Psychiatric Drugs:
Problems and Solutions
Disclosure

I do not have an interest in selling a technology, program, product, and/or service to CME/CE professionals.

I have nothing to disclose with regard to commercial relationships.
The Problems With Psychiatric Drugs: The Disability Data
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)

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 Mental and Behavioural Disorders in Iceland, 1990-2007

Number of New Cases Annually per 100,000 Population

How Do Psychiatric Medications Shape Long-Term Outcomes?
The Evidence for Psychiatric Drugs

Short-term Use

The medications reduce target symptoms of a disorder better than placebo in six-week trials.

Long-term Use

In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications. See antipsychotics in particular.

Clinical Perceptions

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

A. It does not provide evidence that medications improve the long-term course of major mental 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. This heightened risk of relapse is due to the fact that the brain has been changed by exposure to the drug.

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 its clinical perceptions about the efficacy of the drugs isn’t informed by that long-term perspective.
The Effect of Antipsychotics on Long-term Schizophrenia Outcomes: A Case Study
Assessing Long-Term Schizophrenia Outcomes

“After fifty years of neuroleptics, are we able to answer the following simple question: Are neuroleptics effective in treating schizophrenia? [There is] no compelling evidence on the matter, when ‘long-term’ is considered.”

And:

“If we wish to base psychiatry on evidence-based medicine, we run a genuine risk in taking a close look at what has long been considered fact.”

--Emmanuel Stip, European Psychiatry (2002)
The Hippocratic Oath

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

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.)
Bockoven’s 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.”

Outcome studies led researchers to worry that antipsychotics might make people more biologically vulnerable to psychosis over the long-term, and thus increase the chronicity of the disorder.

In 1978, Jonathan Cole wrote a provocative article titled: “Is the Cure Worse than the Disease?”
The Dopamine Supersensitivity Theory

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 Dopamine Supersensitivity Theory

“Neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms . . . An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness.”

Guy Chouinard and Barry Jones, McGill University

Study of Tardive Psychosis:

In 1982, Chouinard and Jones reported that 30% of the 216 schizophrenia outpatients they studied showed sign of tardive psychosis, which meant their psychosis was becoming chronic. When this happens, they wrote, “the illness appears worse” than ever before. “New schizophrenic symptoms of greater severity will appear.”

In 2005, Seeman reported that agents that trigger psychotic-like behavior in animals -- amphetamines, angel dust, lesions to the hippocampus, gene-knockout manipulations -- all cause an increase in D2 receptors that have a “high” affinity for dopamine. These results “imply that there may be many pathways to psychosis, including multiple gene mutations, drug abuse, or brain injury, all of which may converge via D2 HIGH to elicit psychotic symptoms,” Seeman wrote.

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.”

Reviewing the Evidence for the Dopamine-Supersensitivity Theory

• Longer-term studies in the 1970s showed higher relapse rates for drug-exposed patients.

• A biological explanation for this paradoxical result was proposed and assessed in a study of schizophrenia patients.

• Animal models further refined understanding of drug-induced dopamine supersensitivity and researchers at University of Toronto concluded that this was why the medications lost their efficacy over time.
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.”

Summary of MRI Studies

1) Studies in monkeys found that antipsychotics shrink brain volumes.

2) Andreasen found that patients diagnosed with schizophrenia show a decline in brain volumes over time.

3) Andreasen found that this shrinkage was associated with increased negative symptoms, functional impairment and cognitive decline.

4) Andreasen determined that this shrinkage was associated with use of antipsychotics.

5) European researchers have found that shrinkage is more severe in medicated patients.
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 had a “considerably better course and outcome.”

• The WHO researchers concluded that “being in a developed country was a strong predictor of not attaining a complete remission.”

• They also found that “an exceptionally good social outcome characterized the patients” in developing countries.

WHO Findings, Continued

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>
</thead>
<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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Summary of Cross-Cultural Studies With Medication as a Variable

1) In 1970s and 1980s, WHO investigators found that outcomes were significantly better in developing countries, where only 16% were regularly maintained on antipsychotics.

2) In recent global Eli Lilly Study, where all patients are maintained on antipsychotics, patients in developing countries do not have better functional outcomes than patients in developed countries.
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

Long-term Recovery Rates for Schizophrenia Patients

Spectrum of Outcomes in Harrow’s Study

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

Off Antipsychotics
- Recovered: 40%
- Fair: 46%
- Uniformly Poor: 16%

Psychotic Symptoms in Schizophrenia Patients Over the Long Term

Off antipsychotics  On Antipsychotics

10-year followup
- Off antipsychotics: 23%
  - On Antipsychotics: 79%

15-year followup
- Off antipsychotics: 28%
  - On Antipsychotics: 64%

Anxiety Symptoms of Schizophrenia Patients

Cognitive Function of Schizophrenia Patients

“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

Global Adjustment of All Psychotic Patients

“Is very long-term treatment with antipsychotic medications undesirable?”

--Martin Harrow, 2012
Rethinking Antipsychotics: What Does the Evidence Show Would Best Promote Recovery?

My Opinion:

• Avoid immediate use of antipsychotics to identify those who can recover without use of the medications.

• Minimize long-term use.
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>
</tr>
<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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</thead>
<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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychotic symptoms</th>
<th></th>
</tr>
</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>
</tr>
</tbody>
</table>

<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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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
Summary of Effects of Antidepressants on Long-term Outcomes

- Depression has changed from an episodic illness into a chronic one in modern era

- This led Italian psychiatrist Giovanni Fava to propose, in the early 1990s that antidepressants were depressogenic agents over the long term

- Modern studies regularly show better long-term outcomes for unmedicated patients

- Researchers have now proposed a name for this long-term effect: tardive dysphoria
Acknowledgment of 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.”
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
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

Summary of Change in Long-term Bipolar Outcomes in Modern Era

- Prevalence has increased 100-fold in modern era, with antidepressants a primary reason for that increase.

- Bipolar illness runs a much more chronic course than it did in the pre-drug era.

- Disability rates are much higher today than they were in the pre-drug era.
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.

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.”
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 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
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.”
Rethinking Psychiatric Care

A. The field needs to investigate and re-discover the long-term course of major mental disorders prior to the pharmacotherapy era, as epidemiological studies from that era tell of people regularly recovering from acute episodes of mental illness, including psychosis, and often staying well for long periods of time, or even indefinitely.

B. The field needs to incorporate the long-term outcomes literature into its medication protocols, and thus develop protocols that involve using the medications in a more selective, cautious manner. These protocols may involve delaying initial use of medications, and trying to minimize long-term use. (See Western Lapland’s “open dialogue” program.)
“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