Rethinking Psychiatric Care:  
History, Science, and the Long-term Effects of Psychiatric Drugs  

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The Common Wisdom

The introduction of chlorpromazine 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

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

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

Number of New Cases Annually per 100,000 Population

New Cases of Disability in Denmark Due to Mental Illness

One Question Raised by the Disability Data:

How do psychiatric medications affect the long-term course of mental disorders? Do they increase the likelihood that people diagnosed with a major mental disorder will do well over the long-term? Or do they increase the likelihood that people so diagnosed will have a poor long-term outcome?
How Do Psychiatric Medications Act on the Brain?
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
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 monoamine deficit.”--Stephen Stahl, *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.” Kenneth Kendler, Psychological Medicine, 2005.

“In truth, the chemical imbalance notion was always a kind of urban legend, never a theory seriously propounded by well-informed psychiatrists.” Ronald Pies, July 11, 2011 in Psychiatric Times.
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.”

Dopamine function before exposure to antipsychotics

Presynaptic neuron

Dopamine

Dopamine receptors

Postsynaptic neuron
Dopamine function after exposure to antipsychotics

Brain increases receptors to compensate for drug blockade
The Problem With Psychiatric Drugs

1. The etiology of most mental disorders remains unknown, and thus the drugs do not fix known pathologies.

2. The drugs impede the normal functioning of neurotransmitter pathways, which leads to significant side effects.

3. Over the long-term, the drugs induce changes in the brain the opposite of what is intended, and this increases the risk that a person will become chronically ill.
The Consequences of “Oppositional Tolerance”

“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

Recovery Rates for Major Mental Disorders Prior to the Modern Drug Era
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.

Outcomes for Hospitalized Depression in Pre-Drug Era

• Recovery from index episode was expected.

• In four of five long-term studies, more than 50% hospitalized for an index episode were never rehospitalized.

• The average time between recurrent episodes was three years 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
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 mania or even a first depression will not tend toward a more chronic course.”

--George Winokur, Washington University, *Manic Depressive Illness*, 1969
Bipolar Outcomes in the Pre-Drug Era

Swedish Study, 1945

103 manic patients

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 Bipolar 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 majority of mental illnesses, especially the most severe, are largely self-limiting in nature if the patient is not subjected to a demeaning experience or loss of rights and liberties.”

-- Samuel Bockoven, 1975
The Effect of Antipsychotics on Long-term Schizophrenia Outcomes: A Case Study
The Evidence for Antipsychotics

Short-term Use

Antipsychotics 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.

Clinical Perceptions

The physician sees that the medications often work upon initial use, and sees that patients often relapse when they go off the medications.
What’s Missing From The Evidence Base?

A. It does not provide evidence that medications improve the long-term course of schizophrenia (or other psychotic disorders,) particularly in regard to functional outcomes.

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

C. Physicians today no longer have clinical experience with the long-term course of schizophrenia patients off medication.
Recognition that the Evidence Base For Long-term Use of Antipsychotics is Lacking

“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.”

The Hippocratic Oath

In order for a treatment to do no harm, it must improve on natural recovery rates.
• 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.

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.”

Clinicians’ Perceptions

• Patients were returning with great frequency, which was dubbed the “revolving door syndrome.”

• Relapse during drug administration “is greater in severity than when no drugs are given.”

• If patients relapse after quitting antipsychotics, symptoms tend to “persist and intensify.”

Source: Gardos, G. “Maintenance antipsychotic therapy: is the cure worse than the disease?” American Journal of Psychiatry 135 (1978: 1321-4.)
A Retrospective Comparison of Outcomes in Pre-Drug and Drug Era

Relapse Rates Within Five Years of Discharge

1947 cohort: 55%
1967 cohort: 69%

Functional Outcomes

1947 cohort: 76% were successfully living in the community at end of five years

1967 cohort: They were much more “socially dependent”--on welfare and needing other forms of support--than the 1947 cohort.

