

# Psychiatric Drugs:

## Problems and Solutions

# Disclosure

I do not have an interest in selling a technology, program, product, and/or service to CME/CE professionals.

I have nothing to disclose with regard to commercial relationships.

# The Problems With Psychiatric Drugs: The Disability Data

# The Common Wisdom

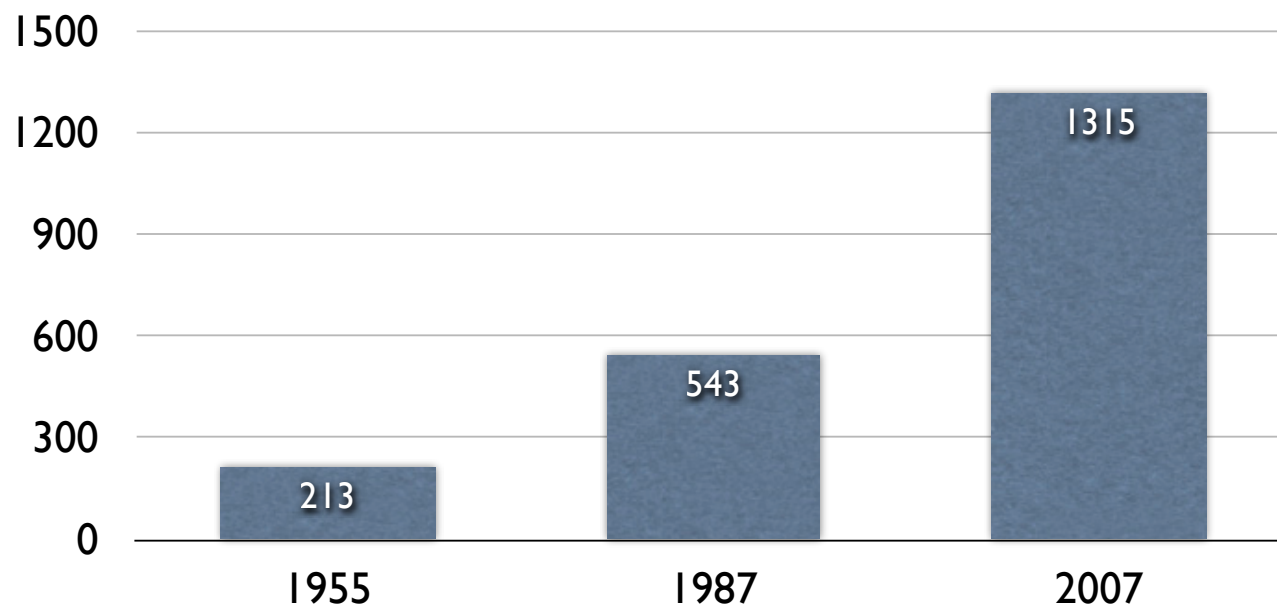
The introduction of Thorazine into asylum medicine in 1955 “initiated a revolution in psychiatry, comparable to the introduction of penicillin in general medicine.”

--Edward Shorter, *A History of Psychiatry*

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

(under government care)

