Rethinking Psychiatric Care:

If We Follow the Scientific Evidence, What Must be Done to Promote Good Long-term Outcomes?

Robert Whitaker, 2011

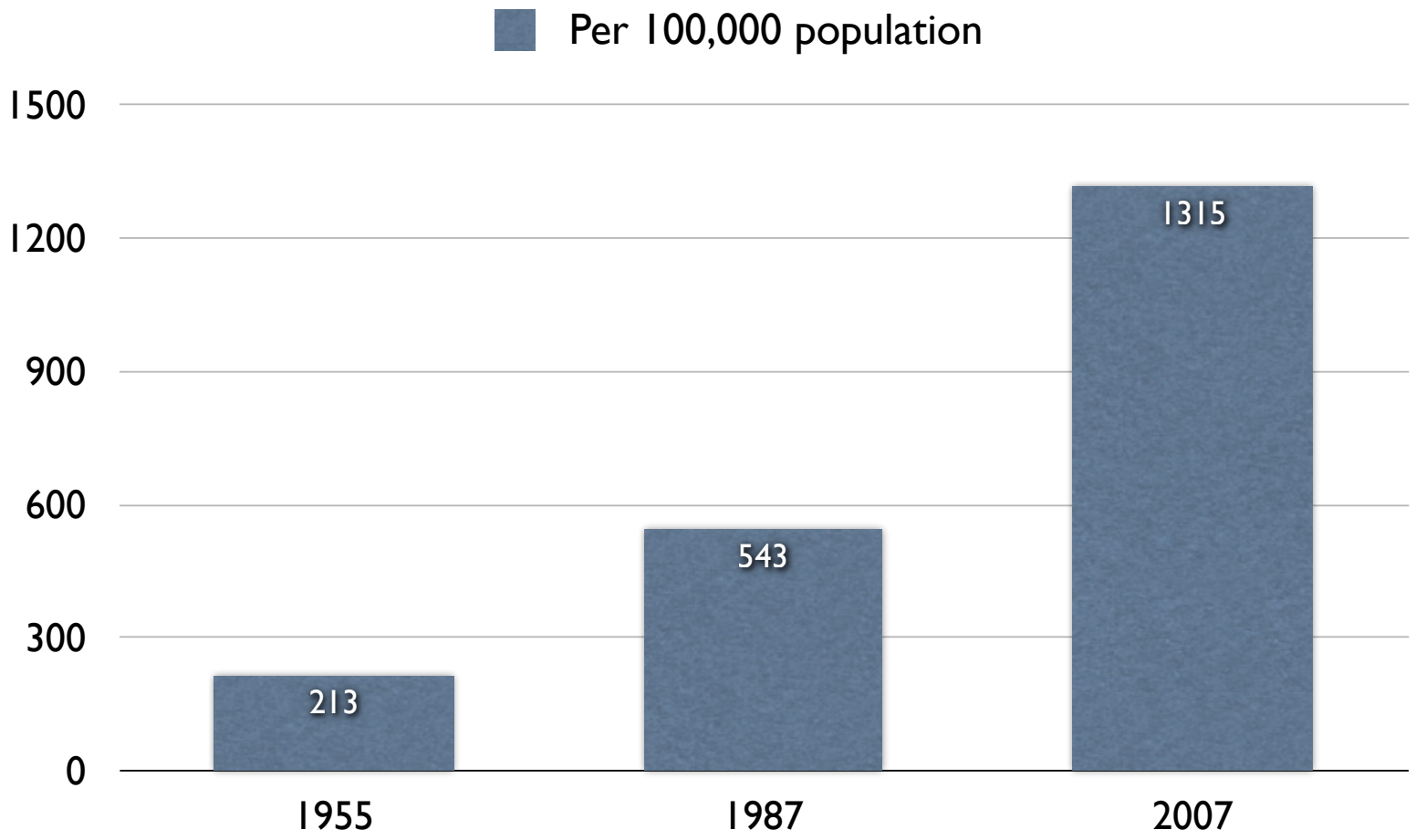
The Common Wisdom

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*

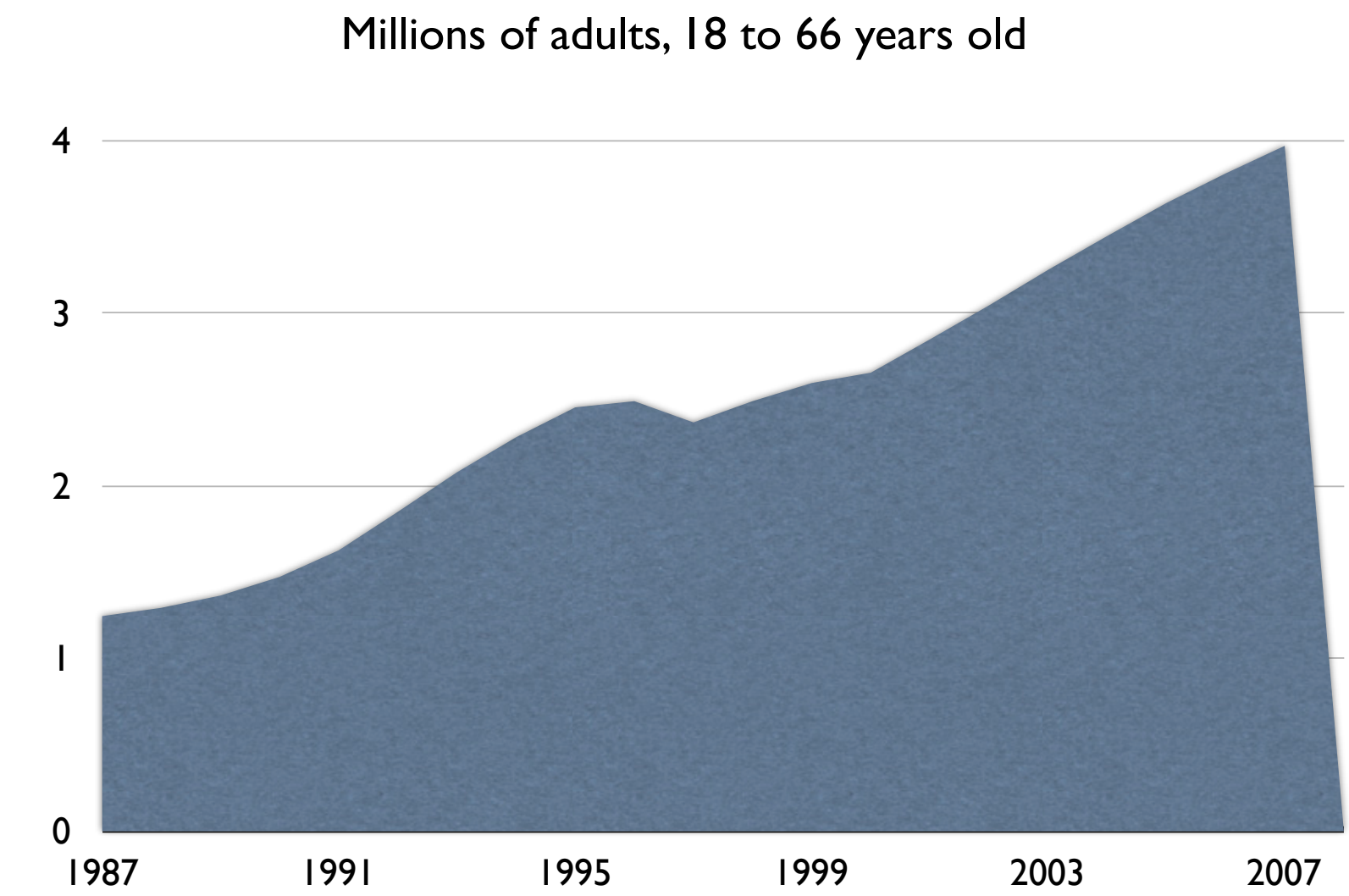
The Disabled Mentally Ill in the United States, 1955-2007

(under government care)