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

<table>
<thead>
<tr>
<th>Medication use (in hospital/after discharge)</th>
<th>Number of Patients</th>
<th>Severity of Illness (1 = best outcome; 7 = worst outcome)</th>
<th>Rehospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>No meds/off</td>
<td>24</td>
<td>1.70</td>
<td>8%</td>
</tr>
<tr>
<td>Antipsychotic/off</td>
<td>17</td>
<td>2.79</td>
<td>47%</td>
</tr>
<tr>
<td>No meds/on</td>
<td>17</td>
<td>3.54</td>
<td>53%</td>
</tr>
<tr>
<td>Antipsychotic/on</td>
<td>22</td>
<td>3.51</td>
<td>73%</td>
</tr>
</tbody>
</table>

Source: Rappaport, M. “Are there schizophrenics for whom drugs may be unnecessary or contraindicated?” *Int Pharmacopsychiatry* 13 (1978):100-11.
Rappaport’s Conclusion:

“Our findings suggest that antipsychotic medication is not the treatment of choice, at least for certain patients, if one is interested in long-term clinical improvement. Many unmedicated-while-in-hospital patients showed greater long-term improvement, less pathology at follow-up, fewer rehospitalizations, and better overall functioning in the community than patients who were given chlorpromazine while in the hospital.”
Loren Mosher’s Soteria Project

Results:

At end of two years, the Soteria patients had “lower psychopathology scores, fewer [hospital] readmissions, and better global adjustment.”

In terms of antipsychotic use, 42% had never been exposed to the drugs, 39% had used them temporarily, and 19% had used them regularly throughout the two-year followup.

Loren Mosher’s Conclusion

“Contrary to popular views, minimal use of antipsychotic medications combined with specially designed psychosocial intervention for patients newly identified with schizophrenia spectrum disorder is not harmful but appears to be advantageous. We think the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined.”
William Carpenter’s In-House NIMH Study, 1977

Results

• Those treated without drugs were discharged sooner than drug-treated patients in a comparison group.

• At the end of one year, only 35 percent of the non-medicated group relapsed within a year after discharge, versus 45% of the medicated group.

• The unmedicated group also suffered less from depression, blunted emotions, and retarded movements.

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.”

The Dopamine Supersensitivity Theory

Dopamine function before exposure to antipsychotics

Presynaptic neuron

Dopamine

Dopamine receptors

Postsynaptic neuron
Dopamine function after exposure to antipsychotics

Presynaptic neuron

Antipsychotic blocks receptors

Dopamine

Postsynaptic neuron

Brain increases receptors to compensate for drug blockade
The Consequences of Dopamine Supersensitivity

“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

Study of Drug-Induced Tardive Psychosis

In 1982, Chouinard and Jones reported that 30% of the 216 schizophrenia outpatients they studied showed signs 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.”

Animal Models of Psychosis and Drug-Induced Dopamine Supersensitivity

In 2005, Philip Seeman at the University of Toronto 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.

Antipsychotics Increase the Density of D2 HIGH Receptors

In this same report, Seeman found that haloperidol and olanzapine both increased the density of D2 HIGH receptors, and thus cause the very biological abnormality that in animal models had been identified as a final pathway to psychosis.
Philip Seeman Tests His D2 High Theory

In rat studies, “we show that during ongoing treatment with clinically relevant doses, haloperidol and olanzapine progressively lose their efficacy ... the loss of efficacy is linked to an increase in D2 receptor number and sensitivity. These results are the first to demonstrate that ‘breakthrough’ supersensitivity during ongoing antipsychotic treatment undermines treatment efficacy.”

WHO Cross-Cultural Studies, 1970s/1980s

• In both studies, which measured outcomes at the end of two years and five years, the patients in the three developing countries, India, Nigeria, and Colombia, had a “considerably better course and outcome” than in the U.S. and six other developed countries.

• 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.

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.

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Clinical Remission</th>
<th>Functional Remission</th>
</tr>
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<tbody>
<tr>
<td>East Asia</td>
<td>84.4%</td>
<td>24.6%</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>79.6%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Latin America</td>
<td>79.4%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Central and Eastern Europe</td>
<td>65.1%</td>
<td>21.6%</td>
</tr>
<tr>
<td>North Europe</td>
<td>60.1%</td>
<td>35.0%</td>
</tr>
<tr>
<td>South Europe</td>
<td>61.3%</td>
<td>20.7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>66.1%</strong></td>
<td><strong>25.4%</strong></td>
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MRI Study in Macaque Monkeys

Finding:

• In macaque monkeys, treatment with either haloperidol or olanzapine for 17 to 27 months led to a “8-11% reduction in mean fresh brain weights” compared to controls.

• The differences (in brain weights and brain volumes) “were observed across all major brain regions, but appeared most robust in the frontal and parietal regions.”

Nancy Andreasen’s MRI Study

In 2003, Andreasen reported that schizophrenia was a “progressive neurodevelopmental disorder” characterized by “progressive reduction in frontal white matter volume.” This decline in brain volumes was seen in MRI imaging tests.

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.

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.

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.”

More Evidence That Antipsychotics Shrink the Brain

In a 2012 review of 43 brain-imaging studies of first-episode psychosis, European researchers determined that a loss of gray matter volume was “significantly more severe in medicated patients.”

