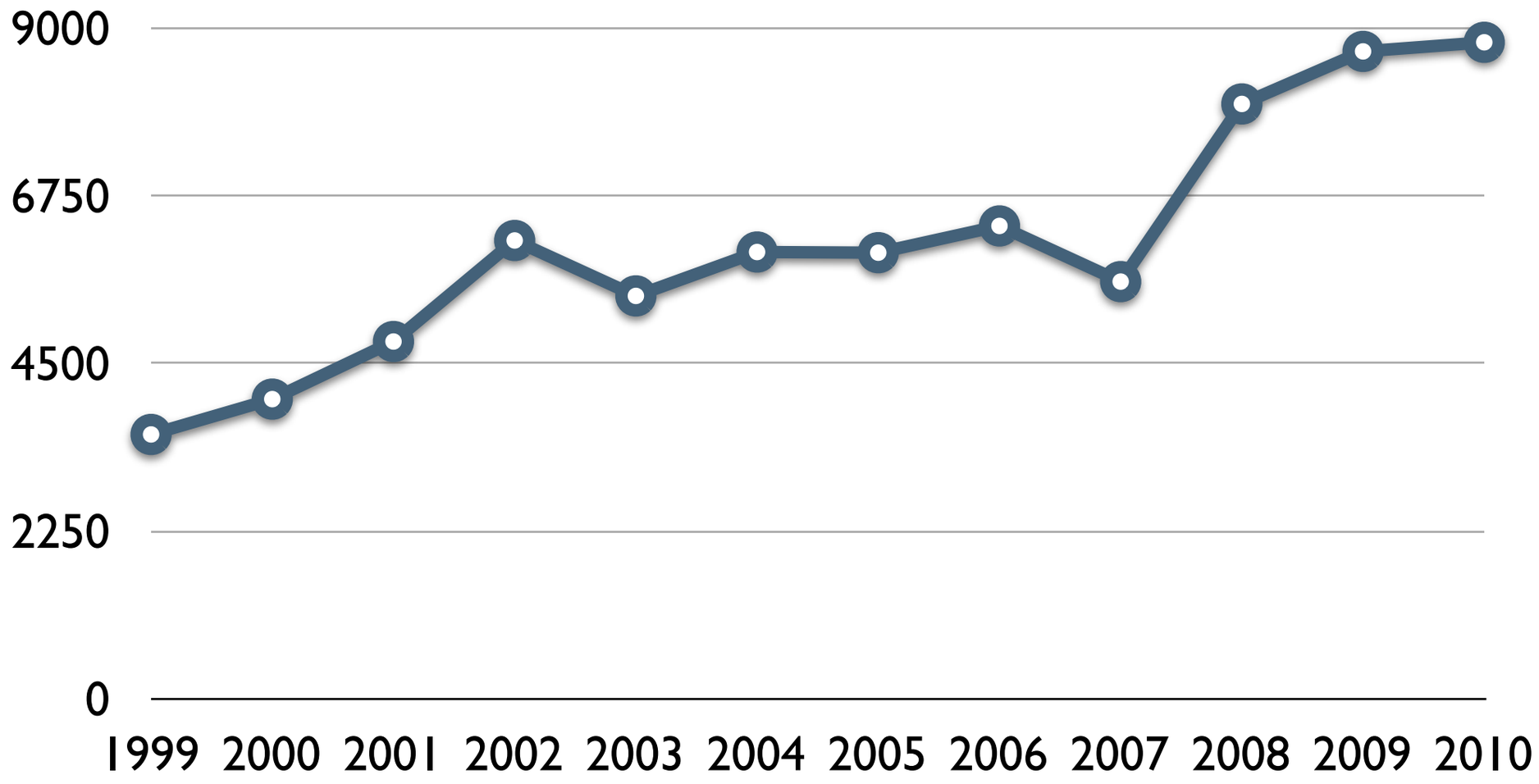
Source: Australian Government, "Characteristics of Disability Support Pension Recipients, June 2011."

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.

One Question Raised by the Disability Data:

How do psychiatric medications affect the long-term course of mental disorders? Do they increase the likelihood that people diagnosed with a major mental disorder will do well over the long-term? Or do they increase the likelihood that people so diagnosed will have a poor long-term outcome?

How Do Psychiatric Medications Act on the Brain?

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 monamine 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." *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."

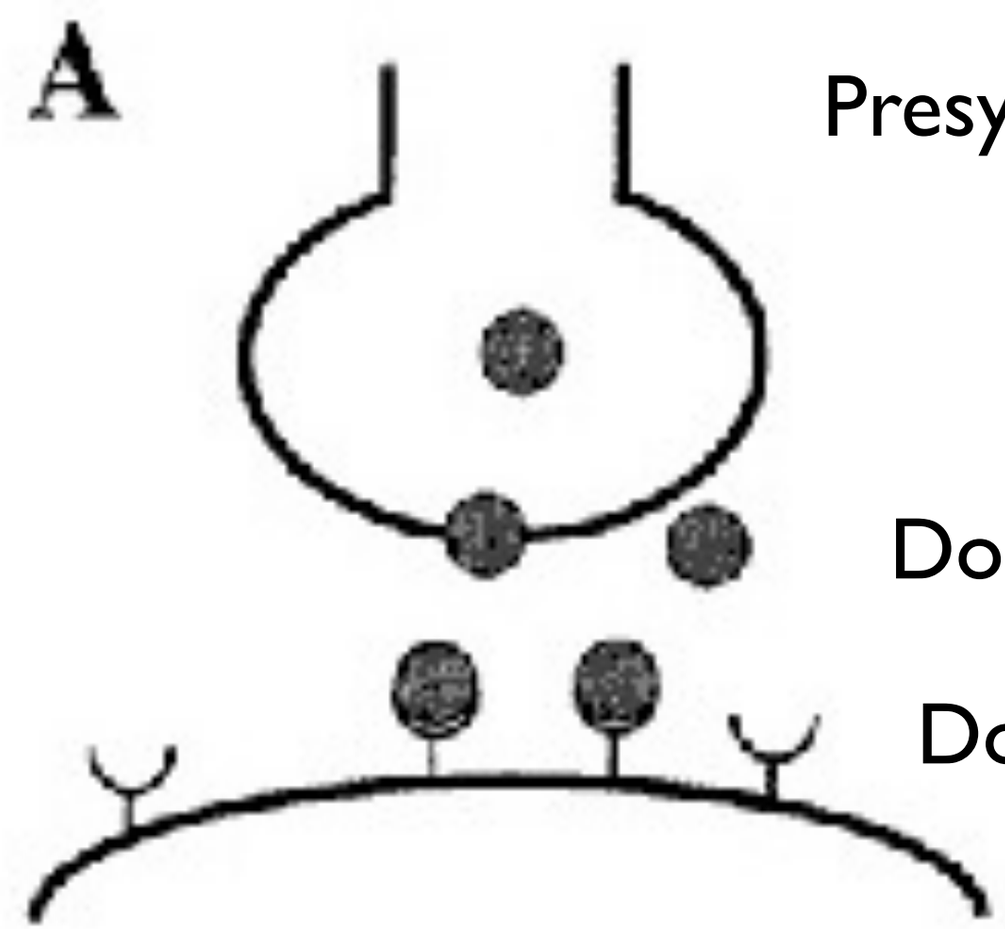
- In response, the brain goes through a series of compensatory adaptations in order "to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu."

- 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."

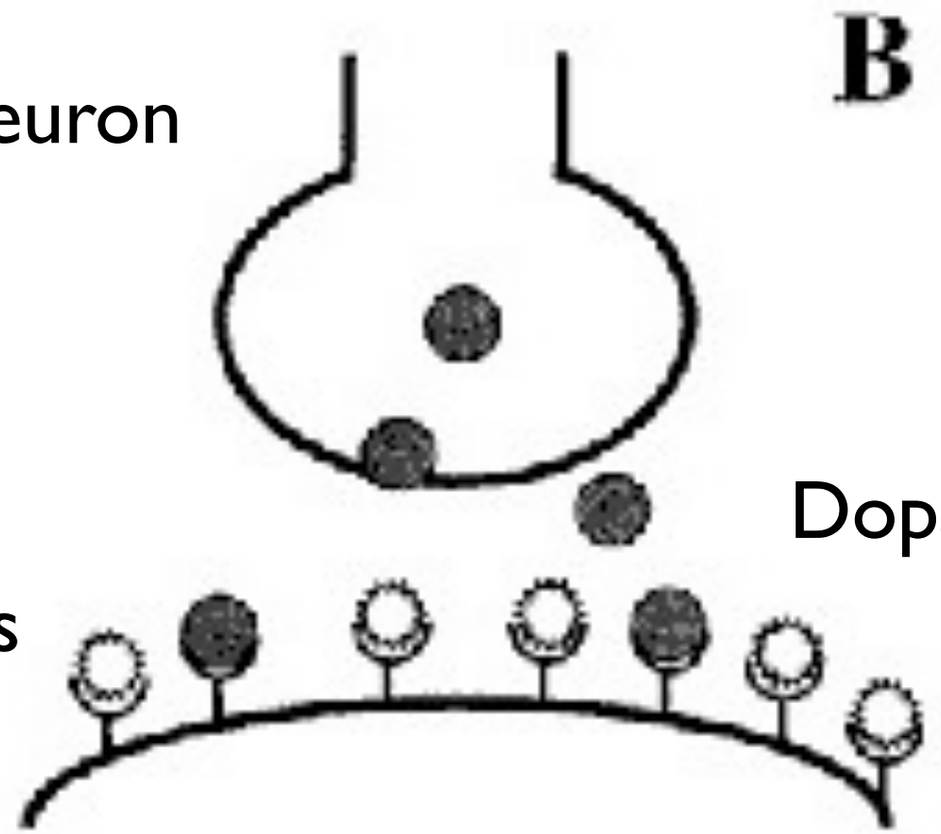
Source: Hyman, S. "Initiation and adaptation: A paradigm for understanding psychotropic drug action." *Am J Psychiatry* 153 (1996):151-61.

