

Affective Disorders in the Age of Prozac

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Depression in the Pre-Antidepressant Era

Who It Affected

Major depression was primarily a disorder of middle-aged and older persons. In 1956, 90% of first admissions to public and private hospitals in the United States for depression were 35 years and older.

Prevalence

In the 1930s and 1940s, fewer than one in a thousand adults suffered an episode of clinical depression each year. (In U.S.)

Hospitalization

In 1955, there were only 7,250 “first admissions” for depression in state and county mental hospitals in the U.S. the total number of depressed patients in the nation’s mental hospitals that year was 38,200.

Short-term Outcomes in the Pre-Antidepressant Era

“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.

“In the treatment of depression, one always has an ally the fact that most depressions terminate in spontaneous remissions. This means that in many cases regardless of what one does the patient eventually will begin to get better.” --Nathan Kline, Journal of the American Medical Association, 1964

Most depressive episodes “will run their course and terminate with virtually complete recovery without specific intervention.” -- Dean Schuyler, head of the depression section at the NIMH, 1974

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, 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.

Depression Was Understood to Be an Episodic Disorder

“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

Conclusion:

Prior to the antidepressant era, clinical depression was primarily a disorder that affected older people and was fairly uncommon. Most of those affected could expect to recover from a depressive episode within 12 months (80% or so), and over the long-term, depression ran an episodic course. Half of first episode patients would never experience another episode severe enough to require rehospitalization, and only 20% or so would become chronically ill.

The Long-term Effects of Antidepressants on Depression

Clinical Perceptions in Early Years of Antidepressant Use

- H.P. Hoheisel, German physician, 1966: Exposure to antidepressants appeared to be “shortening the intervals” between depressive episodes.
- Nikola Schipkowensky, Bulgarian psychiatrist, 1970: The antidepressants were inducing “a change to a more chronic course.”

The Chronicity Worry is Tested

J.D. Van Scheyen, Dutch psychiatry, 1973:

After conducting a study of 94 depressed patients, he concluded that “it was evident, particularly in the female patients, that more systematic long-term antidepressant medication, with or without ECT [electronconvulsive therapy], exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate and a decrease in cycle duration . . . Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?”

An Episodic Illness Turns Chronic in the Antidepressant Era

National Institute of Mental Health Panel on mood disorders, 1985:

“Improved approaches to the description and classification of [mood] disorders and new epidemiologic studies [have] demonstrated the recurrent and chronic nature of these illnesses, and the extent to which they represent a continual source of distress and dysfunction for affected individuals.”

NIMH Trial in 1980s

Four Arms:

Two forms of psychotherapy
Tricyclic (imipramine)
Placebo

16-Week Results

“No significant differences among treatments, including placebo plus clinical management, for the less severely and functionally impaired patients.” Only the severely depressed patients fared better on imipramine.

Source: Shea, M. “Course of depressive symptoms over follow-up.” *Arch Gen Psychiatry* 49 (1992):782-787.

18-Month Results

Stay-well rate highest for psychotherapy groups (30%) and lowest for imipramine group (19%).

Further analysis of results:

If study dropouts were included in the analysis, then the results for the imipramine patients “look even worse . . . patients receiving the antidepressant were most likely to seek treatment following termination, produced the highest probability of relapse, and exhibited the fewest weeks of reduced or minimal symptoms during the follow-up period.”

Source: Shea, M. “Course of depressive symptoms over follow-up.” *Arch Gen Psychiatry* 49 (1992):782-787.

High-Relapse Rates Following Antidepressant Use

In a 1997 meta-analysis, Harvard researchers report that 50% of all drug-withdrawn patients relapsed within 14 months. They also noted that the longer the patient had been on an antidepressant prior to drug withdrawal, the higher the relapse rate.

(In the pre-antidepressant era, this was the relapse rate seen in studies that lasted 15 years or more.)

Source: Viguera, A. "Discontinuing antidepressant treatment in major depression," *Harvard Review of Psychiatry* 5 (1998):293-305.

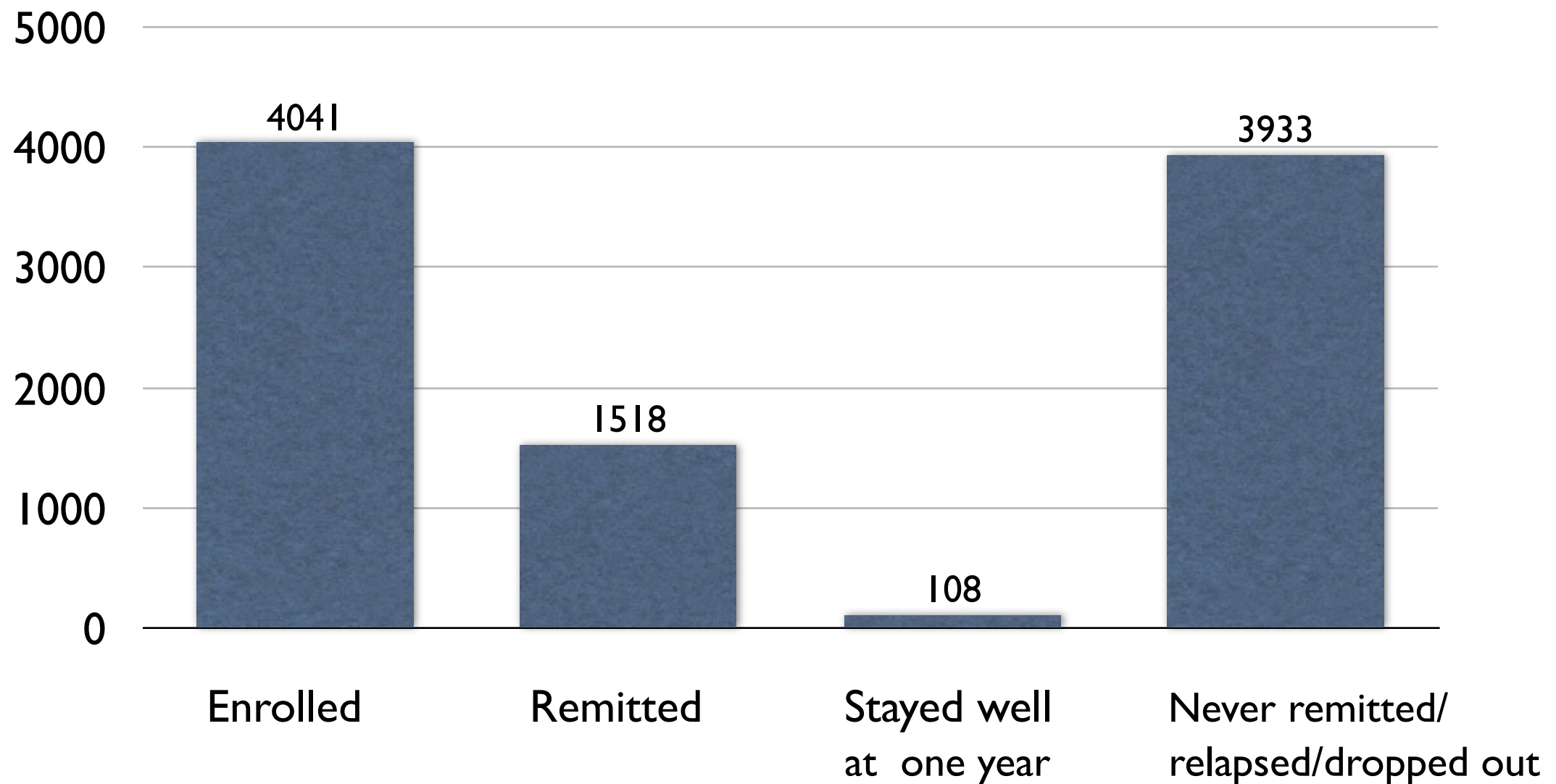
The APA Acknowledges Change in Course of Depression in Modern Era

American Psychiatric Association's Textbook of Psychiatry, 1999:

