THE CASE AGAINST ANTIPSYCHOTICS

A REVIEW OF THEIR LONG-TERM EFFECTS

ROBERT WHITAKER

JULY 2016

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BACKGROUND

In *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs and the Astonishing Rise of Mental Illness in America,* I sought to flesh out the "evidence base" for the long-term use of the main classes of psychiatric medications: antipsychotics, antidepressants, benzodiazepines, and stimulants. An updated edition of that book was published in 2015.

This publication by Mad in America Foundation is designed to present a succinct review of what science has to say about the long-term effects of antipsychotics. Do they reduce psychotic symptoms over the long term? Do they improve functional outcomes? Our hope is that this review can help inform a societal discussion about these drugs and whether their use needs to be rethought.

A slide presentation of much of the information in this publication can be found here.

A video presentation can be seen in two parts: part 1, and part 2

OVERVIEW

It is important for readers to see that this review proceeds in a logical, systematic fashion. This paper is organized into four parts.

1. A presentation of the evidence cited by psychiatry, as an institution, for long-term use of antipsychotics.
2. A critique of that evidence base.
3. A review of research on the long-term effects of antipsychotics. This research is divided into two time periods: 1945 to the early 1980s, and from the early 1980s to today.
4. A response to critics of the argument made in this paper.

This paper, as it reviews the evidence, doesn't challenge psychiatry's "medical model" conception of schizophrenia as a "disease." That conception has shaped psychiatry's research on antipsychotics for 60 years, and given that schizophrenia and other psychotic disorders are seen in this light, the first measure of a drug's effectiveness is whether it can lessen the symptoms of that disease, e.g., lessen the psychotic symptoms. This review could be said to be asking this question: if schizophrenia is conceptualized as a disease, what does research show about how the drugs alter the long-term course of that illness?

The citations are published as endnotes. In addition, we have put up a web page with links to the abstracts of the articles, or with links to the PDFs of the published articles.

Psychiatry's "Evidence Base" for Long-term Use of Antipsychotics

Chlorpromazine, the drug that is remembered today as the first "antipsychotic," was introduced into asylum medicine in 1955. Other antipsychotics were soon introduced, and once psychiatrists began prescribing these drugs, they needed to answer this question: How long should they maintain their patients on the medications?

This led researchers to conduct "relapse studies." One group of patients would be withdrawn from the antipsychotic and the other group maintained on the drug. With great regularity, the withdrawn group relapsed at a higher rate. This was seen as evidence that the medications reduced the risk that the "disease" would return and thus provided a long-term benefit.

In a 2012 paper for the Cochrane Collaboration, Leucht provided a review of this research. He identified 65 relapse studies that had been conducted from 1959 to 2011.[1] The median age of the 6,493 patients in the 65 studies was 40.8 years; their mean duration of illness was 13.6 years. More than half of the studies were in hospitalized patients, and in 54 of the 65 studies, the antipsychotic medication was abruptly withdrawn.

At the end of three months, the relapse rate was 12% for the drug-maintained group versus 37% for the drug-withdrawn group. At the end of one year, the relapse rate was 27% for the drug-maintained group versus 64% for the drug-withdrawn patients. This meta-analysis, Leucht concluded, "clearly demonstrated the superiority of antipsychotic drugs compared to placebo in preventing relapse."

Beyond the relapse studies, psychiatry, as an institution, has little research to point to as providing evidence that the drugs provide a long-term benefit. In recent years, a handful of academic psychiatrists, in response to Anatomy of an Epidemic, have pointed to a longitudinal study in China as providing some evidence that the drugs improve long-term outcomes. That study will be discussed in Part IV of this paper.

But it is the relapse studies that psychiatry, as an institution, has cited as its "evidence base" for long-term use of antipsychotics.

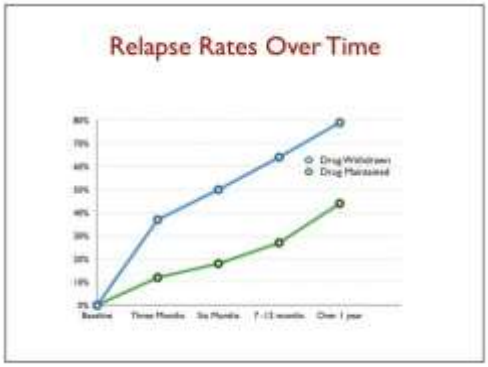
A Critique of Psychiatry's "Evidence Base"

There are many problems that can be identified with the relapse literature. (An in-depth review of Leucht's study, and its limitations, can be found here.) But for the purposes of the larger question being investigated in this paper, which is the effect of antipsychotics on long-term outcomes, the shortcomings of the drug-withdrawal studies can be easily summarized.

1 The high relapse rate for the "placebo" patients in these studies may be, in large part, a drug-withdrawal effect, as opposed to a true "return of the disease." The studies were mostly conducted in older, chronic patients; more than half were in hospitalized patients; and in 80% of the studies, the drug was abruptly withdrawn. This research reveals an excess risk of "relapse"—however that may be defined— for a period of time following drug withdrawal.

Indeed, as can be seen in Leucht's data (below), much of the excess risk occurs within the first three months, when drug-withdrawal effects could be expected to be particularly problematic. After that, the ongoing rate of relapse in the drug-withdrawn group is only slightly greater than for the drug-maintained patients. However, as user stories of withdrawing from antipsychotics will attest, patients may experience withdrawal-type symptoms for many months, which means this confounding factor continues past the three-month mark.

As a result, it can't be known from this research how much of the relapse risk in the drug-withdrawn is due to a withdrawal effect, and how much might rightly be seen as a "return of the disease." This uncertainty makes it impossible to draw conclusions from these studies about the long-term protective effects of antipsychotics against relapse.



2 The relapse studies do not provide any meaningful data on long-term functional outcomes. Are the medicated patients working? Do they have decent social lives? How healthy are they? In the studies conducted in hospitalized patients, only 5% of the drug-maintained patients improved to the point they could be discharged. Data on "quality of life" from this relapse literature was "poor." The data on unemployment was "very poor," and there was no data at all on "satisfaction of care."

3 The relapse studies do not provide any insight into this critical question: How does the spectrum of outcomes seen in medicated patients today compare to the "natural" course of schizophrenia? If patients so diagnosed were never put on the medications, but treated with psychosocial care, what would their long-term outcomes be like? That is the bottom-line regarding the potential efficacy of a medical therapy: does it improve on the natural spectrum of outcomes?

These limitations to the relapse literature are well recognized by many psychiatric researchers. In essence, the relapse studies provide a rationale for clinicians to prescribe antipsychotics on a continual basis, as there can be a high risk of relapse coming off the drugs, but they do not provide evidence on whether that practice improves long-term outcomes for their patients.

In 2002, Emmanuel Stip, a professor of psychiatry at the Université de Montréal, summed up the deficiency in psychiatry's evidence base in this way:

"After fifty years of neuroleptics, are we able to answer the following simple question: Are neuroleptics effective in treating schizophrenia?" There was, he said, "no compelling evidence on the matter, when 'long-term' is considered."[2]

The Case Against Antipsychotics

Stip's editorial can be seen as an invitation to dig further into the scientific literature. If the relapse studies don't provide evidence of the long-term merits of antipsychotics, is there other research that can be found that bears on this question?

And does that research congeal into a coherent narrative?

There is, it turns out, a narrative of science that unfolds in the medical literature, spanning six decades and composed of research of many types, that provides a compelling answer to that question. In a broad sense, this narrative unfolds in three parts.

First, there is the spectrum of outcomes reported for first-episode schizophrenia patients in the decade prior to the introduction of chlorpromazine. This provides a historical foil for assessing whether the new drug led to a notable change in outcomes. Second, there is a line of research, conducted from the late 1950s to the early 1980s, that led

two Canadian researchers to hypothesize that antipsychotics induce biological changes in the brain that worsen psychotic symptoms over time.

Third, there is research since the early 1980s, consisting of cross-cultural studies, MRI studies, animal studies, and longitudinal studies, that provides confirmatory evidence for that hypothesis, and reveals that the medications impair functional outcomes over the long term.

SCHIZOPHRENIA OUTCOMES, 1945-1955

According to the conventional narrative in psychiatry, prior to the discovery of chlorpromazine, people diagnosed with schizophrenia were destined to become chronically ill and confined to a life inside the mental hospital. The natural outcomes for people so diagnosed are dismal, and thus any treatment that improves on this outcome is understood to be helpful.

