Anatomy of a Global Epidemic:

History, Science, and the Long-Term Effects of Psychiatric Medications
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

U.S. Disability in the Prozac Era

Millions of adults, 18 to 66 years old

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

<table>
<thead>
<tr>
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<th>1990</th>
<th>2003</th>
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<tr>
<td>Number treated for psychiatric disorders</td>
<td>11.16 million</td>
<td>21.77 million</td>
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<tr>
<td>Number on government disability due to mental illness</td>
<td>1.47 million</td>
<td>3.25 million</td>
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Source: Surveys on prevalence of psychiatric disorders in 1990 and 2003, and percentage of those with disorders who were treated; SSI and SSDI disability data for 1990 to 2003.
The Disabled Mentally Ill in Iceland, 1976-2001

The proportion of the general population on disability because of depressive and anxiety disorders increased from .4% to .7% from 1976-2001.

The researchers concluded: Increased diagnosis and use of antidepressants “might have been expected to have a public health impact by reducing disability, morbidity and mortality due to depressive disorders . . . however, the cost for society has not been reduced.

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

Number of New Cases per 100,000 Population

Days of Incapacity Due to Mental Disorders in Great Britain, 1985-1995

Millions of Days

The Chemical Imbalance Theory of Mental Disorders

• Arose from understanding of how drugs act on brain (1960s-1970s)

• Investigations of dopamine theory of schizophrenia and serotonin theory of depression started in 1970s
Findings re the Chemical Imbalance Theory of Mental Disorders

A. Serotonin Theory of Depression

• “Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression.” --NIMH, 1984.

• “There is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no real monamine deficit.”--Essential Psychopharmacology, 2000

B. Dopamine Theory of Schizophrenia

• “There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia.” Molecular Psychiatry, 2002

C. Chemical Imbalance Theory of Mental Disorders (in general)

• “We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them.” Psychological Medicine, 2005.
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.”

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.
The Case Against Psychiatric Drugs Over the Long-Term

A review of the long-term outcomes literature shows:

• A worsening of the target symptoms over the long-term (in the aggregate, compared to outcomes in the pre-drug era.)

• New and more severe psychiatric symptoms in a significant percentage of patients

• Physical decline, cognitive problems, and risk of early death
Reconciling the Two Evidence Bases For Psychiatric Medications

A. The relapse studies reflect risks associated with drug-withdrawal effects, rather than just the return of the natural course of the disorder. This high risk of relapse is due to the fact that the brain has been changed by exposure to the drug.

B. The high risk of relapse upon drug withdrawal creates a clinical illusion, which leads physicians to “see” that most patients “need” the medications.

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 they don’t see that mental disorders, if not initially treated with medications, often run an episodic course.
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 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.

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

Recovery from an acute episode:

The depressive symptoms could be expected to lift, although it could take six months or more.

“Depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self-limited.” --Jonathan Cole, NIMH, 1964.

“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
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.

• Conclusion: Depression was an episodic illness, and only a small minority suffered from regular recurrent bouts of major 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.”

• 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 Drug Exposure

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.

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
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.”

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 3% of the patients remitted and then stayed well throughout the 12-month followup. The remaining patients either failed to remit, relapsed during the followup, or dropped out.

Conclusion: “Most individuals with major depressive disorders have a chronic course, often with considerable symptomatology and disability even between episodes.”
Depression in the Netherlands
(Over the course of ten years)

One-Year Outcomes in WHO Screening Study for Depression

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

NIMH’s Study of Untreated Depression

Antidepressants Lessen the Long-Term Benefits of Exercise

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<tr>
<th>Treatment during first 16 weeks</th>
<th>Percentage of patients in remission at end of 16 weeks</th>
<th>Percentage of patents who relapsed in following six months</th>
<th>Percentage of all patients depressed at end of ten months</th>
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<tbody>
<tr>
<td>Zoloft alone</td>
<td>69%</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Zoloft plus exercise</td>
<td>66%</td>
<td>31%</td>
<td>55%</td>
</tr>
<tr>
<td>Exercise alone</td>
<td>60%</td>
<td>8%</td>
<td>30%</td>
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Bipolar in the Pre-Drug Era

Annual Prevalence:
• Between one in 3,000 and one in 10,000

Hospitalized Bipolar Patients in U.S. in 1955
• 13,000
Bipolar Outcomes in the Pre-Drug Era

Swedish Study, 1945
103 manic patients

- Recovered Patients
- Chronically ill

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*
The Bipolar Boom

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 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.


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.”
Worsening Long-term Course of 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

• Slow or incomplete recovery from acute episodes

• 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
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.”


“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 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

Long-term Recovery Rates for Schizophrenia Patients

Global Adjustment of Schizophrenia Patients

![Graph showing the adjustment of schizophrenia patients over time with and without antipsychotic medications.]

Spectrum of Outcomes in Harrow’s Study

On Antipsychotics:
- Recovered: 0%
- Fair: 25%
- Uniformly Poor: 75%

Off Antipsychotics:
- Recovered: 50%
- Fair: 25%
- Uniformly Poor: 25%

Psychotic Symptoms in Schizophrenia Patients Over the Long Term

Global Adjustment of “Other Psychotic” Patients

Global Adjustment of All Psychotic Patients

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

Martin Harrow, page 411.
Five-Year Outcomes for First-Episode Psychotic Patients in Finnish Western Lapland Treated with Open-Dialogue Therapy

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<thead>
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<th>Patients (N=75)</th>
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<tbody>
<tr>
<td>Schizophrenia (N=30)</td>
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<td>Other psychotic disorders (N=45)</td>
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<tr>
<th>Antipsychotic use</th>
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<tbody>
<tr>
<td>Never exposed to antipsychotics</td>
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<tr>
<td>Occasional use during five years</td>
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<tr>
<td>Ongoing use at end of five years</td>
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<table>
<thead>
<tr>
<th>Psychotic symptoms</th>
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<tr>
<td>Never relapsed during five years</td>
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<tr>
<td>Asymptomatic at five-year followup</td>
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<th>Functional outcomes at five years</th>
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<tr>
<td>Working or in school</td>
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<tr>
<td>Unemployed</td>
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<tr>
<td>On disability</td>
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An Epidemic Explained

In the modern era:

• Depression has been transformed from an episodic disorder into a chronic illness, with much higher disability rates

• Use of illicit drugs, stimulants and antidepressants have helped create a 100-fold increase in the prevalence of bipolar illness (in U.S.)

• Functional outcomes for bipolar illness have dramatically deteriorated in modern era.

• More than 50% of schizophrenia patients in 1945-1955 worked; today only 10% or so do.