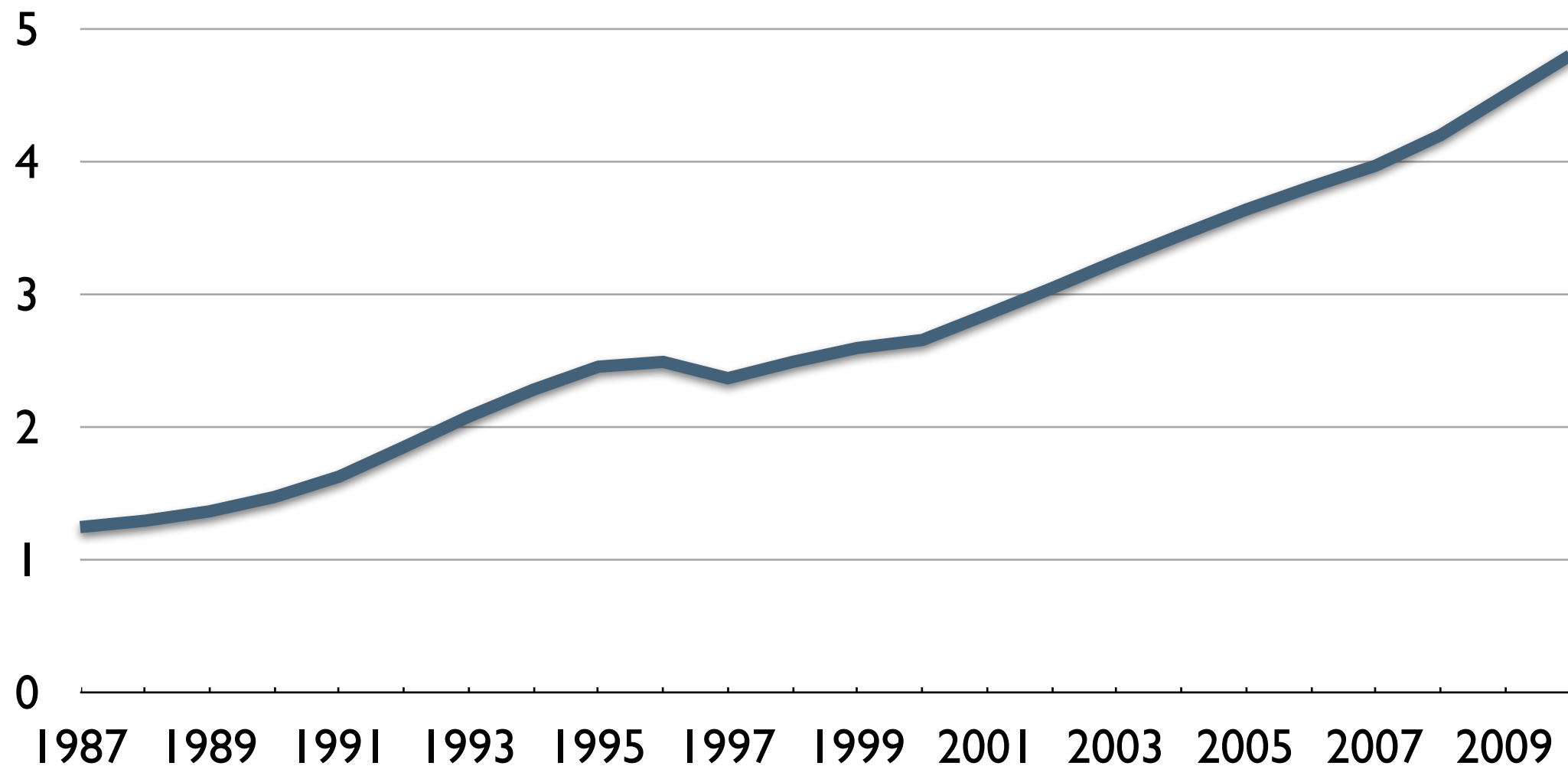


SSRIs In Society: What Are Their Long-term Effects?

Robert Whitaker
April 2013

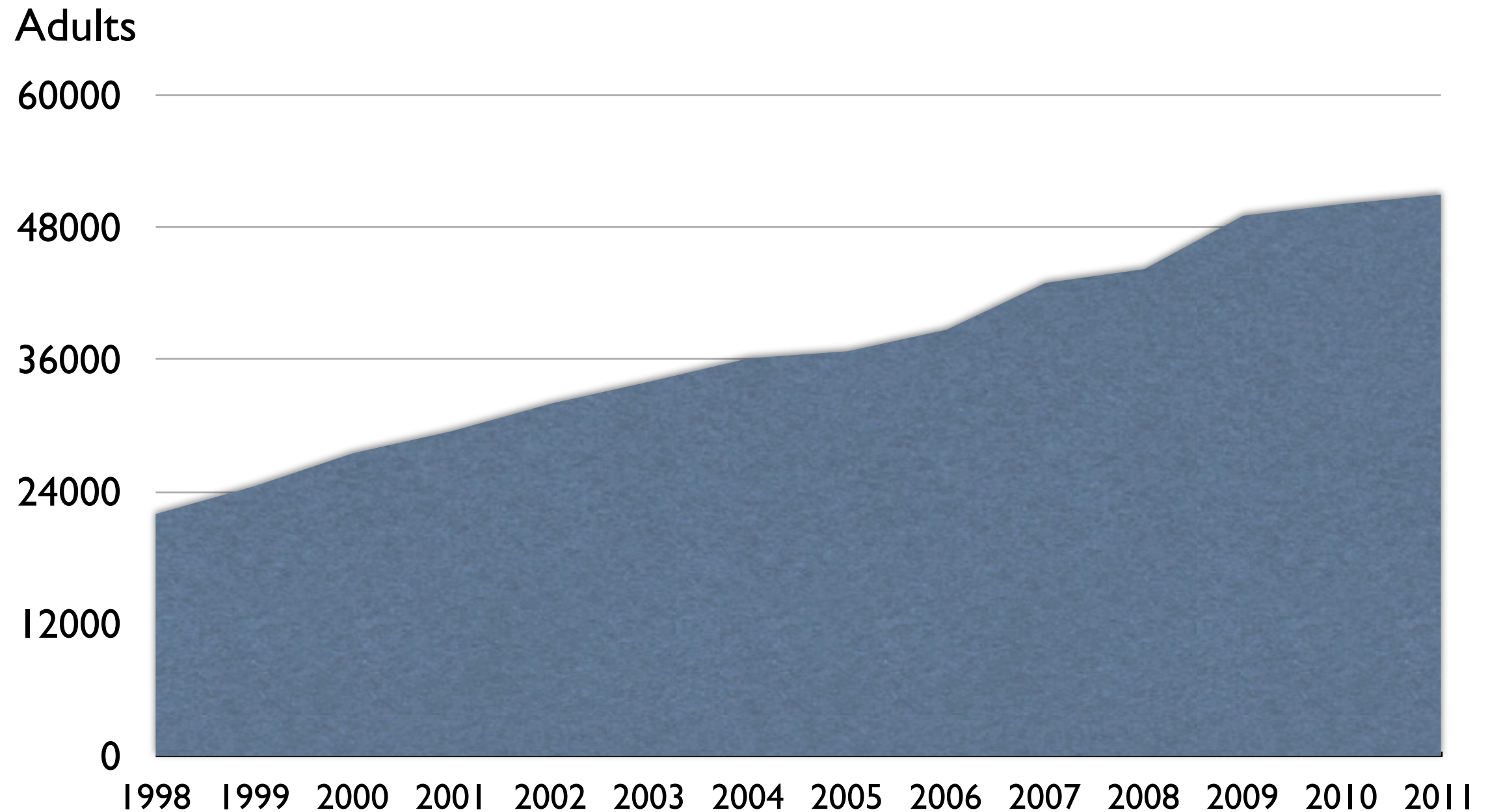
U.S. Disability in the Prozac Era

Millions of adults, 18 to 66 years old



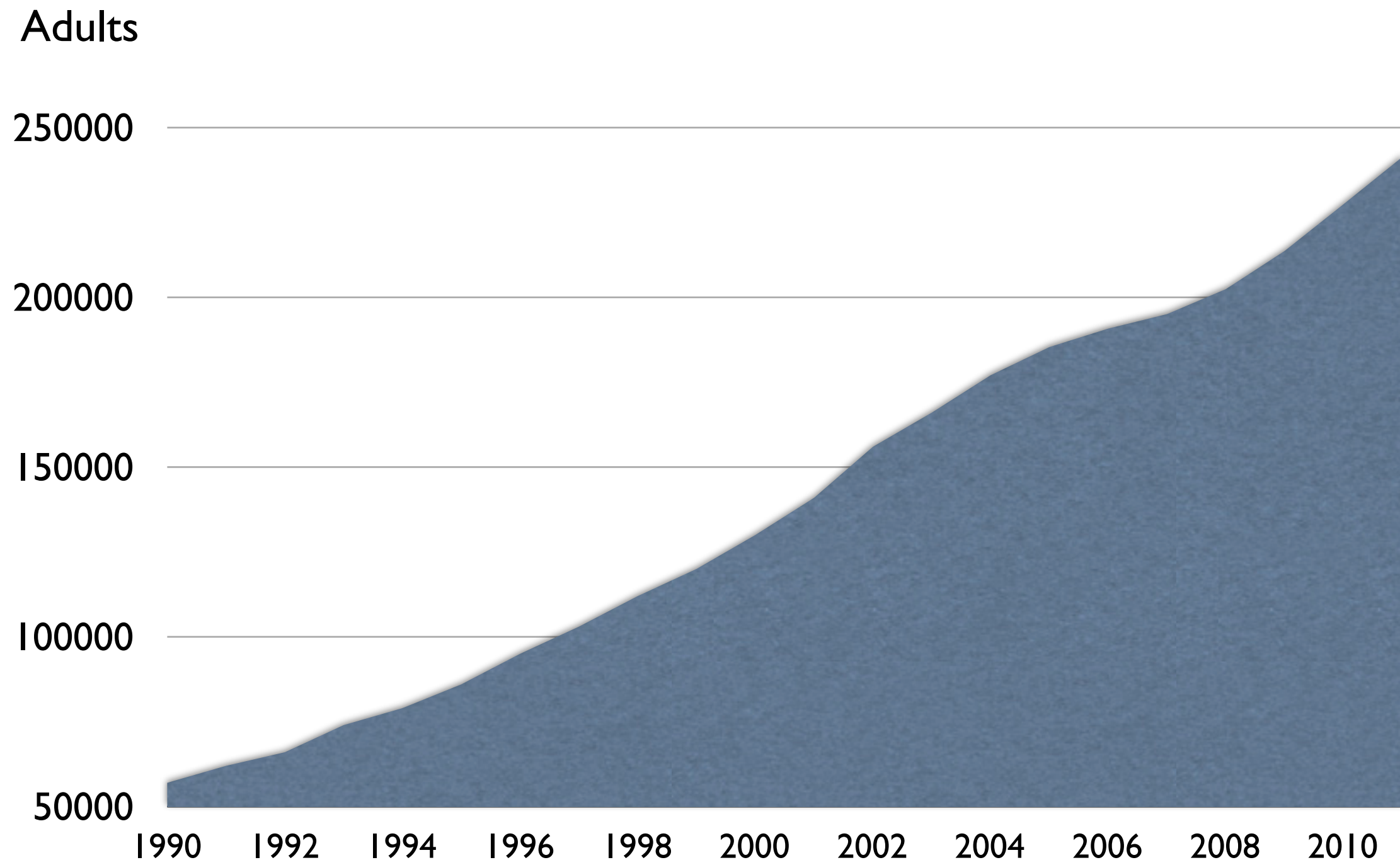
Source: U.S. Social Security Administration Reports, 1987-2010