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

Presynaptic neuron



Antipsychotic blocks receptors

Dopamine

Postsynaptic neuron

Brain increases receptors to compensate for drug blockade

The Problem With Psychiatric Drugs

1. The etiology of most mental disorders remains unknown, and thus the drugs do not fix known pathologies.

2. The drugs impede the normal functioning of neurotransmitter pathways, which leads to significant side effects.

3. Over the long-term, the drugs induce changes in the brain the opposite of what is intended, and this increases the risk that a person will become chronically ill.

The 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.

Recovery Rates for Major Mental Disorders Prior to the Modern Drug Era

Schizophrenia Outcomes, 1945-1955

• At end of three years following hospitalization, 73 percent 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.

Outcomes for Hospitalized Depression in Pre-Drug Era

- Recovery from index episode was expected.

- In four of five long-term studies, more than 50% hospitalized for an index episode were never rehospitalized.

- The average time between recurrent episodes was three years or more.

"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

Long-term Outcomes 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.

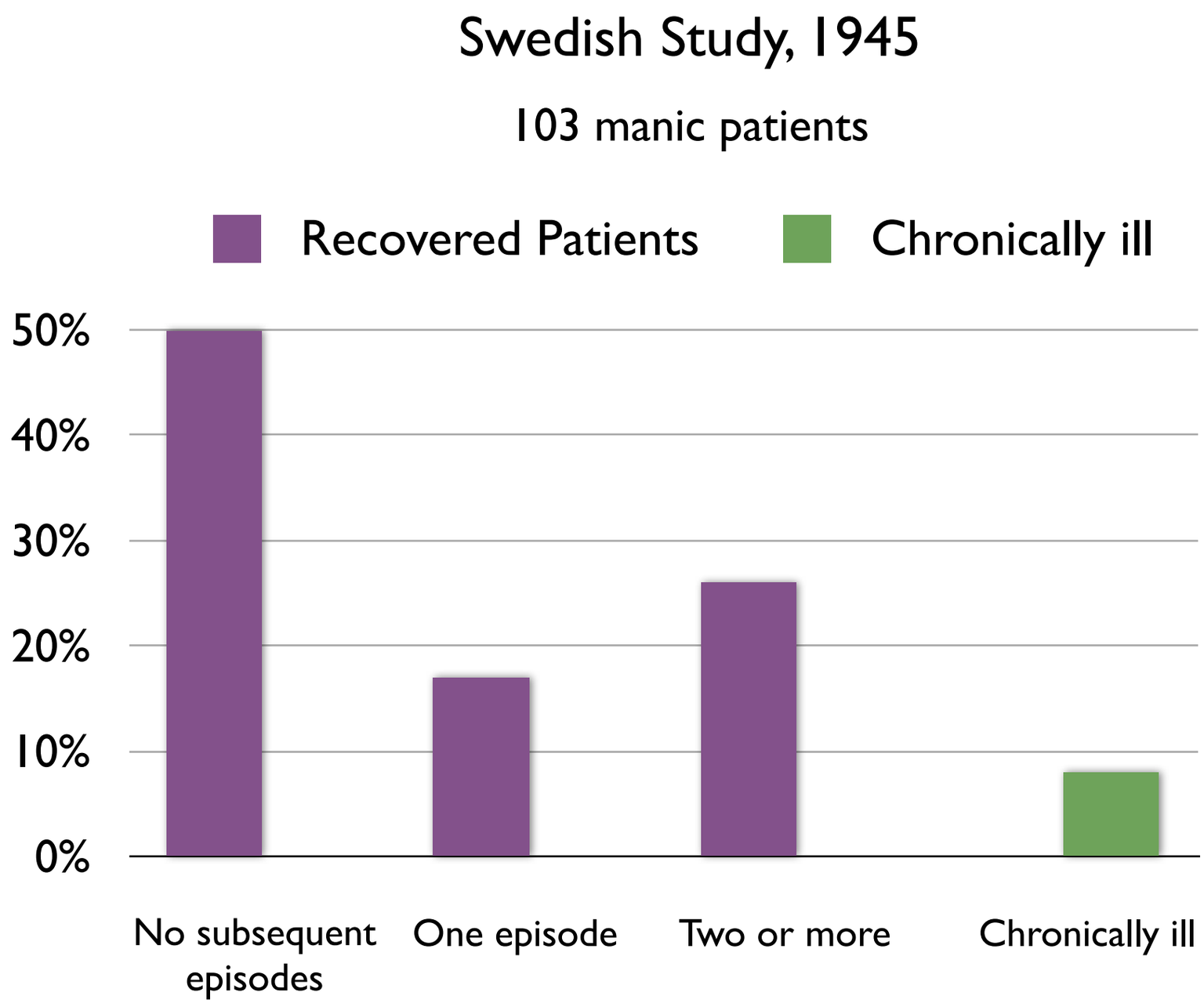
• Horatio Pollock, New York State, 1931. In a long-term study of 2700 first-episode depressed patients, more than half never had another bout of depression that required hospitalization, and only 13% had three or more episodes.

• 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.

"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."

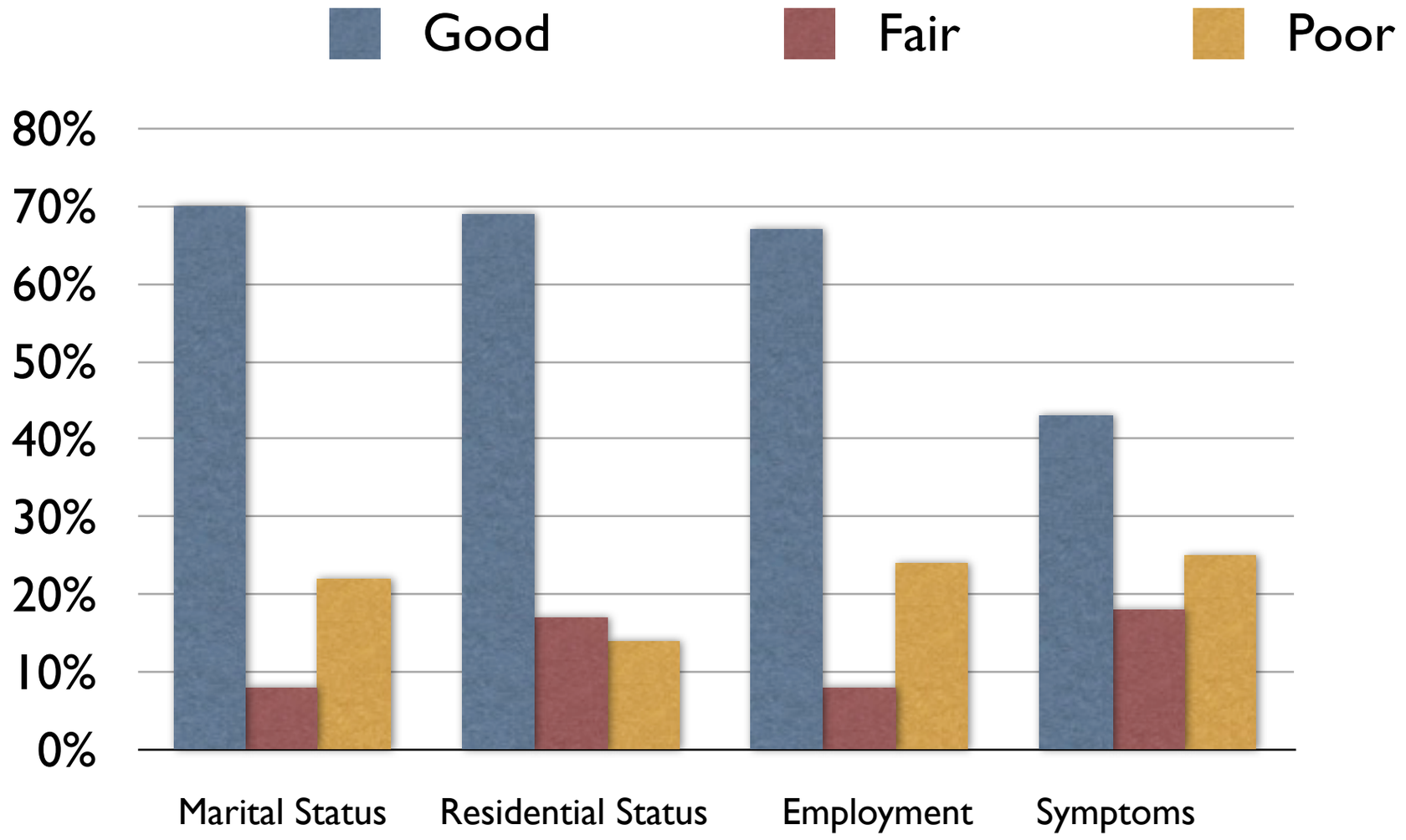
--George Winokur, Washington University,
Manic Depressive Illness, 1969

Bipolar Outcomes in the Pre-Drug Era



Source: Lundquist, G. "Prognosis and course in manic-depressive psychoses." *Acta Psychiat Neurol,* Supp. 35 (1945):7-93.