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

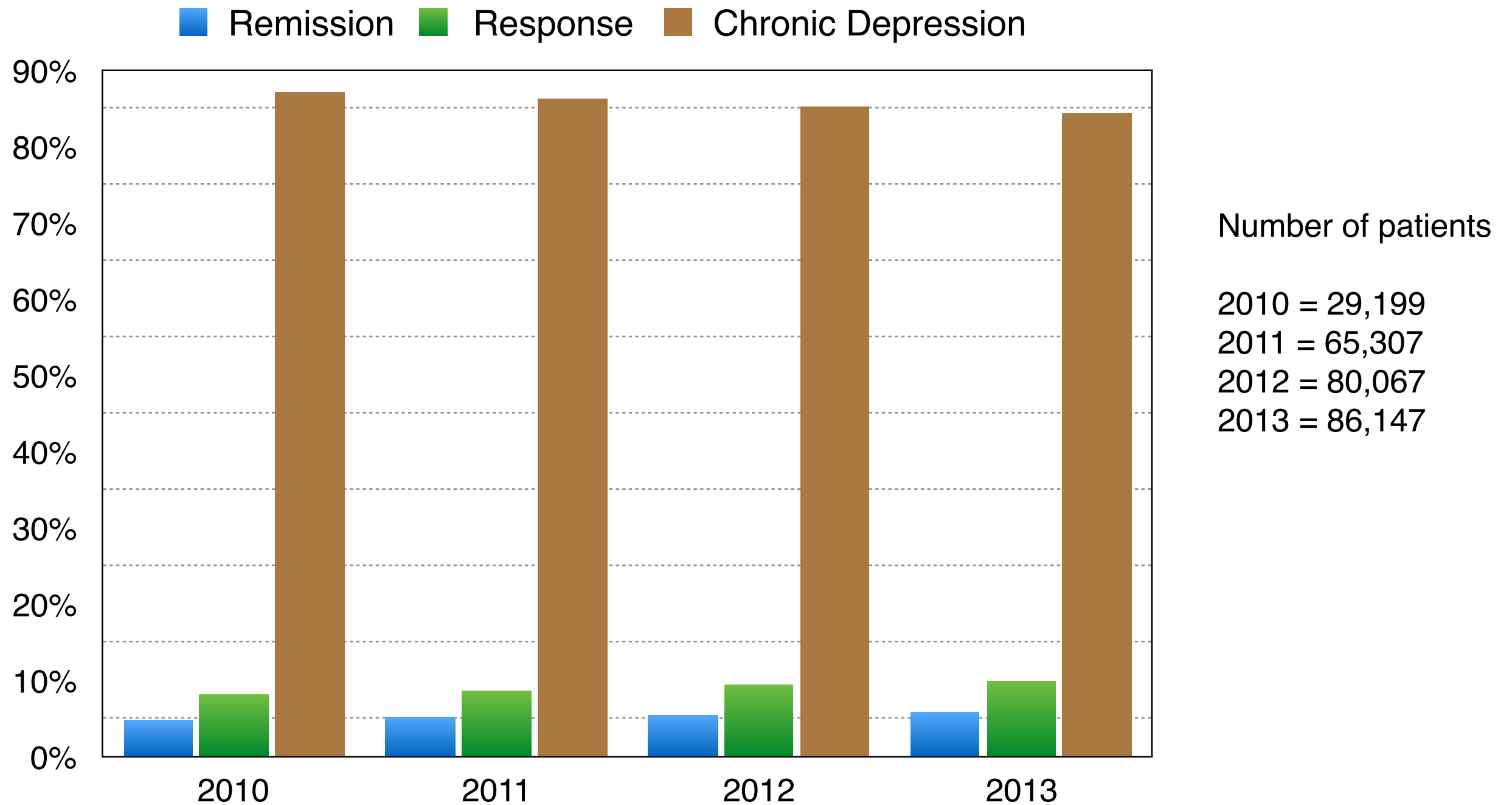
The STAR*D Trial Confirms That Medicated Depression Runs a Chronic Course Today

Number of patients



Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

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



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

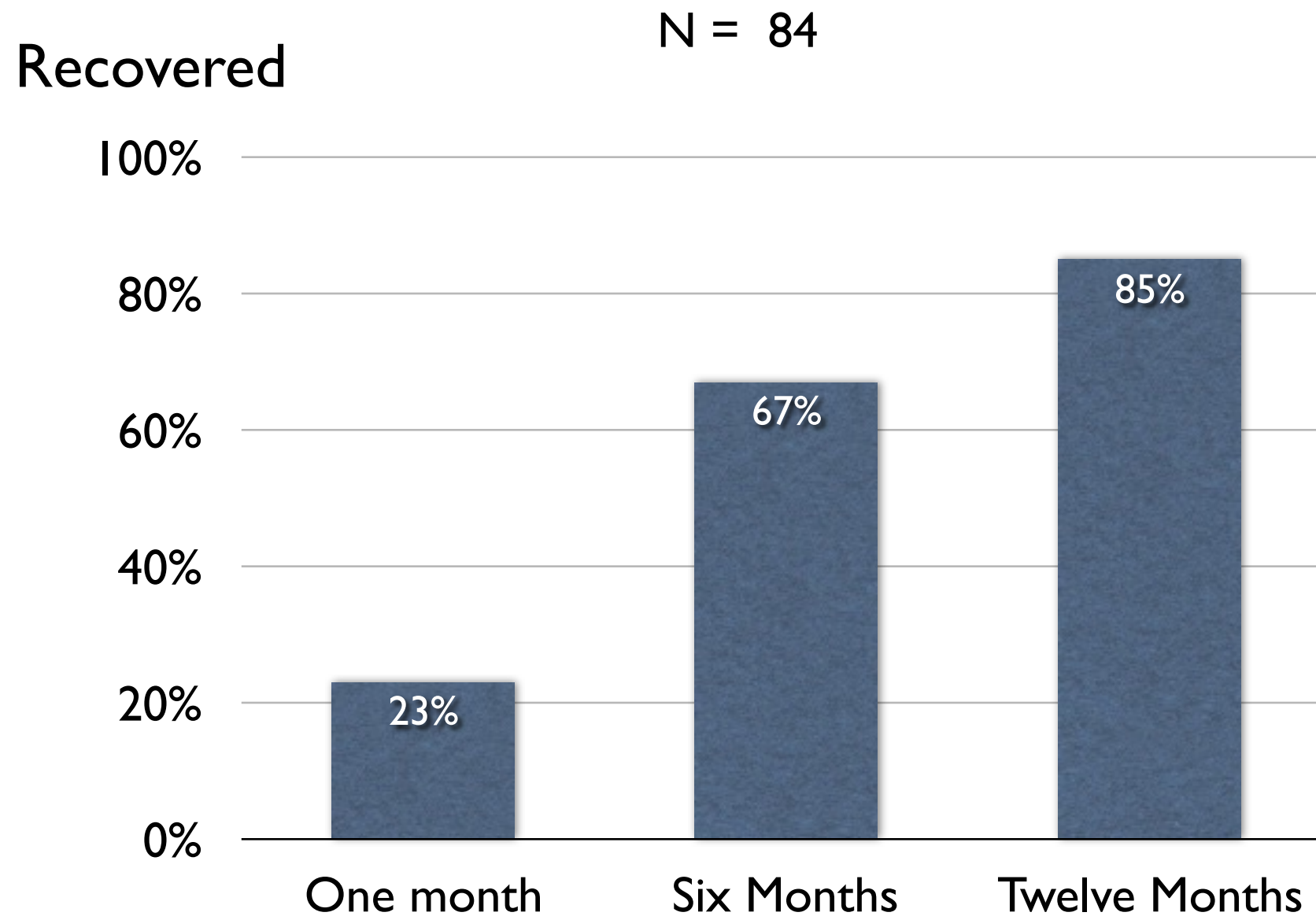
One-Year Remission Rates in NIMH Study of Medicated Depression in “Real-World” Patients

- 126 patients were treated with antidepressants and given emotional and clinical support “specifically designed to maximize clinical outcomes.”
- Only 26% responded to antidepressants (50% reduction in symptoms).
- Only half of those who responded stayed better for a significant period of time
- Only 6% remitted and then remained in remission at the end of one year.

“These findings reveal remarkably low response and remission rates.”

--John Rush, 2004

One-Year Recovery Rates in NIMH Study of Unmedicated Depression



Source: M. Posternak, "The naturalistic course of unipolar major depression in the absence of somatic therapy." *Journal of Nervous and Mental Disease* 194 (2006):324-349.

“If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this.”

--Michael Posternak

The Course of Medicated Depression Today

According to mainstream texts:

- One-third of all unipolar patients are non-responders to antidepressants. This group goes on to have a chronic course.
- Another third are partial responders. However, “resolution of major depressive episode with residual subthreshold depressive symptoms, even the first lifetime episode, appears to be the first step of a more severe, relapsing, and chronic future course.”
- The final third of patients see their symptoms remit over the short term. About half of this group, when maintained on an antidepressant, stay well for long periods of time.

“Only 15% of people with unipolar depression experience a single bout of the illness,” and for the remaining 85%, with each new episode, remissions become “less complete and new recurrences develop with less provocation.”

