

## **Antipsychotics and Schizophrenia/Psychosis**

### **I. The Evidence Base for Current Standard of Care**

- a) In short-term trials, antipsychotics knock down psychotic symptoms better than placebo
- b) In drug withdrawal studies (most with abrupt-withdrawal design), the drug-withdrawn patients relapse at a higher rate than the drug-maintained patients.

However, as Emmanuel Stip noted in a 2002 editorial in *European Psychiatry*, the relapse literature does not provide evidence that antipsychotics are shifting long-term outcomes for the better.

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

### **II. The Evidence that Challenges Conventional Wisdom**

There are five lines of evidence related to long-term outcomes that challenge the conventional wisdom:

1. Evidence that antipsychotics induce a dopamine supersensitivity, which makes the brain more biologically vulnerable to psychosis.
2. MRI studies, which provide evidence that antipsychotics shrink brain volumes, and that this shrinkage is associated with an increase in negative symptoms and functional impairment.
3. Cross-cultural studies, which show better outcomes in developing countries when patients were not regularly maintained on antipsychotics, but do not in studies where all patients are medicated.
4. Martin Harrow’s longitudinal study, which found that over the long-term, unmedicated patients had much better outcomes.
5. The good five-year outcomes in Western Lapland (Finland), where antipsychotics are used in a selective, cautious manner.

### **III. Drug-induced dopamine supersensitivity: Why this worry arose, and how it was tested**

1. First, in the 1960s and 1970s, there were five studies that assessed longer-term outcomes in schizophrenia patients, and each one produced a surprising result.

#### a) NIMH's Study of One-Year Outcomes

This NIMH study looked at one-year outcomes for 299 patients who had been treated either with neuroleptics or placebo upon their admission to a hospital. This was the first long-term study conducted by the NIMH, and the researchers found that patients who received placebo “were less likely to be rehospitalized than those who received any of the three active phenothiazines.”

Schooler, N. “One Year After Discharge.” *American Journal of Psychiatry* 123 (1967): 986-995.

#### b) Bockoven's retrospective study.

In this study, Boston psychiatrists Sanbourne Bockoven and Harry Solomon compared relapse rates in the pre-drug era to those in the drug era, and found that patients in the pre-drug era had done better. Forty-five percent of the patients treated at Boston Psychopathic Hospital in 1947 had not relapsed in the five years following discharge, and 76% were successfully living in the community at the end of that follow-up period. In contrast, only 31% of patients treated in 1967 with drugs at a Boston community health center remained relapse-free for the next five years, and as a group they were much more “socially dependent”—on welfare, etc.—than those in the 1947 cohort.

Bockoven concluded: “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.”

Bockoven, J. “Comparison of Two Five-Year Follow-up Studies.” *American Journal of Psychiatry* 132 (1975): 796-801.

#### c) Maurice Rappaport's Three-Year Study

In this 1978 study, Maurice Rappaport and his colleagues at the University of California, San Francisco randomized 80 young male schizophrenics admitted to

Agnews State Hospital to drug and non-drug groups. Only 27% of the drug-free patients relapsed in the three years following discharge, compared to 62% of the medicated group. Most notably, only two of 24 patients (8 percent) who weren't medicated in the hospital and continued to forgo such treatment after discharge subsequently relapsed. At the end of the study, this group of 24 drug-free patients was functioning at a dramatically higher level than drug-treated patients.

Rappaport wrote: "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."

Rappaport, M. "Are There Schizophrenics for Whom Drugs May be Unnecessary or Contraindicated?" *International Pharmacopsychiatry* 13 (1978):100-111.

#### d) Loren Mosher's Soteria Project

During the 1970s, the head of schizophrenia studies at the NIMH, Loren Mosher, conducted an experiment that compared treatment in a homelike environment (called Soteria), where antipsychotics were minimally used, to conventional treatment in a hospital setting. At the end of two years, the Soteria patients had "lower psychopathology scores, fewer (hospital) readmissions, and better global adjustment" than those treated conventionally with antipsychotics. Only 31% of the patients treated without drugs in the Soteria House who remained off neuroleptics after leaving the program relapsed over the next two years.