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

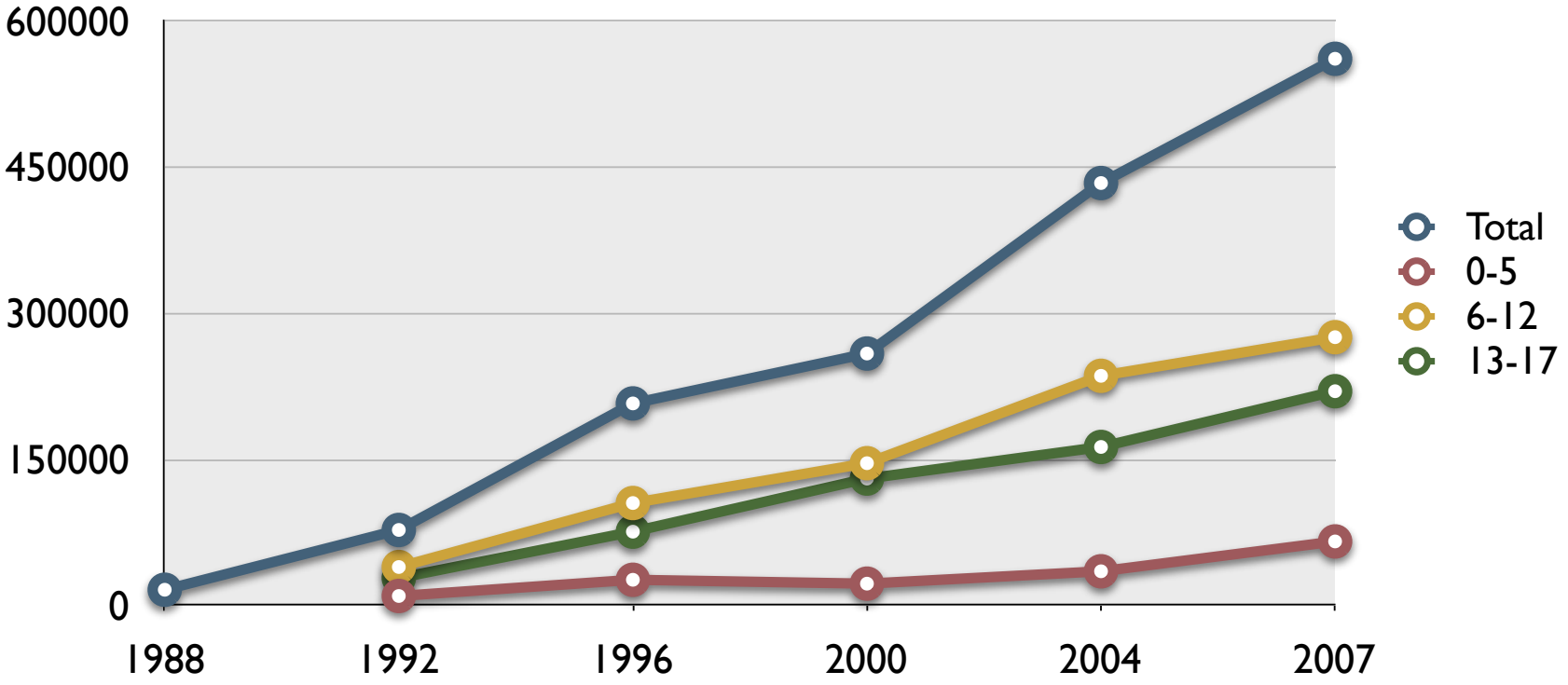
U.S. Disability in the Prozac Era



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

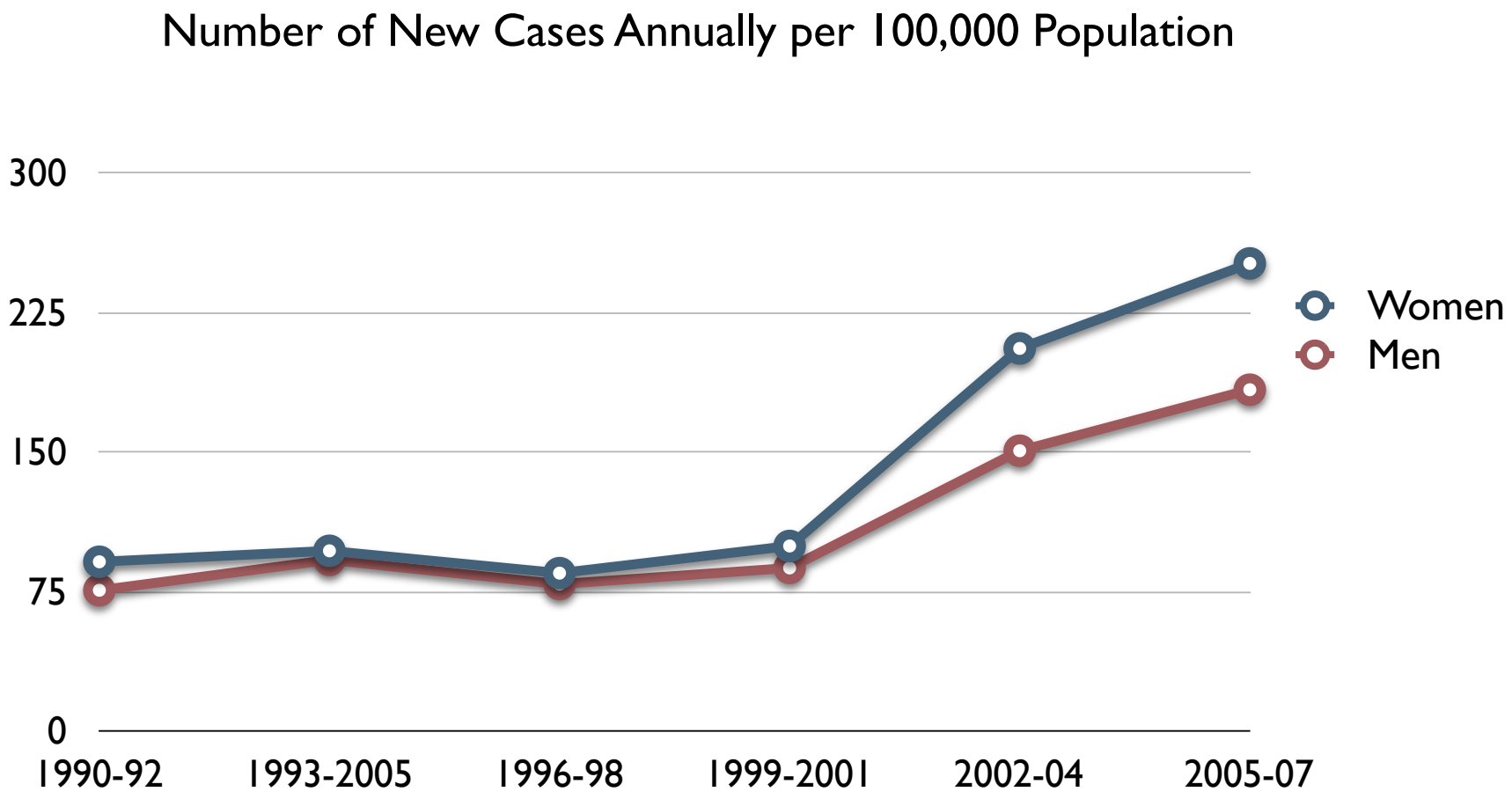
The Epidemic in Children