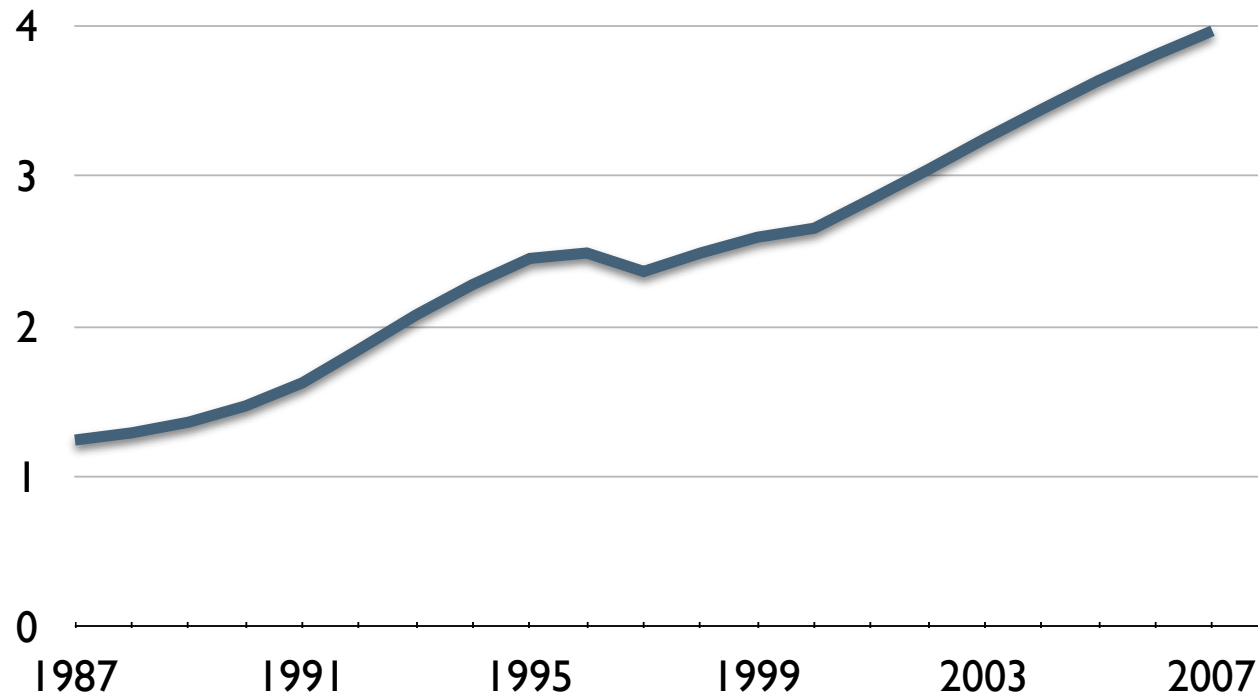
■ Per 100,000 population



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

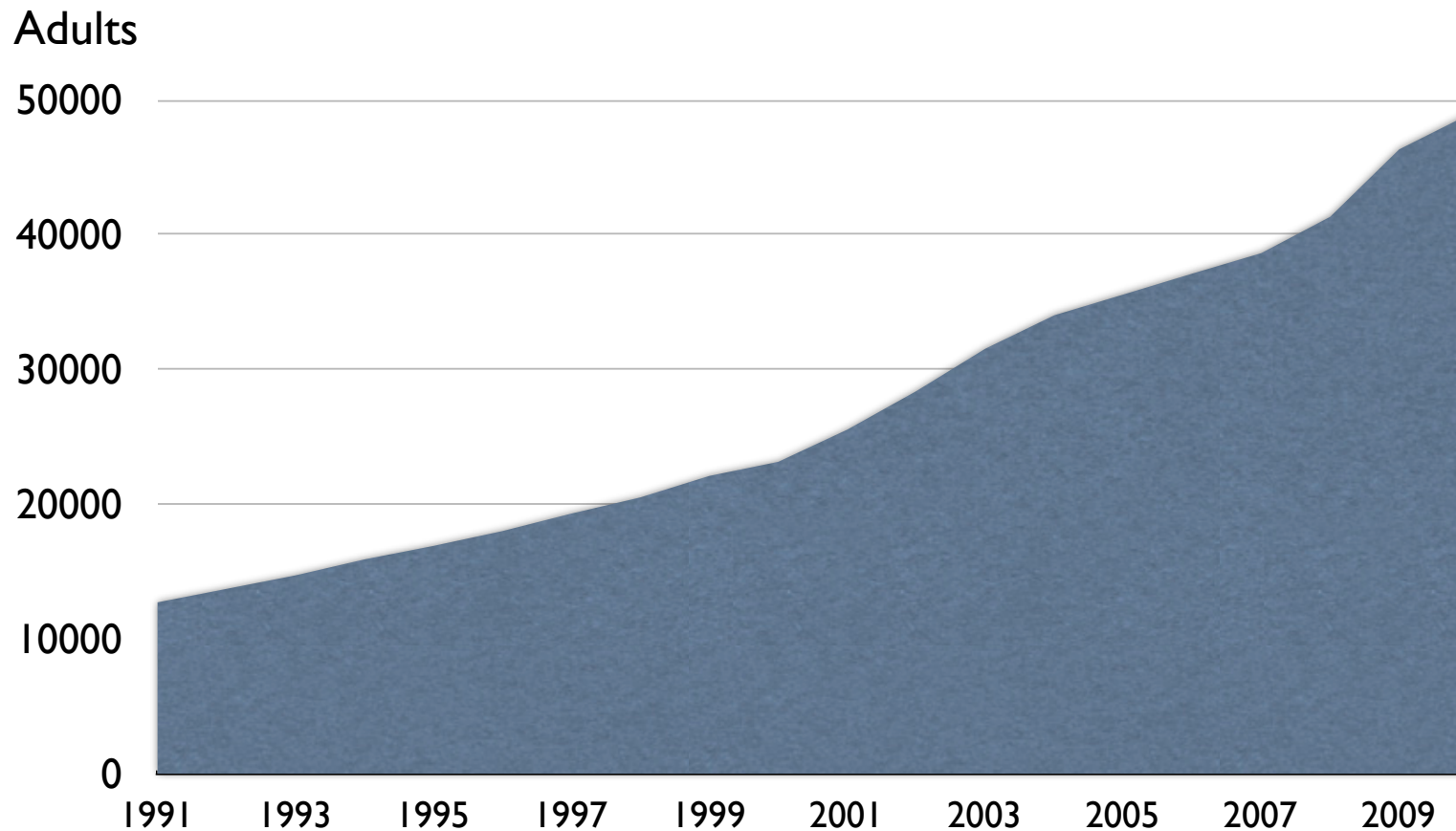
# U.S. Disability in the Prozac Era

Millions of adults, 18 to 66 years old



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

Adults

250000

200000

150000

100000

50000

1990

1992

1994

1996

1998

2000

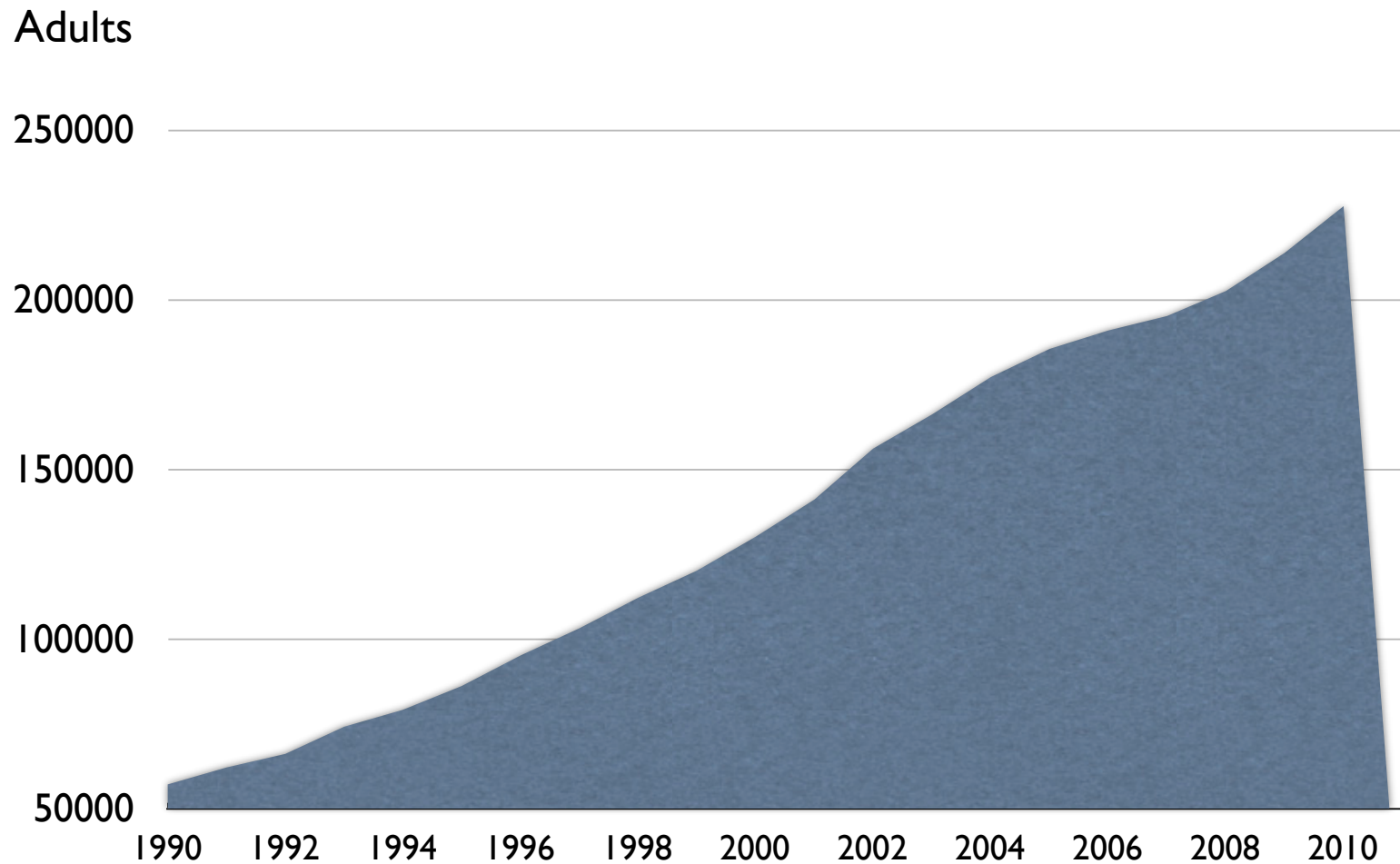
2002

2004

2006

2008

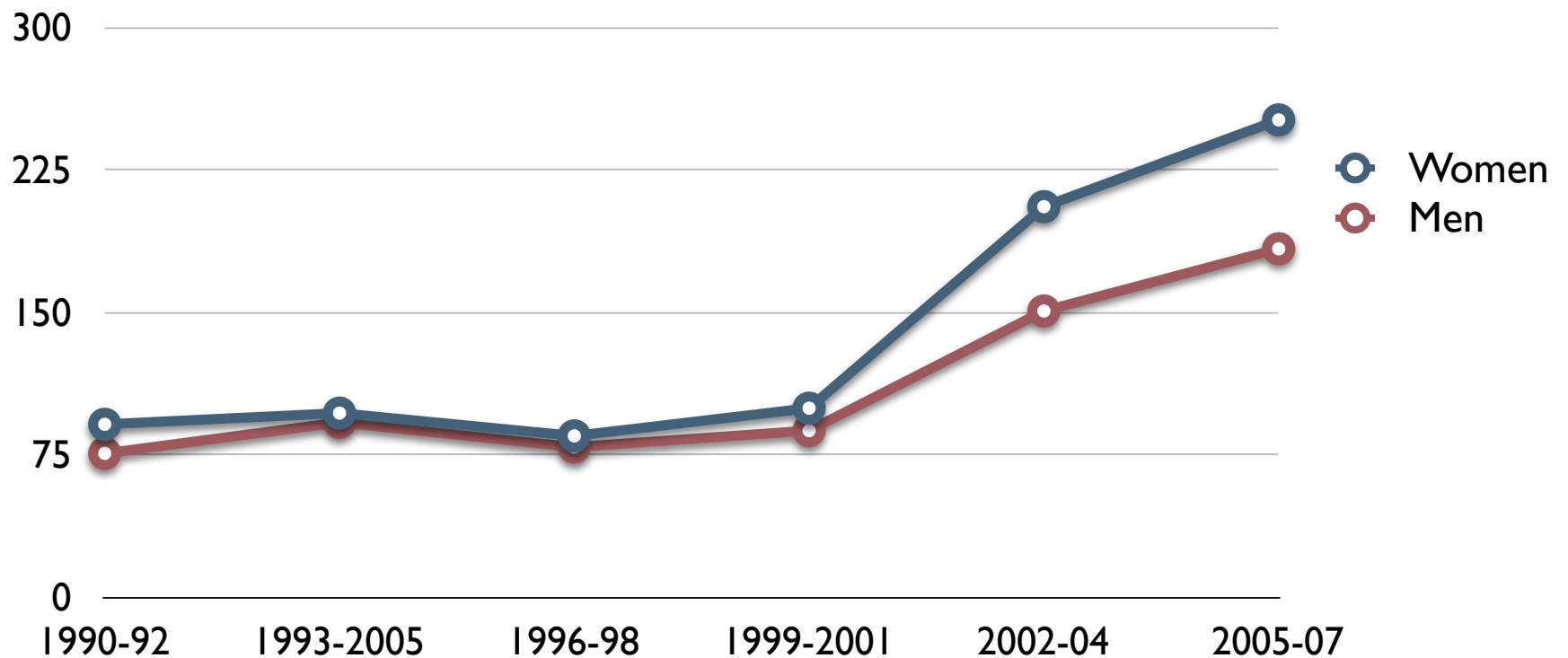
2010





# 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.

# How Do Psychiatric Medications Shape Long-Term Outcomes?

# The Evidence for Psychiatric Drugs

## **Short-term Use**

The medications 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. See antipsychotics in particular.