Disability Due to Psychiatric Disorders in New Zealand, 1998-2011



Source: New Zealand Ministry of Social Development, "National Benefits Factsheets," 2004-2011.

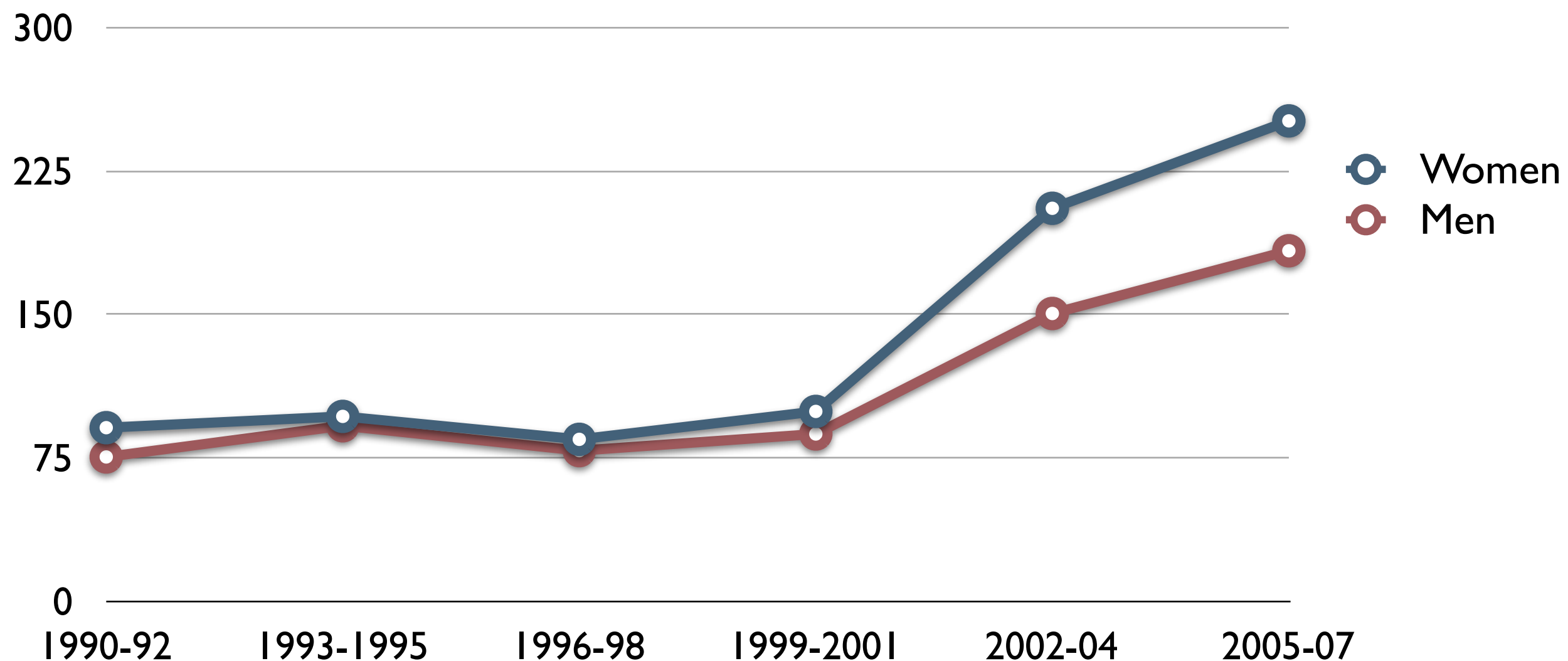
Disability Due to Psychiatric Disorders in Australia, 1990-2011



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

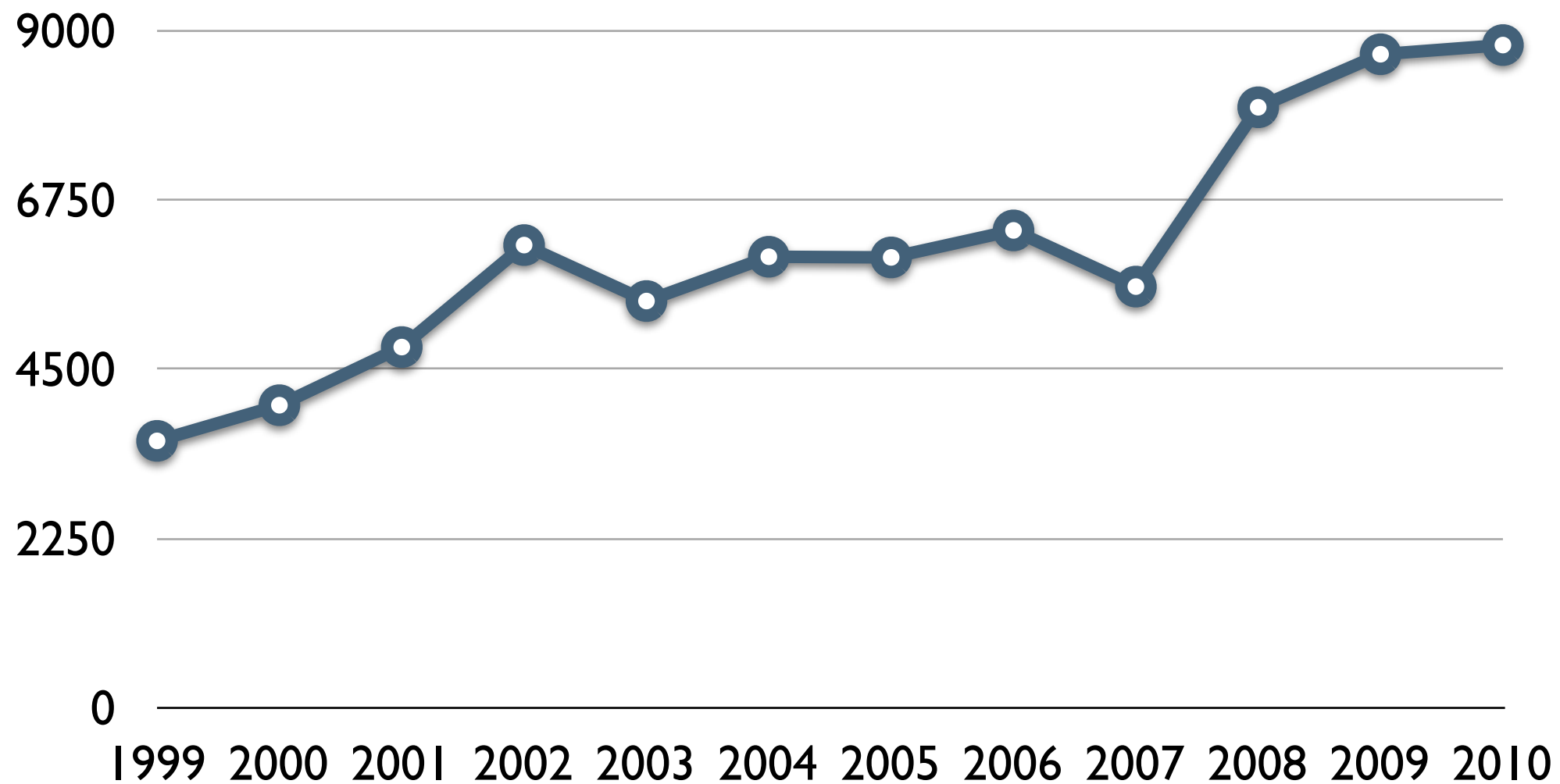
Disability Due to Mental and Behavioural Disorders in Iceland, 1990-2007