Children on SSI Disability Due to Mental Illness



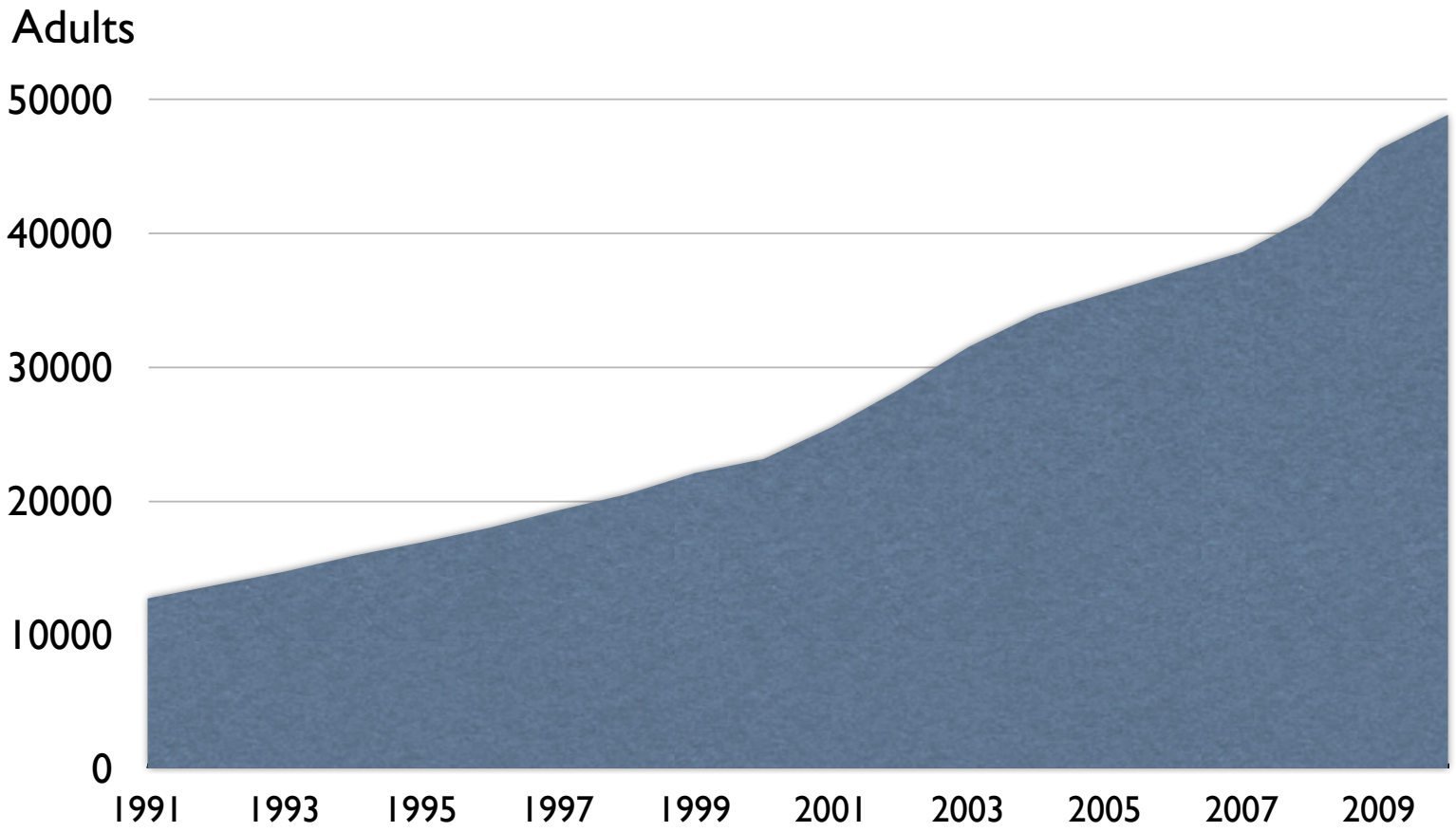
Prior to 1992, the government's SSI reports did not break down recipients into subgroups by age. Source: Social Security Administration reports, 1988-2007.