## **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 major mental 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. This heightened risk of relapse is due to the fact that the brain has been changed by exposure to the drug.

C. The medical profession no longer has an understanding of the “natural course” of major mental disorders, such as depression, bipolar disorder, and psychotic disorders, and thus its clinical perceptions about the efficacy of the drugs isn't informed by that long-term perspective.

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

# Assessing Long-Term Schizophrenia Outcomes

“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.

# Bockoven's 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.

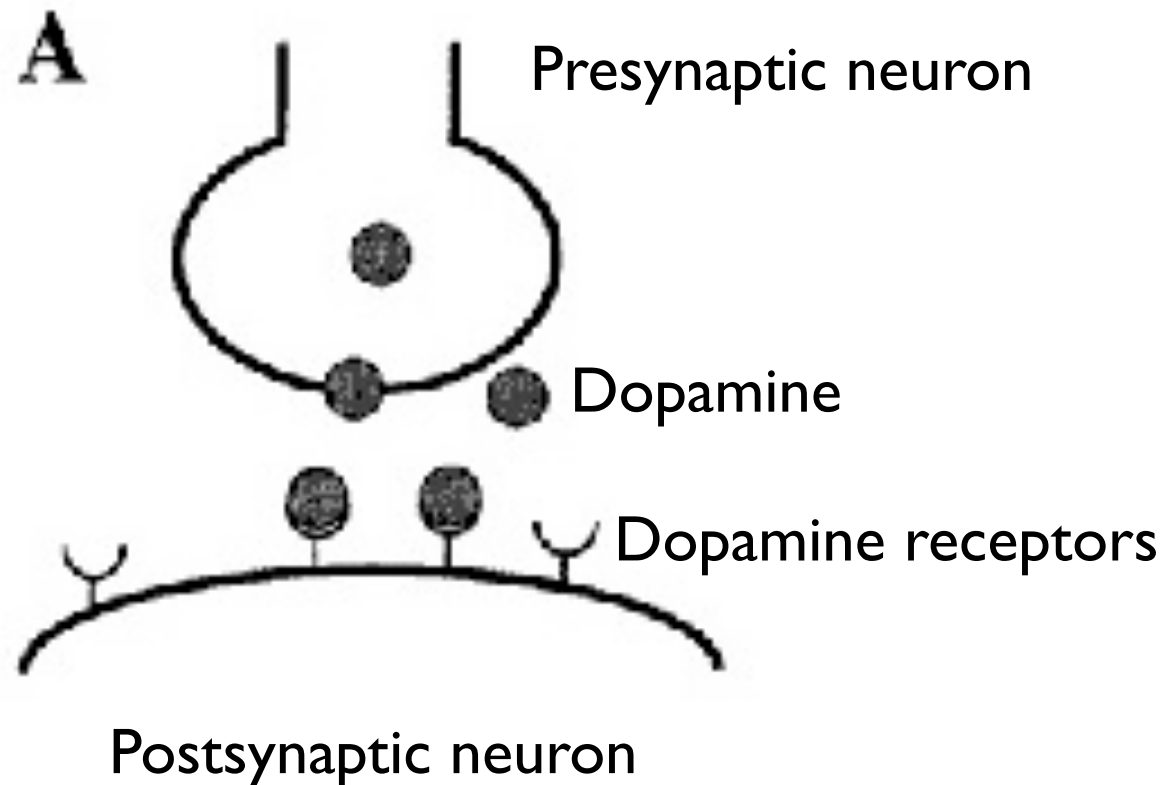
# Summary of First 25 Years

Outcome studies led researchers to worry that antipsychotics might make people more biologically vulnerable to psychosis over the long-term, and thus increase the chronicity of the disorder.