--American Psychiatric Association Textbook, 1999

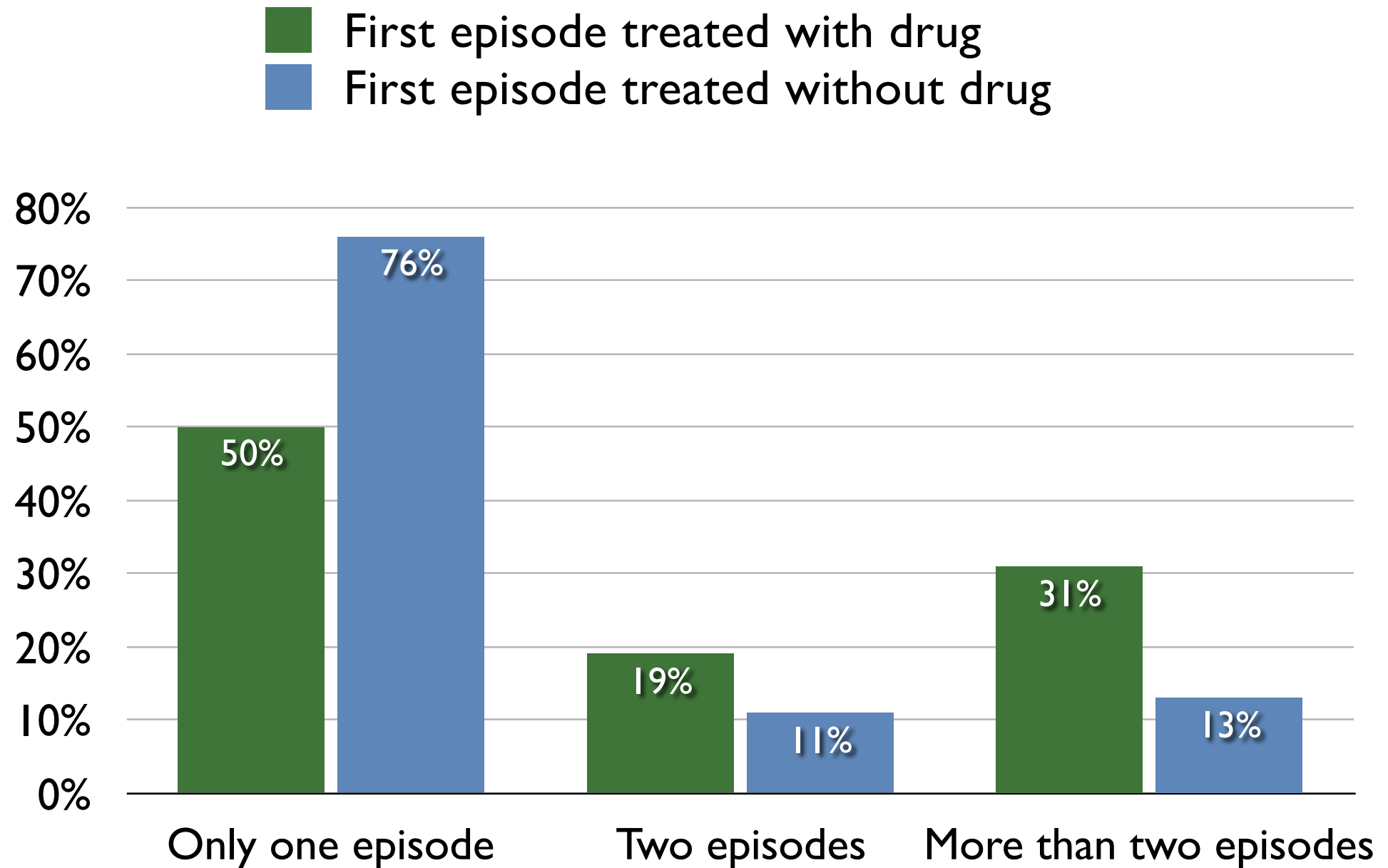
Are Antidepressants Depressogenic Over the Long-Term?

“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

Depression in the Netherlands

(Over the course of ten years)



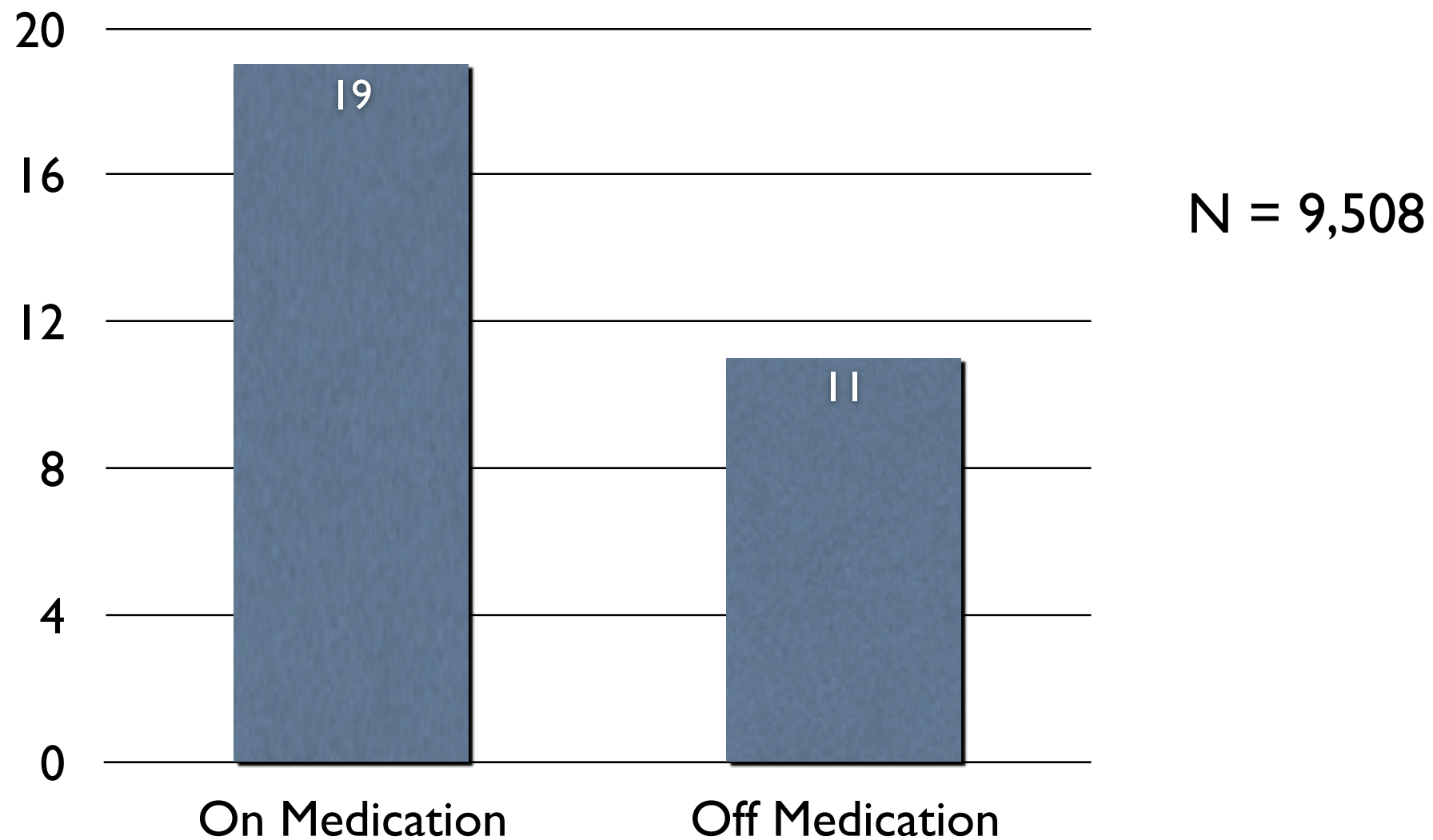
Source: E. Weel-Baumgarten, "Treatment of depression related to recurrence," *J Clin Psychiatry & Therapeutics* 25 (2000):61-66.

“Even when a diagnosis of Major Depressive Disorder has been made, spontaneous recovery should be considered for a number of cases in general practice and watchful waiting could prove worthwhile.”