Functional Bipolar Outcomes in the Pre-Drug Era



Outcomes for 100 manic patients first hospitalized in U.S., 1935-1945, and followed for 30 to 40 years. A good rating for each category meant that the patient was married or widowed, owned home or lived with family members, was employed or had retired, and had no psychiatric symptoms. Seventy percent of the patients had good functional outcomes, and half were asymptomatic. Source: Tsuang, M. "Long-term outcome of major psychoses." *Arch Gen Psych* 36 (1979):1295-1301.

Summary of Bipolar Outcomes in Pre-Drug Era

There is "no basis to consider that manic depressive psychosis permanently affected those who suffered from it. In this way, it is of course different from schizophrenia." While some people suffered multiple episodes, each episode was usually only a "few months in duration" and "in a significant number of patients, only one episode of illness occurs." Once patients recovered, they usually had "no difficulty resuming their usual occupations."

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

"The majority of mental illnesses, especially the most severe, are largely self-limiting in nature if the patient is not subjected to a demeaning experience or loss of rights and liberties."

-- Samuel Bockoven, 1975

The Effect of Antipsychotics on Long-term Schizophrenia Outcomes: A Case 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.

Clinical Perceptions

The physician sees that the medications often work upon initial use, and sees that patients often relapse when they go off the medications.

What's Missing From The Evidence Base?

A. It does not provide evidence that medications improve the long-term course of schizophrenia (or other psychotic disorders,) particularly in regard to functional outcomes.

B. The relapse studies reflect risks associated with drug-withdrawal effects, rather than just the return of the natural course of the disorder.

C. Physicians today no longer have clinical experience with the long-term course of schizophrenia patients off medication.

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)

The Hippocratic Oath

In order for a treatment to do no harm, it must improve on natural recovery rates.

Schizophrenia Outcomes, 1945-1955

• At end of three years following hospitalization, 73 percent 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.

The First Hint of a Paradox

NIMH's First Followup Study (1967):

At the end of one year, patients who were treated with placebo upon initial hospitalization "were less likely to be rehospitalized than those who received any of the three active phenothiazines."

Source: Schooler, C. "One year after discharge." *Am J of Psychiatry* 123 (1967):986-95.

Clinicians' Perceptions

- Patients were returning with great frequency, which was dubbed the "revolving door syndrome."

- Relapse during drug administration "is greater in severity than when no drugs are given."

- If patients relapse after quitting antipsychotics, symptoms tend to "persist and intensify."

Source: Gardos, G. "Maintenance antipsychotic therapy: is the cure worse than the disease?" *American Journal of Psychiatry* 135 (1978: 1321-4.

A Retrospective Comparison of Outcomes in Pre-Drug and Drug Era

Relapse Rates Within Five Years of Discharge

1947 cohort: 55%
1967 cohort: 69%

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.

Source: Bockoven, J. "Comparison of two five-year follow-up studies," *Am J Psychiatry* 132 (1975): 796-801.

Bockoven's Conclusion:

"Rather unexpectedly, these data suggest that psychotropic drugs may not be indispensable. Their extended use in aftercare may prolong the social dependency of many discharged patients."

Rappaport's Study: Three-Year Outcomes

Medication use (in hospital/after discharge)	Number of Patients	Severity of Illness (1= best outcome; 7 = worst outcome)	Rehospitalization
No meds/off	24	1.70	8%
Antipsychotic/off	17	2.79	47%
No meds/on	17	3.54	53%
Antipsychotic/on	22	3.51	73%

Source: Rappaport, M. "Are there schizophrenics for whom drugs may be unnecessary or contraindicated?" *Int Pharmacopsychiatry* 13 (1978):100-11.

Rappaport's Conclusion:

"Our findings suggest that antipsychotic medication is not the treatment of choice, at least for certain patients, if one is interested in long-term clinical improvement. Many unmedicated-while-in-hospital patients showed greater long-term improvement, less pathology at follow-up, fewer rehospitalizations, and better overall functioning in the community than patients who were given chlorpromazine while in the hospital."

Loren Mosher's Soteria Project

Results:

At end of two years, the Soteria patients had "lower psychopathology scores, fewer [hospital] readmissions, and better global adjustment."

In terms of antipsychotic use, 42% had never been exposed to the drugs, 39% had used them temporarily, and 19% had used them regularly throughout the two-year followup.

Source: Bola, J. "Treatment of acute psychosis without neuroleptics." *J Nerv Ment Disease* 191 (2003):219-29.

Loren Mosher's Conclusion

"Contrary to popular views, minimal use of antipsychotic medications combined with specially designed psychosocial intervention for patients newly identified with schizophrenia spectrum disorder is not harmful but appears to be advantageous. We think the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined."

William Carpenter's In-House NIMH Study, 1977

Results

• Those treated without drugs were discharged sooner than drug-treated patients in a comparison group.

• At the end of one year, only 35 percent of the non-medicated group relapsed within a year after discharge, versus 45% of the medicated group.

• The unmedicated group also suffered less from depression, blunted emotions, and retarded movements.

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

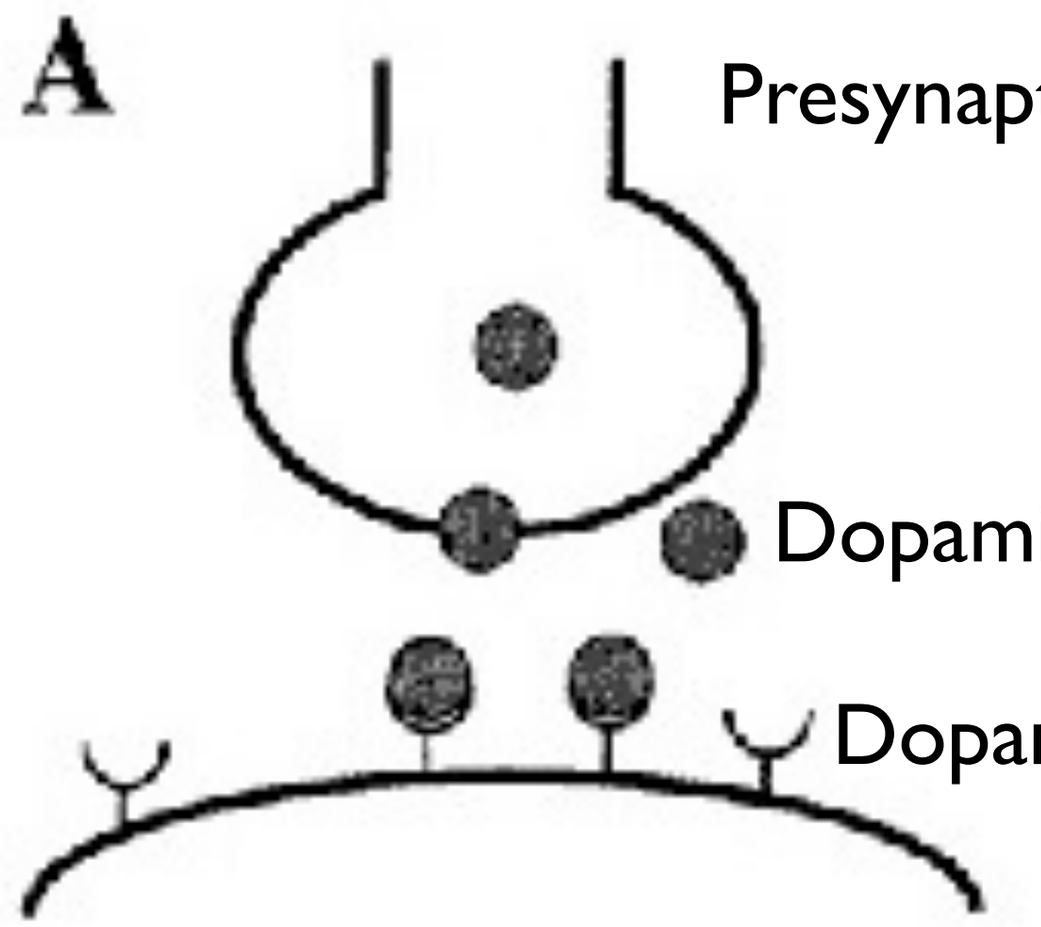
William Carpenter Raises a Question:

"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.