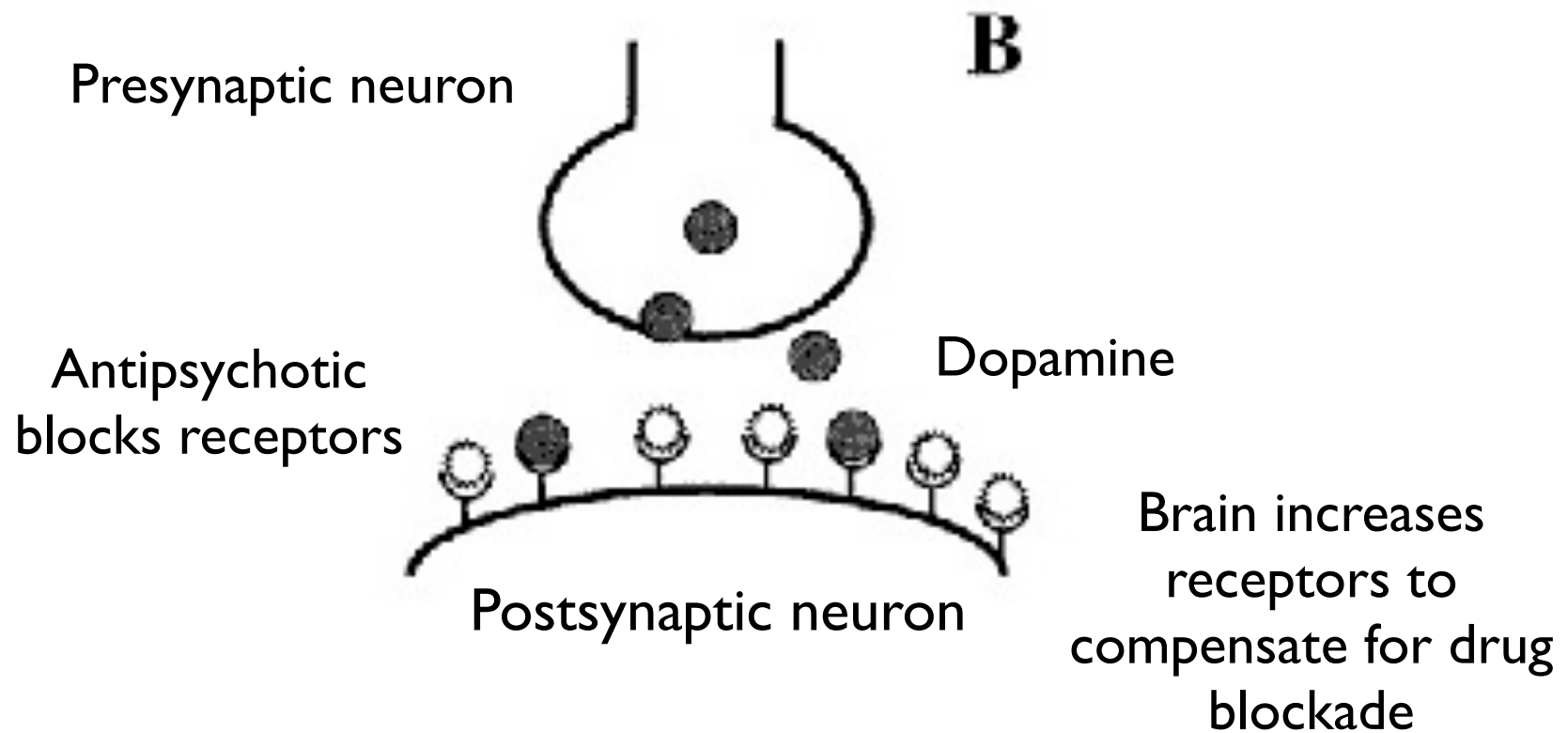
In 1978, Jonathan Cole wrote a provocative article titled: “Is the Cure Worse than the Disease?”

# The Dopamine Supersensitivity Theory

Dopamine function before exposure to antipsychotics



# Dopamine function after exposure to antipsychotics



# The Dopamine Supersensitivity Theory

“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 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 psychosis, 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.

# Philip Seeman's D2 HIGH Theory

In 2005, Seeman 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.

# Reviewing the Evidence for the Dopamine-Supersensitivity Theory

- Longer-term studies in the 1970s showed higher relapse rates for drug-exposed patients.
- A biological explanation for this paradoxical result was proposed and assessed in a study of schizophrenia patients.
- Animal models further refined understanding of drug-induced dopamine supersensitivity and researchers at University of Toronto concluded that this was why the medications lost their efficacy over time.

# 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.” *Neuropsychopharmacology* (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 antipsychotic medications.” *Neuroscience and Biobehavioral Review*, in press as of 9/04/2012.

# Summary of MRI Studies

- 1) Studies in monkeys found that antipsychotics shrink brain volumes.
- 2) Andreasen found that patients diagnosed with schizophrenia show a decline in brain volumes over time.
- 3) Andreasen found that this shrinkage was associated with increased negative symptoms, functional impairment and cognitive decline.
- 4) Andreasen determined that this shrinkage was associated with use of antipsychotics.
- 5) European researchers have found that shrinkage is more severe in medicated patients.

# 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 had a “considerably better course and outcome.”
- 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%
<b>Total</b>	<b>66.1%</b>	<b>25.4%</b>

Source: Haro, "Cross-national clinical and functional remission rates." *Brit J of Psychiatry* 2011, 199: 194-201.

# Summary of Cross-Cultural Studies With Medication as a Variable

- 1) In 1970s and 1980s, WHO investigators found that outcomes were significantly better in developing countries, where only 16% were regularly maintained on antipsychotics.
- 2) In recent global Eli Lilly Study, where all patients are maintained on antipsychotics, patients in developing countries do not have better functional outcomes than patients in developed countries.

## 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

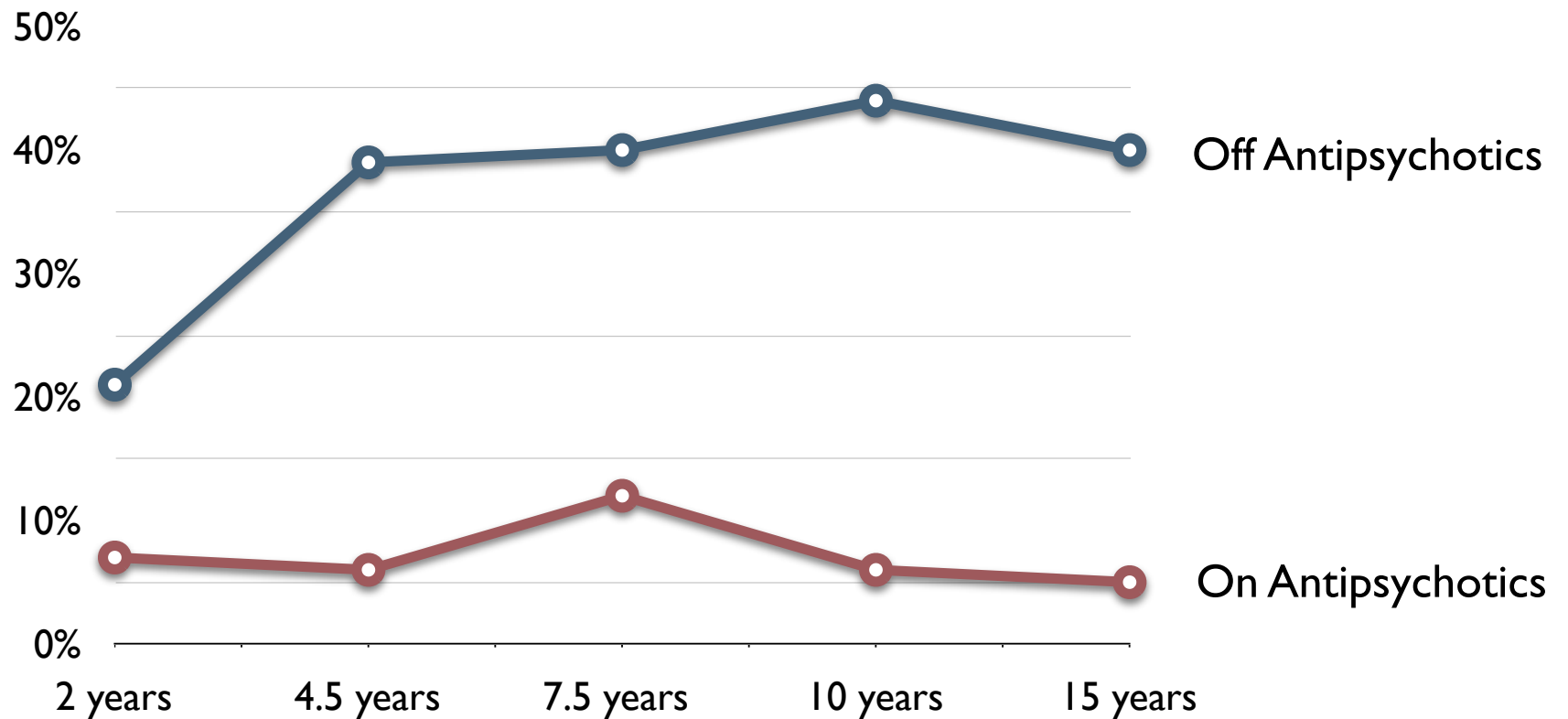
## Patient Enrollment

- 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.