Mosher and Bola wrote: "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 that the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined."

Mathews, S. "A Non-Neuroleptic Treatment for Schizophrenia." *Schizophrenia Bulletin* 5 (1979), 322-332.

Mosher, L. "Community Residential Treatment for Schizophrenia." *Hospital and Community Psychiatry* 29 (1978), 715-723

Mosher, L. "The Treatment of Acute Psychosis Without Neuroleptics." *International*

*Journal of Social Psychiatry* 41 (1995), 157-173.

Bola, J. "Treatment of Acute Psychosis Without Neuroleptics." *The Journal of Nervous and Mental Disease* 191 (2003):219-229.

e) NIMH's In-House Study, led by William Carpenter

In this 1977 NIMH study, outcomes for 49 schizophrenia patients, treated in an experimental hospital program that provided them with psychosocial support but didn't use antipsychotics were compared to outcomes for a cohort of patients treated conventionally with antipsychotics. Only 35% of the non-medicated patients relapsed within a year after discharge, compared to 45% of those treated with medication. The medicated patients also suffered more from depression, blunted emotions, and retarded movements.

Carpenter, W. "The Treatment of Acute Schizophrenia Without Drugs." *American Journal of Psychiatry* 134 (1977): 14-20.

2. In the late 1970s, the surprising outcomes from the studies cited above led researchers at the top of the NIMH (beyond Loren Mosher) to question the long-term use of antipsychotics, and to worry that antipsychotics were inducing a biological change that increased the patient's vulnerability to psychosis over the long run.

a) Jonathan Cole

In 1977, Jonathan Cole, the former head of the NIMH Psychopharmacology Service Center, concluded that given the myriad of problems caused by antipsychotics, "every chronic schizophrenic outpatient maintained on an antipsychotic medication should have the benefit of an adequate trial without drugs." He titled his article, "Is the Cure Worse than the Disease?"

Cole, J. "Maintenance Antipsychotic Therapy." *American Journal of Psychiatry* 132 (1977): 32-6.

b) William Carpenter

William Carpenter raised this profound 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.”

Carpenter, W. “The Treatment of Acute Schizophrenia Without Drugs.” *American Journal of Psychiatry* 134 (1977): 14-20.

3. With this question now having been raised, two researchers at McGill University, Guy Chouinard and Barry Jones, presented a biological explanation for why antipsychotics would make patients more biologically vulnerable to psychosis. They dubbed it “drug-induced” supersensitivity psychosis.”

a) They set forth their hypothesis:

In several articles, they noted that because the drugs dampen dopamine activity, the brain tries to compensate by becoming “supersensitive” to dopamine. In particular, the drugs trigger an increase in the density of dopamine receptors. This perturbation in dopamine function, over the long term, makes the patients more biologically prone to psychosis and to worse relapses upon drug withdrawal, they argued.

Chouinard and Jones concluded: “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.”

Muller, P. “Dopaminergic Supersensitivity After Neuroleptics.” *Psychopharmacology* 60 (1978):1-11.

Chouinard, G. “Neuroleptic-Induced Supersensitivity Psychosis” *American Journal of Psychiatry* 135 (1978):1409-1410.

Chouinard, G. “Neuroleptic-Induced Supersensitivity Psychosis:” *American Journal of Psychiatry* 137 (1980):16-20.

b) Chouinard and Jones then tested their hypothesis.

They reasoned that just as some patients treated long-term with antipsychotics develop tardive dyskinesia, which is a sign of dysfunction in the basal ganglia, some patients develop a tardive psychosis, as a result of drug-induced dysfunction in the limbic system. In 1982, Chouinard and Jones reported that 30% of 216 schizophrenia outpatients showed signs of tardive psychosis, which meant that their psychosis was

becoming chronic. When this sets in, “the illness appears worse” than ever before, they wrote. “New schizophrenic symptoms of greater severity will appear.”