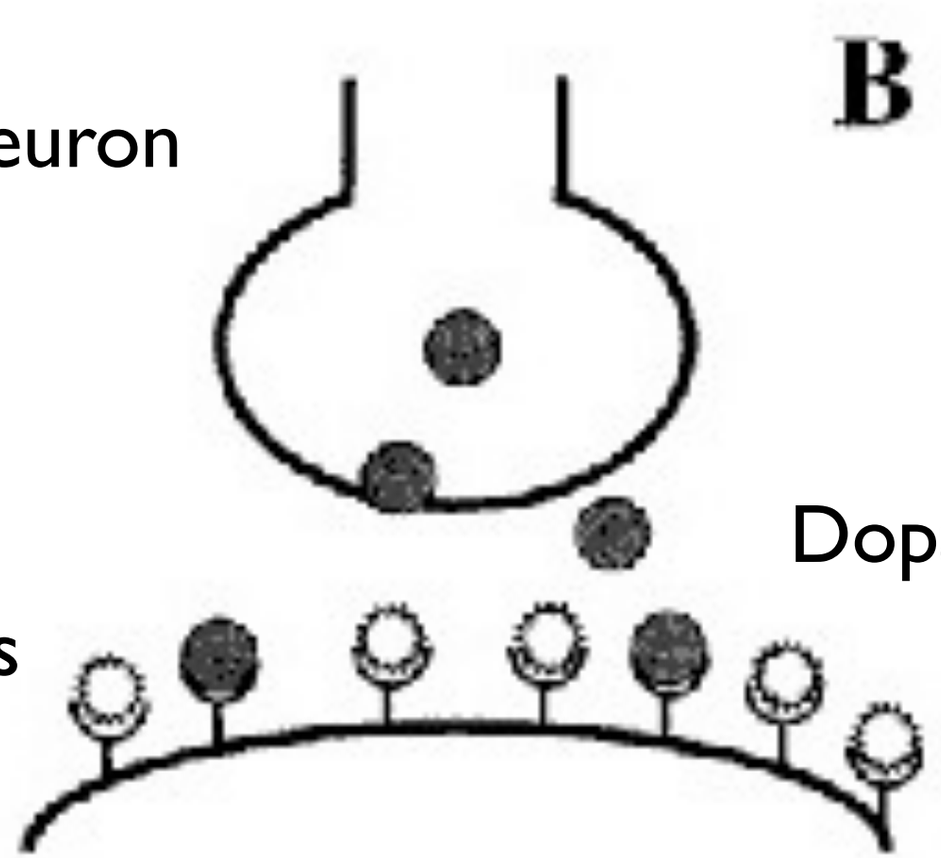
The Dopamine Supersensitivity Theory

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

Presynaptic neuron



Antipsychotic blocks receptors

Dopamine

Postsynaptic neuron

Brain increases receptors to compensate for drug blockade

The Consequences of Dopamine Supersensitivity

"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."

Guy Chouinard and Barry Jones, McGill University

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.

Study of Drug-Induced Tardive Psychosis

In 1982, Chouinard and Jones reported that 30% of the 216 schizophrenia outpatients they studied showed sign of tardive psychosis, which meant their psychosis was becoming chronic. When this happens, they wrote, "the illness appears worse" than ever before. "New schizophrenic symptoms of greater severity will appear."

Source: Chouinard, C. "Neuroleptic-induced supersensitivity psychos, the 'Hump Course,' and tardive dyskinesia." *J Clin Psychopharmacology* 2 (1982):143-44. Also, Chouinard, C. "Severe cases of neuroleptic-induced supersensitivity psychosis," *Schiz Res* 5 (1991):21-33.

Animal Models of Psychosis and Drug-Induced Dopamine Supersensitivity

In 2005, Philip Seeman at the University of Toronto reported that agents that trigger psychotic-like behavior in animals -- amphetamines, angel dust, lesions to the hippocampus, gene-knockout manipulations -- all cause an increase in D2 receptors that have a "high" affinity for dopamine. These results "imply that there may be many pathways to psychosis, including multiple gene mutations, drug abuse, or brain injury, all of which may converge via D2 HIGH to elicit psychotic symptoms," Seeman wrote.

Source: Seeman, P. "Dopamine supersensitivity correlates with D2 HIGH states, implying many paths to psychosis. Proceedings of the Nat Acad of Science 102 (2005): 3513-18. Samaha, A. "Breakthrough dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time." *J Neuroscience* 27 (2007):2979-86.

Antipsychotics Increase the Density of D2 HIGH Receptors

In this same report, Seeman found that haloperidol and olanzapine both increased the density of D2 HIGH receptors, and thus cause the very biological abnormality that in animal models had been identified as a final pathway to psychosis.

Philip Seeman Tests His D2 High Theory

In rat studies, "we show that during ongoing treatment with clinically relevant doses, haloperidol and olanzapine progressively lose their efficacy . . . the loss of efficacy is linked to an increase in D2 receptor number and sensitivity. These results are the first to demonstrate that 'breakthrough' supersensitivity during ongoing antipsychotic treatment undermines treatment efficacy."

Source: Samaha, A. "Breakthrough dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time." *J Neuroscience* 27 (2007):2979-86.

WHO Cross-Cultural Studies, 1970s/1980s

• In both studies, which measured outcomes at the end of two years and five years, the patients in the three developing countries, India, Nigeria, and Colombia, had a "considerably better course and outcome" than in the U.S. and six other developed countries.

•The WHO researchers concluded that "being in a developed country was a strong predictor of not attaining a complete remission."

• They also found that "an exceptionally good social outcome characterized the patients" in developing countries.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." *Psychological Medicine* 20, monograph (1992):1-95.

WHO Findings, Continued

Medication usage:

16% of patients in the developing countries were regularly maintained on antipsychotics, versus 61% of the patients in rich countries.

15-year to 20-year followup:

The "outcome differential" held up for "general clinical state, symptomatology, disability, and social functioning." In the developing countries, 53% of schizophrenia patients were "never psychotic" anymore, and 73% were employed.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." Psychological Medicine 20, monograph (1992):1-95. See table on page 64 for medication usage. For followup, see Hopper, K. "Revisiting the developed versus developing country distinction in course and outcome in schizophrenia." *Schizophrenia Bulletin* 26 (2000):835-46.

Eli-Lilly's Global Study

Study details

- 11,078 schizophrenia patients in 37 countries
- All patients treated with olanzapine or another antipsychotic
- Symptoms and functional remission assessed for three years

Outcomes

Region	Clinical Remission	Functional Remission
East Asia	84.4%	24.6%
North Africa and Middle East	79.6%	17.8%
Latin America	79.4%	28.7%
Central and Eastern Europe	65.1%	21.6%
North Europe	60.1%	35.0%
South Europe	61.3%	20.7%
Total	66.1%	25.4%

Source: Haro, "Cross-national clinical and functional remission rates." *Brit J of Psychiatry* 2011, 1999: 194-201.

MRI Study in Macaque Monkeys

Finding:

- In macaque monkeys, treatment with either haloperidol or olanzapine for 17 to 27 months led to a "8-11% reduction in mean fresh brain weights" compared to controls.

- The differences (in brain weights and brain volumes) "were observed across all major brain regions, but appeared most robust in the frontal and parietal regions."

Source: Dorph-Petersen. "The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation." Neuropsychopharmaology (2005) 30: 1649-1661.

Nancy Andreasen's MRI Study

In 2003, Andreasen reported that schizophrenia was a "progressive neurodevelopmental disorder" characterized by "progressive reduction in frontal white matter volume." This decline in brain volumes was seen in MRI imaging tests.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." *Arch Gen Psych* 60 (2003):585-94.

In 2003 and 2005, Andreasen reported that this brain shrinkage was associated with a worsening of negative symptoms, increased functional impairment, and, after five years, cognitive decline.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." *Arch Gen Psych* 60 (2003):585-94. Andreasen, N. "Longitudinal changes in neurocognition during the first decade of schizophrenia illness." *International Congress on Schizophrenia Research* (2005):348.

In 2011, Andreasen reported that this shrinkage was drug-related. Use of the old neuroleptics, the atypical antipsychotics, and clozapine were all "associated with smaller brain tissue volumes," with decreases in both white and grey matter. The severity of illness and substance abuse had "minimal or no effect'" on brain volumes.

Ho, B. "Long-term antipsychotic treatment and brain volumes." *Arch Gen Psychiatry* 68 (2011):128-37.