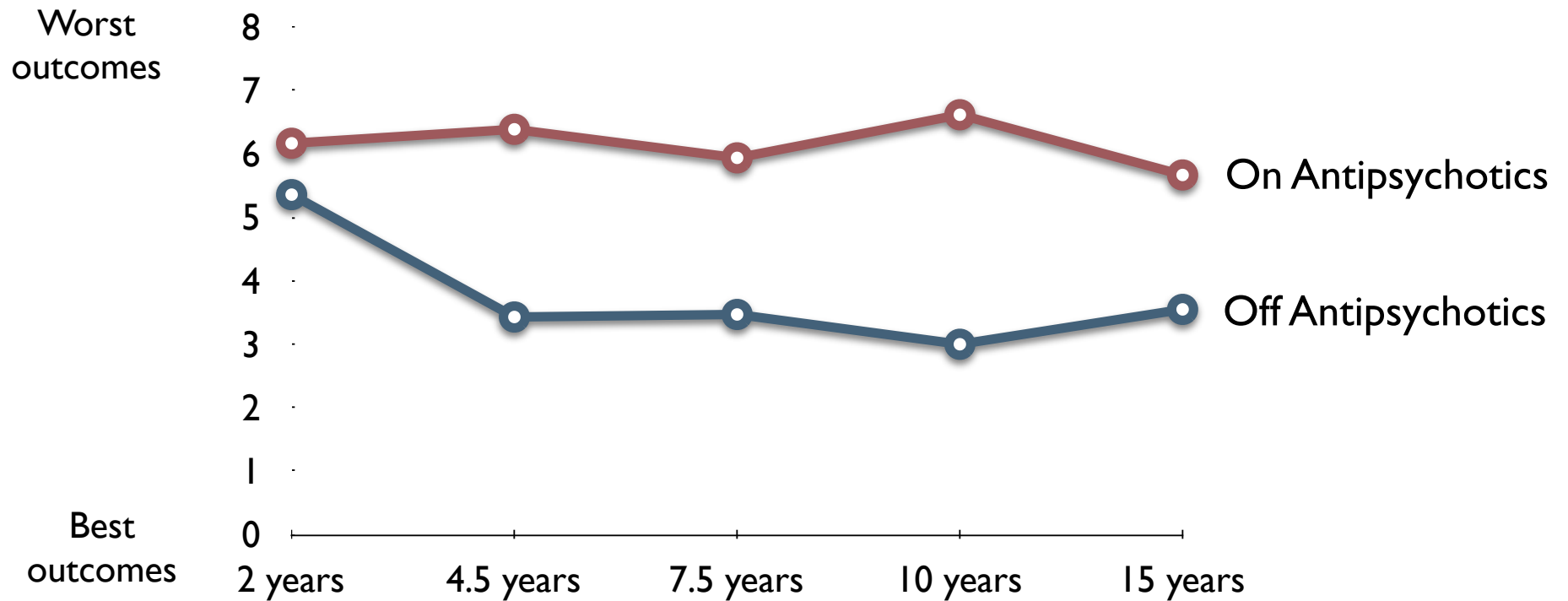


# Long-term Recovery Rates for Schizophrenia Patients



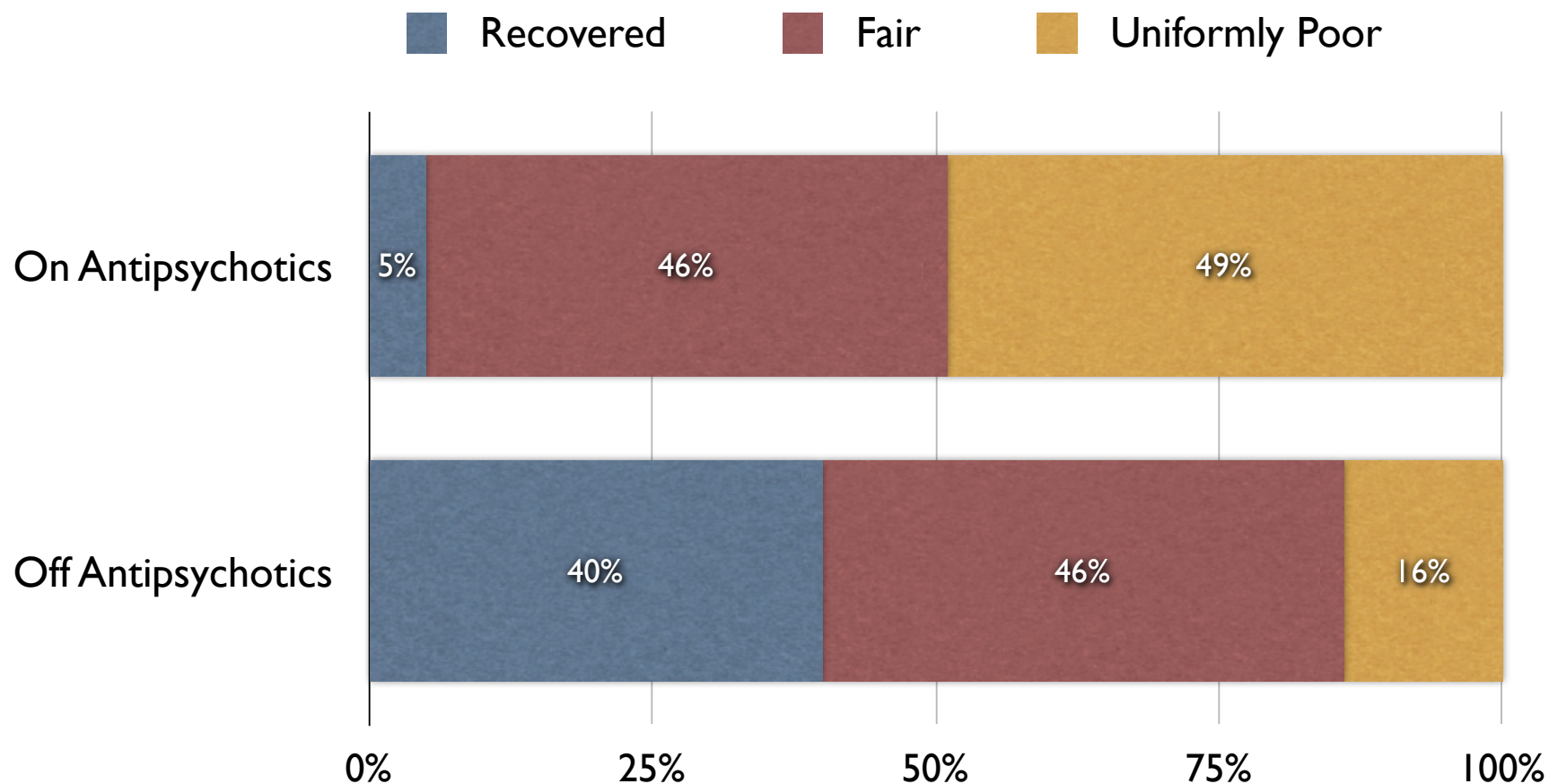
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