However, a review of outcomes for first-episode schizophrenia patients from 1945 to 1955 reveals a very different understanding. Specifically:

- At Warren State Hospital in Pennsylvania, 62 percent of first episode psychotic patients admitted between 1946 and 1950 were discharged within 12 months. At the end of three years, 73% were living outside of the hospital.[3]
- At Delaware State Hospital, 85% of first-episode schizophrenia patients admitted from 1948 to 1950 were discharged within five years, and on January 1, 1956—six years or more after initial hospitalization—70 percent were successfully living in the community.[4]
- At Hillside Hospital in Queens, more than half of the 87 schizophrenia patients discharged in 1950 never relapsed during the next four years[5].

There are three conclusions to be drawn from this data. The first is that a majority of patients hospitalized for a first episode of schizophrenia from 1945 to 1955 recovered within 12 months to a point they could be discharged. The second is that more than two-thirds of first-episode patients could be expected to be living in the community five years after initial hospitalization, and this was at a time when there was no disability system to provide financial support to people who are unable to work for one reason or another. The third is that only a third of first-episode patients would become chronically ill and unable to function outside the mental hospital.

Those were the outcomes for hospitalized patients diagnosed with first-episode schizophrenia in the pre-antipsychotic era. This spectrum of outcomes serves as a historical foil for the introduction of antipsychotics. And given the conventional narrative about the drugs' merits, we could expect that the arrival of chlorpromazine and other antipsychotics would lead to an improvement in this spectrum of outcomes, a leap forward that would be captured by the research literature. The percentage of first episode patients who recovered and could live independently in the community, without government assistance, could be expected to increase.

RESEARCH FROM THE 1950S TO 1980S

A paradox appears

In 1961, the National Institute of Mental Health conducted what it deemed the first well-controlled study of antipsychotics. In the trial, which was conducted at nine hospitals, 270 patients were given chlorpromazine or another phenothiazine (the chemical name for first-generation antipsychotics), and 74 were randomized to placebo. At the end of six weeks, the drug-treated patients had a greater reduction of their psychotic symptoms, and, in general, were doing better than the placebo patients. This was evidence of the drugs' short-term efficacy[6].

However, many of the placebo patients also improved during the six weeks. Most of the patients were then discharged and followed for one year. At the end of that time, the investigators were startled to discover that "patients who received placebo treatment [in the hospital] were less likely to be re-hospitalized than those who received any of the three active phenothiazines."[7]

Here, at this very first moment in the outcomes literature for antipsychotics, there is the hint of a paradox: While the drugs appeared to be effective over the short term, perhaps they made people more vulnerable to psychosis over the long term, and thus the higher rehospitalization rates for drug-treated patients at the end of one year.

The clinicians' perspective

When a new therapy is introduced, physicians have their past clinical experience as a measure for assessing its merits. They can observe a change in the course of the "disease" in their patients, and assess whether they are now faring better.

Once antipsychotics were regularly used, many psychiatrists did report that their psychotic patients were now getting better faster than before. But soon, hospital staff and psychiatrists observed that their discharged patients were returning to the hospital in great numbers, a rehospitalization pattern they dubbed the "revolving door syndrome." In addition, at least a few psychiatrists worried that relapses when people were on antipsychotics were "greater in severity than when no drugs are given."8 As the same time, if patients relapsed after quitting the medications, observed Jonathan Cole, director of the Psychopharmacology Service Center at the National Institute of Mental Health (NIMH), their psychotic symptoms tended to "persist and intensify." [9]

All of this produced a sense of uncertainty within psychiatry. In general, psychiatrists during the 1960s and 1970s voiced their belief that the drugs provided a benefit, of some sort, to their patients. However, at the same time, there were a number of clinicians who worried that something might be amiss. In this narrative of science, their concerns simply comprise another data point, which is to say that they represent a yellow flag of caution.

A retrospective study

With such concerns in mind, J. Sanbourne Bockoven and Harry Solomon conducted a retrospective study to assess whether outcomes had improved since the arrival of chlorpromazine. They determined that 45% of the psychotic patients treated in 1947 at Boston Psychopathic Hospital with psychosocial care didn't relapse in the next five years and that 76% were successfully living in the community at the end of that period. In contrast, only 31% of the patients treated at the hospital in 1967 with psychosocial care and antipsychotics remained relapse-free for five years, and as a group they were much more "socially dependent"—on welfare and needing other forms of support.

Bockoven and Solomon had looked back at the past for understanding, and concluded that outcomes for schizophrenia patients treated with medications were worse than they had been in the pre-drug era. "Rather unexpectedly, these data suggest that psychotropic drugs may not be indispensable," they wrote. "Their extended use in aftercare may prolong the social dependency of many discharged patients."[10]

Experimental studies in the 1970s

During the 1970s, with questions about the merits of antipsychotics hanging in the air, the NIMH funded three studies designed to assess their longer-term merits.

a) Agnews State Hospital study

In one study, Maurice Rappaport, at the University of California in San Francisco, randomized 80 young males newly diagnosed with schizophrenia at Agnews State Hospital into drug and non-drug groups. Although symptoms abated more quickly in those treated with antipsychotics, both groups, on average, stayed only six weeks in the

hospital. Rappaport then followed the patients for three years, during which time they could choose whether to take an antipsychotic. As such, he ended up with four groups at the end of three years:

a) those treated without antipsychotics in the hospital who stayed off the drugs during the follow-up.

b) those treated without antipsychotics in the hospital who then used drugs in the follow-up.

c) those treated with antipsychotics in the hospital who got off the drugs in the follow-up.

d) those treated with antipsychotics in the hospital who stayed on the drugs during the follow-up.

At the end of three years, it was the first group—the never-exposedto-antipsychotics group—that had by far the best outcomes. Only two of the 24 patients in this group relapsed during the 3-year follow-up (8%.) In contrast, the patients that arguably fared the worst were the last group—those on antipsychotics throughout the study. Seventy-three percent of this group had been re-hospitalized.

Rappaport's Study: Three-Year Outcomes

Medication use (in hospital/after discharge)	Number of Patients	Severity of Illness	Rehospitalization
No meds/off	24	1.7	8%
Antipsychotic/off	17	2.79	47%
No meds/on	17	3.54	53%
Antipsychotic/on	22	3.51	73%

Source: Rappaport, M. "Are there schizophrenics for whom drugs may be unnecessary or contraindicated?" Int Pharmacopsychiatry 13 (1978):100-11.

Given this data, Rappaport and colleagues drew the obvious 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," they wrote. "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."[11]

As can be seen, a majority of patients randomized to the no-drug arm in the hospital were able to recover and did well over the long term (24 of 41 treated without medication in the hospital). That outcome also echoed findings from the pre-drug era, when roughly two-thirds of first-episode schizophrenia patients would be living in the community five years after their initial hospitalization.

b) The Soteria project

The Soteria experiment was led by Loren Mosher, head of schizophrenia studies at the NIMH. Patients diagnosed with schizophrenia, or a variant of it, were either treated conventionally with antipsychotics in a hospital setting or sent to a Victorian house, known as Soteria, which was staffed by ordinary people. At Soteria, patients were not immediately treated with antipsychotics (although, if necessary, they would be given benzodiazepines to help them sleep.) The patients would be put on an antipsychotic only if, after a few weeks of living at the Soteria house, they had failed to improve.

Eventually, Mosher opened two such houses, with a total of 82 patients treated during the 10-year experiment. By the end of six weeks, psychotic symptoms had abated as much in the Soteria patients as in the hospitalized patients. At the end of two years, the Soteria patients had "lower psychopathology scores, fewer [hospital] readmissions, and better global adjustment."[12] In terms of their antipsychotic use during the two years, 42% of the Soteria patients had never been exposed to the medications, 39% had used them on a temporary basis, and 19% had used them on a constant basis.

Mosher and Bola concluded: "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."[13]

c) The NIMH's psychotherapy study

The third study, which was led by William Carpenter at the NIMH's clinical research facility in Bethesda, Maryland, compared one-year outcomes for 27 schizophrenia patients treated with psychotherapy and no antipsychotics to 22 treated with psychotherapy and antipsychotics. Those treated without drugs were discharged sooner, had a slightly lower relapse rate at the end of one year (35% to 45%), and also suffered less from depression, blunted emotions, and retarded movements. Given the better outcomes for the unmedicated group, Carpenter speculated that perhaps the medicated patients, because of the sedating effects of the drugs, were less able to "learn" from their psychotic experiences, and thus, over the long term, were "less able to cope with subsequent life stresses."[14]

In sum, three longer term studies funded by the NIMH in the 1970s produced the same result: Outcomes were better in the experimental arms where antipsychotics were much less used, or not used at all. The outcomes for the unmedicated patients were also mindful of longterm outcomes in the 1945 to 1955 era, when two-thirds lived in the community, without government support.