--E.M. van Weel-Baumgarten, 2000

Five-Year Outcomes in Canada

Number of Weeks
Depressed Each Year



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

One possible interpretation of results:

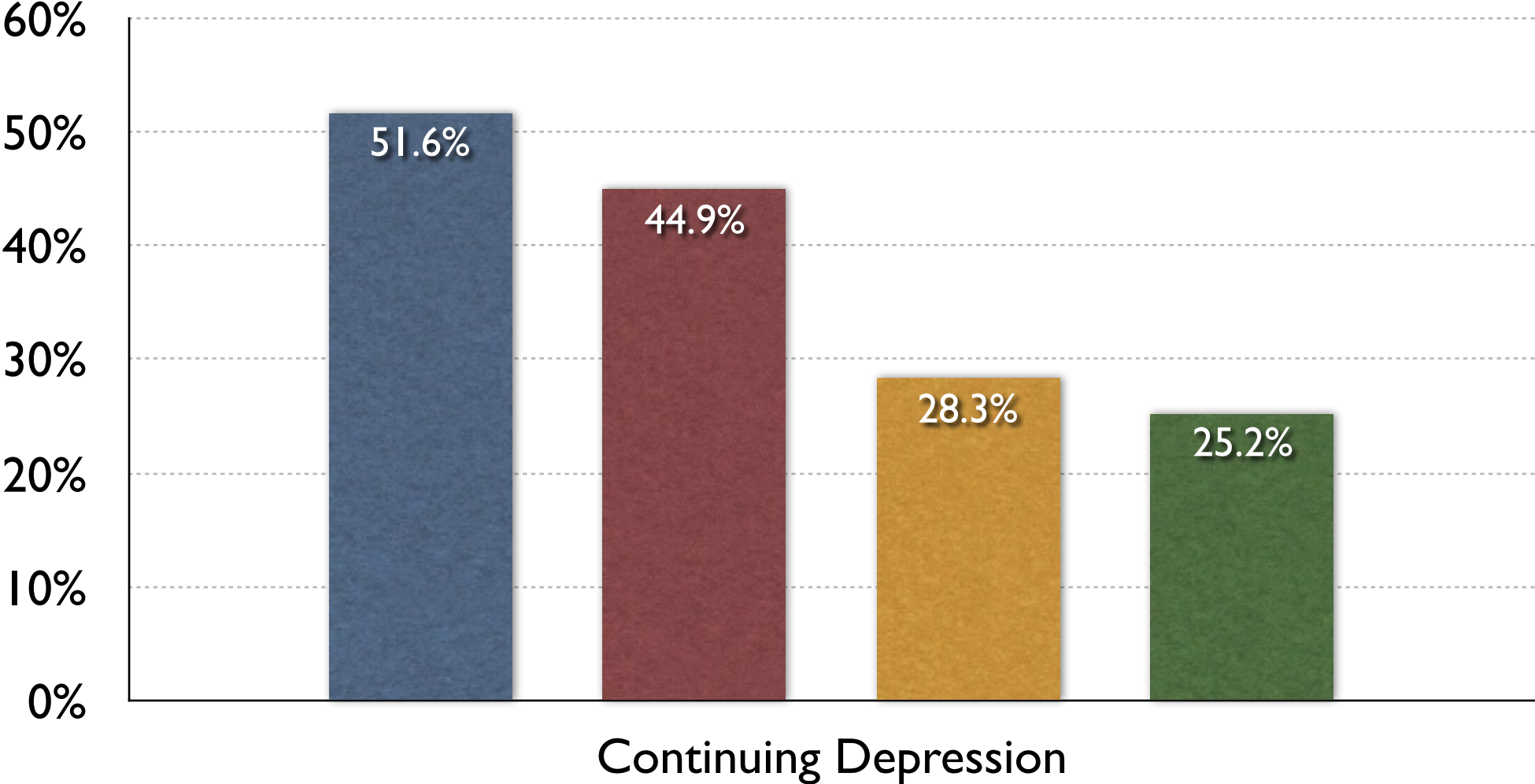
These findings are consistent with Giovanni Fava's hypothesis that "antidepressant treatment may lead to a deterioration in the long-term course of mood disorders."

--Scott Patten

One-Year Outcomes in WHO Screening Study for Depression

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

N = 740

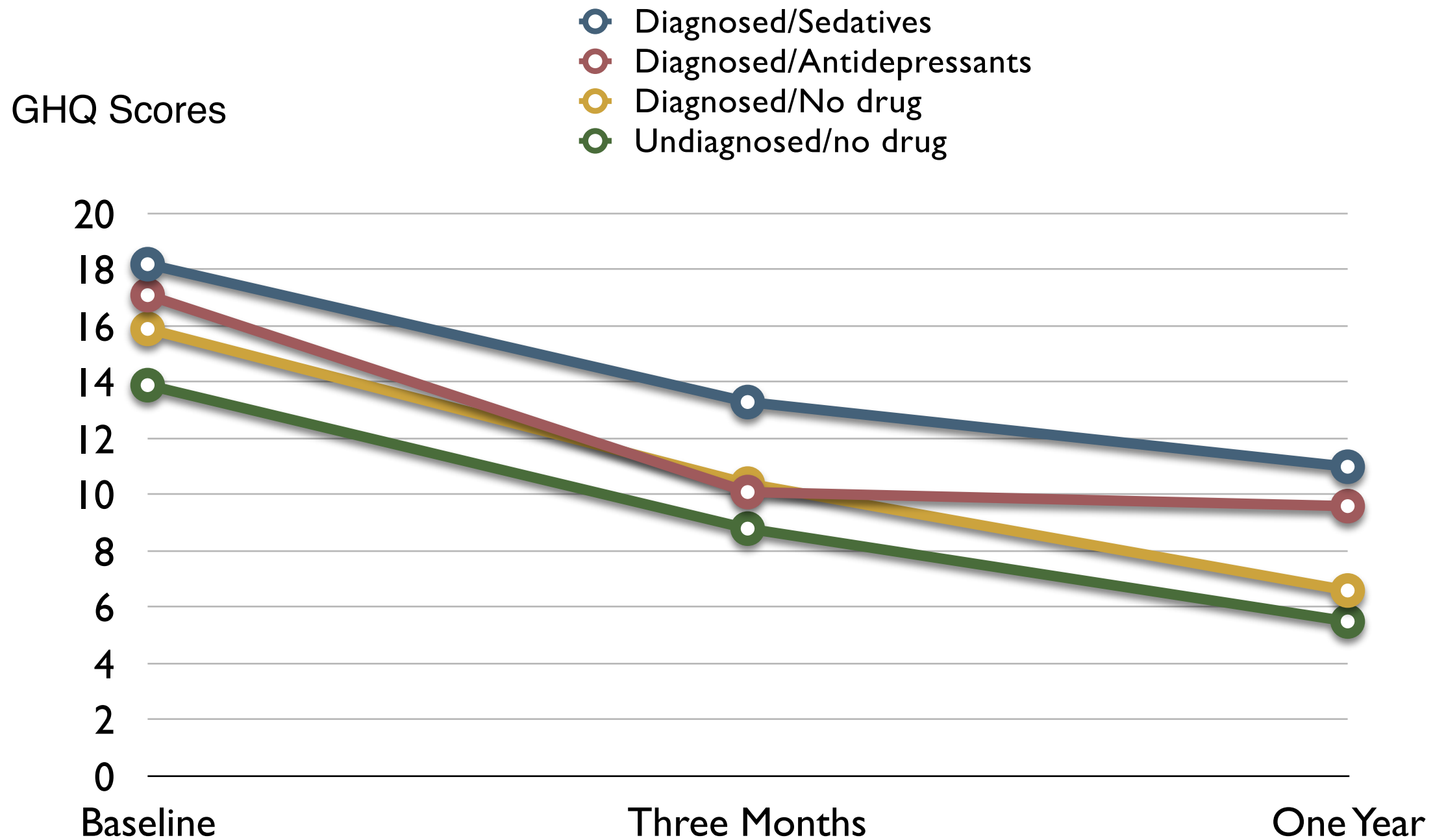


Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

“Patients not given drugs had milder illnesses but did significantly better than those receiving drugs, both in terms of symptoms lost and their diagnostic status.” This was so “even after adjustment for initial scores on each instrument.”