# Global Adjustment of Schizophrenia Patients



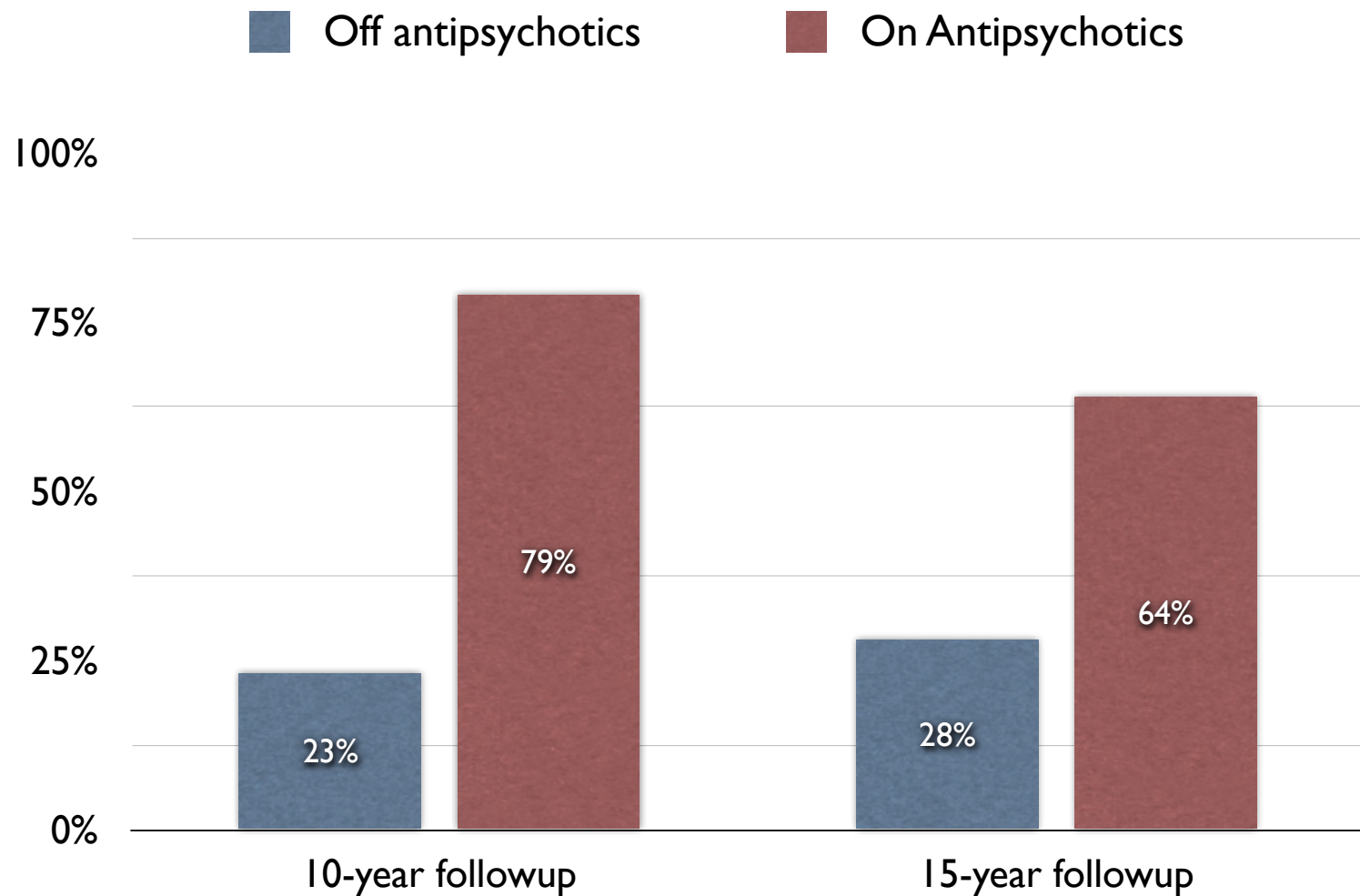
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

# Spectrum of Outcomes in Harrow's Study



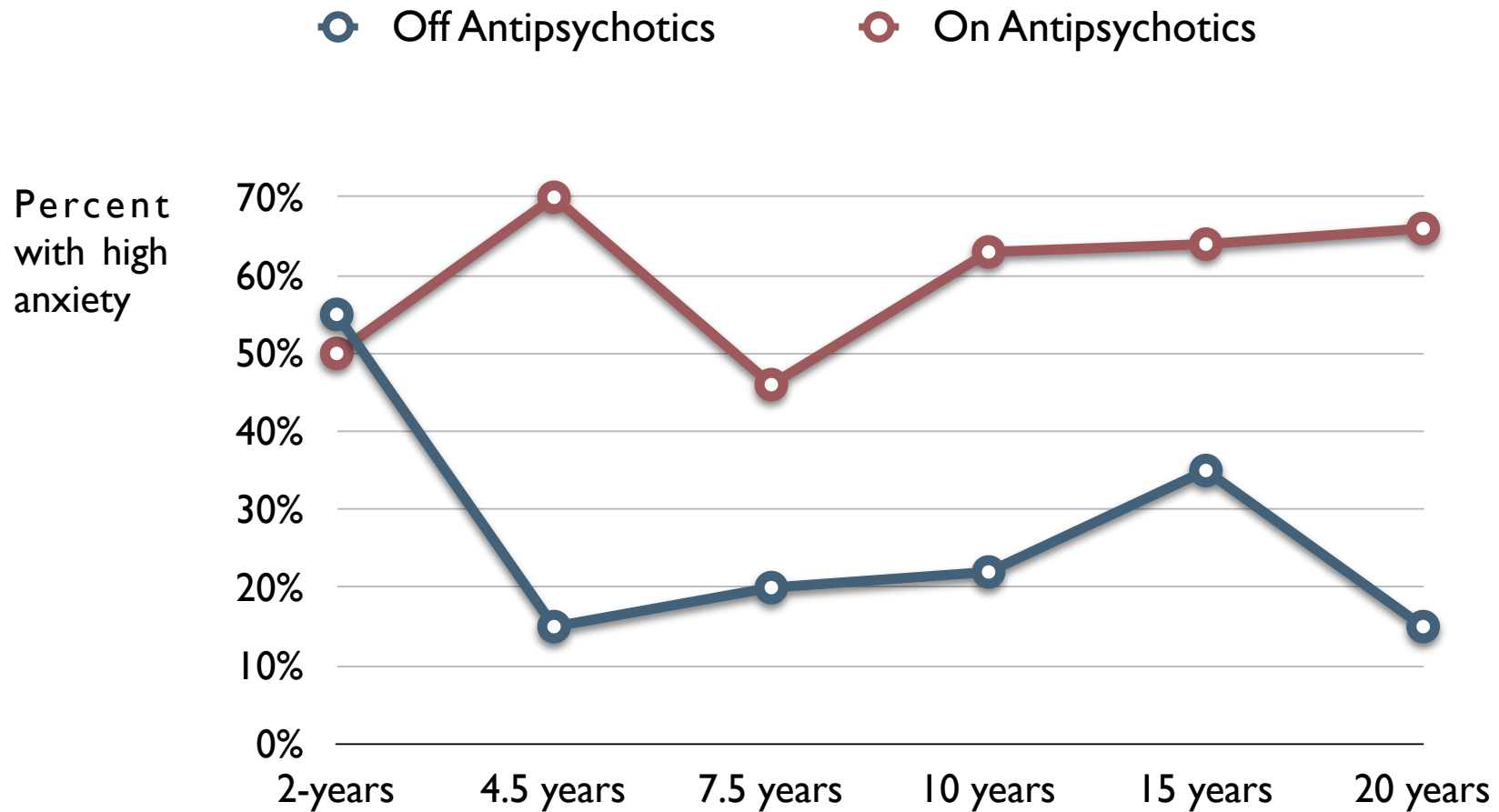
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