A question is posed

The findings from these studies presented psychiatry with an outcomes puzzle.

Specifically:

- In six-week studies, the drugs had been found to be effective in knocking down psychotic symptoms better than placebo.
- In drug withdrawal studies, the patients withdrawn from the drugs relapsed at higher rates.
- Yet, over the long term, the drugs appeared to increase the chronicity of psychotic symptoms (relapse rates), and worsen functional outcomes.

In his 1977 paper on the psychotherapy experiment, Carpenter summed up the conundrum:

"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 natural course of the illness."

This question presented psychiatry with a moment of truth. If antipsychotics made patients more vulnerable to relapse, then what benefit—over the long-term—did they provide? This was the very symptom the drugs were supposed to treat. If they didn't provide this benefit, then there would only be harms to be chalked up, and it was well known that antipsychotics caused a diverse range of problematic adverse effects.

A paradox explained

In the late 1970s, two physicians at McGill University, Guy Chouinard and Barry Jones, put forth a biological explanation for why antipsychotics might make people more biologically vulnerable to psychosis. The drugs, it turned out, were inducing the very biological abnormality hypothesized to cause schizophrenia in the first place. Research into the dopamine hypothesis of schizophrenia had come to a startling conclusion.

In the 1960s, researchers discovered that chlorpromazine and other antipsychotics blocked dopamine receptors in the brain. In particular, at a therapeutic dose, they blocked 70% to 90% of D2 receptors (a subtype of dopamine receptor)[15], [16] This blockade thwarted the activity of dopamine pathways in the brain, which made patients lethargic and often gave them Parkinsonian symptoms. It was also thought to be the mechanism that reduced psychotic symptoms.

Once researchers made this discovery, they hypothesized that perhaps schizophrenia and other psychotic disorders were due to too much dopamine activity in the brain, and thus the drugs—by blocking such activity—were helping to normalize it. They noted that amphetamines, which increase dopamine activity, could induce psychosis, and this was seen as additional evidence supporting the hypothesis.

Having developed this theory, researchers then needed to assess whether it was true. Did people diagnosed with schizophrenia have overactive dopamine systems? There were two ways that might be so.

The transmission of neuronal messages in the brain occurs in this way: A presynaptic neuron releases a "chemical messenger"—such as dopamine, serotonin, or a number of other neurotransmitters—into the tiny gap between neurons, known as the synaptic cleft. The neurotransmitter binds with receptors on the receiving neuron, which is

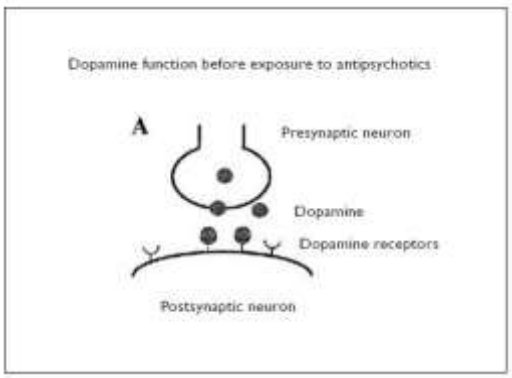
known as the postsynaptic neuron. In the case of dopamine, this causes the second neuron to fire. The chemical messenger must then be removed from the synaptic cleft, and this is done in two ways: either it is taken back up into the presynaptic neuron and stored for reuse, or an enzyme metabolizes it and the metabolites are carted off as waste (with these metabolites showing up in the cerebrospinal fluid.)

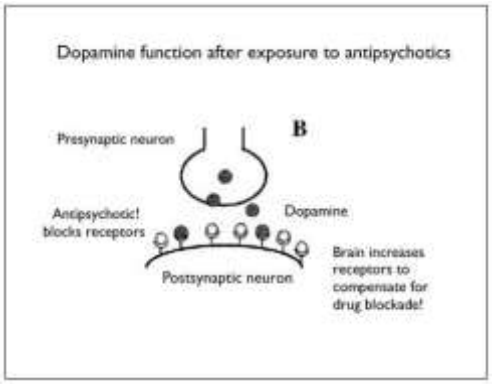
Once researchers raised the dopamine hyperactivity theory of schizophrenia, their first thought was that perhaps the presynaptic neurons were releasing too much dopamine into the synaptic cleft. To investigate this possibility, they measured the levels of dopamine metabolites in the cerebrospinal fluid of schizophrenia patients, and discovered that, prior to being medicated, their levels were normal. However, after being put on an antipsychotic, their dopamine metabolites increased to abnormal levels, for at least a short period of time. [17, 18, 19]

This finding led researchers to put together a new understanding of how the brain responded to the drug's blockade of dopamine receptors. The drug acted as a brake on dopamine transmission, and in compensatory response, the brain's presynaptic neurons, trying to maintain the normal functioning of their dopaminergic pathways, increased their output of dopamine. This compensatory response seemed to last four weeks or so, and then it appeared to decline.

At that point, researchers turned their attention to measuring the density of dopamine receptors on postsynaptic neurons in schizophrenia patients. Perhaps this was the pathology—an abnormally high number of dopamine receptors—that led to psychosis. They found that, at autopsy, schizophrenia patients indeed had an abnormally high number of such receptors. This would lead to a hyperactive dopamine system.20 But, once again, the same question arose: Was this abnormality due to the disease, or a compensatory reaction to the drug? Researchers subsequently determined that it was a compensatory reaction to the medications. [21, 22, 23, 24, 25, 26, 27] The drug, they said, caused an "upregulation" of the receptors.

The graphics below illustrate this process:





This understanding of the effects of antipsychotics on the brain began to come clear by the end of the 1970s, and the conclusion to be drawn was this: the drugs caused the very abnormalities—an increase in the release of dopamine and an increase in the density of D2 receptors—that had been hypothesized to cause psychotic symptoms in the first place. The first compensatory response appeared to burn out after a while, but researchers came to understand that the second one—the increase in dopamine receptors—persisted.

In a series of articles in the late 1970s and 1980s, Chouinard and Jones argued that this drug-induced dopamine super-sensitivity would have these three effects:[28, 29]

- When patients tried to go off the medications, they would be at increased risk of relapse.
- Over time, this biological change could increase the frequency of psychotic symptoms, at least in some patients. These patients could be said to have developed a "tardive psychosis."
- When tardive psychosis developed, this led to an increase in the severity of psychotic symptoms.

Having presented this hypothesis, Chouinard and Jones conducted a study of 216 patients, who on average had been taking antipsychotics for ten years. They found that 30% had developed tardive psychosis.[30] When this sets in, they wrote, "the illness appears worse" than ever before. "New schizophrenic or original symptoms of greater severity will appear."[31]

Summary of the research from 1950s to 1980s

As can be seen in this brief review, studies of antipsychotics during this period ultimately led to this unsettling conclusion: the drugs were increasing the chronicity of psychotic symptoms, and impairing functional outcomes. That would explain the increased rate of rehospitalization at the end of one year in the NIMH's nine-hospital study; it would explain why clinicians were soon telling of a "revolving door syndrome;" it would explain the outcomes in Bockoven's retrospective study; and it would explain the outcomes in the three experimental studies conducted in the 1970s. Those results all seemed paradoxical until research into the biological effects of the drugs revealed that they induced a dopamine supersensitivity, which could make patients more biologically vulnerable to psychosis.

This understanding also revealed that the relapse studies were measuring the risk of relapse in patients whose brains had been changed by the drugs, and in ways that made them more prone to psychotic symptoms. This understanding revealed how that line of research was leading psychiatry astray.

RESEARCH FROM THE 1980S TO TODAY

In many ways, the first thirty years of research produced a record of good science. The various studies produced unexpected results, which were uncomfortable for psychiatry to consider, and eventually researchers put together a biological explanation for the poor results. Researchers had followed a trail of science to a surprising end.

However, this was an explanation that imperiled psychiatry's own narrative, which was that antipsychotics had ushered in a psychopharmacological revolution, a great advance in care. Science and institutional needs were in conflict, and the latter won out. Rather than curtail its use of antipsychotics, the field pushed aside this worry about drug-induced dopamine super-sensitivity, and instead focused on the relapse studies as the evidence it would heed. That was the research that showed its drugs worked.