Number of New Cases Annually per 100,000 Population



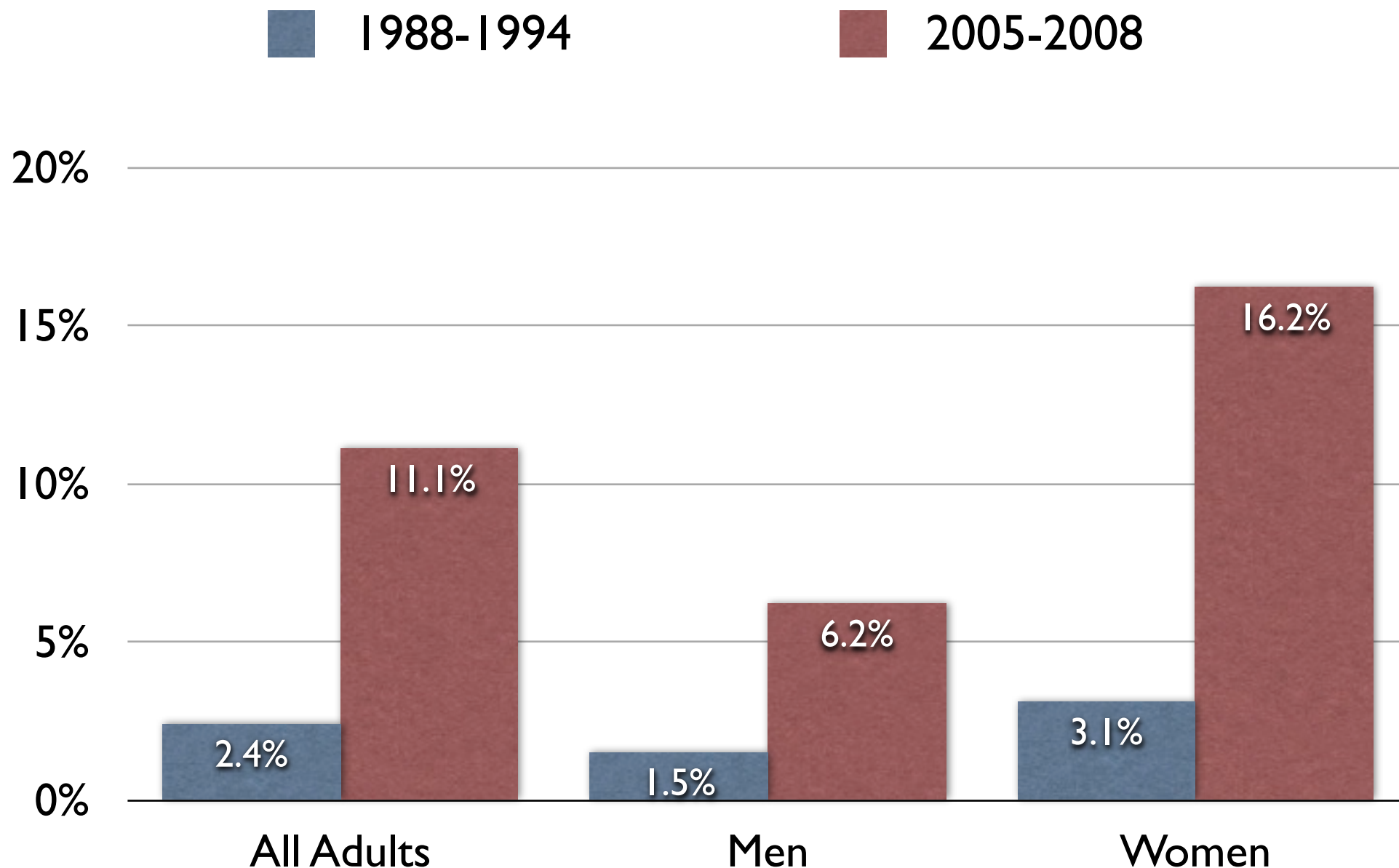
Source: Thoriacius, S. "Increased incidence of disability due to mental and behavioural disorders in Iceland, 1990-2007." *J Ment Health* (2010) 19: 176-83.

New Cases of Disability in Denmark Due to Mental Illness



Antidepressants: A Case Study of Their Short-term Efficacy and Long-term Effects

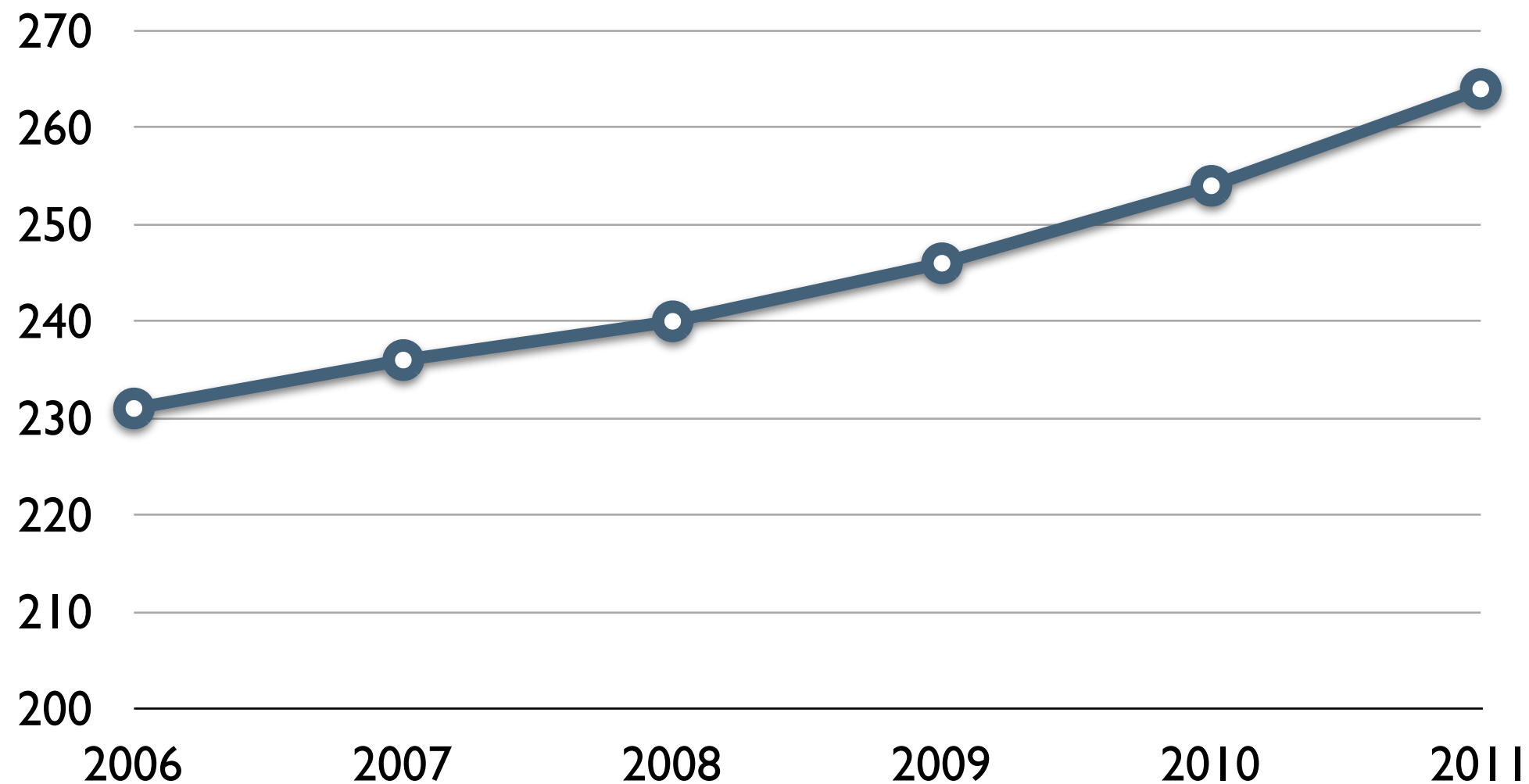
Increase in Usage of Antidepressants in the Prozac Era



Source: Centers for Disease Control and Prevention, National Center for Health Statistics. *Health, United States, 2010*.

U.S. Prescriptions for Antidepressants, 2006-2011

In Millions



Source: IMS Health, Top Therapeutic Classes by U.S. Dispensed Prescriptions

The Cost of Depression to Employers

Annual medical spending for an employee with depression is \$2185 higher than for an employee without depression.

In a study of ten modifiable health risk factors, depression was found to be the most expensive to employers.

Source: R. Goetzel. "Ten Modifiable Health Risk Factors Are Linked to More than One-Fifth of Employer-Employee Health Care Spending." HOPE/Health Affairs 11 (2012).

Is Depression Due to A Chemical Imbalance in the Brain?

Findings Re the Chemical Imbalance 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

“After more than a decade of PET studies, monamine depletion studies, and genetic association analyses examining polymorphisms in monoaminergic genes, there is little evidence to implicate true deficits in serotonergic, noradrenergic, or dopaminergic neurotransmission in the pathophysiology of depression. This is not surprising, as there is no a priori reason that the mechanism of action of a treatment is the opposite of disease pathophysiology.”

Eric Nestler, “Linking Molecules to Mood,” 2010.

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.

What Compensatory Adaptations Are Triggered by An SSRI?

- There is a decrease in the release of serotonin by presynaptic neurons, at least for a period of time.
- The postsynaptic neurons decrease the density of receptors for serotonin, an adaptive process known as “downregulation” of receptors.
- In mouse studies, over the long-term there is a depletion of serotonin in the forebrain.