# Psychotic Symptoms in Schizophrenia Patients Over the Long Term



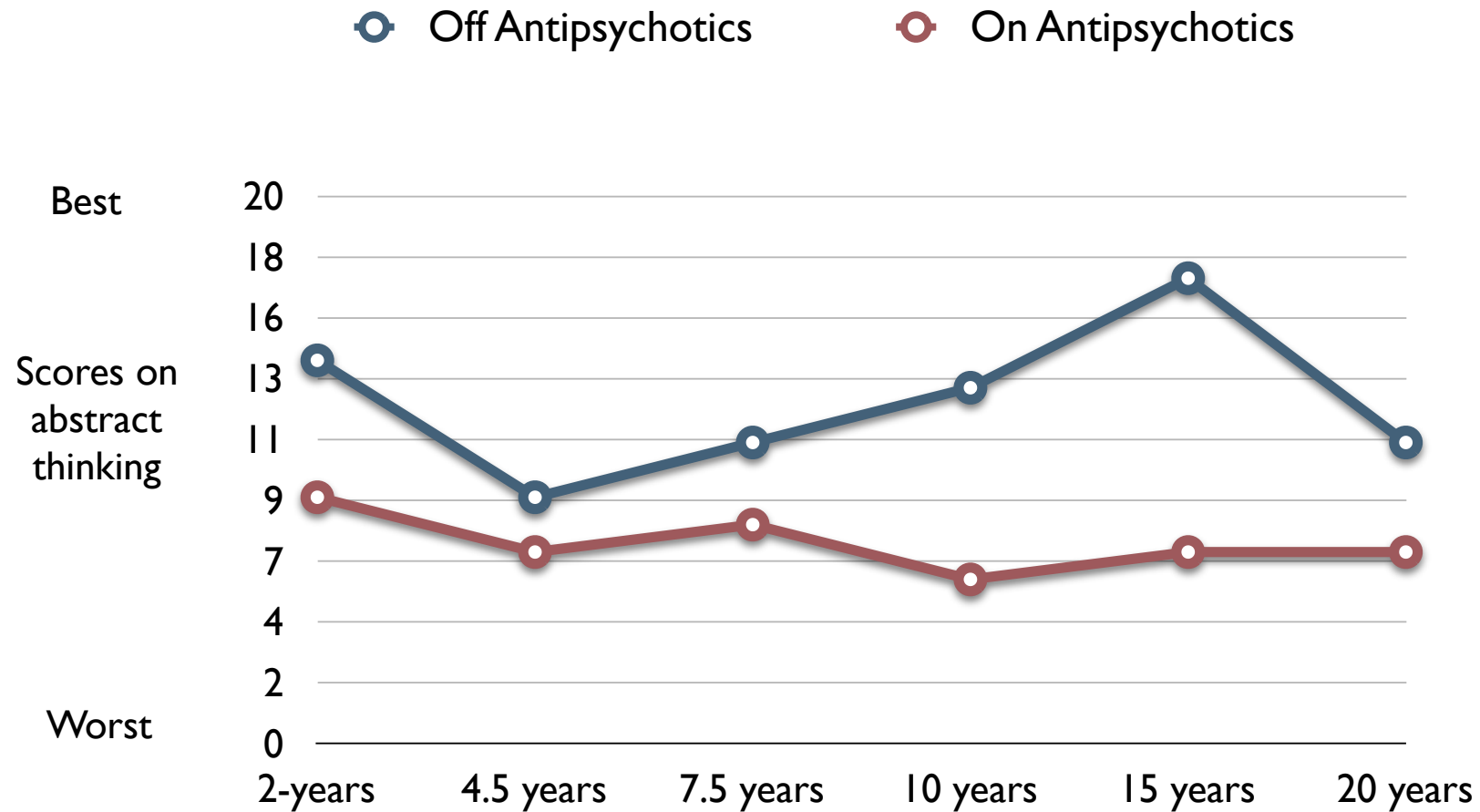
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

# 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.

“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.”

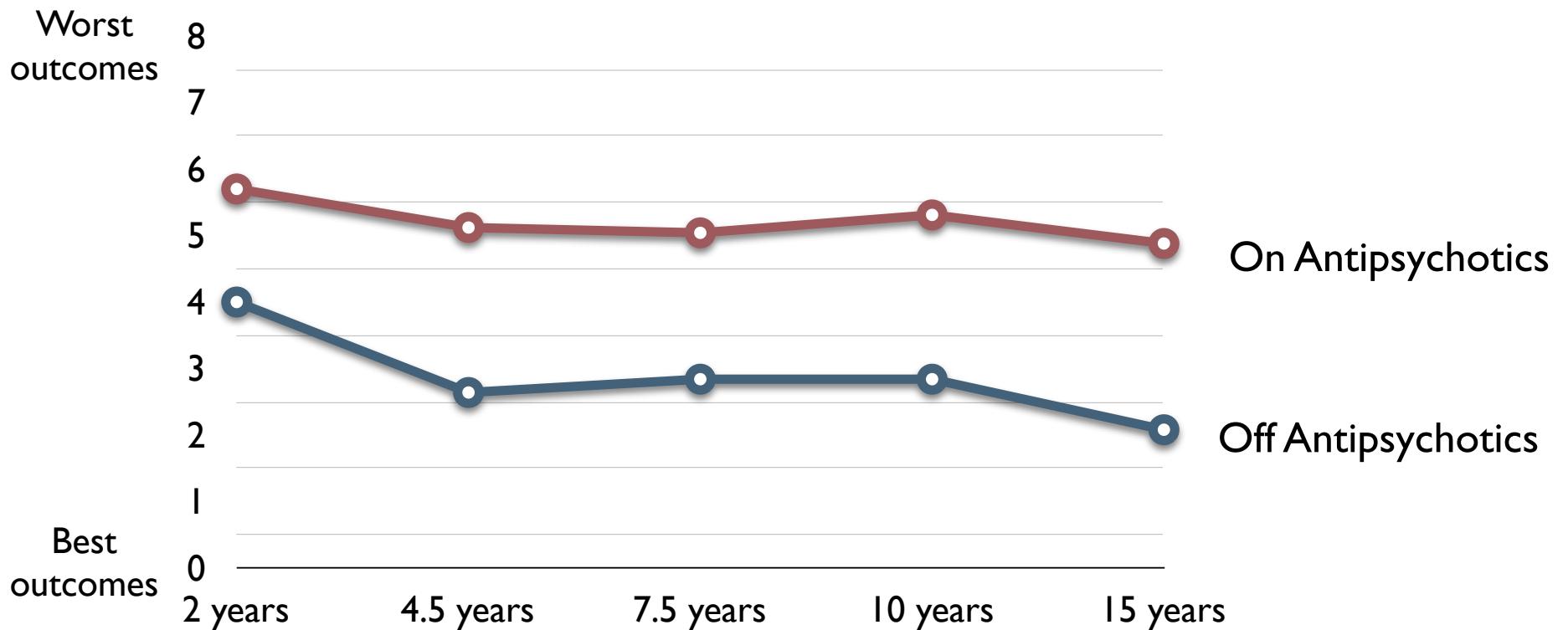
Martin Harrow, page 411.