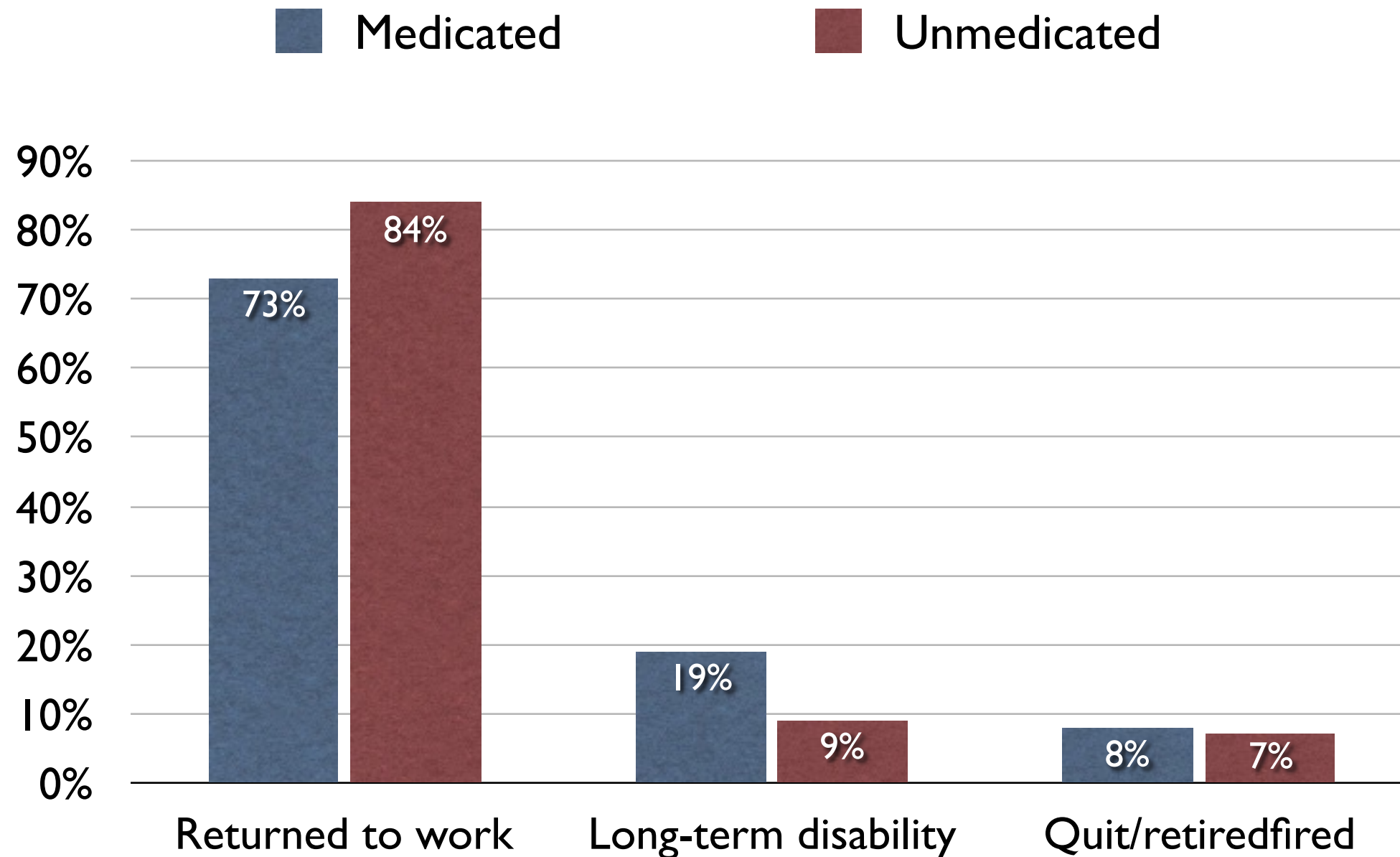
--D. Goldberg

WHO Screening Study for Depression



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

Canadian Study of Risk of Long-term Disability for Depressed Workers

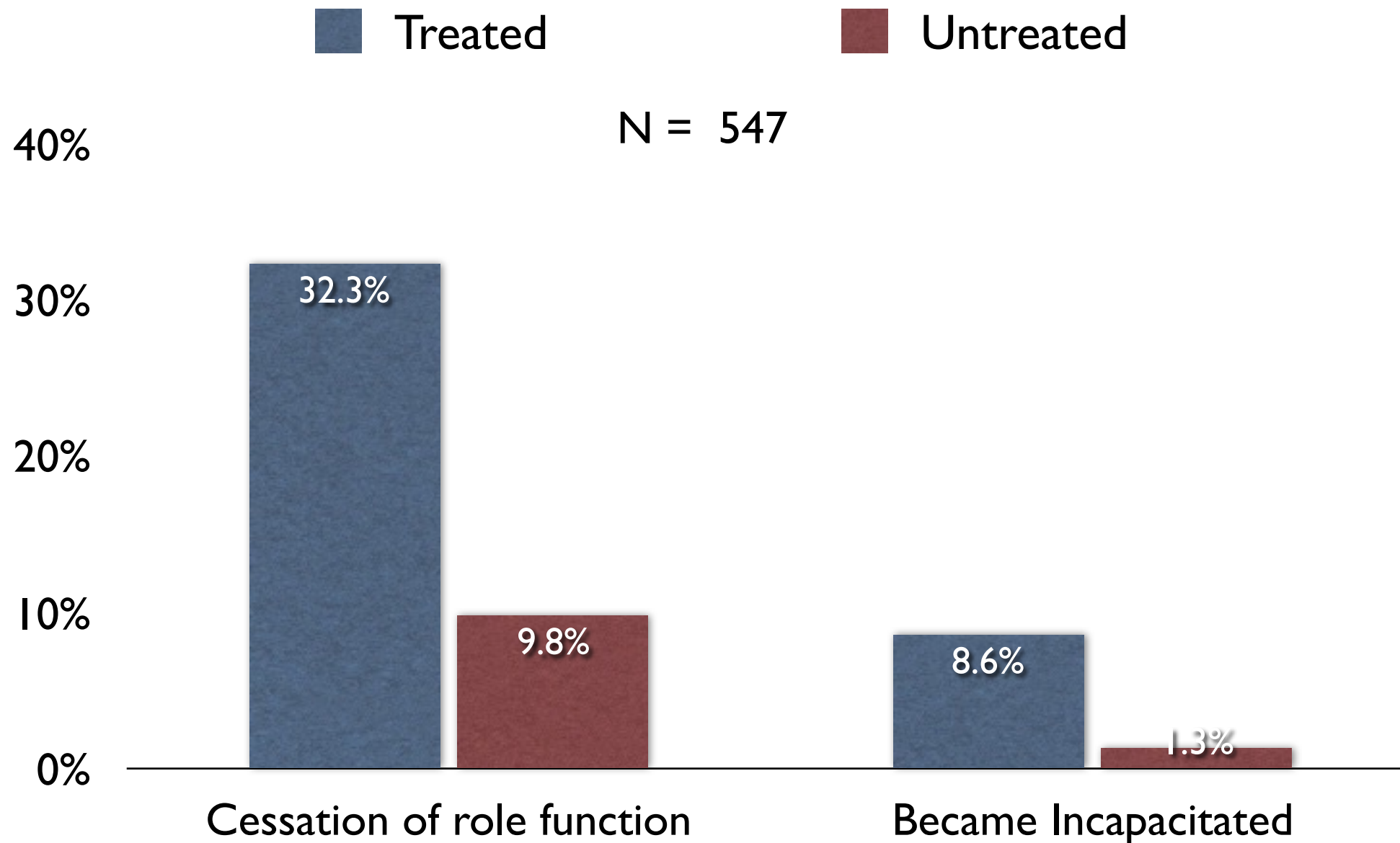


Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.

“Does the lack of antidepressant use reflect a resistance to adopting a sick role and consequently a more rapid return to work?”

--Carolyn Dewa

Six-Year Outcomes in NIMH Study of Untreated Depression



Source: W. Coryell. "Characteristics and significance of untreated major depressive disorder." *American Journal of Psychiatry* 152 (1995):1124-29.

“The untreated individuals described here had milder and shorter-lived illnesses [than those who were treated], and, despite the absence of treatment, did not show significant changes in socioeconomic status.”

--William Coryell

Antidepressants Lessen the Long-Term Benefits of Exercise

Treatment during first 16 weeks	Percentage of patients in remission at end of 16 weeks	Percentage of patents who relapsed in following six months	Percentage of all patients depressed at end of ten months
Zoloft alone	69%	38%	52%
Zoloft plus exercise	66%	31%	55%
Exercise alone	60%	8%	30%

Source: Babyak, M. "Exercise treatment for major depression." *Psychosomatic Medicine* 62 (2000):633-8.

A Biological Explanation for Why Antidepressants May Be Depressogenic Agents Over the Long-Term

The Problem

- Over time, antidepressants induce brain changes that “are the opposite of what the medication originally produced.” Rather than raise serotonin levels, the drugs over the long-term impair serotonergic pathways in the brain.

Animal Evidence

- In studies with rats, long-term treatment with an SSRI led to markedly reduced serotonin in “nine areas of the brain.” In addition, treatment with an SSRI leads to a reduced density of receptors for serotonin in the brain.
- In experiments with animals, such impairments in serotonergic functions are “associated with increased depressive and anxious behaviors.”