The Efficacy of Antidepressants Over the Short Term

Recovery From a Depressive Episode Before the Antidepressant Era

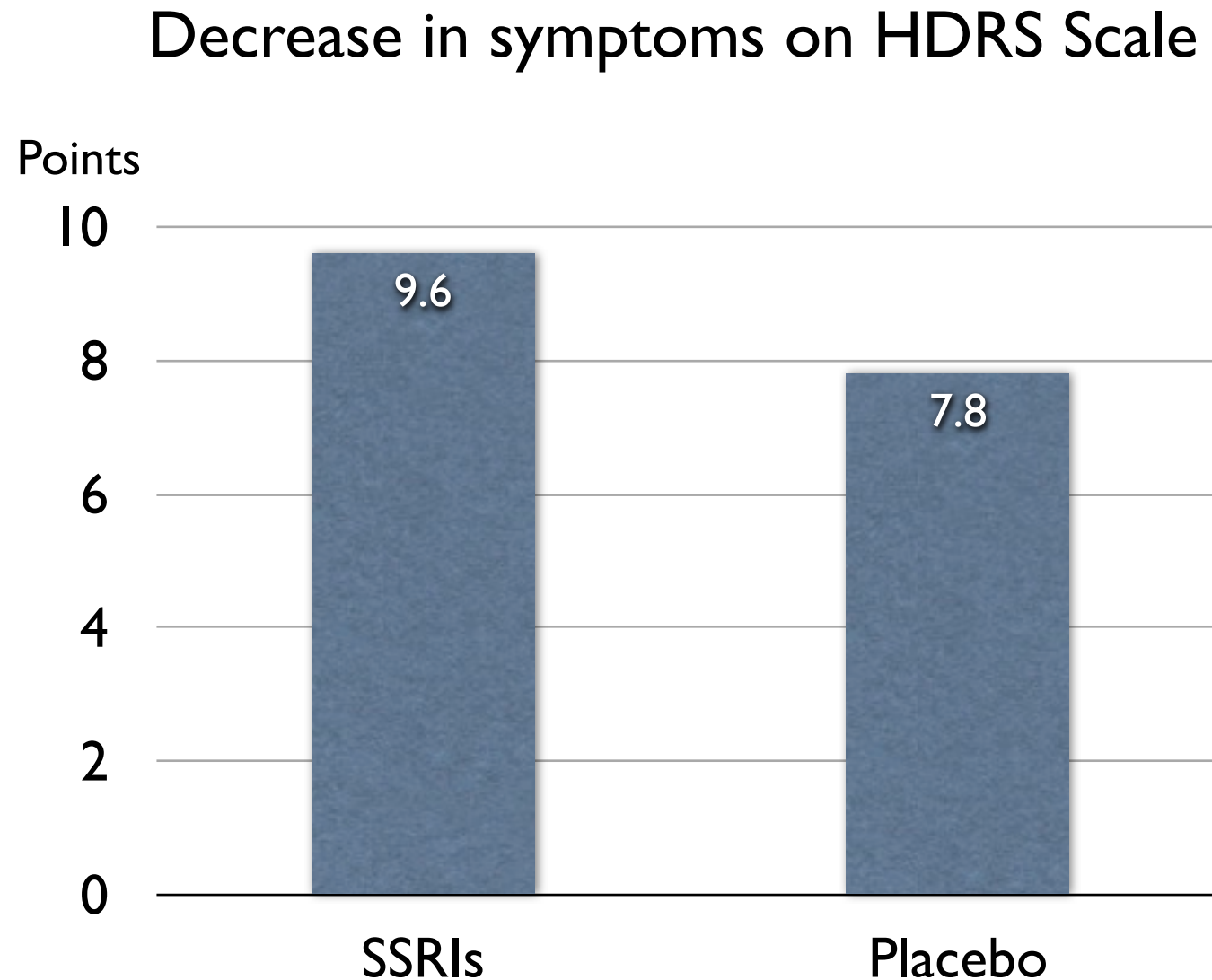
“Depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self-limited.”

--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

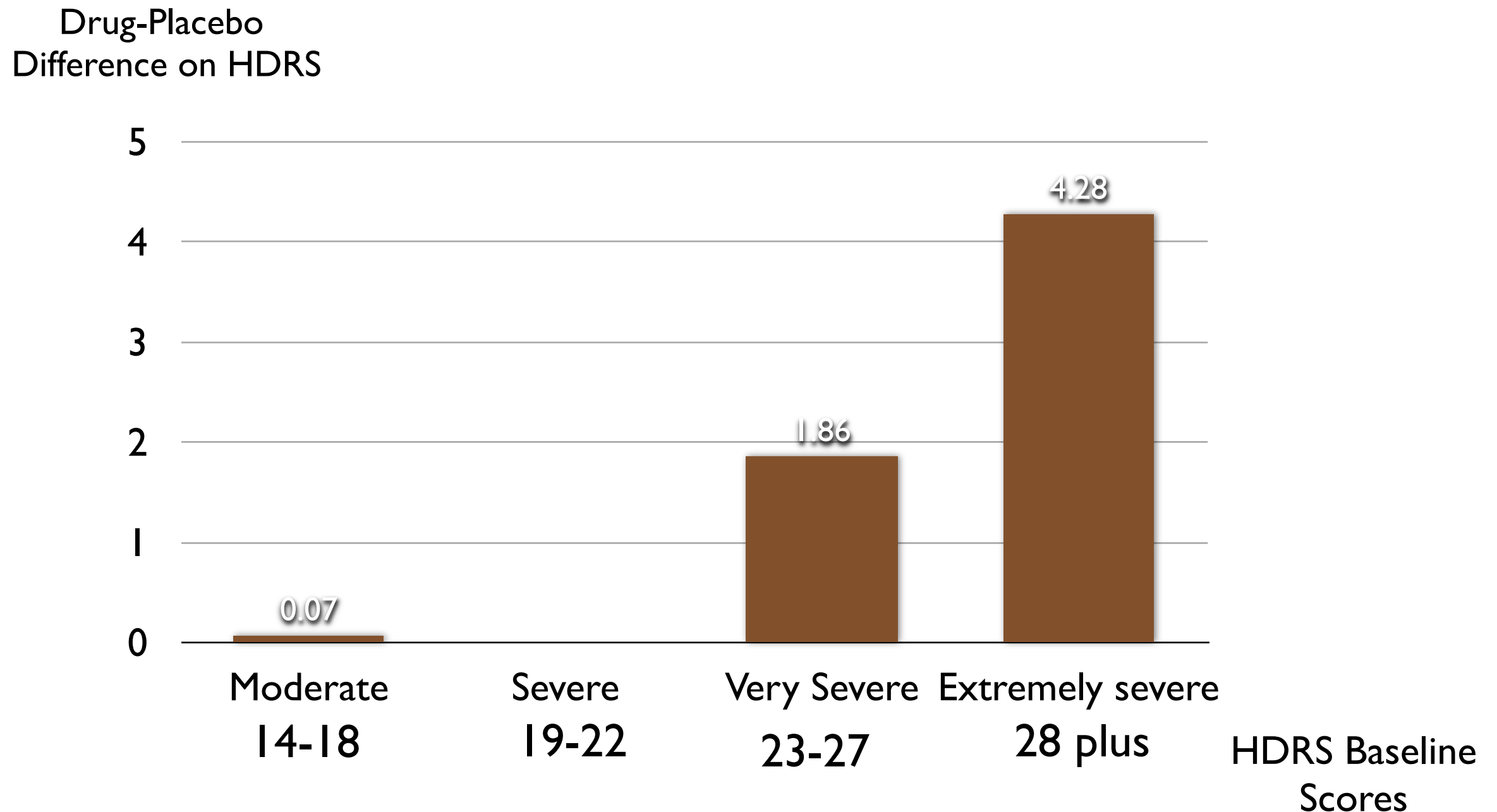
Efficacy of Four SSRIs In Clinical Trials



The National Institute of Clinical Excellence in Britain determined that a three-point difference was needed on the Hamilton scale to demonstrate a “clinically significant benefit.” Difference here is 1.8 points. The four SSRIs were Prozac, Effexor, Serzone, and Paxil.

Source: I. Kirsch, “Initial severity and antidepressant benefits,” *PLoS Medicine* 5 (2008):260-68.

Efficacy of Four SSRIs According to Severity of Illness



Source: I. Kirsch, "Initial severity and antidepressant benefits," *PLoS Medicine* 5 (2008):260-68.

Meta-analysis of FDA Trials

- In patients with HRSD baseline score less than 25: “Drug/placebo differences did not meet either of the 2 thresholds for clinical significance proposed by NICE.”
- In patients with HRSD baseline scores above 25: Antidepressant medication “was markedly superior to placebo.”

Source: J. Fournier. “Antidepressant drug effects and depression severity.” *JAMA* 303 (2010): 47-53.

Because of these findings, the National Institute of Clinical Excellence in Britain does not recommend the prescribing of antidepressants as a first-line therapy for mild to moderate depression.

The Long-term Effects of Antidepressants on Depression

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 depression will not tend toward a more chronic course.”

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

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.”

Source: Van Scheyen, J.D. “Recurrent vital depressions,” *Psychiatria, Neurologia, Neurochirurgia* 76 (1973):93-112.

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?”

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.

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

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.”

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 Depression Runs a Chronic Course Today

Findings from the National Institute of Mental Health's STAR*D study, which was the "largest study" of depression ever conducted:

- Only 38% of the patients properly enrolled in the trial remitted during one of the four stages of drug treatment.
- Only seven percent of the patients who remitted and were entered into the 12-month followup stayed well and in the trial. (108 of 1518). The remaining 93% relapsed or dropped out.
- The bottom line: Of the 4,041 patients who entered the trial, only 3% remitted and then stayed well throughout the 12-month followup (108 of 4,041.) The remaining patients either failed to remit, relapsed during the followup, or dropped out.

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

Outcomes in Real-World Patients

In a 2004 study funded by the NIMH:

- 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.

Source: J. Rush. “One-year clinical outcomes of depressed public sector outpatients,” *Biological Psychiatry* 56 (2004):46-53.

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

--John Rush, 2004

Real World Outcomes in Minnesota

In 2009, only 1,131 of 23,887 patients treated for major depression or dysthymia were in remission at the end of one year.