This leads to a new question today. As we review the research literature from the 1980s forward, does it provide confirmatory evidence of the dopamine super-sensitivity hypothesis advanced by Chouinard and Jones? Or to put it another way, does research since the 1980s provide evidence that antipsychotics increase psychotic symptoms and impair functioning over the long term, or, conversely, does research show they provide a benefit in these realms?

There is research of many types that, collectively, provide an answer to that question.

Cross-cultural studies

In 1969, the World Health Organization launched a study that compared schizophrenia outcomes in three developing countries, India, Nigeria, and Colombia, to outcomes in the United States and five other developed countries. At the end of five years, the outcomes were much better for patients in the developing countries.[32]

This result stunned the WHO investigators, who struggled to explain the reason for this disparity in outcomes. The WHO launched a second study, two years in length, and this time they decided to measure usage of antipsychotics. The researchers hypothesized that perhaps patients in the developing countries were more medication compliant, and this was a reason for their better outcomes.

The results in the second study were much the same. At the end of two years, nearly two-thirds of the patients in the developing countries had good outcomes, and slightly more than one-third had become chronically ill. In the rich countries, only 37 percent of the patients had good outcomes, and 59 percent had become chronically ill. "The findings of a better outcome of patients in developing countries was confirmed," the WHO scientists wrote. "Being in a developed country was a strong predictor of not attaining a complete remission." [33]

However, the medication hypothesis did not pan out. In the developing countries, the researchers reported, only 16% of the patients regularly took antipsychotics, versus 61% of the patients in the developed nations. The outcomes were the best in India and Nigeria, where usage of medication was the lowest, and the worst in Moscow, which had the highest medication use and highest percentage of patients who became chronically ill.[34]

In 1997, the WHO investigators interviewed the patients in the two studies once more. After fifteen years, 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.[35]

The researchers didn't report on medication use in this follow-up study. But the connection was clear: In the countries where few people had been regularly maintained on antipsychotics (16%), long-term outcomes were much better than in the countries where continual medication use was the standard of care.

That is a result consistent with the finding that, over the long-term, the medications increase the chronicity of psychotic disorders and impair functioning.

MRI studies

The advent of MRI technology in the 1990s enabled researchers to study brain volume changes in patients diagnosed with schizophrenia and other psychotic disorders, with such changes measured over time. By the late 1990s, investigators had reported that antipsychotics caused basal ganglion structures and the thalamus to swell, and the frontal lobes to shrink, with these changes in brain volumes "dose related." [36, 37, 38] Then, in 1998, Raquel Gur, from the University of Pennsylvania, reported that the swelling of the basal ganglia and thalamus was "associated with greater severity of both negative and positive symptoms." [39]

This was disconcerting news: the brain volume changes induced by antipsychotics were associated with a worsening of the very symptoms the drugs were supposed to treat.

Soon Nancy Andreasen, who was then editor-in-chief of the American Journal of Psychiatry, weighed in with her findings from a study of 500 schizophrenia patients. In 2003, she reported that their frontal lobes shrank over time, and that this shrinkage was associated with a worsening of negative symptoms and functional impairment, and after five years, with a worsening of cognitive abilities.[40]

While Andreasen initially attributed this shrinkage of the frontal lobes to a disease process, in 2011 she announced that long-term use of the old standard antipsychotics, the new atypicals, and clozapine were all "associated with smaller brain tissue volumes." She found that this brain shrinkage was dose related; the more drug a person was given, the greater the association "with smaller grey matter volumes." A loss in white matter volume was also "most evident among patients who received more antipsychotic treatment." Illness severity and substance abuse had "minimal or no effects" on brain volumes, she concluded.[41]

Numerous studies have now reported that antipsychotic induce changes in brain volumes, which, German investigators concluded in 2014, "exert adverse effects on neurocognition, negative and positive symptoms and psychosocial functioning."[42]

The MRI studies tell of a clear iatrogenic process. Antipsychotics cause changes in brain volumes that are associated with a worsening of negative and positive symptoms, and a worsening of functional impairment.

Animal models of psychosis

As part of their investigations of schizophrenia, researchers have studied in rats and other animals the brain changes induced by various drugs—amphetamines, angel dust, etc.—that can trigger delusions and hallucinations in humans. Philip Seeman, at the University of Toronto, also developed other methods—such as lesions to the hippocampus and "knocking out" certain genes—for inducing psychotic-like behaviors in rats. In 2005, Seeman reported that while the initial insult in these animal models of psychosis had been wildly different, they all ultimately triggered an increase in D2 receptors that had a "HIGH affinity" for dopamine.[43]

This animal model provided a new understanding of the possible "biology" of psychosis. Although researchers had not found that schizophrenia patients suffered from overactive dopamine systems, as a matter of course, Seeman's research suggested that there was a transient change in the activity of D2 receptors during times of acute psychotic episodes. They jumped into a "HIGH" state. Seeman reasoned that this is why antipsychotics initially work: They block D2 receptors, and thus they block this transient HIGH activity in the dopamine system.

However, in his research, Seeman also found that if he gave antipsychotics—including the newer atypical antipsychotics—to rats, this eventually doubled the density of their "HIGH affinity" D2 receptors. Over the long term, the drugs caused the very biological abnormality that he had identified as the common final pathway to psychosis in his animal models. This, he concluded, was why "antipsychotics so often fail" over the long-term.

To further test this thought, Seeman administered amphetamines to rats, which increased their locomotion (a symptom in his animal model of psychosis), and then gave the rats either haloperidol or olanzapine. At first, the antipsychotic blocked the rats' increased movement. The drug worked. But fairly quickly, the rats' hyperlocomotion returned, evidence that the antipsychotic had lost its "efficacy."

Moreover, the loss of efficacy was linked to the antipsychotic-induced "increase in D2 receptor number and sensitivity," Seeman reported.

Thirty years after Chouinard and Jones had set forth their "dopamine supersensitivity" theory, Seeman—through his animal research—had come to the same conclusion. His findings, he wrote in 2007, demonstrated "that continued antipsychotic treatment and D2 receptor blockade induces neuroadaptations that lead to antipsychotic failure." [44]

Harrow's longitudinal study

In the late 1970s, Martin Harrow, a psychologist at the University of Illinois College of Medicine, together with psychiatrist Thomas Jobe, enrolled 200 psychotic patients into what became the best long-term, prospective study of schizophrenia and other psychotic disorders ever conducted in the United States. The median age of the patients was 22 years and nine months; 67% were experiencing either a first or second hospitalization. Harrow and Jobe mostly followed a young cohort of patients early in the course of their illness.

The 200 patients were recruited from two Chicago hospitals. One was private and the other public, as this ensured that the group would be economically diverse. All were treated conventionally with antipsychotics in the hospital and discharged. Then, over the next 20 years, Harrow and Jobe periodically assessed how well they were doing. Were

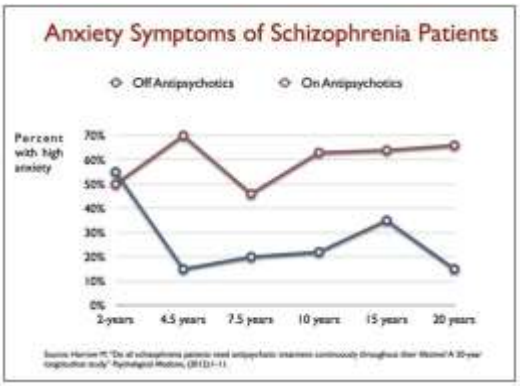
they symptomatic? In recovery? Employed? At every follow-up - at 2 years, 4.5 years, 10 years, 15 years, and 20 years—they also assessed the patients' use of antipsychotic medications.