Nancy Andreasen, former editor of the *American Journal of Psychiatry*, on antipsychotics:

"What exactly do these drugs do? They block basal ganglia activity. The prefrontal cortex doesn't get the input it needs and is being shut down by drugs. That reduces psychotic symptoms. It also causes the prefrontal cortex to slowly atrophy."

--*New York Times*, September 16, 2008

More Evidence That Antipsychotics Shrink the Brain

In a 2012 review of 43 brain-imaging studies of first-episode psychosis, European researchers determined that a loss of gray matter volume was "significantly more severe in medicated patients."

Source: J. Radua. "Multimodal meta-analysis of structural and functional changes in first episode psychosis and the effects of antispychotic medications." *Neuroscience and Biobehavioral Review*, in press as of 9/04/2012.

Dueling Histories: Which Is Predictive of Outcomes in Long-Term Observational Studies?

If the conventional wisdom is correct, then medicated schizophrenia patients should have markedly better outcomes.

If the science reviewed here is predictive, then medicated patients, in the aggregate, should suffer more persistent psychotic symptoms and have worse global outcomes.

Martin Harrow's Long-Term Study of Psychotic Patients

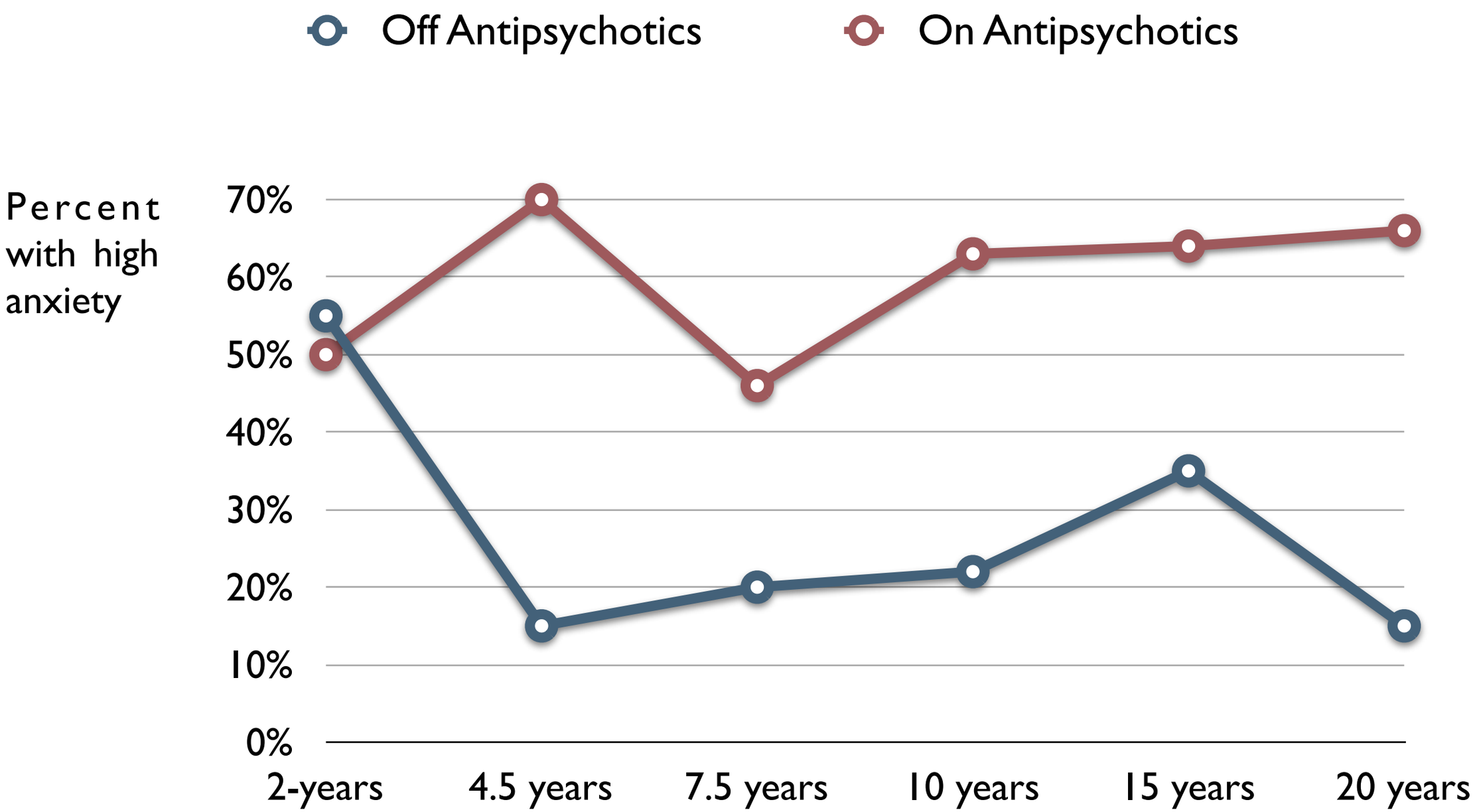
Patient Enrollment

- 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

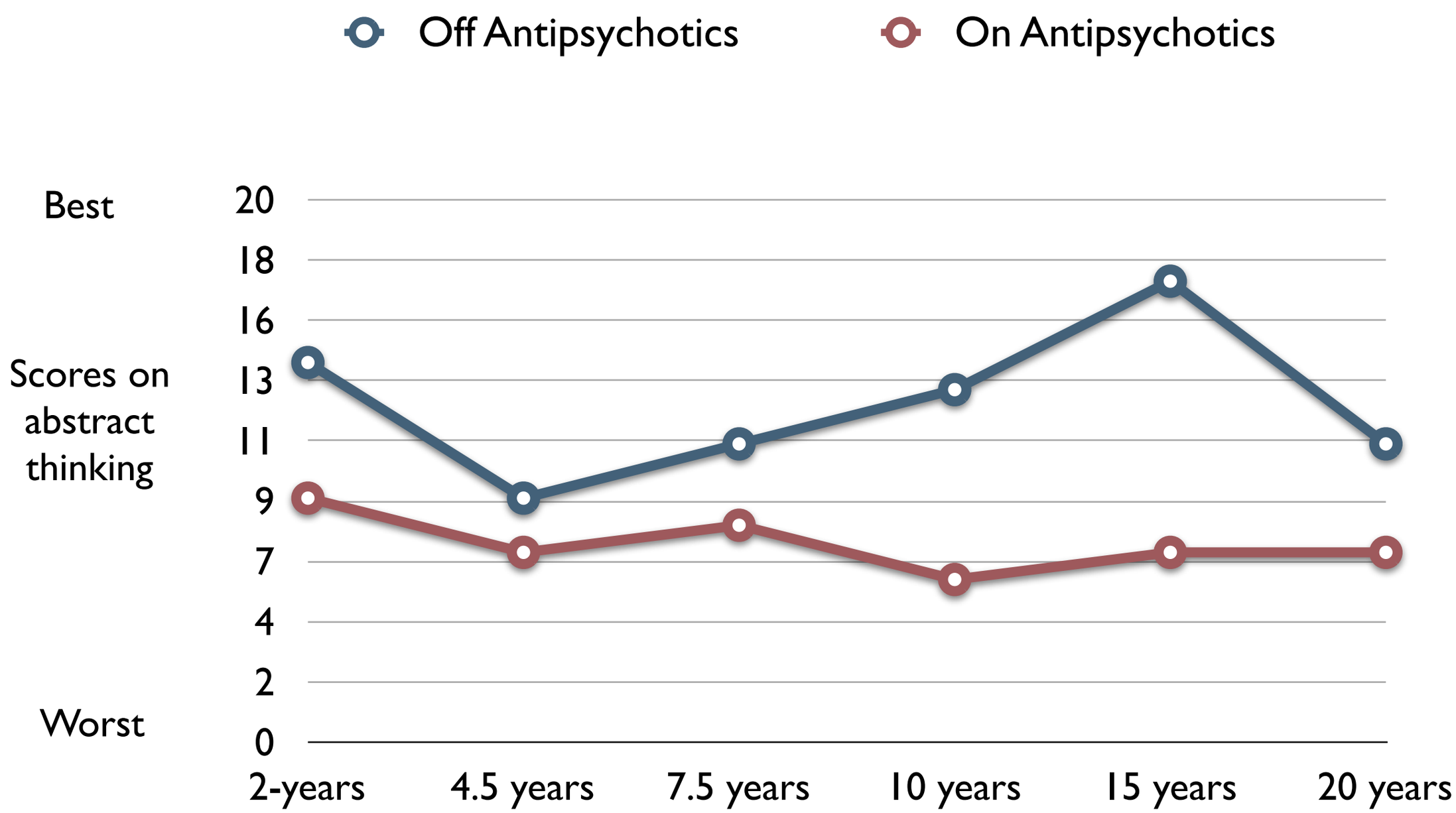
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Anxiety Symptoms of Schizophrenia Patients