Source: MN Community Measures, *2010 Health Care Quality Report*

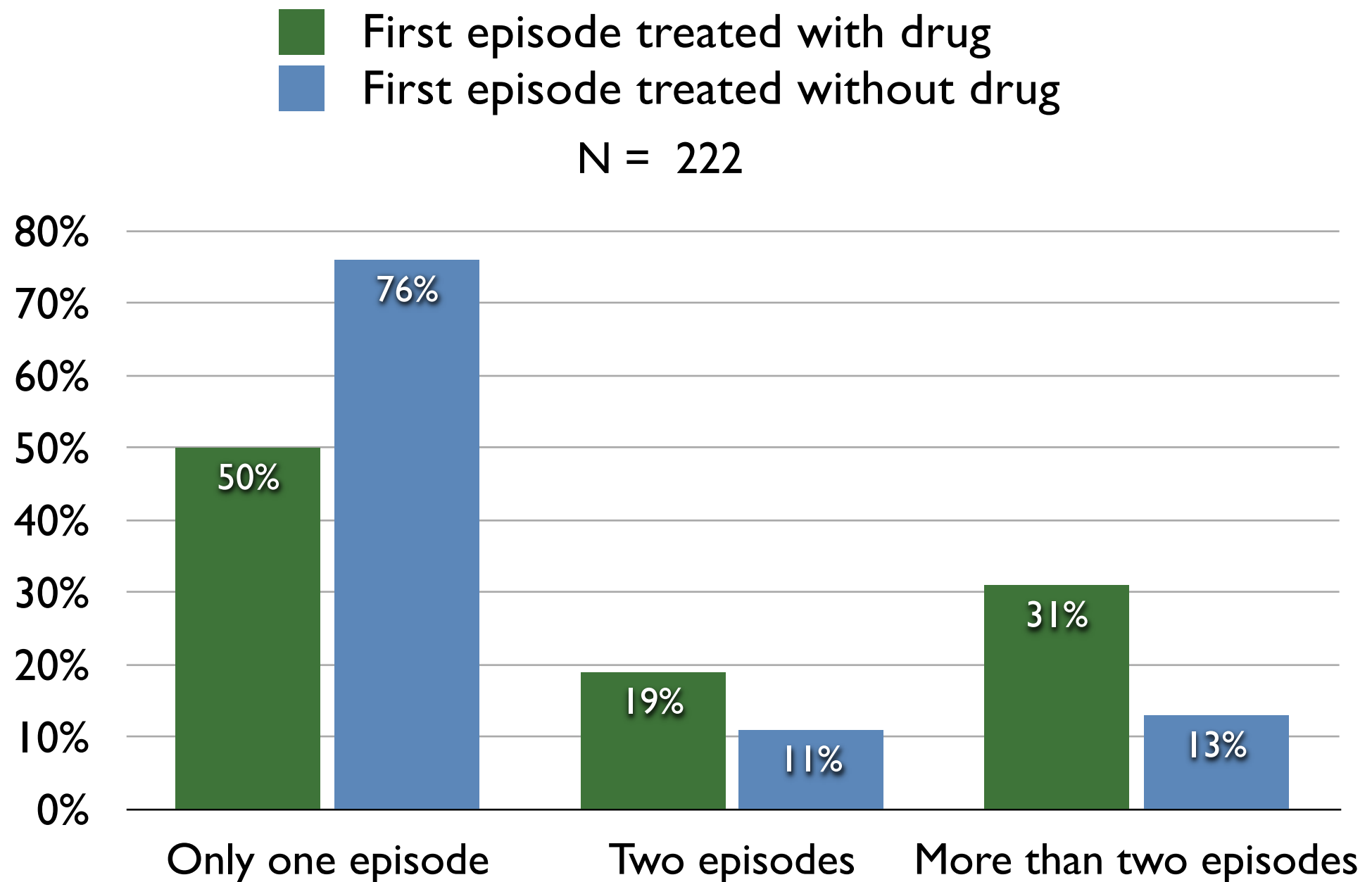
Are Antidepressants Depressogenic Over the Long-Term?

“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

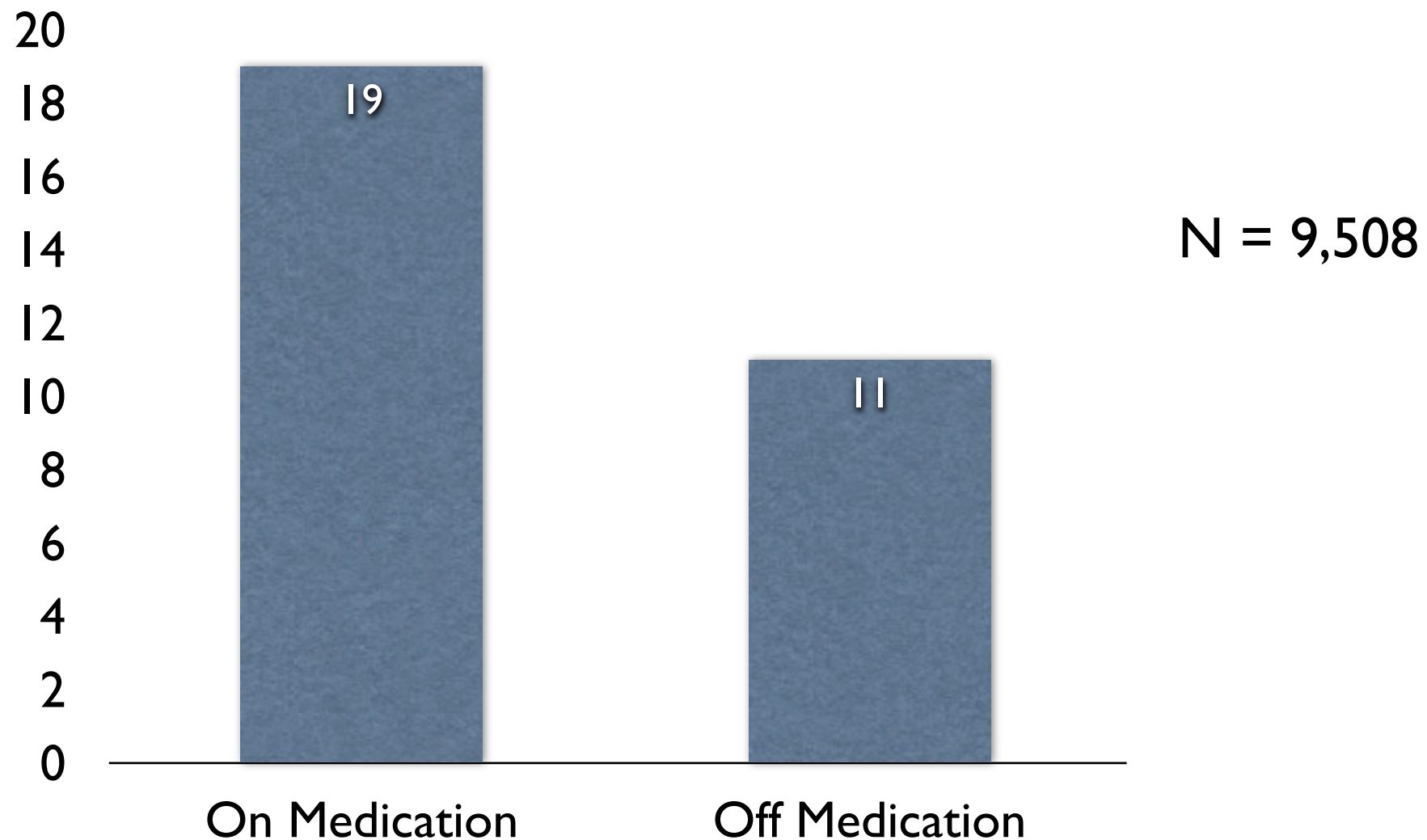
(Over the course of ten years)



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

Five-Year Outcomes in Canada

Number of Weeks
Depressed Each Year

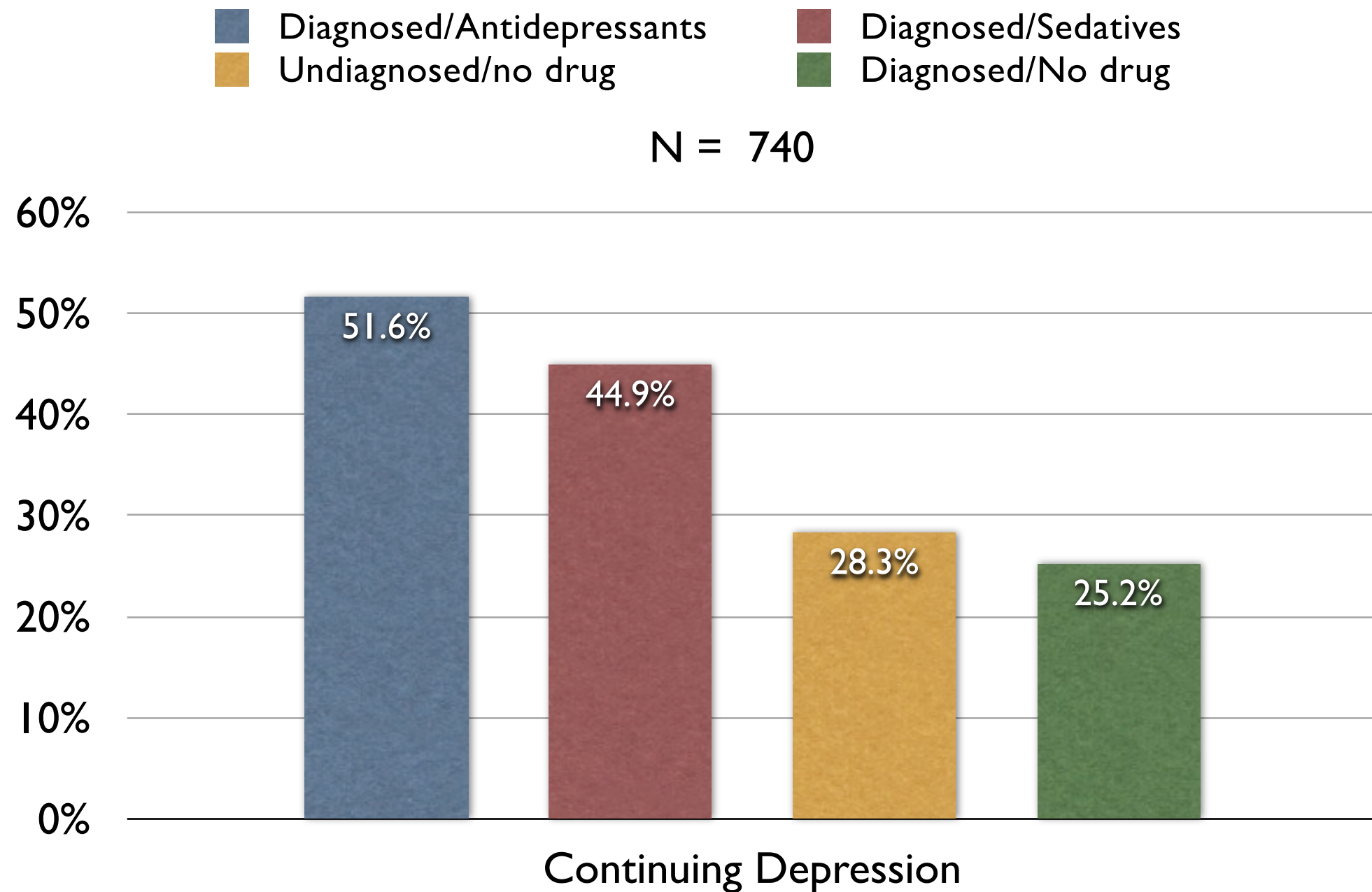


Source: S. Patten, "The Impact of antidepressant treatment on population health." *Population Health Metrics* 2 (2004): 9.