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



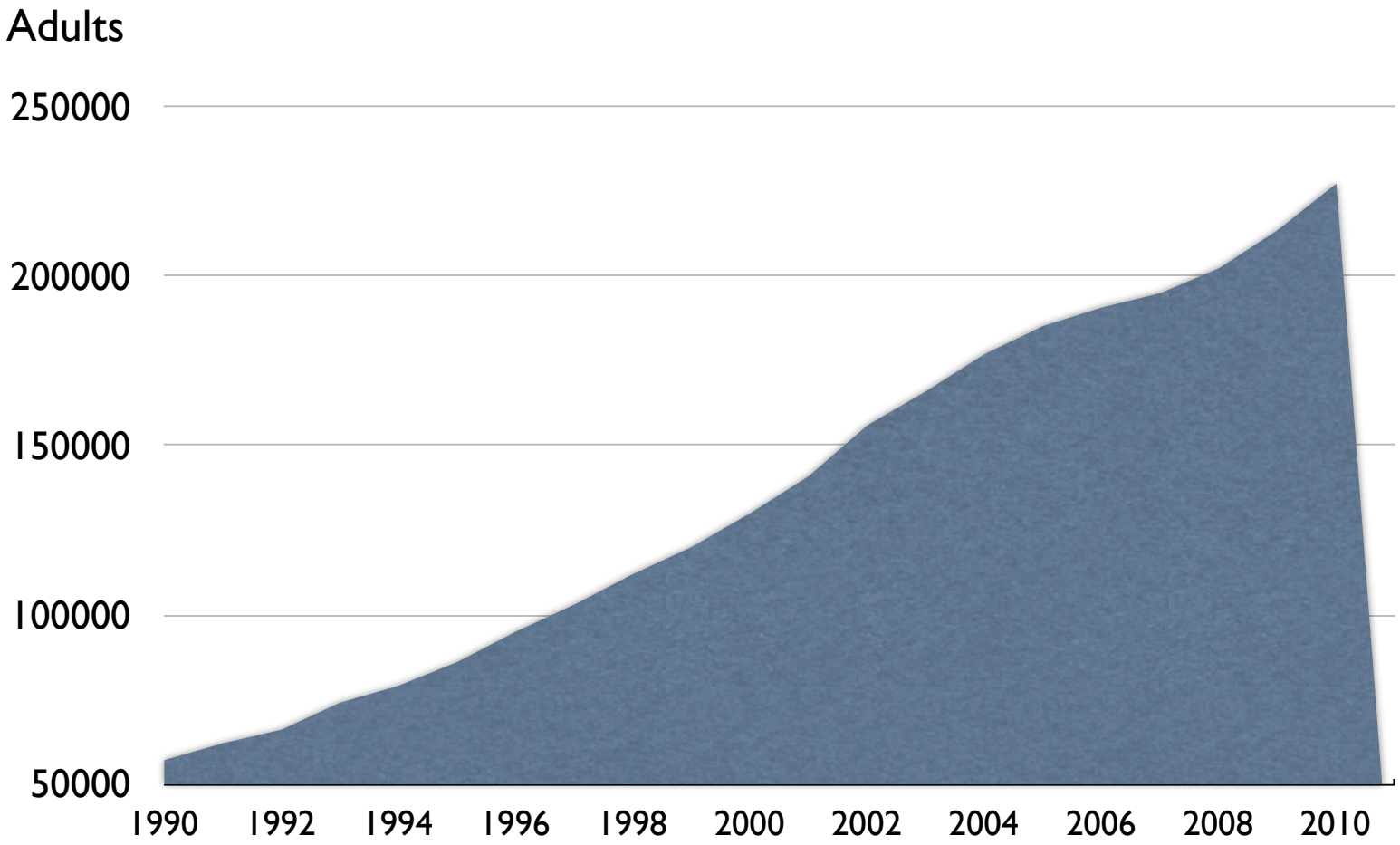
Source: Thoriacius, S. "Increased incidence of disability due to mental and behavioural disorders in Iceland, 1990-2007." *J Ment Health* (2010) 19: 176-83.