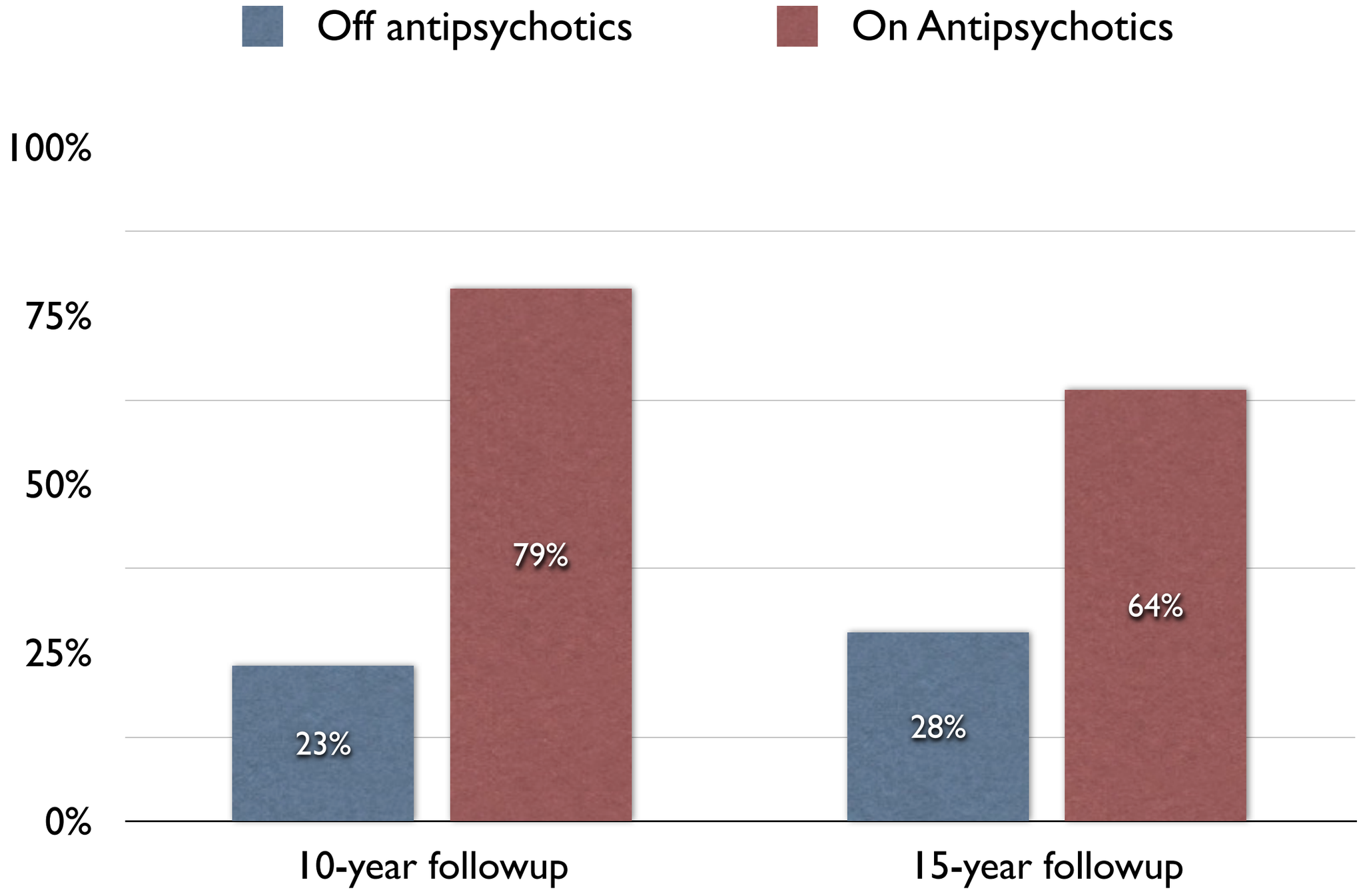
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Cognitive Function of Schizophrenia Patients



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

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



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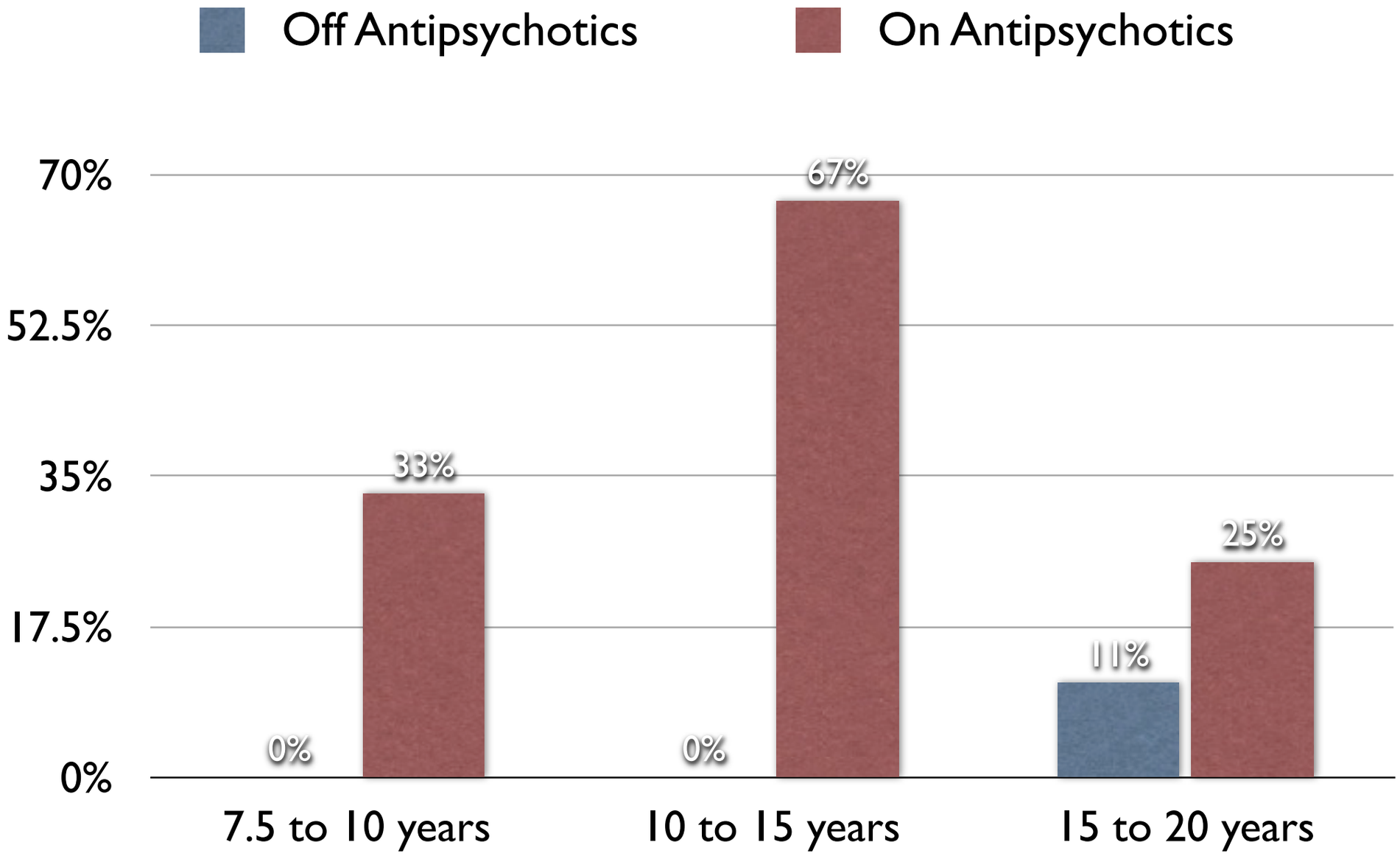
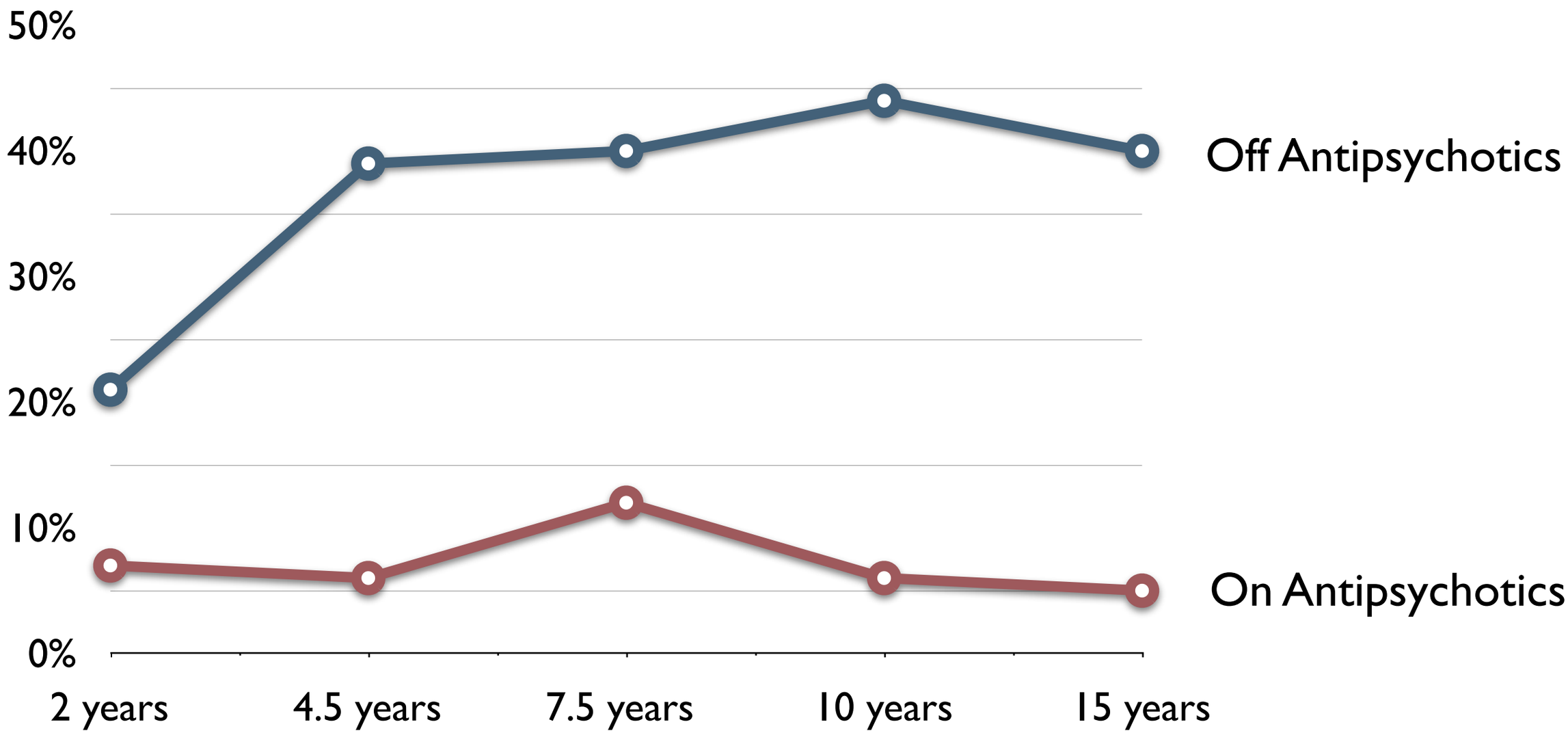
Relapse Rates Once Patients Are Stable



Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal 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.

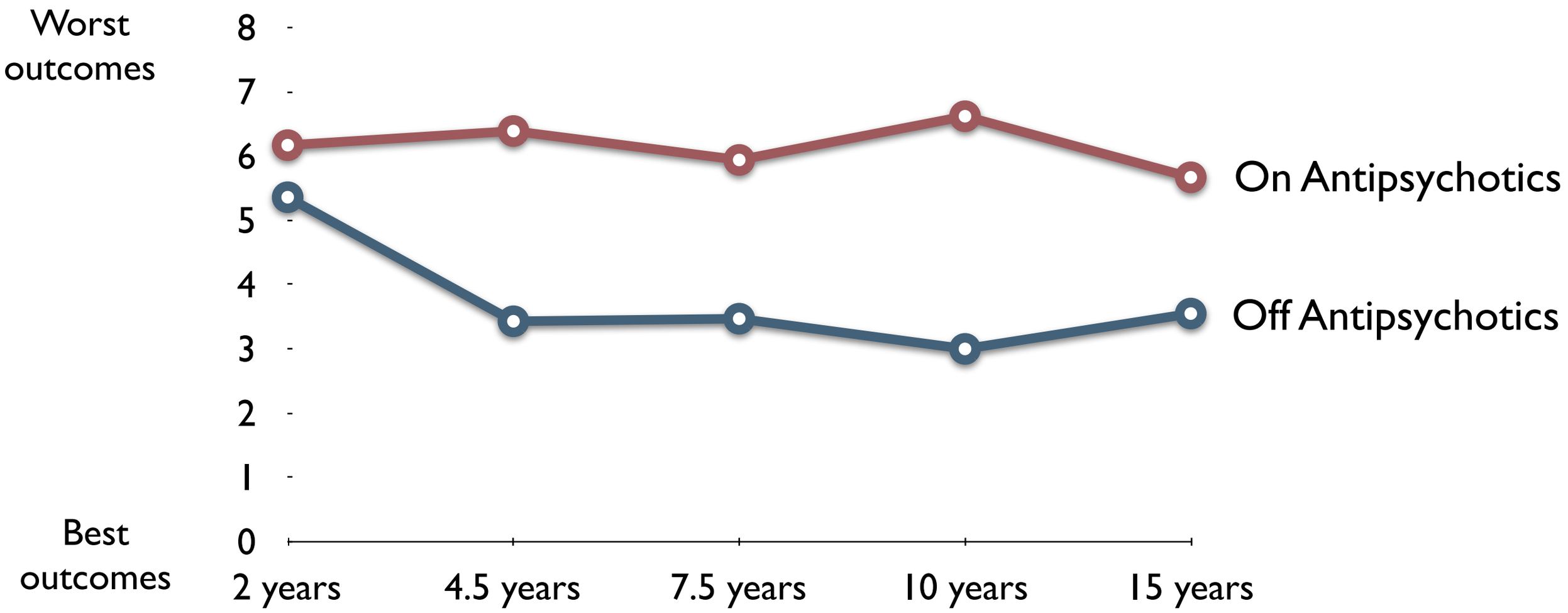
More on Recovery Rates

Medication compliant patients throughout 20 years: 17% had one period of recovery.

Those off antipsychotics by year two who then remained off throughout next 18 years: 87% had two or more sustained periods of recovery.

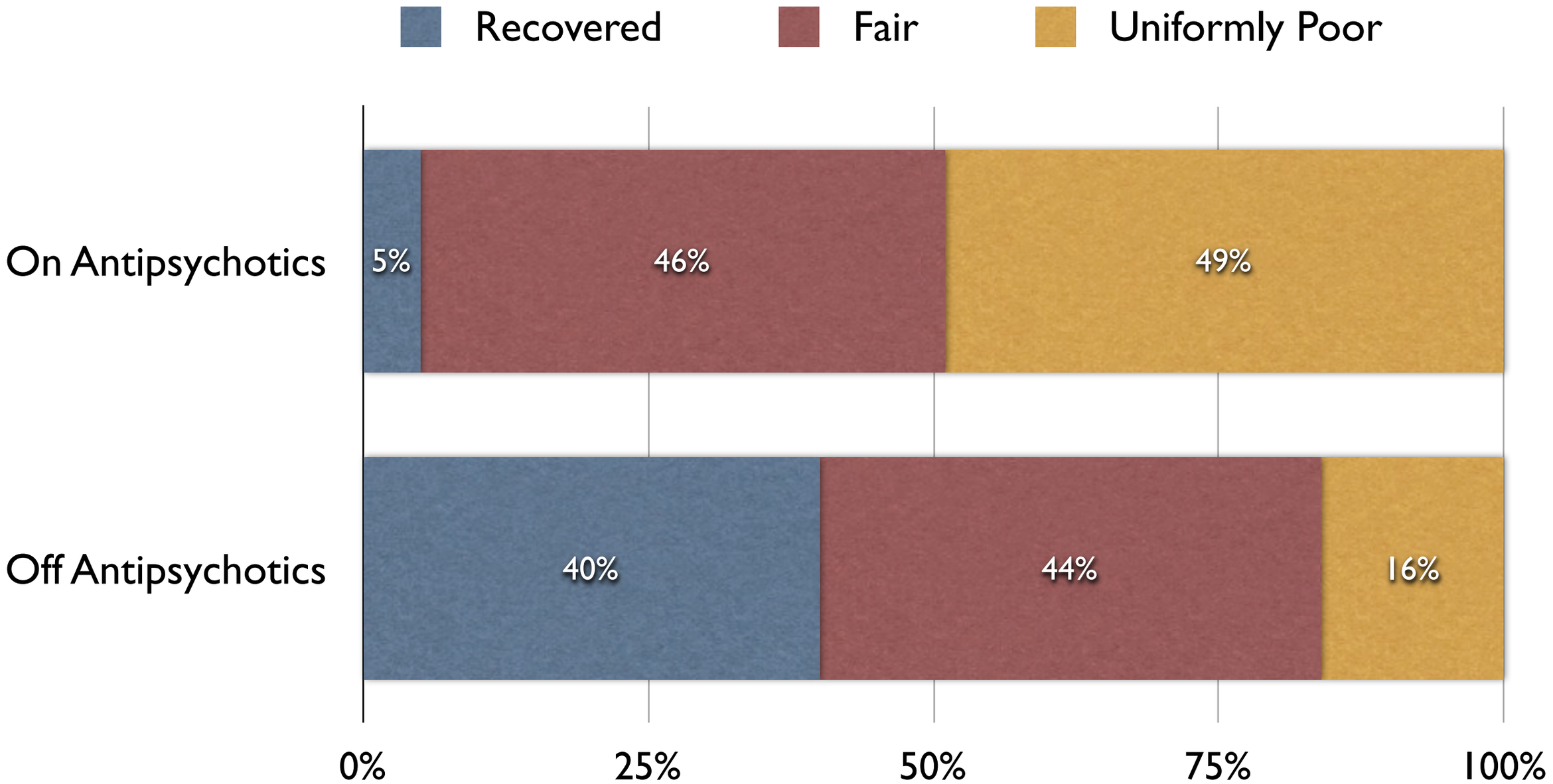
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Global Adjustment of 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.