At the end of 15 years, Harrow and Jobe still had 145 of the original cohort of 200 patients in their study, which is an extremely high retention rate. Sixty-four were diagnosed with schizophrenia, and the remaining 81 had milder psychotic disorders. Among those diagnosed with schizophrenia, 24 had stopped taking antipsychotics by year two, and at least 15 of this group remained off the drugs throughout the follow-ups. Nearly half of those with milder psychotic disorders stopped taking antipsychotic medications during the study.[45]

Here are the outcomes for the schizophrenia patients, with Harrow reporting results at both 15 and 20 years:

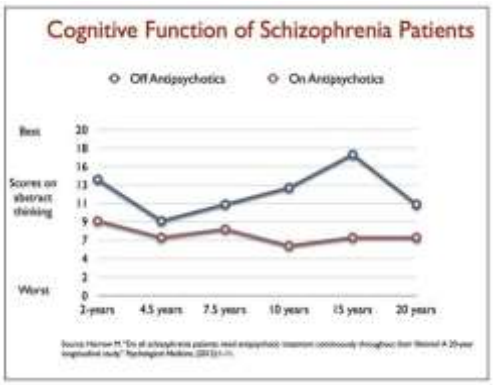
a) Anxiety symptoms

At the two-year mark, anxiety symptoms for the medicated and unmedicated patients were the same. But then, over the next 2.5 years, anxiety symptoms noticeably abated in the unmedicated group, and worsened in the medicated patients. This difference in anxiety levels remained throughout the study. [46]



b) Cognitive function

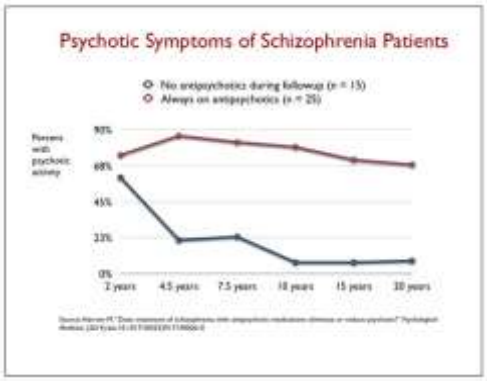
Throughout the twenty years, those off medication had better cognitive function. [47]



c) Psychotic symptoms

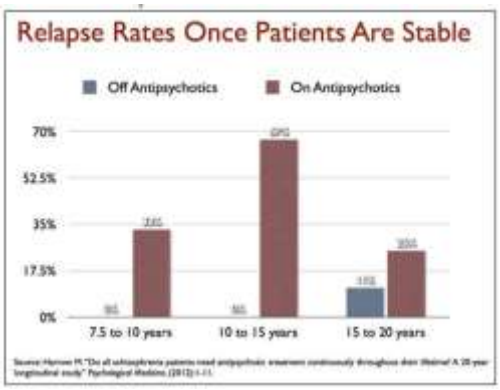
The patients on medication were much more likely to be psychotic at the 10-year and 15-year follow-ups.[48]

Harrow also reported on the prevalence of psychotic symptoms in those patients who quit taking antipsychotics by year two and stayed off the drugs throughout the study compared to those who were "medication compliant" throughout the 20 years. At the end of year two, there was little difference between the two groups; at least 60% were actively psychotic. However, during the next 30 months, psychotic symptoms dramatically decreased in the off-med group, while they increased in the medicated group. Eighty-six percent of the medication-compliant patients were psychotic at the 4.5-year follow-up, compared to 21% of those who had stayed off antipsychotics. This dramatic difference remained throughout the study.[49]



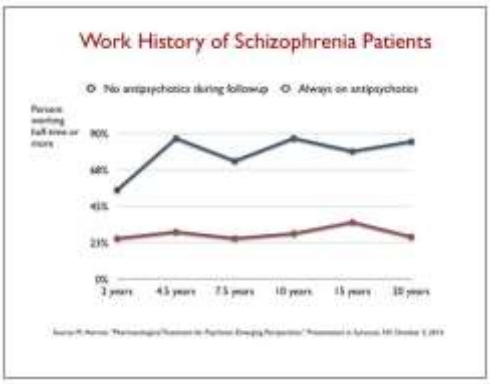
d) Relapse rates

In a similar vein, Harrow found that once patients were stable off medication, they were likely to remain stable for extended periods (or throughout the study), whereas even those patients who were stable on medication at a follow-up had fairly high subsequent relapse rates. None of the off-med patients who were stable at the 7.5-year follow-up relapsed in the next 7.5 years.[50]



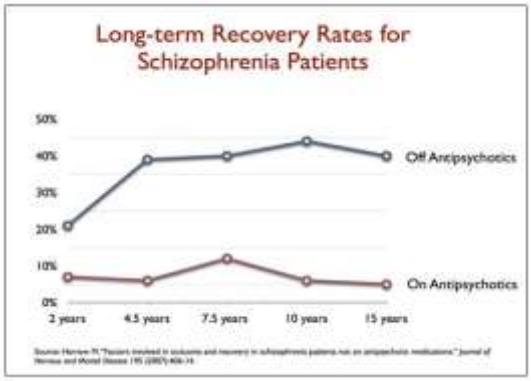
e) Work history

Those who didn't take antipsychotics throughout the study had much better work records than the medication-compliant patients. Seventy to 90% percent of the unmedicated patients were working more than half time at the multiple follow-ups starting with year 4.5, compared to about 25% of the medicated patients.[51]



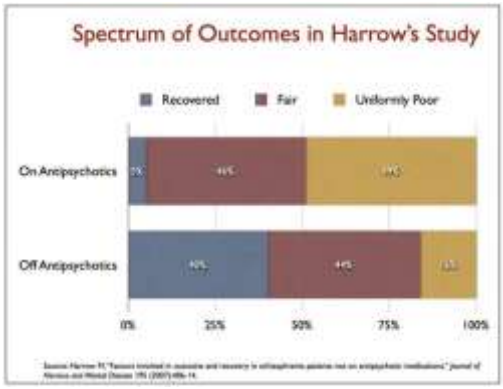
f) Recovery rates

To be judged to be in "recovery," a patient had to be asymptomatic, with no hospitalizations in the previous year, working or in school more than half time, and with decent social relationships At the end of two years, 21% of those off meds were in recovery versus 7% on meds. Over the next 30 months, the off-med group continued to improve, such that 39% were in recovery at the end of 4.5 years, versus 6% in the on-med group. This seven-fold higher recovery rate for the off-med group remained throughout the study.[52]



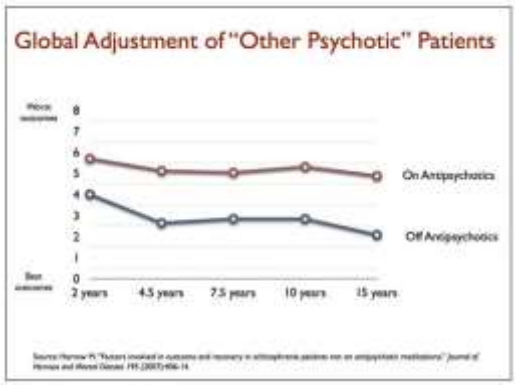
g) Overall outcomes

At the end of 15 years, Harrow sorted outcomes into three broad categories: recovered, fair, and uniformly poor. The spectrum of outcomes was much worse for the medicated cohort, with nearly half ending up in the "uniformly poor" category.[53]



h) Outcomes for patients with milder psychotic disorders

The results for the patients diagnosed with milder psychotic disorders were much the same. The off-medication patients had markedly better global outcomes.[54]



i) Summary of findings

The first purpose of antipsychotic treatment is to keep psychotic symptoms under control. Before Harrow's work, research had presented two different views of the drugs' long-term effects in this regard. The relapse literature led psychiatry to believe that the drugs achieved that purpose of reducing psychotic symptoms, whereas the dopamine supersensitivity theory—and Philip Seeman's animal-model—predicted that the drugs would have the opposite effect over the long term.

Harrow's results confirmed that the latter was true. Harrow discovered that patients off medication regularly recovered from their psychotic symptoms over time (2-year to 4.5-year outcomes), and that once this happened, they had very low relapse rates. At the same time, a majority of the patients on medication regularly remained psychotic, and even those who did recover often relapsed. Harrow's results provide a clear picture of how antipsychotics worsen psychotic symptoms over the long term.

Beyond that, the medicated patients did worse on every domain that was measured. They were much more likely to be anxious; they had worse cognitive function; they were much less likely to be working and in recovery; and they had much worse global outcomes.

This divergence in outcomes was true for every cohort of patients. Harrow divided his schizophrenia patients into good prognosis groups and bad prognosis groups, and in each group, it was the off-medication group that did better. There is one other comparison that can be made. Throughout the study, there were, in essence, four major groups in Harrow's study: schizophrenia on and off meds, and those with milder psychotic disorders on and off meds. Here is how their outcomes stacked up:[55]

At initial diagnosis, those with milder disorders could be expected to have a better long-term course than those diagnosed with schizophrenia. Yet, in this study, those with milder disorders who stayed on antipsychotics had worse outcomes than schizophrenia patients who got off the medication. That outcome contradicts the diagnostic expectation, and there is a treatment variable that explains it: Antipsychotics worsen long-term outcomes, and significantly so, over the long term.