Chouinard, G. “Neuroleptic-induced supersensitivity psychosis, the “hump course,” and tardive dyskinesia.” *Journal of Clinical Psychopharmacology* 2 (1982):143-4.

Chouinard, C. “Severe cases of neuroleptic-induced supersensitivity psychosis,” *Schiz Res* 5 (1991):21-33.

#### 4. Philip Seeman’s animal models of psychosis

After Chouinard and Jones presented their hypothesis and tested it, psychiatry, by and large, didn’t pursue further investigations. However, Philip Seeman at the University of Toronto subsequently developed animal models of psychosis, and he has now reported three important findings:

In his model of psychosis, the various means he uses to trigger psychosis—illicit drugs, gene knockouts, lesions to the hippocampus—all ultimately cause an increase in D2 receptors that have a “high affinity” for dopamine. He wrote: 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.

However, Seeman also reported that both haloperidol and olanzapine cause this same change, i.e., they dramatically increase the density of D2 receptors with a “HIGH” affinity for dopamine.

Finally, he then conducted a study, in rats, to determine whether this drug-induced change led to “treatment failure” over time. Although the antipsychotics initially blocked the “psychotic” behavior in rats, over time—as this drug-induced D2 HIGH sensitivity developed—the drugs lost their efficacy.

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Seeman wrote: “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.”

Seeman, P. “Dopamine supersensitivity correlates with D2 HIGH states, implying many paths to psychosis. *Proceedings of the Nat Acad of Science* 102 (2005): 3513-18.

Samaha, A. “Breakthrough dopamine supersensitivity during ongoing antipsychotic

treatment leads to treatment failure over time.” *J Neuroscience* 27 (2007):2979-86.

#### **IV. MRI Studies of Brain Volumes**

##### 1. Background data

In the 1990s, several researchers reported that standard antipsychotics shrunk the frontal lobes, and there was also a report by Rachel Gur that the drugs caused an enlargement of the basal ganglia, and that this enlargement was associated with a worsening of the negative and positive symptoms of schizophrenia.

##### 2. Study in monkeys

In a study with macaque monkeys, researchers reported that, 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.”

Dorph-Petersen. “The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation.” *Neuropsychopharmacology* (2005) 30: 1649-1661.

##### 3. Nancy Andreasen’s MRI Study

In 1989, Nancy Andreasen, who was editor in chief of the *American Journal of Psychiatry*, began a long-term study of more than 500 schizophrenia patients. Here is a summary of her findings:

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, she 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.

In 2008, she said: “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.”

Ho, B. “Progressive structural brain abnormalities and their relationship to clinical outcome.” *Arch Gen Psych* 60 (2003):585-94.

Andreasen, N. “Longitudinal changes in neurocognition during the first decade of schizophrenia illness.” *International Congress on Schizophrenia Research* (2005):348.

Ho, B. “Long-term antipsychotic treatment and brain volumes.” *Arch Gen Psychiatry* 68 (2011):128-37.

## **V. Cross-Cultural Studies**

### **1. The World Health Organization studies.**

The first World Health Organization study that compared schizophrenia outcomes in "developed" and "developing" countries was called The International Pilot Study of Schizophrenia. It began in 1968, and involved 1202 patients in nine countries. At both two-year and five-year follow-ups, the patients in the poor countries were doing much better. The researchers concluded that schizophrenia patients in the poor countries "had a considerably better course and outcome than (patients) in developed countries. This remained true whether clinical outcomes, social outcomes, or a combination of the two was considered." Two-thirds of the patients in India and Nigeria were asymptomatic at the end of five years. The WHO investigators, however, were unable to identify a variable that explained this notable difference in outcomes. See pages 132, 142, 143.

Leff, J. “The International Pilot Study of Schizophrenia.” *Psychological Medicine* 22 (1992):131-145.