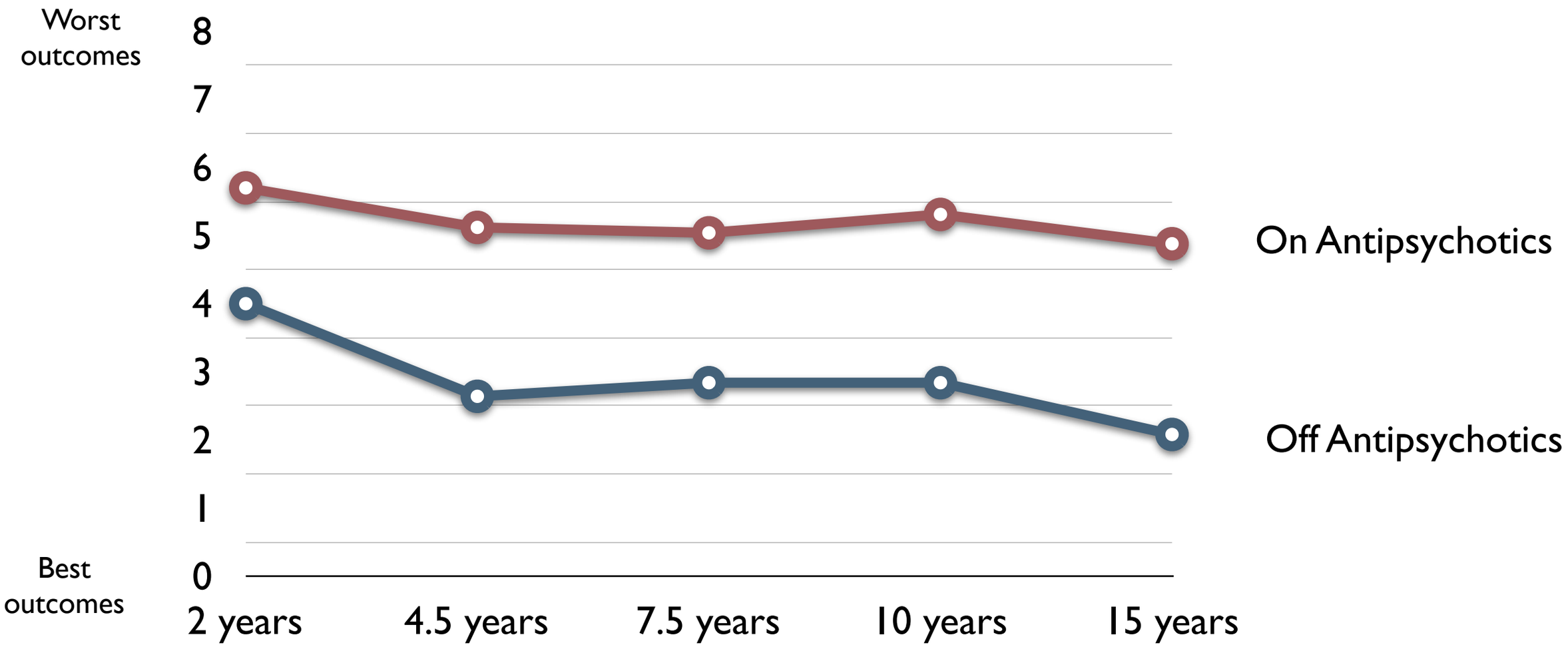
"In addition, global outcome for the group of patients with schizophrenia who were on antipsychotics was compared with the off-medication schizophrenia patients with similar prognostic status. Starting with the 4.5-year follow-up and extending to the 15-year follow-up, the off-medication subgroup tended to show better global outcomes at each followup."

Martin Harrow, page 411.

"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."

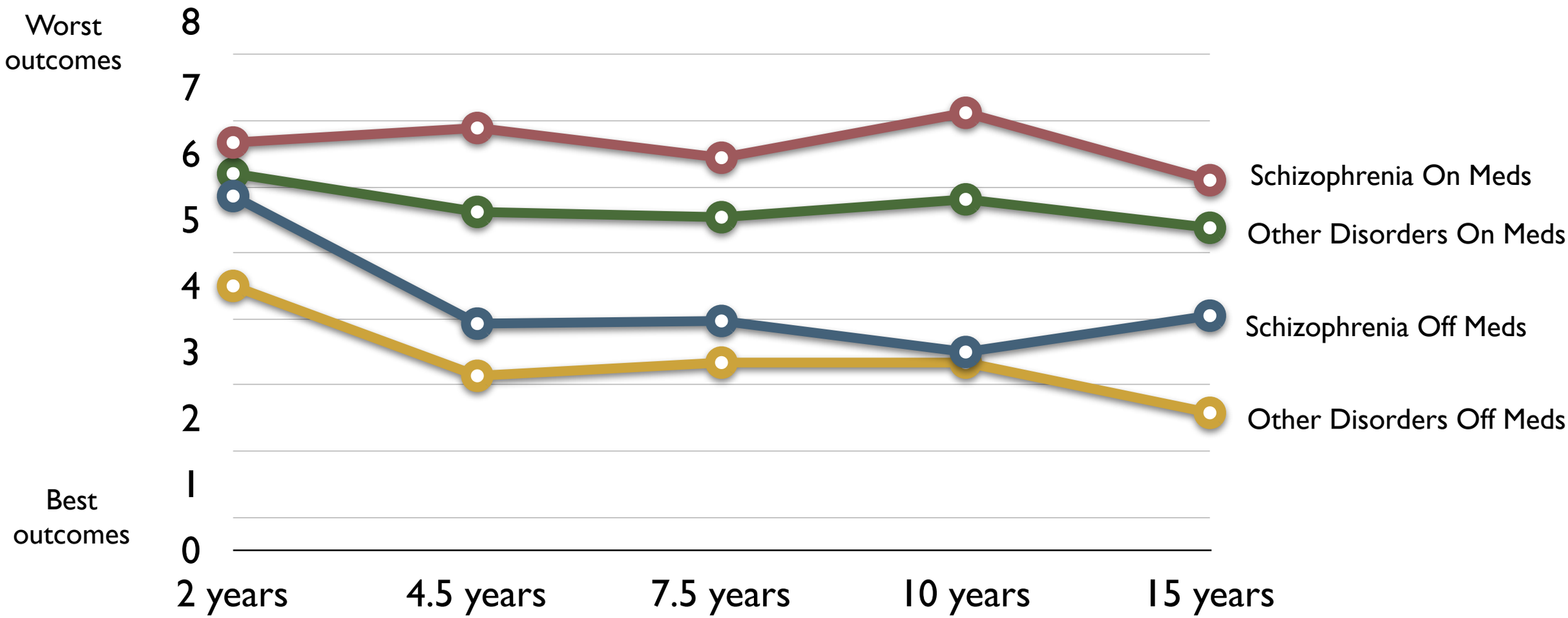
--Martin Harrow, American Psychiatric Association annual meeting, 2008

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.

Summary of Harrow's Findings

Those who stayed on antipsychotics:

- Were much more psychotic
- Were much more anxious
- Had worse cognitive function
- Had much lower recovery rates
- Were much more likely to have a "uniformly poor" outcome
- Had worse global outcomes

And:

- Schizophrenia patients off antipsychotics had much better outcomes than patients with milder psychotic disorders who stayed on the drugs.

"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

The Pieces of the Puzzle: Do They Fit Together?

1. In the first long-term study conducted by the NIMH, rehospitalization rates were higher for those treated initially with an antipsychotic.

2. A retrospective study at Boston Psychopathic Hospital in the 1970s found that outcomes had deteriorated in the drug era.

3. Three studies in the 1970s that compared conventional drug treatment to experimental treatment that involved using antipsychotics in a limited fashion all found better outcomes in the experimental group.

4. Researchers at McGill University then stepped forward with a biological explanation for why antipsychotics made patients more biologically vulnerable to psychosis and thus increased the risk of relapse.

5. A cross-cultural study by the World Health Organization found much better outcomes in three developing countries where patients weren't regularly maintained on antipsychotics.

6. MRI studies have revealed that antipsychotics shrink the brain. This shrinkage is associated with a worsening of outcomes.

7. Harrow's long-term, prospective study found that patients off antipsychotics had much better outcomes.

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

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.