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

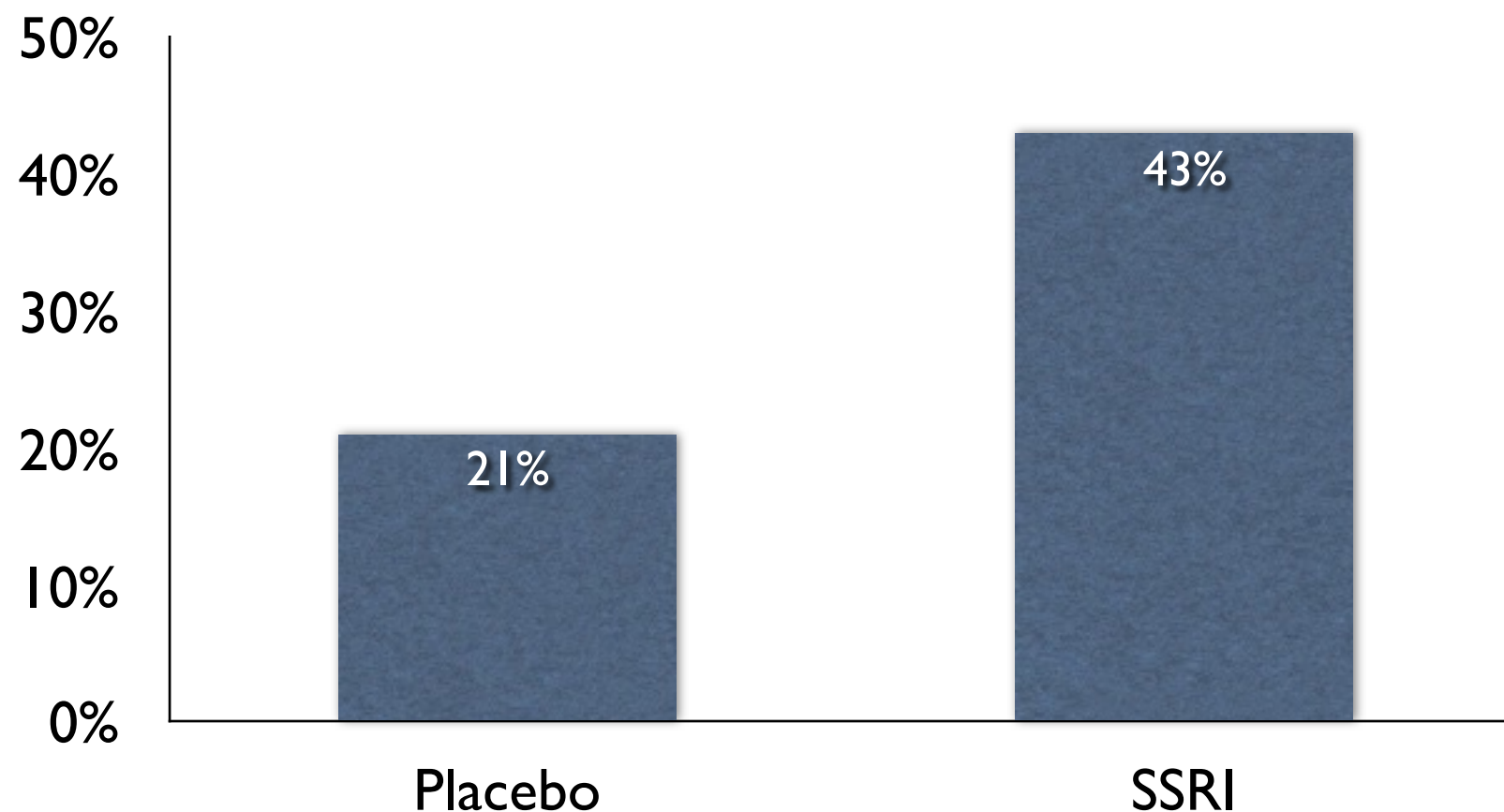
“When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible.”

Giovanni Fava, 2011

Source: G. Fava. “The mechanisms of tolerance in antidepressant action.” *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35 (2011): 1593-1602.

Putting the Depressogenic Hypothesis to the Test

Three-month relapse rate after initial remission:
placebo vs. SSRI-withdrawn patients

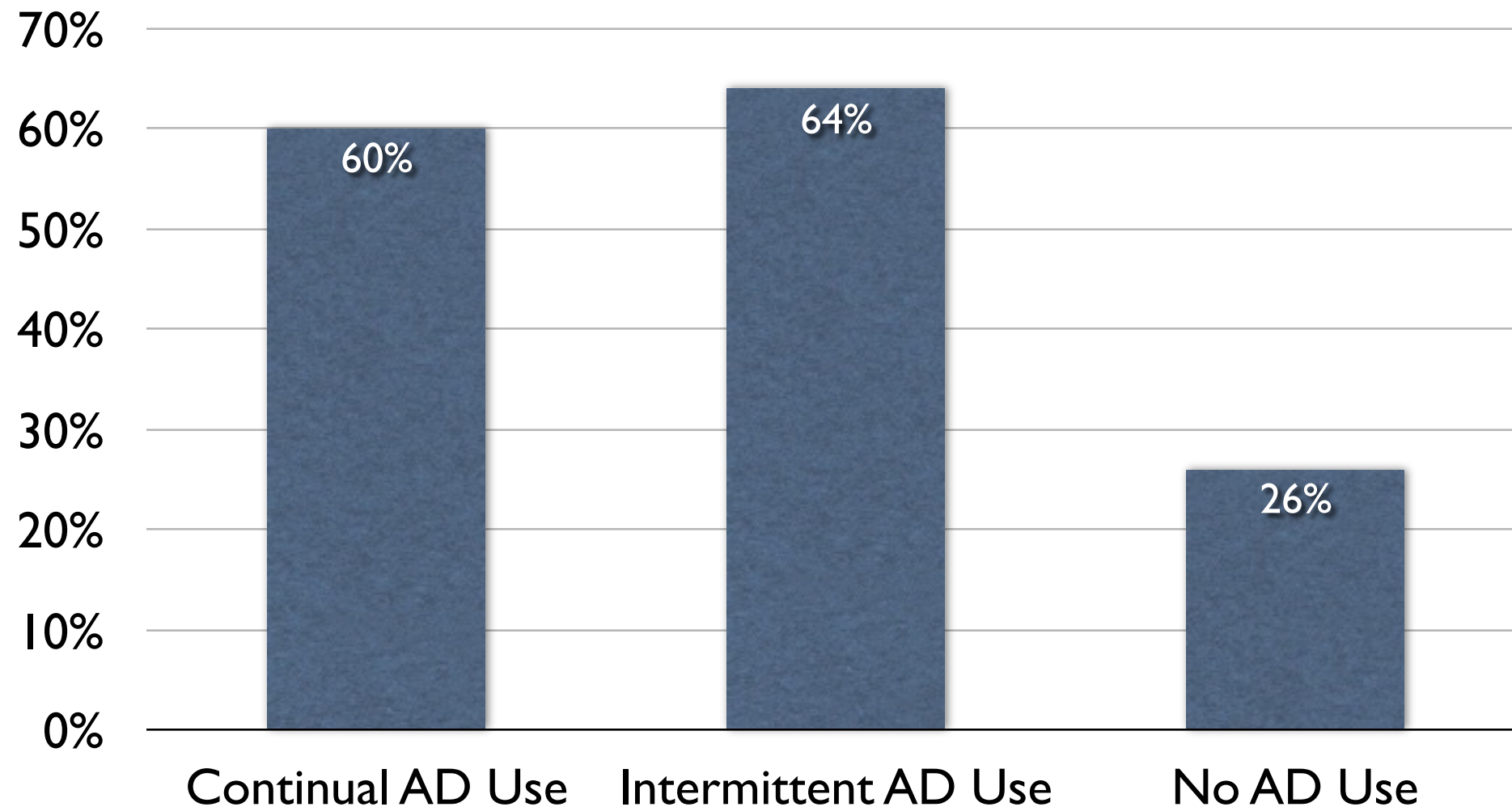


Source: P.Andrews: "Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good." *Frontiers in Psychology* 3 (2012): 1-18.

“The more antidepressants perturb monoamine levels in the brain, the more the brain appears to push back, which increases the risk of relapse when the drug is discontinued . . . antidepressant use appears to increase [biological] susceptibility to depression.”

--Paul Andrews, 2012

Two-Year Relapse Rates for Remitted Patients in the Netherlands



Source: C. Bockting. "Continuation and maintenance use of antidepressants in recurrent depression." *Psychotherapy and Psychosomatics* 77 (2008): 17-26.

“Continued antidepressant treatment may oppose the initial acute effects of [the] antidepressant . . . neurobiological mechanism(s) may be involved in increasing vulnerability” to relapse.