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

Anxiety Symptoms of Schizophrenia Patients

Cognitive Function of Schizophrenia Patients

Psychotic Symptoms in Schizophrenia Patients Over the Long Term

Relapse Rates Once Patients Are Stable

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Off Antipsychotics</th>
<th>On Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 to 10 years</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td>10 to 15 years</td>
<td>0%</td>
<td>67%</td>
</tr>
<tr>
<td>15 to 20 years</td>
<td>0%</td>
<td>25%</td>
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Long-term Recovery Rates for Schizophrenia Patients

Medication compliant patients throughout 20 years: 17% had one period of recovery.

Those off antipsychotics by year two who then remained off throughout next 18 years: 87% had two or more sustained periods of recovery.

Global Adjustment of Schizophrenia Patients

Spectrum of Outcomes in Harrow’s Study

On Antipsychotics
- Recovered: 5%
- Fair: 46%
- Uniformly Poor: 49%

Off Antipsychotics
- Recovered: 40%
- Fair: 44%
- Uniformly Poor: 16%

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

Martin Harrow, page 411.
“I conclude that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics.”

--Martin Harrow, American Psychiatric Association annual meeting, 2008
Global Adjustment of “Other Psychotic” Patients

![Graph showing outcomes of patients on and off antipsychotics over time]

Global Adjustment of All Psychotic Patients

Summary of Harrow’s Findings

Those who stayed on antipsychotics:

- Were much more psychotic
- Were much more anxious
- Had worse cognitive function
- Had much lower recovery rates
- Were much more likely to have a “uniformly poor” outcome
- Had worse global outcomes

And:

- Schizophrenia patients off antipsychotics had much better outcomes than patients with milder psychotic disorders who stayed on the drugs.
“How unique among medical treatments is it that the apparent efficacy of antipsychotics could diminish over time or become ineffective or harmful? There are many examples for other medications of similar long-term effects, with this often occurring as the body readjusts, biologically, to the medications.”

--Martin Harrow, 2013
The Pieces of the Puzzle: Do They Fit Together?

1. In the first long-term study conducted by the NIMH, rehospitalization rates were higher for those treated initially with an antipsychotic.

2. A retrospective study at Boston Psychopathic Hospital in the 1970s found that outcomes had deteriorated in the drug era.

3. Three studies in the 1970s that compared conventional drug treatment to experimental treatment that involved using antipsychotics in a limited fashion all found better outcomes in the experimental group.

4. Researchers at McGill University then stepped forward with a biological explanation for why antipsychotics made patients more biologically vulnerable to psychosis and thus increased the risk of relapse.
5. A cross-cultural study by the World Health Organization found much better outcomes in three developing countries where patients weren’t regularly maintained on antipsychotics.

6. MRI studies have revealed that antipsychotics shrink the brain. This shrinkage is associated with a worsening of outcomes.

7. Harrow’s long-term, prospective study found that patients off antipsychotics had much better outcomes.
A Call to Rethink Antipsychotics

“It is time to reappraise the assumption that antipsychotics must always be the first line of treatment for people with psychosis. This is not a wild cry from the distant outback, but a considered opinion by influential researchers . . . [there is] an increasing body of evidence that the adverse effects of [antipsychotic] treatment are, to put it simply, not worth the candle.”

--Peter Tyrer, Editor

British Journal of Psychiatry, August 2012
### Outcomes with Selective Use Of Antipsychotics

#### Five-Year Outcomes for First-Episode Psychotic Patients in Finnish Western Lapland Treated with Open-Dialogue Therapy

<table>
<thead>
<tr>
<th>Patients (N=75)</th>
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<tbody>
<tr>
<td>Schizophrenia (N=30)</td>
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<tr>
<td>Other psychotic disorders (N=45)</td>
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<table>
<thead>
<tr>
<th>Antipsychotic use</th>
<th></th>
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<tbody>
<tr>
<td>Never exposed to antipsychotics</td>
<td>67%</td>
</tr>
<tr>
<td>Occasional use during five years</td>
<td>33%</td>
</tr>
<tr>
<td>Ongoing use at end of five years</td>
<td>20%</td>
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<table>
<thead>
<tr>
<th>Psychotic symptoms</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Never relapsed during five years</td>
<td>67%</td>
</tr>
<tr>
<td>Asymptomatic at five-year followup</td>
<td>79%</td>
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<table>
<thead>
<tr>
<th>Functional outcomes at five years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Working or in school</td>
<td>73%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>7%</td>
</tr>
<tr>
<td>On disability</td>
<td>20%</td>
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