After Harrow published his 20-year data, he raised the obvious question. "How unique among medical treatments is it that the apparent efficacy of antipsychotics could diminish over time or become ineffective or harmful?" he wrote. "There are many examples for other medications of similar long-term effects, with this often occurring as the body readjusts, biologically, to the medications."[56]

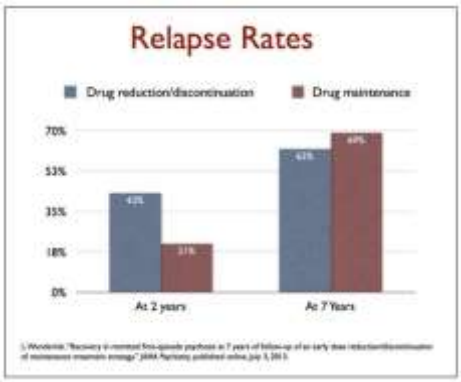
Wunderink's randomized study

After Harrow published his results, American psychiatry, as an institution, responded by discounting his results for this reason: his was not a randomized study. It was those with a better prognosis that got off the drugs, they said, and this explained the disparate results. While this was not an interpretation consistent with Harrow's data, American psychiatry nevertheless settled on it to discount the results.

However, in 2013, Lex Wunderink of the Netherlands conducted a randomized study of 128 first-episode patients that served as a partial response to that criticism. The patients had been stabilized on antipsychotics and were then randomized to "treatment as usual" or to a drug-tapering treatment designed to get patients down to a low dosage or off medication altogether, and then followed for seven years. Here are the results:[57]

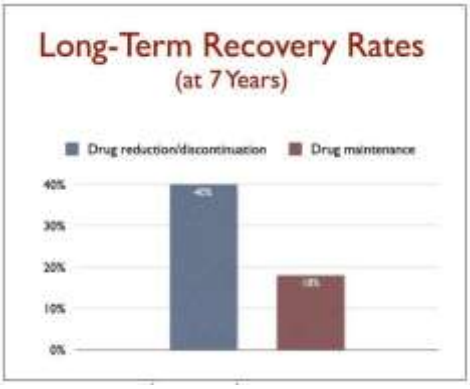
a) Relapse rates

Relapse was defined as an exacerbation of symptoms for at least one week. At the end of two years, the relapse rate was higher for those randomized to the low-dose/discontinuation group (43% to 21%.) However, by the end of seven years, the relapse rate was slightly higher for those randomized to treatment as usual (69% to 62%.)



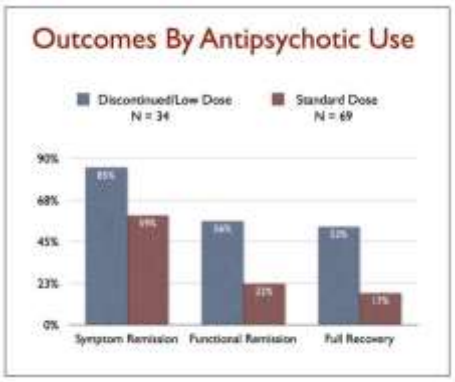
b) Recovery rates

In terms of functional outcomes, at the end of seven years the recovery rate was more than twice as high for those randomized to the drugreduction/discontinuation group.



c) Long-term outcomes by antipsychotic use

The seven-year results, grouped according to randomized cohorts, provided evidence of the long-term benefit of a treatment protocol that provided support for drug tapering following initial stabilization on an antipsychotic. However, there is another way to assess the long-term outcomes in this study. Some patients randomized to conventional drug treatment stopped taking antipsychotics during the seven years; conversely, some patients randomized to the discontinuation arm eventually began taking a conventional dose of an antipsychotic. The patients can thus be grouped according to ongoing medication use, much like in the Harrow study. At the end of seven years, the patients on a low dose or off antipsychotics were three times more likely to be enjoying a "full recovery" than those on the medication.



Wunderink drew two conclusions from his results. The first was that long-term antipsychotic use "might compromise important mental functions, such as alertness, curiosity, drive, and activity levels, and aspects of executive functional capacity." The second was that psychiatry, in its outcome studies, had long focused on symptom reduction over shorter periods of time, and that it should instead focus on "recovery or functional remission rates as their primary outcome and should also include long-term follow-up for more than 2 years, even up to 7 years or longer."

Australia's medication compliance study

In Australia, investigators hypothesized that providing services that increased medication compliance would lead to better long-term outcomes. Eighty-one first episode patients stabilized on medications were randomized to treatment as usual or to a "specialized therapy" designed to increased medication adherence. Although the therapy did increase compliance over the 30-month study, the increased use of medication was associated with "decreases in psychosocial functioning and increases in negative symptoms."[58]

A hypothesis confirmed

Research in the 1960s and 1970s led to a worry that antipsychotics induced a biological change in the brain that made patients more biologically vulnerable to psychosis, and ultimately could lead to the development of "tardive psychosis" in a significant percentage of patients. The research appeared to tell of a drug treatment that, over the long-term, worsened psychotic symptoms and impaired functional capacities, making patients more "socially dependent" than before their advent.

The research since 1980, which consists of studies of both first-generation and second-generation antipsychotics, serves as a confirmation of that hypothesis. The studies are of many types, and they all support the same conclusion: On the whole, these drugs increase the chronicity of schizophrenia and other psychotic disorders, and impair functional recovery as well.

SUMMARY OF THE CASE AGAINST ANTIPSYCHOTICS

As Stip noted in his 2002 paper, there is no compelling evidence in the literature that antipsychotics improve long-term outcomes. The relapse studies do not provide such evidence, and there is no other body of research that does. However, as can be seen in this paper, there is a history of science, stretching across six decades, that consistently tells of a medical treatment that, in the aggregate, does more harm than good.

Here is a chronological presentation of that history of science:

- The first long-term study reveals a higher rehospitalization rate for patients treated initially with antipsychotics.
- Psychiatrists and other hospital staff describe a new "revolving door syndrome" seen in drug-treated patients.
- Bockoven's retrospective study finds a decline in functional outcomes in the antipsychotic era.
- Three experimental studies funded by the NIMH in the 1970s tell of better outcomes with treatment that minimizes antipsychotic use.
- One of the lead investigators in those studies, William Carpenter, raises the possibility that antipsychotics induce a change that makes patients more biologically vulnerable to psychosis.
- Guy Chouinard and Barry Jones, drawing on an emerging understanding of how antipsychotics change the brain, provide a biological explanation of why that would be so. They then test their hypothesis and find that a significant percentage of medicated patients suffer from drug-induced tardive psychosis.
- In cross-cultural studies conducted by the World Health Organization, schizophrenia outcomes are found to be much better in developing countries where only a small percentage of patients are regularly maintained on antipsychotics.
- MRI studies reveal that antipsychotics induce changes in brain volumes that are associated with a worsening of positive and negative symptoms, and adverse cognitive effects.
- Animal-model studies lead Philip Seeman to conclude that drug-induced dopamine supersensitivity explains why antipsychotics "fail over time."
- Longitudinal studies in the United States, the Netherlands, and Australia all find that less use of antipsychotics, or no use of the drugs, is associated with better outcomes.

That is a robust body of evidence. In order to argue that antipsychotics do not worsen long-term outcomes in the aggregate, all of this evidence would have to be explained away. This entire history of science would need to be discounted.

In addition, this review has focused on the benefit side of the risk-benefit equation for antipsychotics. The drugs are supposed to provide the benefit of reducing psychotic symptoms. But the research reveals that, over the long term, this benefit turns into a negative, and so, over the long-term, there are only negatives to be chalked up: the increased chronicity of psychotic symptoms, the impaired functional outcomes, the worse cognitive functioning, and, of course, a broad range of "side effects," such as tardive dyskinesia, metabolic problems, sexual dysfunction, and so forth. Such is the bottom-line arithmetic that makes the case against antipsychotics.

PROOF OF PRINCIPLE

The evidence base for a class of medications becomes a foil for developing guidelines for their use. In this instance, the evidence tells of drugs that may provide a short-term benefit, but, on the whole, worsen long-term outcomes. However, there may be individuals who respond well to antipsychotics over the long term and thus benefit from this treatment. As such, the challenge for psychiatry (and society) is to incorporate this evidence into prescribing practices that seek to minimize long-term use and reserve such care for the smaller cohort that may benefit from maintenance therapy.