--C. Bockting, 2008

Summing up the Evidence That Antidepressants Are Depressogenic Over the Long Term

- Depression has changed from an episodic illness to a chronic one during the antidepressant era.
- In naturalistic studies, the unmedicated patients have better long-term outcomes.
- Investigators have proposed a biological explanation for why antidepressants are depressogenic over the long term.

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.

Other Adverse Effects of SSRIs

On Mood

- Emotional blunting, apathy
- Mania
- Conversion to bipolar

Neurocognitive Effects

- Mild cognitive impairment
- Driving accidents
- Neuronal structural damage

•Gastrointestinal Effects

- Diarrhea
- Constipation
- Upset stomach

Vascular Effects

- Gastrointestinal bleeding

Movement

- Tics
- Fatigue
- Tardive dyskinesia

Sleep

- Suppression of REM sleep

Reproductive Functioning

- Sexual dysfunction

Fetal Development

- Congenital abnormalities
- Preterm births

The Burden of Depression on Society Today

In the United States

- Major depressive disorder is now the leading cause of disability in the United States for people ages 15 to 44.
- According to the NIMH, it affects 15 million American adults. Researchers at Johns Hopkins School of Public Health reported in 2008 that 58% of this group is “severely impaired.”
- Nearly nine million adults are now disabled, to some extent, by this condition.

Globally

- According to the World Health Organization, depression is now the leading cause of disability worldwide.

The Bipolar Boom

Annual Prevalence in the Pre-Lithium Era

- One in 3000 to one in 10,000

Prevalence Today:

- One in 50 adults

Gateways to Bipolar Today

- Illicit drugs (marijuana, cocaine, hallucinogens, etc.)
- Stimulants and antidepressants
- Expanded Diagnostics

Antidepressants Increase the Risk that a Unipolar Patient will Convert to a a Bipolar Diagnosis

1956: First case report of antidepressant-induced mania is published

1985: Swiss investigators tracking change in the patient mix at Burgholzli psychiatric hospital report that the percentage with manic symptoms jumped dramatically following the introduction of antidepressants. “Bipolar disorders increased; more patients were admitted with frequent episodes.”

1993: An American Psychiatric Association guide to depression warns: “All antidepressant treatments, including ECT, may provoke manic or hypomanic episodes.”

Yale Investigators Quantify the Risk of Conversion to a Bipolar Diagnosis with Antidepressant Use

Study design: Yale Investigators analyzed the records of 87,920 patients, ages 0 to 29, initially diagnosed with an anxiety or non bipolar mood disorder from 1997-2001. The median follow-up time was 41 weeks. They reported on the number of patients who converted to a bipolar diagnosis according to whether they were “exposed” to an antidepressant.

Converters to a Bipolar Diagnosis

Age	Not Exposed	Exposed	NNH
15-19	698 (4.8%)	1093 (10.9%)	16
20-24	390 (4.3%)	591 (7.6%)	31
25-29	333 (2.7%)	587 (6.2%)	29
15-29	1421 (4.1%)	2271 (8.3%)	23

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

Increase in Bipolar Diagnoses in United States, 1994 to 2003

Number of office-based visits with a diagnosis of bipolar disorder

	1994-1995	2002-2003	Increase in rate
Youth (0-19 years)	25 per 100,000	1003 per 100,000	40-fold increase
20 years and older	905 per 100,000	1,679 per 100,000	85% increase

Source: Moreno, C. "National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth." *Arch Gen Psychiatry* (2007) 64: 1032-39.

In a survey of members of the Depressive and Manic-Depressive Association, 60 percent of those with a bipolar diagnosis had initially fallen ill with major depression and had turned bipolar after exposure to an antidepressant.

Source: R. El-Mallakh. "Use of antidepressants to treat depression in bipolar disorder." *Psychiatric Services* 53 (2002): 58-84.

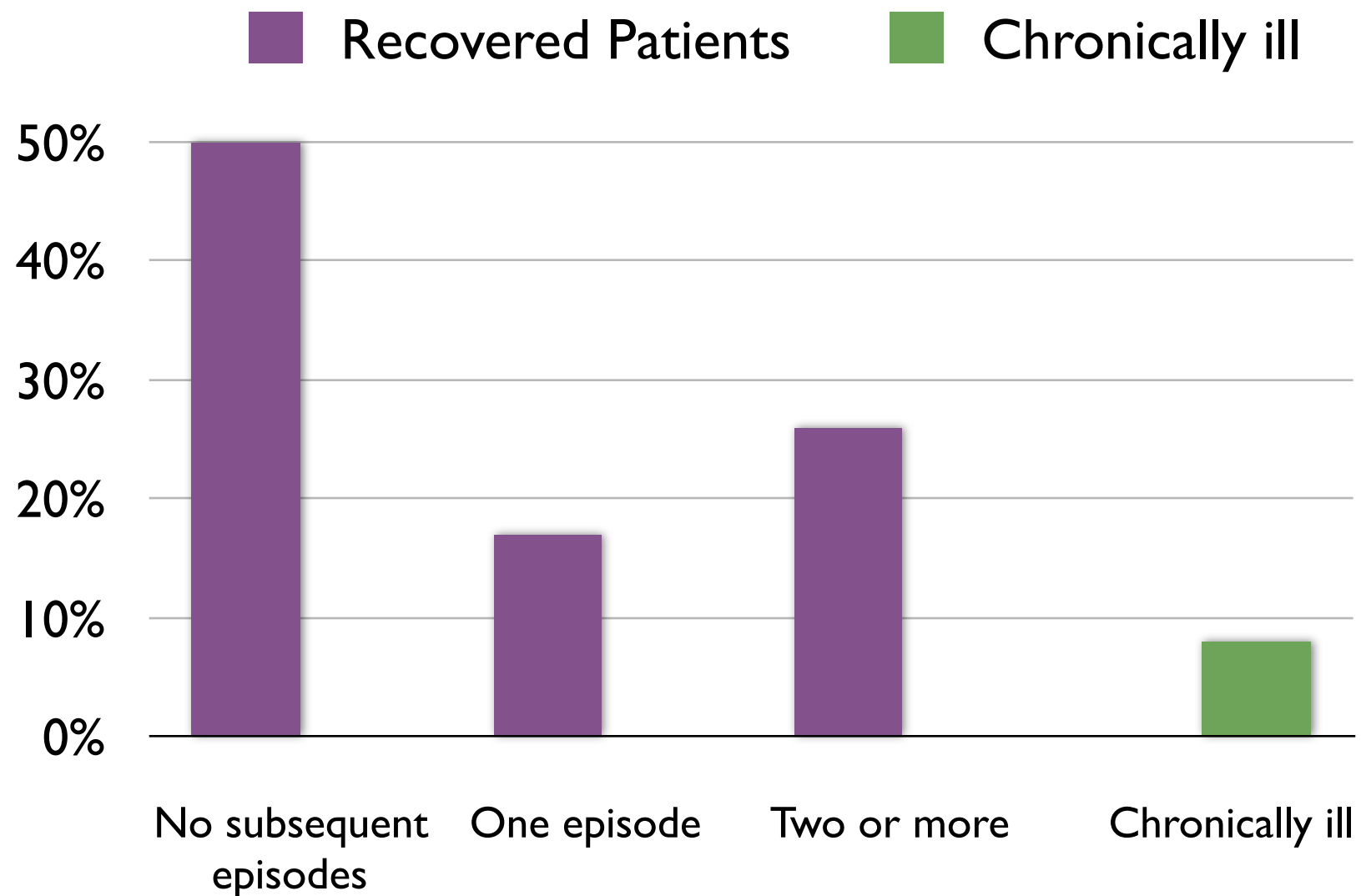
Fred Goodwin, former director of the National Institute of Mental Health, 2005:

“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.”