The second WHO study of this type was called the Determinants of Outcome of Severe Mental Disorders. It involved 1379 patients from 10 countries, and was designed as a follow-up study to the International Pilot Study of Schizophrenia. The patients in this study were first-episode patients, and 86% had been ill fewer than 12 months. This study confirmed the findings of the first: two-year outcomes were much better for the patients in the poor countries. In broad terms, 37 percent of the patients in the poor countries (India, Nigeria and Colombia) had a single psychotic episode and then fully recovered; another 26.7% of the patients in the poor countries had two or more psychotic episodes but still were in "complete remission" at the end of the two years. In other words, 63.7% of the patients in the poor countries were doing fairly well at the



end of two years. In contrast, only 36.9% of the patients in the U.S. and six other developed countries were doing fairly well at the end of two years. The researchers concluded that "being in a developed country was a strong predictor of not attaining a complete remission."

Although the WHO researchers didn't identify a variable that would explain this difference in outcomes, they did note that in the developing countries, only 15.9% of patients were continuously maintained on neuroleptics, compared to 61% of patients in the U.S. and other developed countries.

Jablensky, A. "Schizophrenia: Manifestations, Incidence and Course in Different Cultures." *Psychological Medicine, supplement 20* (1992):1-95.

## 2. The 15-year to 20-year followup of the patients in the WHO studies

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.

Hopper, K. "Revisiting the developed versus developing country distinction in course and outcome in schizophrenia." *Schizophrenia Bulletin* 26 (2000):835-46.

## 3. Eli Lilly's Global Study of Schizophrenia Outcomes

This is an Eli Lilly funded study of 11,078 schizophrenia patients in 37 countries. All patients were treated with olanzapine or another antipsychotic. In this study, functional outcomes of patients in non-European countries were as poor as in European countries (or even worse), with only around 25% enjoying functional remission. (The superiority in functional outcomes found by the WHO in developing countries has disappeared in this study where all patients are medicated.)

Haro, "Cross-national clinical and functional remission rates." *Brit J of Psychiatry* 2011, 1999: 194-201.

## **VI. Martin Harrow's Longitudinal Study**

In this prospective study, Martin Harrow followed 64 schizophrenia patients and 81 diagnosed with a milder psychotic disorder for 15 years. A close examination of his data reveals the following results:

- At the end of 15 years, 40% of the schizophrenia patients off medication were in recovery, versus 5% of those on medication.
- At the end of 15 years, only 16% of schizophrenia patients off medication had a “uniformly poor” outcome, compared to 49% of those on medication.
- At the 10-year and 15-year follow-ups, the on-medication patients were two to three times more likely to still be experience psychotic symptoms
- The bad-prognosis schizophrenia patients off medication did better than the bad-prognosis patients on medication
- The good-prognosis schizophrenia patients off medication did better than the good-prognosis patients on medication
- Among those with milder psychotic disorders, the off-medication group did better
- The schizophrenia patients off medication did better over the long-term than the milder-disorders group that stayed on antipsychotic medications.

Harrow M. “Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications.” *Journal of Nervous and Mental Disease* 195 (2007):406-14.

## **VII. Outcomes in Western Lapland**

In Western Lapland, a region in northern Finland, psychiatrists developed a treatment called open-dialogue therapy that involves treating first-episode psychotic patients with a selective medication protocol. Initial use of antipsychotics is delayed to see if the patient can get better without going on the medications. If antipsychotic medication is subsequently seen as needed, patients may still be kept on the medication for only a shorter period of time. Western Lapland has been using this medication protocol since 1992, and has reported five-year outcomes for several cohorts of patients.

In this particular study of first-episode nonaffective psychotic patients, at the end of five years, 82% of the patients did not have psychotic symptoms, 86% had returned to their studies or were working, and only 14% were on a disability allowance. Only 29% of the patients had ever been exposed to an antipsychotic drug during the five years, and only 17% were on antipsychotics at the end of the study.

Seikkula, J. “Five-Year Experience of First-Episode Nonaffective Psychosis in Open-Dialogue Approach.” *Psychotherapy Research* 16 (2006):214-228.