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

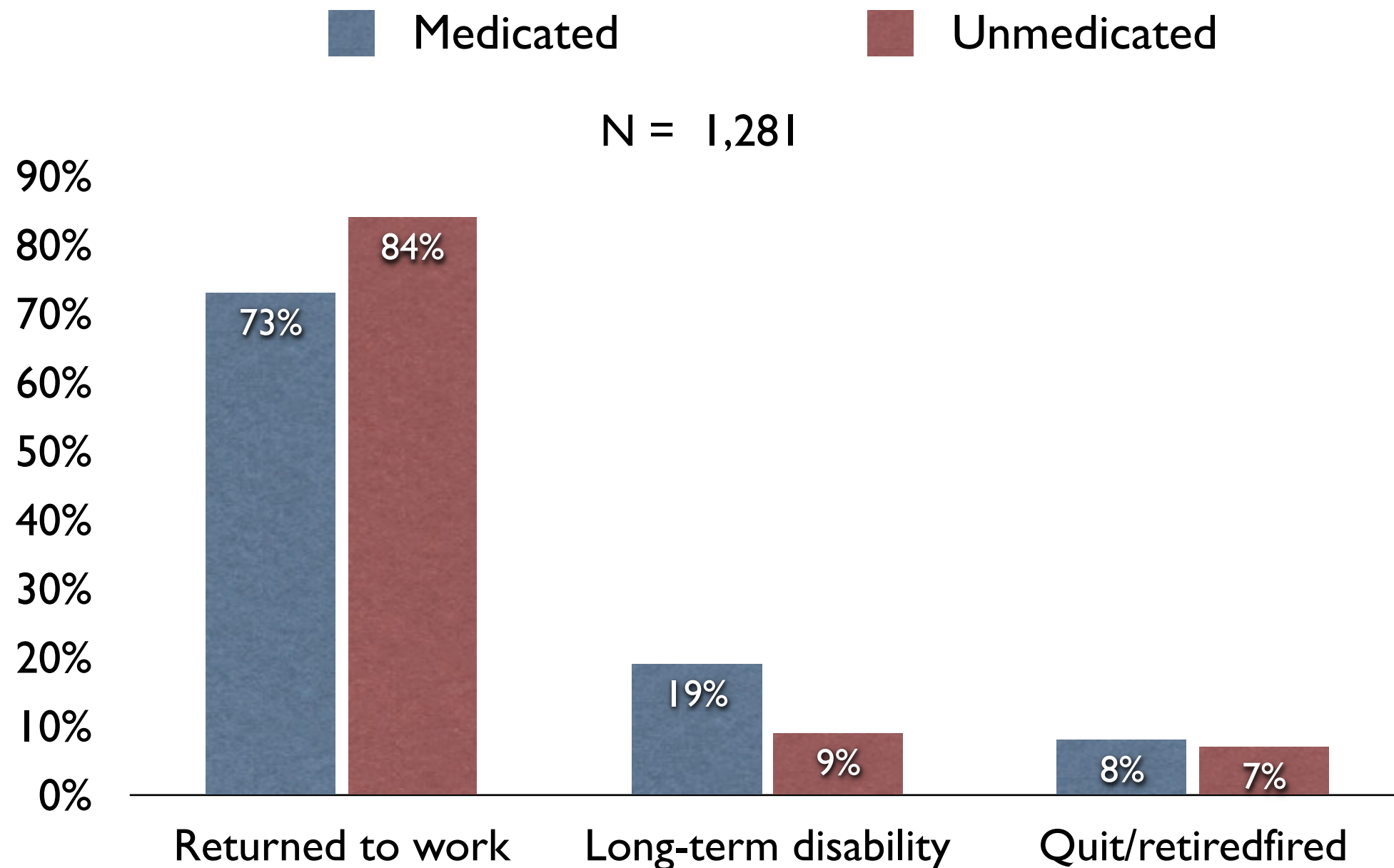


Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

This “study does not support the view that failure to recognize depression has serious adverse consequences.”

--D. Goldberg

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

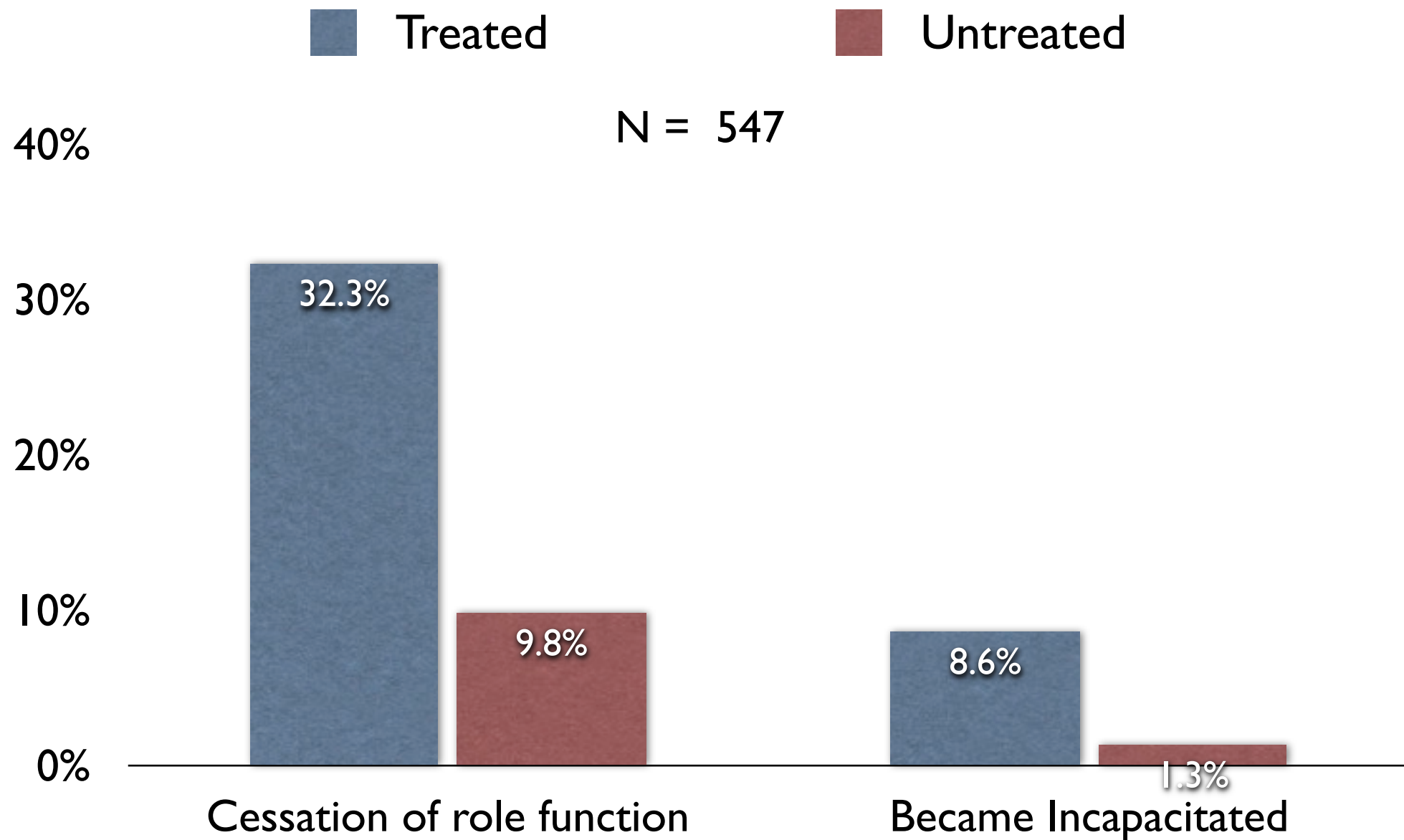


Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.