Bipolar Outcomes in the Pre-Drug Era

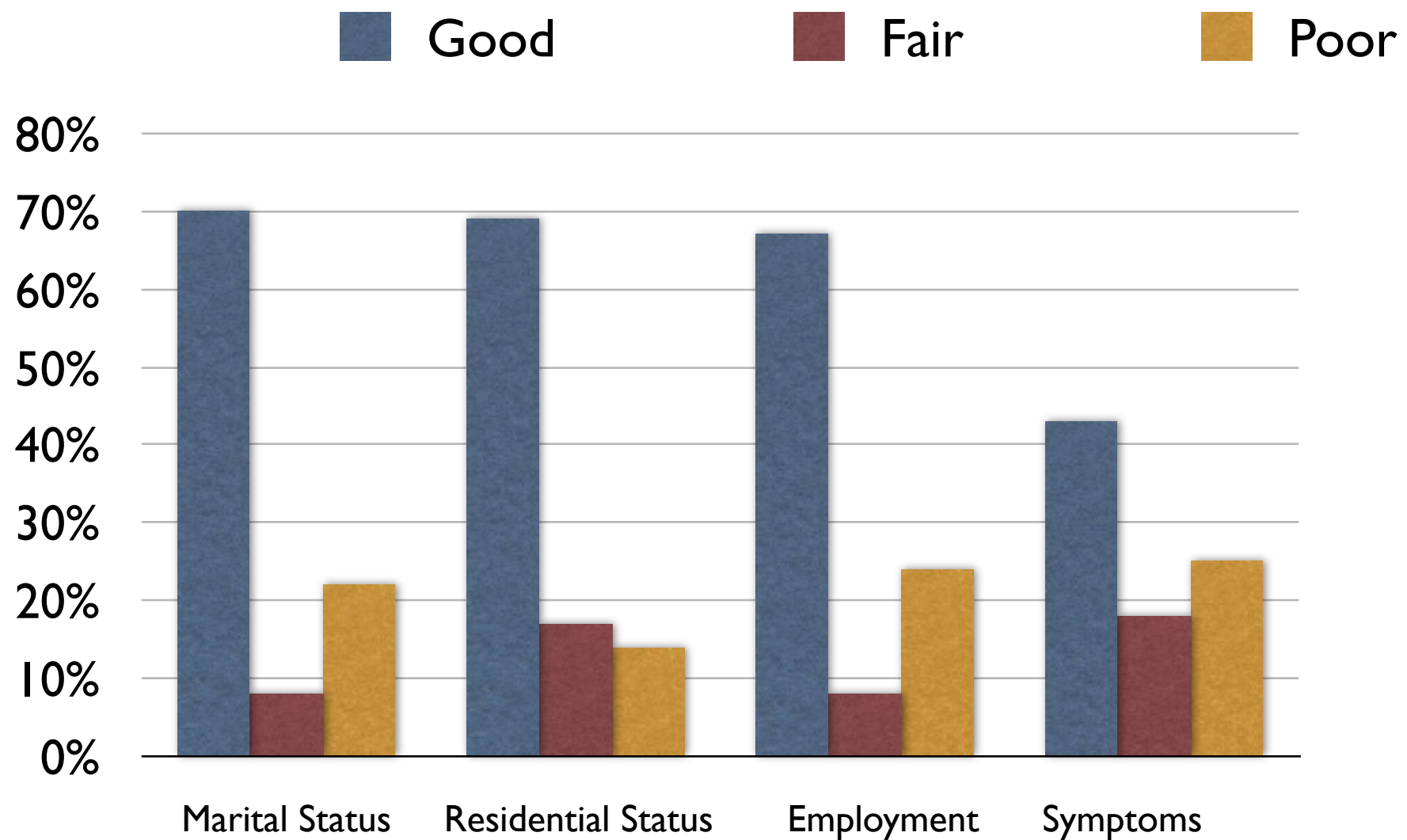
Swedish Study, 1945

103 manic patients



Source: Lundquist, G. "Prognosis and course in manic-depressive psychoses." *Acta Psychiatr 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 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

“It is now well established that bipolar disorders are chronic, with a course characterized by frequent affective episode recurrence.”

--Lewis Judd, 2008

Experts Recognize the Decline in Bipolar Outcomes

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.”

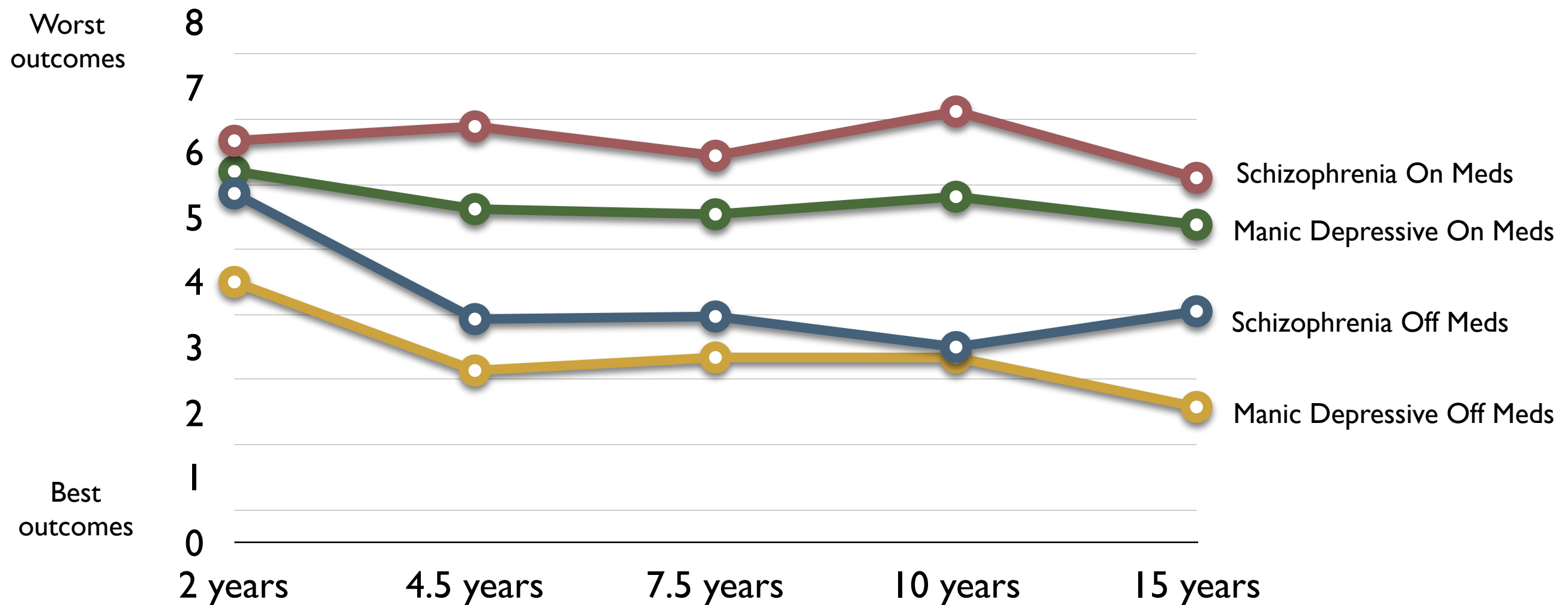
Ross Baldessarini, Harvard Medical School, 2007.

“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.”

Martin Harrow's 15-Year Study: Outcomes for Manic-Depressive Group



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.

The Burden of Bipolar Illness on Society Today

- In 1955, there were 12,750 adults hospitalized with bipolar illness in the United States. Today there are nearly six million adults in the United States with this diagnosis.
- According to the Johns Hopkins School of Public Health, 83 percent of people diagnosed with bipolar are “severely impaired” in some facet of their lives. (5 million adults.)
- Bipolar illness is now said to be the sixth leading cause of medical-related disability in the world.

Same Prevalence + More Treatment = Soaring Numbers of Adults Disabled by Affective Disorders in U.S.

	1991	2002
U.S. adult population	188 million	214 million
Prevalence of anxiety, mood and substance disorders	29.4%	30.5%
Number with anxiety, mood and substance disorders	55.3 million	65.3 million
Percentage treated for those disorders	20.3%	32.7%
Number treated for those disorders	11.2 million	21.4 million
Number on disability due to affective disorders	292,000	940,000
Percentage with those disorders on disability	1 of 188	1 of 69

Source: Survey on prevalence and treatment of anxiety, mood and substance use disorders in 1991 and 2002; Social Security disability data for 1991 and 1992; estimate of percentage of disabled mentally ill with affective disorders in 1991; report on number of people with affective disorders on disability rolls in 2002.

A Failed Paradigm of Care

“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

British Journal of Psychiatry, August 2012

Is “Oppositional Tolerance” a Universal Concern With Psychiatric Drugs?

“Continued drug treatment may induce processes that are the opposite of what the medication originally produced.” This may “cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible.”

-Rif El-Mallakh, University of Louisville, 2011

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

Alternatives

The Opportunity:

History and science are telling us that there is a natural capacity to recover from depression, and that even bipolar disorder runs an episodic course, with fairly good long-term outcomes.

The Challenge:

How do we provide therapies that assist that enhance that natural capacity to recovery?

Possibilities:

- Exercise
- Diet/nutrition
- Psychosocial therapies
- Etc.

The Problem With Psychiatric Drugs

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

From the Co-founder of the Cochrane Collaboration:

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

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

–Peter C. Gøtzsche, 2013

Co-founder of the Cochrane Collaboration

Director of the Nordic Cochrane Center