“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

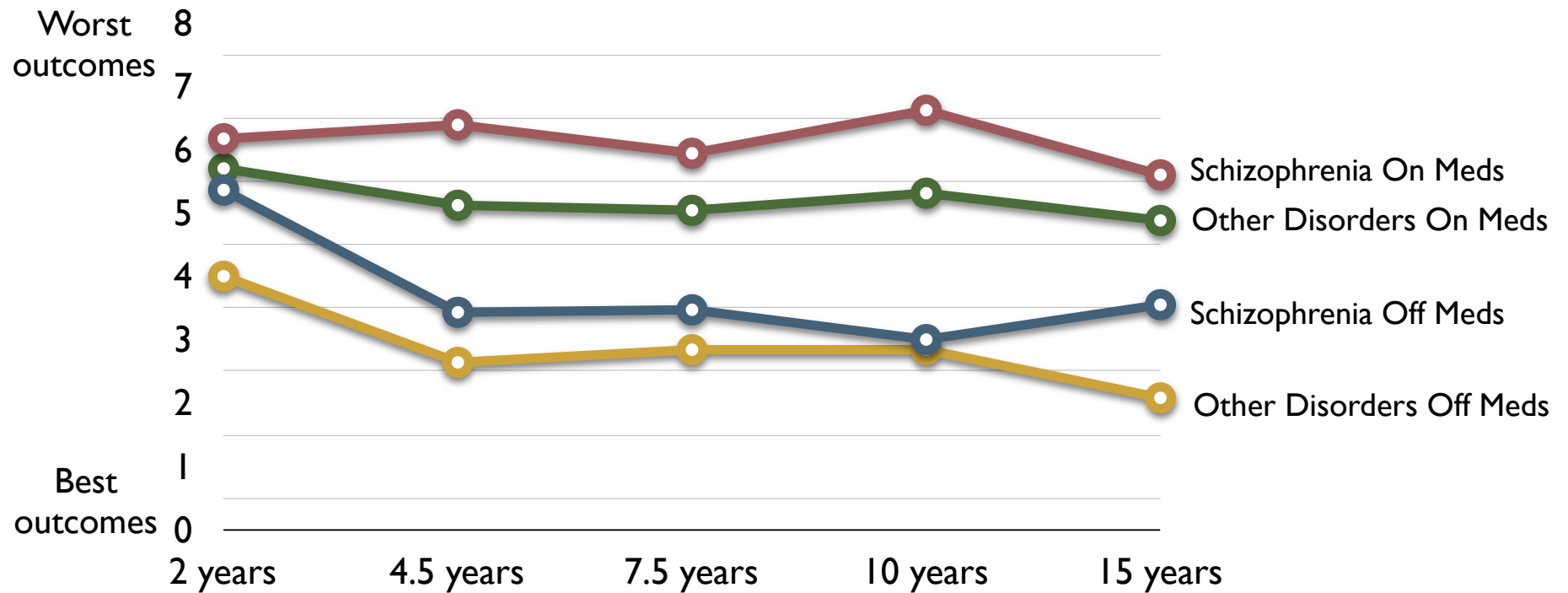


# Global Adjustment of “Other Psychotic” Patients



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.

“Is very long-term treatment with antipsychotic medications undesirable?”

--Martin Harrow, 2012

# Rethinking Antipsychotics: What Does the Evidence Show Would Best Promote Recovery?

## My Opinion:

- Avoid immediate use of antipsychotics to identify those who can recover without use of the medications.
- Minimize long-term use.

## 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.

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# 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

# Summary of Effects of Antidepressants on Long-term Outcomes

- Depression has changed from an episodic illness into a chronic one in modern era
- This led Italian psychiatrist Giovanni Fava to propose, in the early 1990s that antidepressants were depressogenic agents over the long term
- Modern studies regularly show better long-term outcomes for unmedicated patients
- Researchers have now proposed a name for this long-term effect: tardive dysphoria

## Acknowledgment of 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.”



# Are Antidepressants Depressogenic Over the Long-Term?

“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

# 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.

## Summary of Change in Long-term Bipolar Outcomes in Modern Era

- Prevalence has increased 100-fold in modern era, with antidepressants a primary reason for that increase
- Bipolar illness runs a much more chronic course than it did in the pre-drug era
- Disability rates are much higher today than they were in the pre-drug era

# The Antidepressant Pathway

In 2004, Yale University investigators reviewed the records of 87,290 patients diagnosed with depression or anxiety between 1997 and 2001, and those treated with antidepressants converted to bipolar at the rate of 7.7% per year, which was three times greater than those not exposed to the drugs. As a result, 20 to 40% of unipolar depressed patients in the U.S. who stay on antidepressants long-term convert to bipolar illness.

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

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.”

# Summary of 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*

## Worsening Long-term Course of Bipolar Illness in Drug Era

“The general impression of clinicians today is that the course of recurrences of manic-depressive illness has substantially changed in the last 20 years. The recurrences of many patients have become more frequent. One sees more manias and hypomanias . . . more rapid cyclers and more chronic depressions.”

--Anthansious Koukoulos, 1983

# The Modern Course of Bipolar Illness

- More recurrent episodes and more rapid cycling
- Low-level depression between episodes
- Only 33% enjoy good functional outcomes (compared to 70% to 85% in pre-drug era)
- Long-term cognitive impairment (which wasn't seen in pre-drug era)
- Physical problems related to long-term medication use
- Risk of early death



**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.”

# Rethinking Psychiatric Care

A. The field needs to investigate and re-discover the long-term course of major mental disorders prior to the pharmacotherapy era, as epidemiological studies from that era tell of people regularly recovering from acute episodes of mental illness, including psychosis, and often staying well for long periods of time, or even indefinitely.

B. The field needs to incorporate the long-term outcomes literature into its medication protocols, and thus develop protocols that involve using the medications in a more selective, cautious manner. These protocols may involve delaying initial use of medications, and trying to minimize long-term use. (See Western Lapland's "open dialogue" program.)

“The time has now come to call an end to the psychopharmacological revolution of 1952 . . . all revolutions have to come to an end, and the psychopharmacological one now has to meld into a quieter world where drug therapy, which has had quite a battering in recent years and needs our support, will be joined by other approaches as equal partners, preferably working together in harness rather than in conflict.”

--Peter Tyrer, Editor  
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