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



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 psychiatric medications improve the long-term course of mental disorders, particularly in regard to functional outcomes.

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

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

A Case Study

The Effect of Antipsychotics on the Long-term Course of Schizophrenia and Other Psychotic Disorders

Assessing Long-Term 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)

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.

Bockoven's Retrospective Comparison of Outcomes in Pre-Drug and Drug Era

1947 cohort: 45% didn't relapse within five years of discharge, and 76% were successfully living in the community at the end of that period.

1967 cohort: 31% didn't relapse within five years of discharge, and as a group 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
Placebo/off	24	1.7	8%
Antipsychotic/off	17	2.79	47%
Placebo/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.

Rapport'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

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

- 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

"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 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.

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 Double the Density of D2 HIGH Receptors

In this same report, Seeman found that haloperidol and olanzapine both doubled 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 concluded that this was why the medications failed over time

MRI Study in Macaque Monkeys

- 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 of Schizophrenia Patients

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

WHO Cross-Cultural Studies in 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.

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.

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

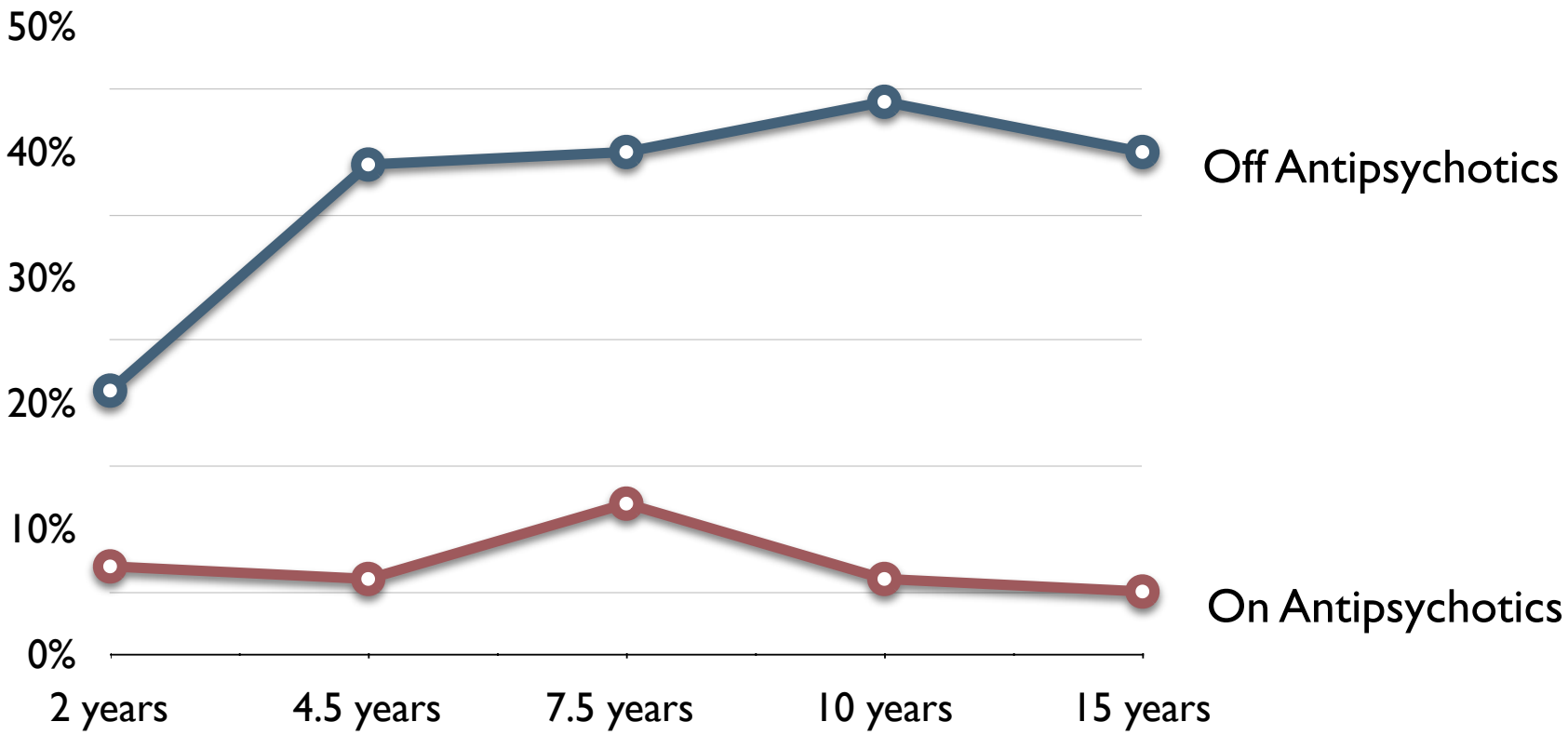
Patient Enrollment

- 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

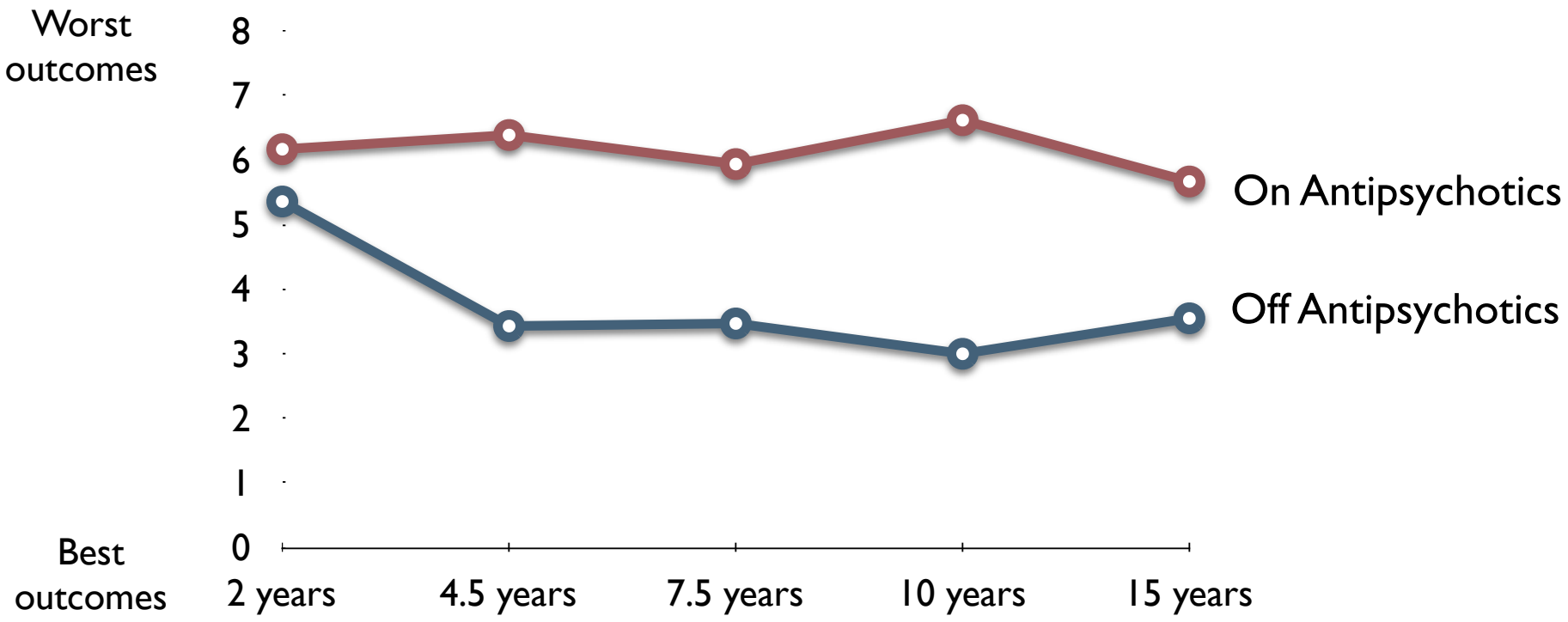
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Long-term Recovery Rates for Schizophrenia Patients



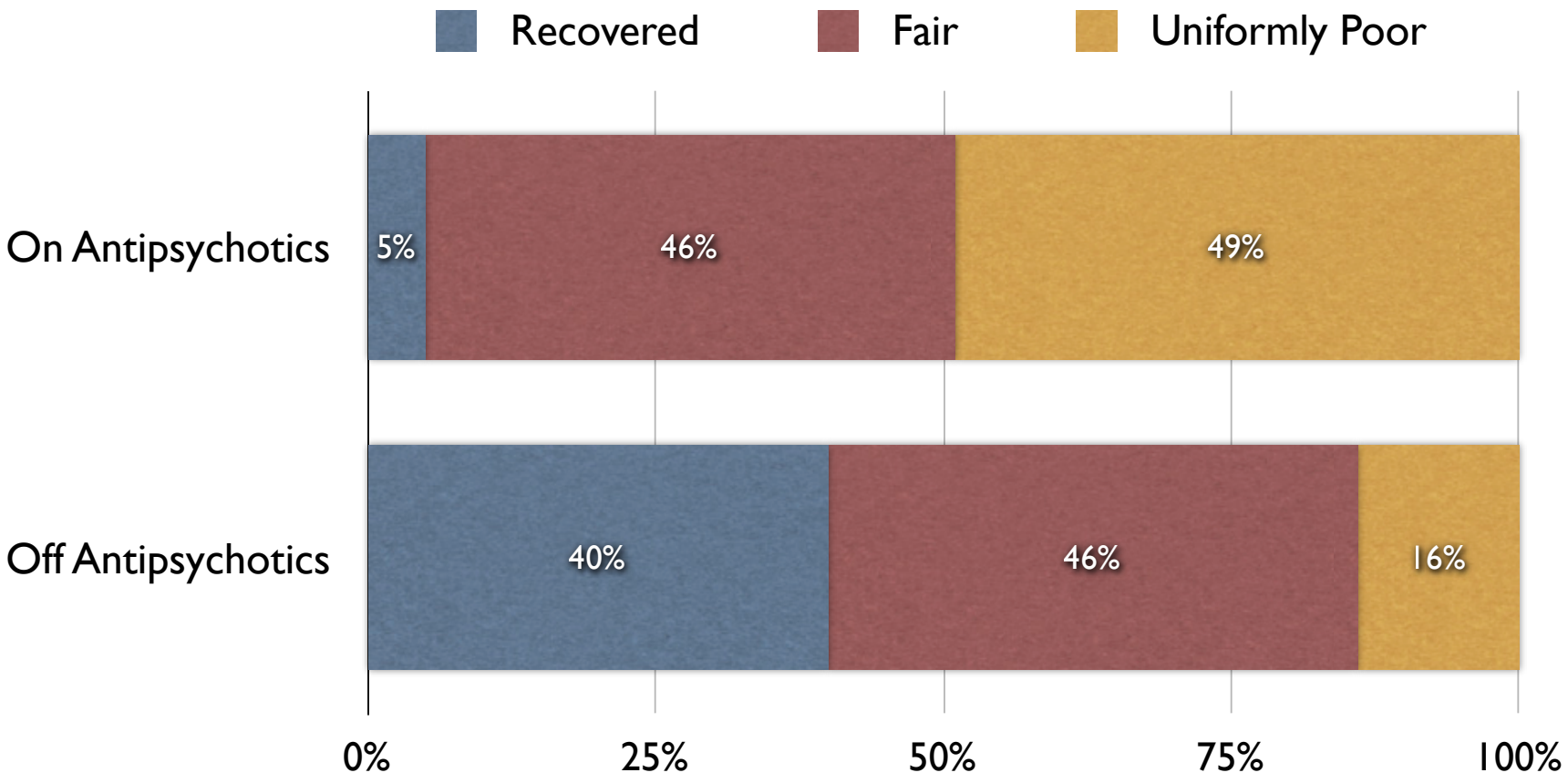
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Global Adjustment of Schizophrenia Patients