“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

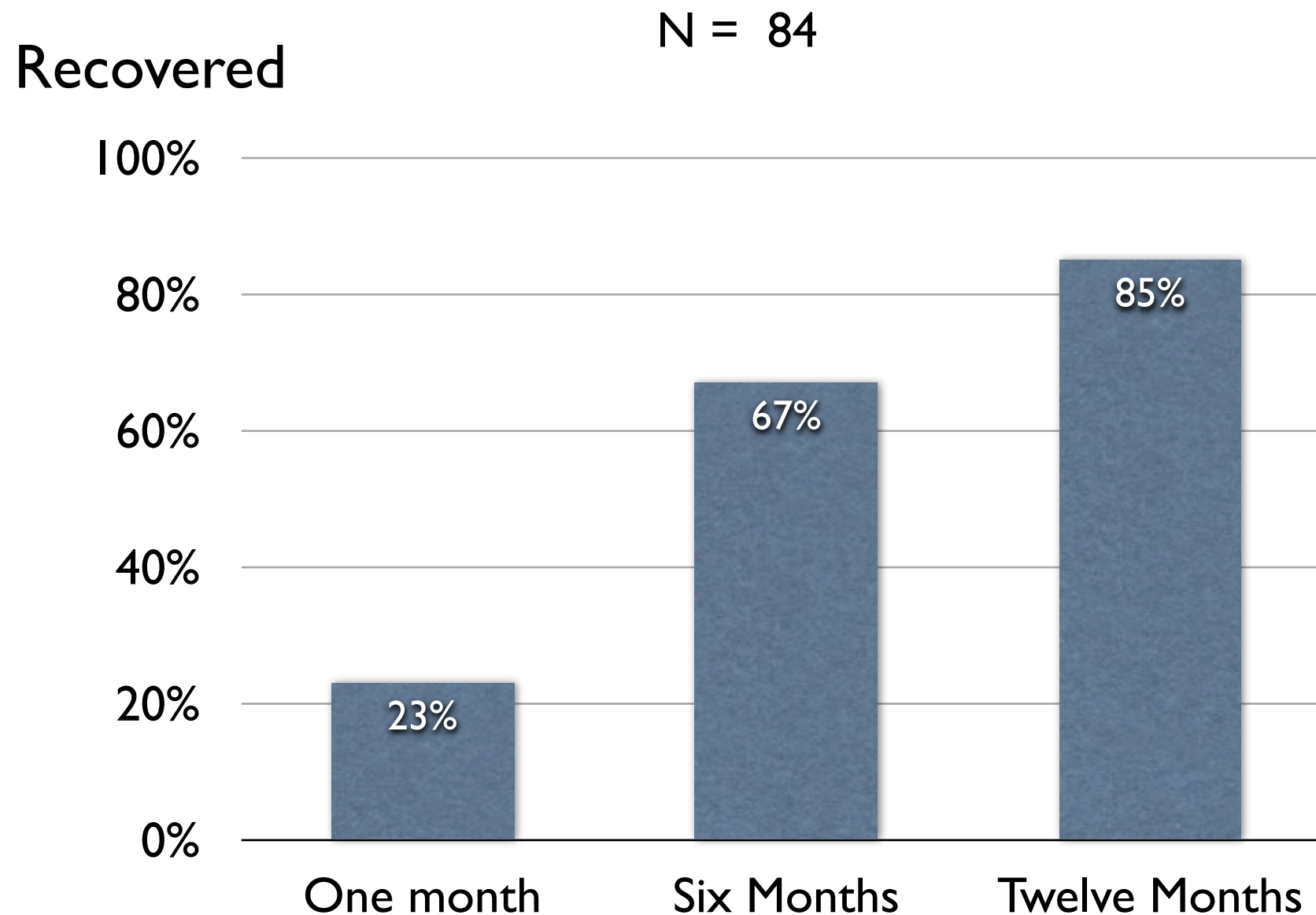


Source: W. Coryell. "Characteristics and significance of untreated major depressive disorder." *American Journal of Psychiatry* 152 (1995):1124-29.

“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

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

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.

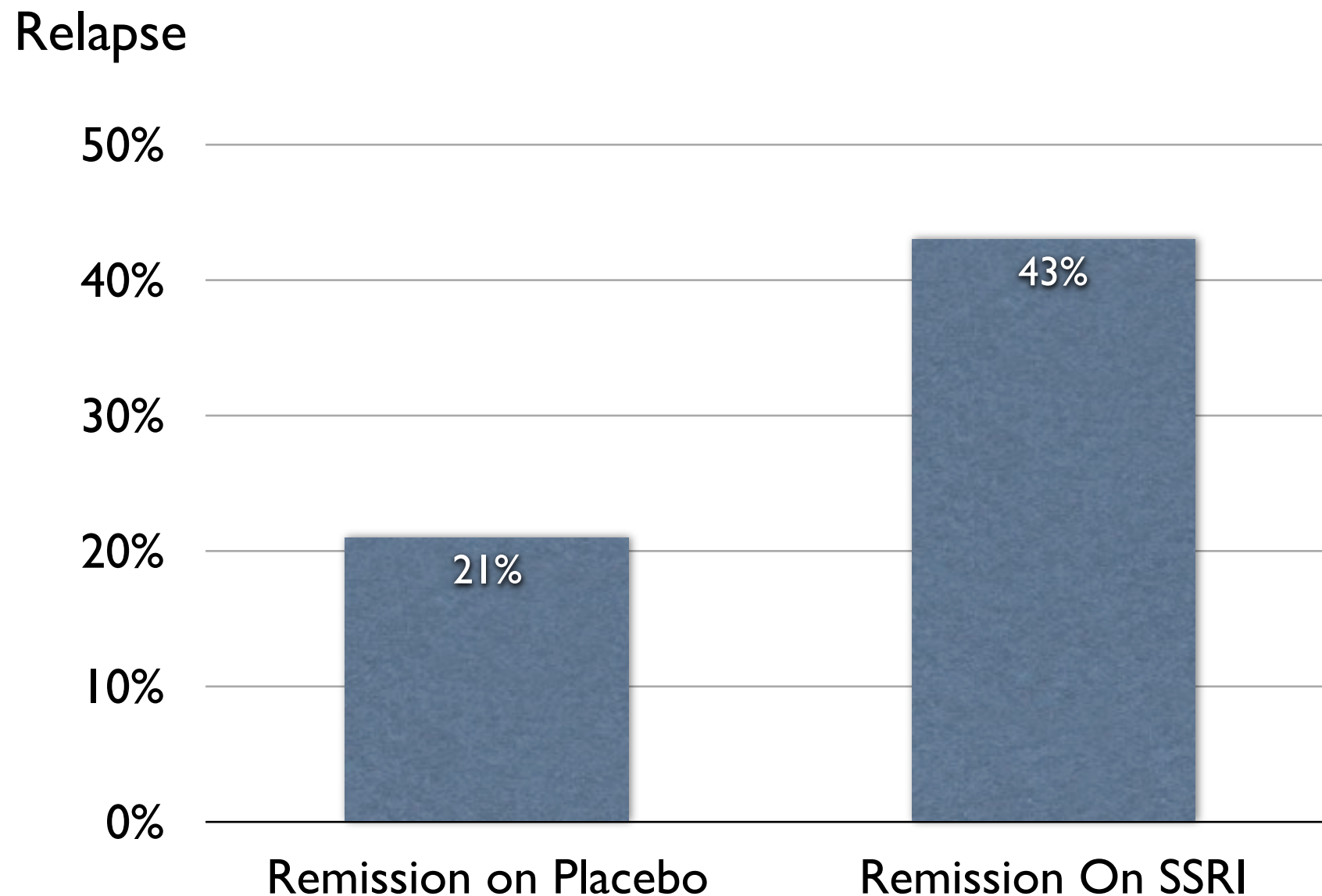
Why Are SSRIs Depressogenic Over the Long Term?

“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.

Three-Month Risk of Relapse After Initial Remission: Placebo vs. SSRI-Withdrawn Patients

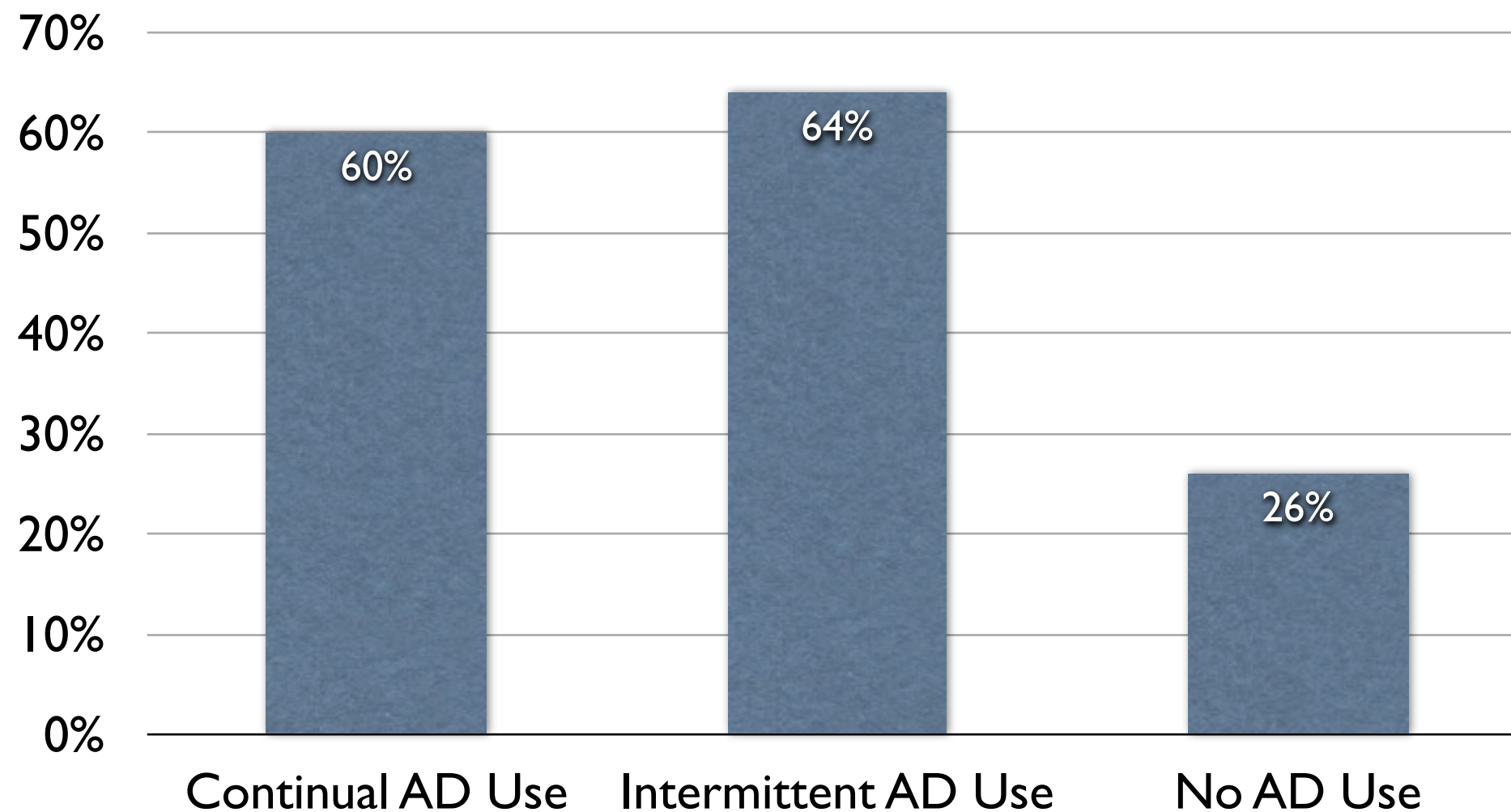


Source: P.Andrews: “*Primum non nocere*: an evolutionary analysis of whether antidepressants do more harm than good.” *Frontiers in Psychology* 3 (2012): 1-18.