In northern Finland, the developers of Open Dialogue Therapy began employing a "selective use" model for prescribing antipsychotics in the early 1990s. At the end of five years, 67% of their patients have never been exposed to an antipsychotic, and only 20% use the drugs on a continual basis. Their reported outcomes with this model of care are greatly superior to the norm in the developed world: 80% are asymptomatic at the end of five years and working or in school, and only 20% have become chronically ill.[59]

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

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

Source: Seikkula, J. "Five-year experience of first-episode nonaffective psychosis in open-dialogue approach." Psychotherapy Research 16 (2006):214-28.

In this narrative of science, the Open Dialogue results serve as a proof of principle. There is a history of research that tells of the need to use antipsychotics in a selective manner, and Open Dialogue provides an example of the better outcomes than can be achieved by doing so.

ANSWERING THE CRITICS

General criticisms

The central elements of this argument were first set forth in Anatomy of an Epidemic, which was published in 2010. As could be expected, there have been many critics of the book. Reviewing those criticisms provides a valuable opportunity to further assess the merits of this "case against antipsychotics." If this case is flawed, the critics should be able to make a compelling argument of why the evidence presented here can be fairly discounted, and they should be able to point to evidence of the drugs' long-term efficacy that has been left out from this presentation.

The critics have made these arguments:

- The relapse studies provide some evidence of a long-term benefit.
- Much of the research reviewed here is old.
- Martin Harrow's study was not randomized. The patients who stopped taking the medication were "less ill" and this explains their superior results.
- A longitudinal study in rural China, which reported better outcomes for patients exposed to antipsychotics, provides evidence that the drugs improve long-term outcomes.

These criticisms, and my response, can be reviewed in detail on madinamerica.com (see answering critics, and this blog.) But, in short, these criticisms are easily answered.

On the relapse literature: As noted earlier in this paper, the shortcomings of the relapse literature are well known. Those studies chart the exacerbation of symptoms that often occurs after antipsychotics are withdrawn. They do not provide data on how well medicated and non-medicated patients are functioning, or even how symptomatic they are, across longer periods of time.

These studies are old: The fact that this case against antipsychotics unfolds over time, across six decades, and in a consistent manner, is precisely what makes the case so strong. The older research is part of a larger scientific inquiry that leads to the conclusion that these drugs impair recovery rates over the long term. And without the inclusion of the past, it becomes difficult to understand the present. The research conducted in the past 35 years builds upon the research that was done in the first 25 years.

The dismissal of Harrow: The less-ill explanation for Harrow's results is belied by the actual data. There is a comparison of the less ill with the more severely ill at baseline, and here is what it shows: those who were less ill who stayed on the medications (the milder disorders group) fared worse than the more severely ill who got off the drugs (the schizophrenia group.) It was the more severely ill who had better outcomes. That is the very comparison that makes the Harrow findings so compelling: what variable can explain this fact other than that it is due to the medications worsening outcomes over the long term?

The longitudinal study in China: When I gave a Grand Rounds presentation at Massachusetts General Hospital in 2011, psychiatrist Andrew Nierenberg, in his "rebuttal," pointed to longitudinal study in rural China as evidence that the drugs have a long-term benefit. Ronald Pies, former editor-in-chief of Psychiatric Times, has done so as well, and he cited a 2015 report for this belief. [60]

In the study, Hong Kong investigators surveyed a rural community of 100,000 in China, and identified 510 people who met the criteria for a diagnosis of schizophrenia. This was in 1994, and at this baseline moment, there were 156 who had never been treated and 354 who had received antipsychotic medication at least once, and thus were deemed the "treated" group.

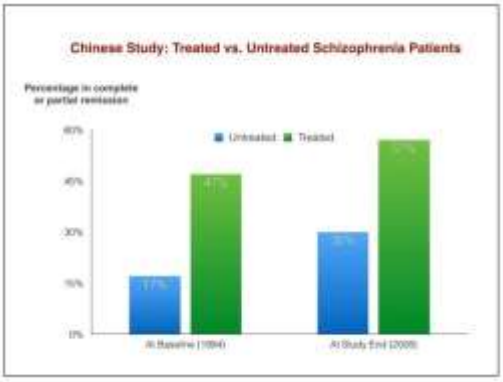
The first thing to note about this study is that those in the "untreated" group were on average 48 years old and had been ill for 14 years. Anyone in this rural community who, in the years before 1994, had suffered a psychotic episode and recovered without treatment would not have shown up in this study. In layman's terms, the investigators had identified a group of "chronically crazy" people for their "untreated" group they would now follow for 14 years.

The second thing to note is that the untreated and treated cohorts—at baseline— were not at all similar. Compared to the treated patients, the "untreated" group were "significantly older, less likely to be married, more likely to have no family caregiver and to live alone, had a lower education level, and fewer family members."

The untreated group also came from families with a significantly lower economic status, and they were more likely to have been abused by their families. In addition, the never-treated group was more severely ill at baseline: they had a "longer duration of illness; higher mean scores on the PANSS positive subscale; and had higher PANSS negative

subscale and general mental scores." Eighty-three percent had "marked symptoms/or were deteriorated," compared to 54% of those in the treated group.

At the end of 14 years, the treated group—which simply meant that they had exposure to antipsychotics at some point in their lives, as there was no reporting on how regular they used such medication—was still doing better. Fifty-seven percent were now in complete or partial remission, up from 47% at the start of the study (an increase of 10%). Thirty percent of the untreated group were in complete or partial remission at the end of the study, and while that was still lower than the treated cohort, it meant that there had been an increase of 13% in this good outcomes category.



Thus, in this longitudinal study that several critics cited as a refutation of the literature presented in Anatomy of an Epidemic, the percentage of the untreated group who improved was actually greater than for the treated patients, but since they had been so much more severely ill at baseline, with so many worse prognostic factors, their collective outcomes were still worse at the end of 2008.

Readers of this paper can decide whether such a study serves as an effective counter to Harrow and the larger case against antipsychotics made in this paper. There are apparently leading American psychiatrists who see it this way.

Journal review

In 2015, Nancy Sohler, from the City College of New York, and researchers from Columbia University, motivated by their reading of Anatomy of an Epidemic, sought to answer this question: Is there evidence that antipsychotics do more harm than good over the long-term? Their published article represented a methodological review of this question, and thus can be seen as of greater scientific importance to this discussion than the general criticisms cited above.[61]

Sohler and her colleagues searched for studies of psychotic patients at least two years in length that, in some fashion, compared outcomes in those who received antipsychotic medication to those who did not. They identified 18 reports, published in English, that met these criteria.

They concluded that this literature was "inadequate to test the hypothesis." There were design flaws and inadequate reporting of data in the 18 studies that made it impossible to draw a conclusion one way or the other about the long-term effects of antipsychotics. New research was needed to "establish a sufficient evidence base to understand its benefit/risk balance for patients with schizophrenia," they wrote.

Even at first glance, Sohler's study provides a rationale for rethinking the use of antipsychotics. If there is a lack of evidence that antipsychotics provide a long-term benefit, then—given that the drugs have so many adverse effects—there is reason to rethink treatment protocols that urge long-term use. At the same time, Sohler's article does raise a challenge to the "case against antipsychotics" presented in this paper: does their review show that there is, in fact, an absence of research supporting a conclusion that antipsychotics, on the whole, worsen long-term outcomes?

The answer to that question consists of two parts.

First, the evidence presented in this Mad in America Foundation paper (and in Anatomy of An Epidemic) is of many types, and that, I believe, is what makes the case against antipsychotics so compelling: the evidence for harm done comes from many different kinds of research. However, Sohler focused on a particular slice of that evidence base, which had the effect of excluding the first NIMH study; Carpenter's psychotherapy study; the WHO cross-cultural studies; the dopamine supersensitivity worries; Chouinard's reports of drug-induced tardive psychosis; and the MRI studies. It is that larger body of evidence that needs to be considered.

Second, a close look at the 18 studies reviewed by Sohler reveals that their results, in fact, fit within the larger narrative of science reported in this Mad in America Foundation paper. Sohler and her colleagues cut out a slice of the evidence base, and while this slice may have been deemed insufficient to adequately test the "doing harm" hypothesis, the studies nevertheless reveal the same "evidence-based" landscape as laid out in this paper. As such, their work, in my opinion, adds another data point in the case against antipsychotics.