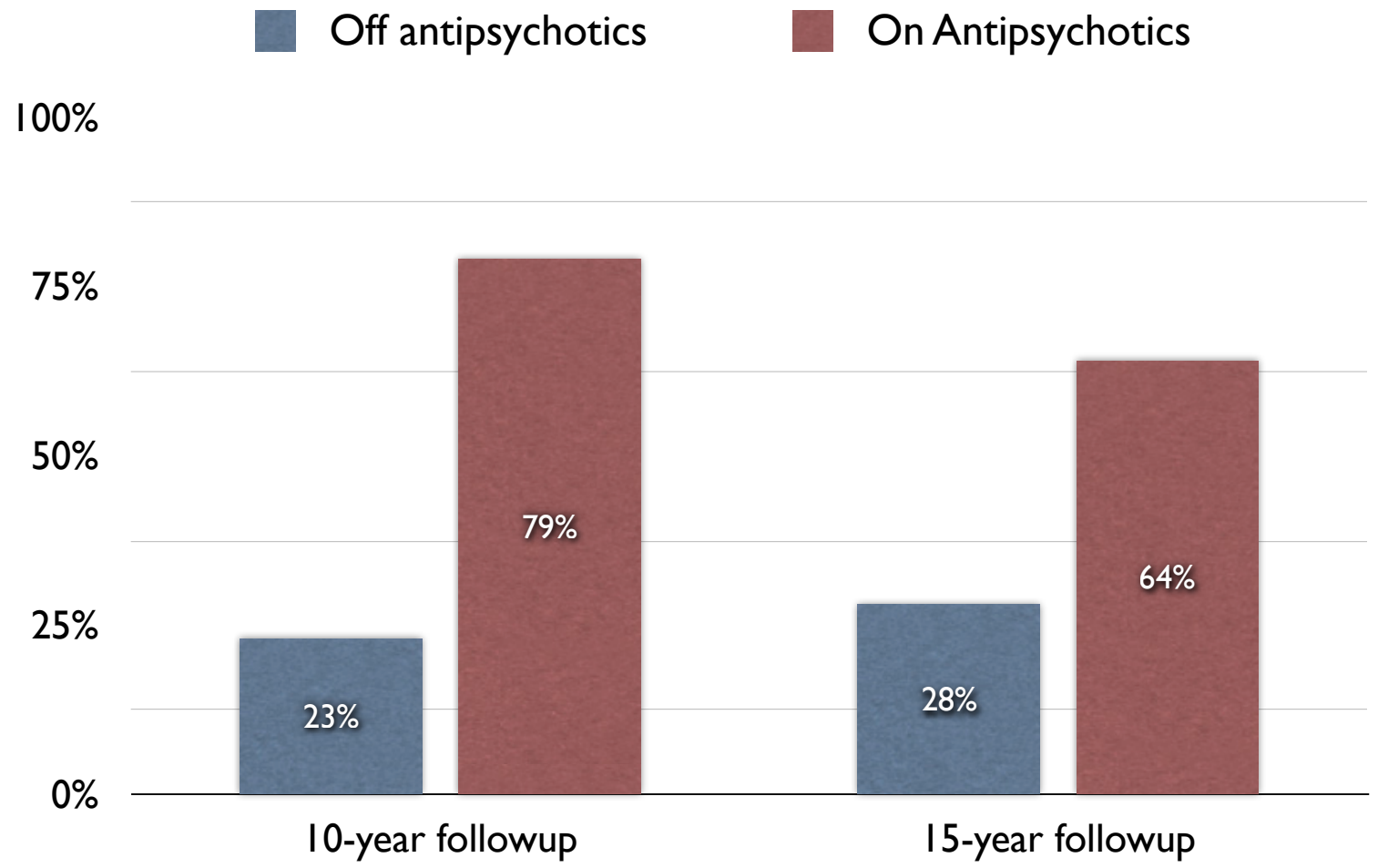
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Spectrum of Outcomes in Harrow's Study



