Antipsychotics in Open-Dialogue Therapy: A Best Use Model of Care

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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In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications.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.
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.)
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>
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</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.”
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.

“Patients reported experiencing more anguish with our treatment approach, whereas they felt a greater sense of frustration and of being ‘frozen in the psychosis’ in settings emphasizing drug treatment . . . insofar as the psychotic break contains potential for helping the patient alter pathological conflicts within himself and establish a more adaptive equilibrium with his environment, our present-day practice of immediate and massive pharmacological intervention may be exacting a price in terms of producing ‘recovered’ patients with greater rigidity of character structure who are less able to cope with subsequent life stresses.”

--William Carpenter
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.”

Summary of First 25 Years

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

![Diagram showing presynaptic and postsynaptic neurons with dopamine and receptors labeled.]

A 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 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.”

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

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<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>Total</td>
<td>66.1%</td>
<td>25.4%</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.
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

Off Antipsychotics

On Antipsychotics

Cognitive Function of Schizophrenia Patients

Psychotic Symptoms in Schizophrenia Patients Over the Long Term

Global Adjustment of Schizophrenia Patients

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: 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

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

--Martin Harrow, 2012
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*
Five-Year Outcomes for First-Episode Psychotic Patients in Finnish Western Lapland Treated with Open-Dialogue Therapy

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<thead>
<tr>
<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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<table>
<thead>
<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>
</tr>
<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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<tbody>
<tr>
<td>Never relapsed during five years</td>
</tr>
<tr>
<td>Asymptomatic at five-year followup</td>
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<table>
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<tr>
<th>Functional outcomes at five years</th>
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<tbody>
<tr>
<td>Working or in school</td>
</tr>
<tr>
<td>Unemployed</td>
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<tr>
<td>On disability</td>
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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