“The more antidepressants perturb monamine 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

- 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.

Adverse Effects of SSRIs

On Mood

- Increased risk of long-term depression
- Emotional blunting, apathy
- Mania
- Conversion to bipolar

Neurocognitive Effects

- Mild cognitive impairment
- Driving accidents
- Neuronal structural damage

Gastrointestinal Effects

- Diarrhea
- Constipation
- Upset stomach

Movement

- Tics
- Fatigue
- Tardive dyskinesia

Sleep

- Suppression of REM sleep

Reproductive Functioning

- Sexual dysfunction

Fetal Development

- Congenital abnormalities
- Preterm births

The Bipolar Boom

Annual Prevalence in the Pre-Lithium Era

- One in 3000 to one in 10,900

Prevalence Today:

- One in 50 adults

Gateways to Bipolar Today

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

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 an antidepressant 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.”

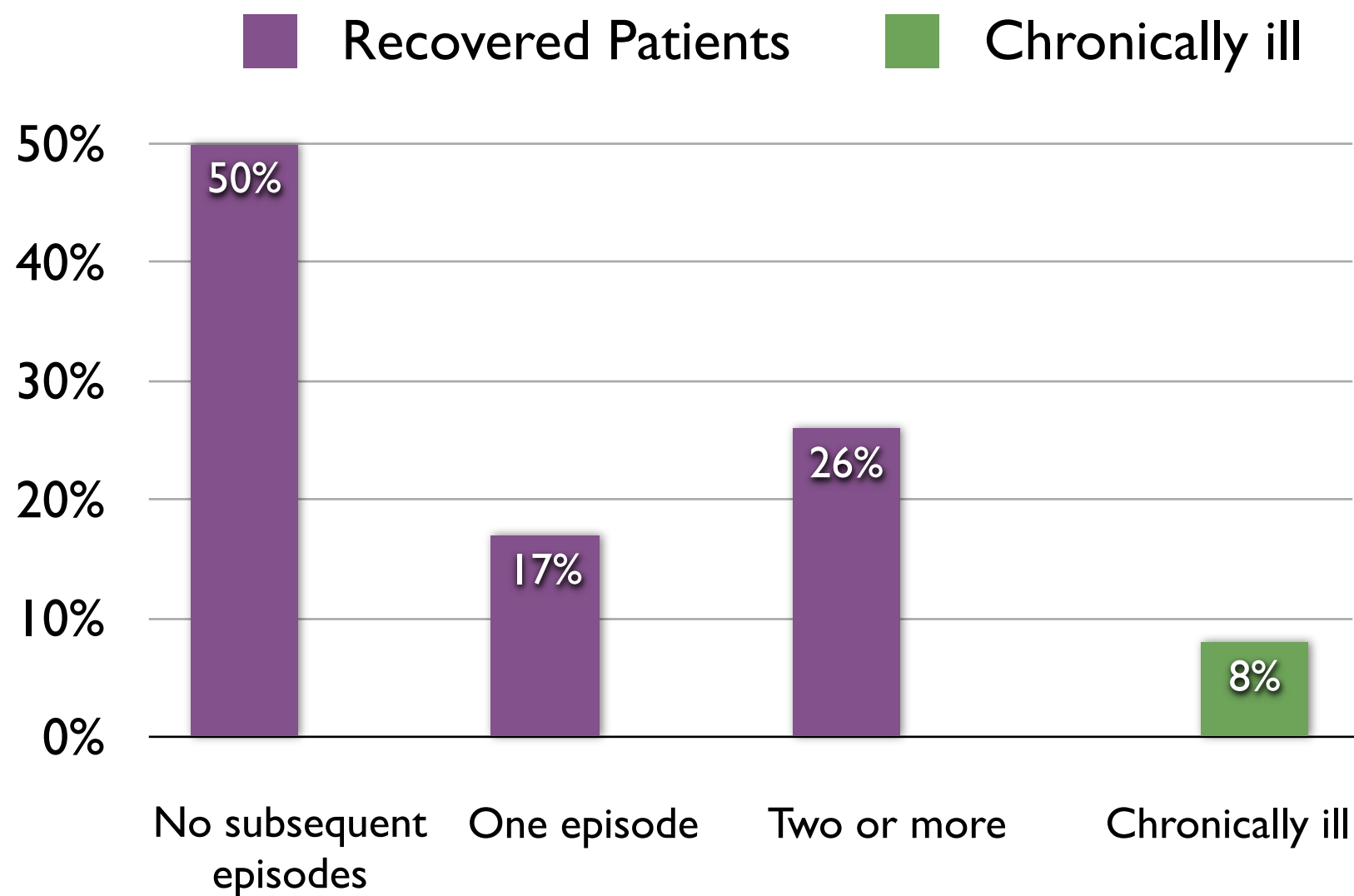
In a survey of members of the Depressive and Manic-Depressive Association, 60 percent of those with a bipolar diagnosis had initially fallen ill with major depression and had turned bipolar after exposure to an antidepressant.

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

Bipolar Outcomes in the Pre-Drug Era

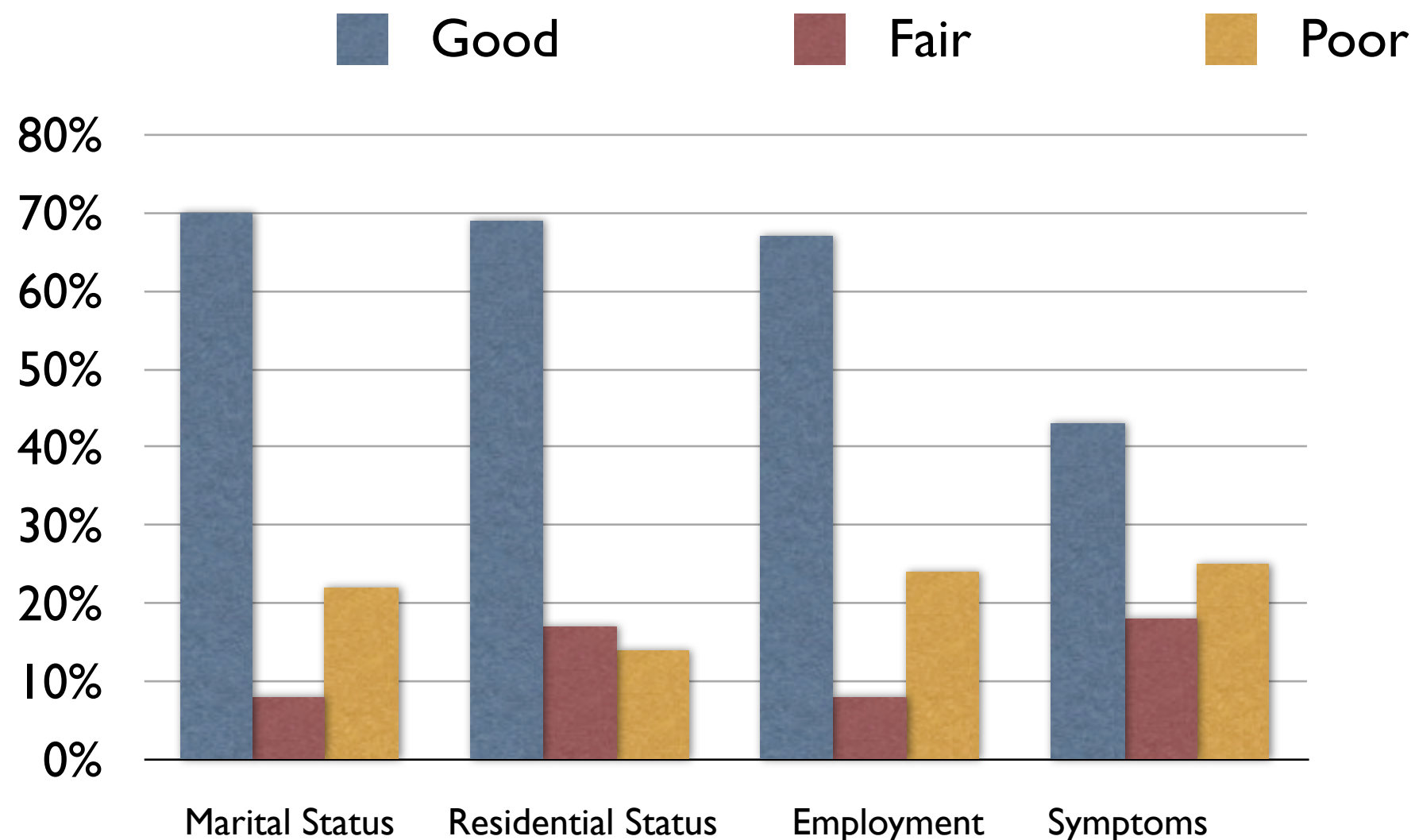
Swedish Study, 1945

103 manic patients



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 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.”

--Anthony Kouloukoulas, 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.”

Increased Treatment and Disability In U.S., 1990 to 2003

| | 1990 | 2003 |
|---|---------------|---------------|
| Number with anxiety, mood and substance disorders | 55 million | 66 million |
| Number treated for those disorders | 11.16 million | 21.77 million |
| Number on government disability due to mental illness | 1.47 million | 3.25 million |

Source: Surveys on prevalence of affective disorders in 1990 and 2003, and percentage of those with disorders who were treated; SSI and SSDI disability data for 1990 to 2003.

Questions

1. There were 264 million prescriptions written for antidepressant in the U.S. in 2011. Is there an evidence base that justifies this widespread use?
2. If the short-term and long-term data reviewed here were incorporated into clinical care guidelines for treating depression, what would those guidelines recommend?
3. Is there any evidence to be found that shows that SSRIs have decreased the burden of mental illness in any society that has embraced the use of these drugs? Or does the available evidence show that the opposite is true?

4. What are the medical costs of patients in the five years before exposure to an SSRI, compared to the first five years after exposure?
5. What percentage of people who are prescribed an SSRI end up on disability in the next 10 years?
6. Is there a risk of early dementia with SSRI use?
7. Is there a risk of early mortality with SSRI use?