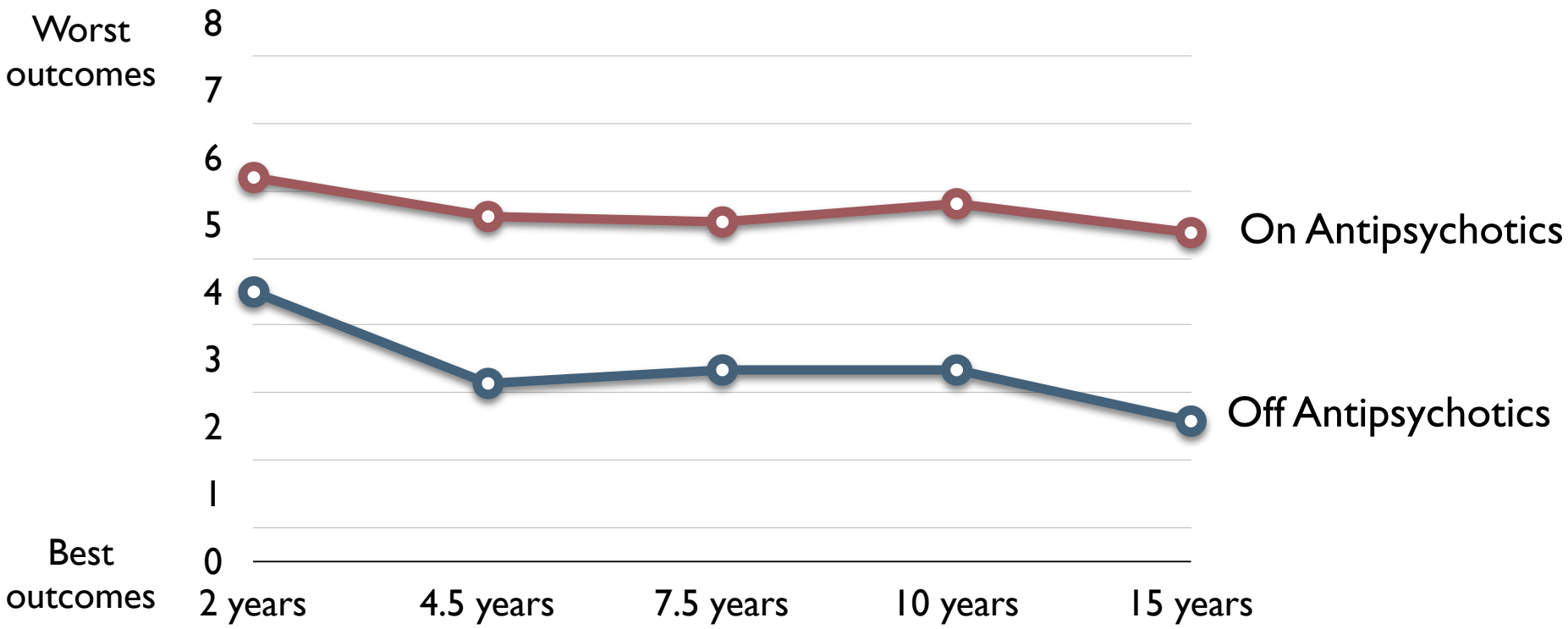
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



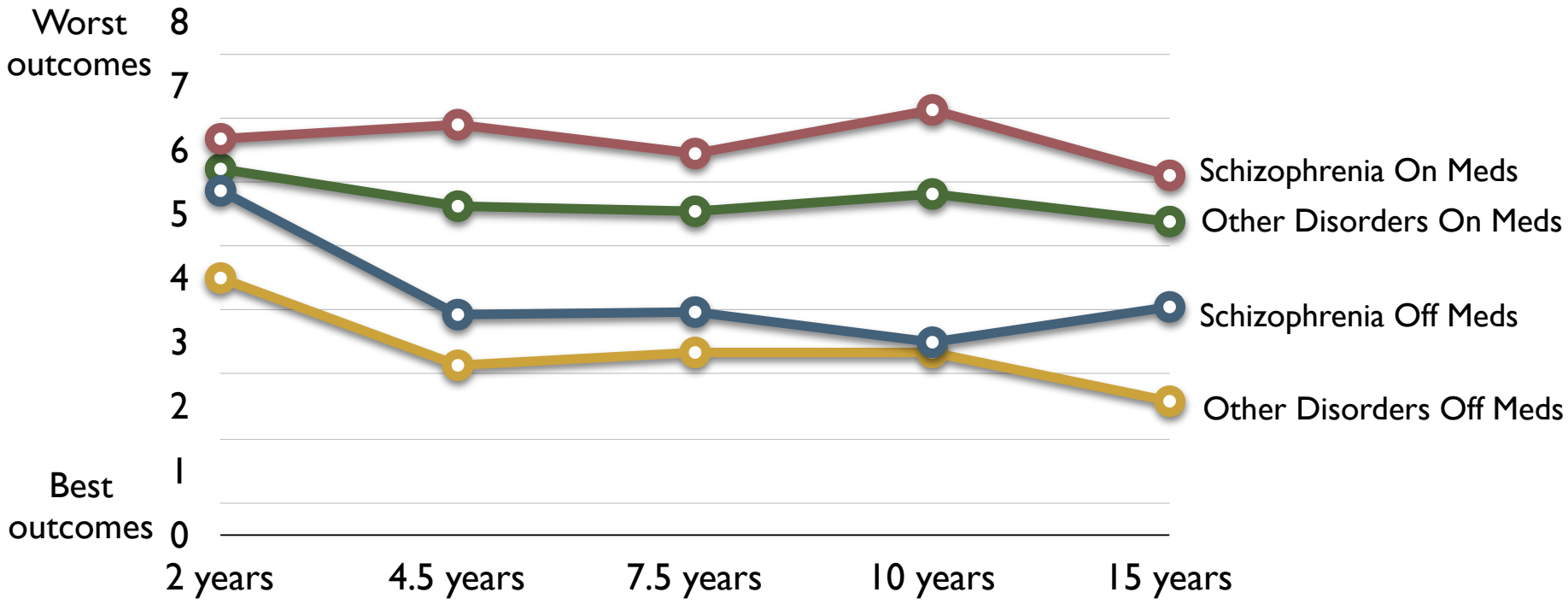
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

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.

"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

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.

Summary of Outcomes For Affective Disorders

- Depression has been transformed from an episodic illness into a chronic one in the modern drug era.

- The prevalence of bipolar disorder in adults has increased roughly one-hundred fold.

- Bipolar outcomes have notably deteriorated in modern era.

Why Don't We Know This?

Solutions

1. Long-term outcomes data needs to be presented, evaluated, and discussed.

2. Apply the Hippocratic Oath.

In order for a treatment to "do no harm," the treatment must improve on the "natural" recovery rates for a disorder. Psychiatric drugs do not meet that standard over the long-term, and thus their use needs to be rethought.

3. Fund and study programs that involve providing patients with psychosocial care and involve using medications in a much more selective, limited manner (a la open dialogue therapy.)