Here is a quick synopsis of the 18 studies, grouped by type:

1) Retrospective studies

Sohler identified four studies that assessed outcomes before and after the introduction of chlorpromazine. One of the four was Bockoven's (cited above), which, at the end of five years, found a slightly lower relapse rate and much better functional outcomes for the pre-chlorpromazine group. In the three other studies:

- A British study of 100 schizophrenia patients found that those treated in 1956/57, had, if anything, a "higher rate of readmission" in the three years following discharge than those treated in 1952/53, prior to the introduction of the phenothiazines. This study did not assess functional outcomes.[62]
- A Norwegian study of hospital admission and discharge records in 1948/52 and in 1955/1959 determined that while there may have been a slight improvement in discharge rates after chlorpromazine arrived in asylum medicine, the total number of readmissions "increased 41.6%," which the researchers described as "characteristic of the drug period." This study did not assess functional outcomes for the discharged patients.[63]
- In a study of 221 first-episode schizophrenia patients admitted into Scottish hospitals from 1949 to 1957, with patients followed for three years, there was no difference in the percentage that suffered a single "attack" (about 70% of all patients in both the pre-drug and post-drug eras), but among all discharged patients, there was an "increased relapse frequency" in males following the introduction of chlorpromazine. This study did not assess functional outcomes for the discharged patients.[64]

All four studies hinted at the same change in the long-term course of schizophrenia following the introduction of chlorpromazine, with relapses—and thus readmissions—to the hospital increasing. Only one study assessed functional outcomes, and that one found a marked increase in the patients' social dependence in the era of antipsychotics.

2) Drug-withdrawal studies

Sohler reviewed five drug-withdrawal studies that followed the patients for two years or more. In all of the studies, the relapse rate was higher for those withdrawn from the medication.65, 66, 67, 68, 69 This was consistent with Leucht's meta-analysis of this literature (reviewed earlier in this paper.)

As can be seen in Leucht's meta-analysis (above), much of this excess risk occurs within the first three months of withdrawal. Moreover, these five long-term studies did not provide an ongoing assessment of psychotic symptoms. Once a patient had been judged to have relapsed, which meant an exacerbation of symptoms, that became his or her final primary "outcome." Any patient who suffered a flare-up of symptoms following drug withdrawal and yet then began to gradually recover off medication over a longer period of time would still be seen as having "relapsed."

Indeed, Sohler's inclusion of these studies in her survey of "long term" studies of medicated and unmedicated patients reveals how this relapse literature is misunderstood. These studies recorded, over a period of two years or more, the occurrence of a first episode of symptom exacerbation, e.g. relapse, in patients either maintained on an antipsychotic or withdrawn from the drug, and charted the cumulative percentage of patients who relapsed over this time. As such, these studies did not assess the outcomes for the patients at the end of two years at all.

The minute a person relapsed, whether in the first week, or first month, or first three months, that became the person's final status in these studies. They became part of the "cumulative" percentage that relapsed.

As such, what the inclusion of these studies by Sohler in her review does is illustrate—and powerfully so—why "long-term" relapse studies do not provide evidence of whether the drugs are effective over the long-term. These studies, in terms of their primary "outcome," do not follow patients for the length of the study and report on their continuing status. They simply assess how often a first-episode of symptom exacerbation occurs following the initial randomization, and in a two-year study, chart the total percentage of patients in each group who suffered such an episode by study end.

3) Partial drug-withdrawal studies

Two studies in Sohler's review compared regular drug maintenance to "intermittent" use of neuroleptics. In 1987, American researchers reported an "extensive similarity" in outcomes at the end of two years;[70] German investigators reported in 1993 a higher relapse rate at the end of two years for the intermittent group.[71]

4) Experimental treatments

Sohler identified three studies of first-episode patients that involved initially treating patients either with drugs or no drugs, and followed the patients for at least two years. Two of the three, Rappaport and Mosher, were reviewed above, and both reported superior long-term outcomes for treatment that minimized long-term use of antipsychotics.

The third study was by Philip May. He randomized 228 first episode schizophrenia patients, who were admitted to a hospital from 1959 to 1962, to five different treatments: electroshock, an antipsychotic, psychotherapy, psychotherapy plus drug, and milieu therapy. The initial outcome was discharge from the hospital, and anyone who was released from the hospital within the first year while still on the randomized form of treatment was deemed a "success." The highest success rate was drug plus psychotherapy (95%), and the lowest was milieu (58%).[72]

Upon discharge, most patients were treated with an antipsychotic. This study was not designed to assess the long-term effects of different forms of continuing treatment, May noted, but rather whether different in-hospital treatments had a long-term effect.

At the end of five years, although there was no "startling difference in follow-up outcome between the five original treatment groups, there was an overall tendency for the drug-alone and ECT groups to have the best, and for the psychotherapy alone group to have the worst." On the whole, May reported, "it seems that whatever treatment our patients received, the long-term outcome was, in general, grim."

May also charted the long-term outcomes for the "successes" in each of the five treatment groups. Although the milieu group had the lowest percentage of in-hospital successes (58%), these patients "functioned over the follow-up at least as well, if not better, than the successes for the other treatments."

May's study is often cited by leaders in American psychiatry as evidence that schizophrenia patients do poorly without medications. But if May's results are carefully parsed, they reveal these two findings:

- Over the short term, the drugs are more effective than placebo in knocking down psychotic symptoms.
- At the same time, there is a significant percentage of hospitalized patients who can recover from a first episode without the use of antipsychotic medication (58%).

Beyond that, this study doesn't provide much insight into the long-term effects of these medications. Most patients were prescribed antipsychotics, and in general, their outcomes were poor, May reported.

5) Longitudinal studies

Sohler identified three longitudinal studies fit for review: Harrow's, Wunderink's, and a study of patients in Northern Finland. Both Harrow and Wunderink reported superior long-term outcomes for non-medicated patients (or patients who got down to a very low dose.)

In the Finnish study, researchers identified a group of 70 patients who were born in 1966 and diagnosed as adults with schizophrenic psychoses. They assessed the patients at the start of the study, when they were 34 years old (with a mean duration of illness of 10.4 years at that point), and followed them for nine more years.[73]

At initial assessment, the 24 patients off medication were doing better than the 46 patients on antipsychotics: they were much more likely to be working, more likely to be in remission, and had better clinical outcomes. During the follow-up, 46% of the non-medicated patients suffered a relapse, compared to 56% of the medicated group. Those who used antipsychotics less than 50% of the time were more likely to be functioning well, in remission, and to have a good clinical outcome than those who used medications more than half the time.[74]

This study doesn't contradict the findings in Harrow and Wunderink, but rather provides an additional data point: in an initial assessment of patients of similar age who had been diagnosed with schizophrenia on average 10 years earlier, it was the non-medicated patients who were doing better, particularly in their functional outcomes. In the nine-year follow-up, patients who used antipsychotics less than 50% of the time had the best outcomes—socially and clinically.

6) Database study

In this study, Finnish investigators mined a national database of drug prescriptions, which could be linked to individual patients, to assess the relative effectiveness of antipsychotic drugs for 2230 adults hospitalized for a first episode of schizophrenia or schizoaffective disorder from 1995 to 2001. 75 The patients were treated in the hospitals with antipsychotics, and the investigators then charted their medication use for every 30-day period following discharge. Any relapse or death during a 30-day period was chalked up to outcomes for the particular antipsychotic they were on, or to "no antipsychotic drugs" if they were off medication during that month.

Given this methodology, anyone who came off a medication and relapsed would show up in the outcomes for "no antipsychotic drugs." In a similar vein, if someone committed suicide after discontinuing a medication, this was chalked up to the outcomes for "no antipsychotics," and if someone became ill from adverse effects of the drugs and went off them in the last months of life, the death would be attributed to "no antipsychotics."

With outcomes categorized in this way, the investigators reported that relapse rates were higher for patients during the 30-day periods when they weren't taking antipsychotic drugs, and that mortality "was more than 10 times higher in patients not taking drugs than in patients currently taking drugs."

As can be seen, this study doesn't provide information about how patients off antipsychotics for long periods fare in comparison to those who take such medications. It also is a study based on mining a database, as opposed to studying a distinct patient cohort. But in terms of how it might fit into the "evidence base" for antipsychotics presented in this paper, the results may provide another signal that when patients discontinue antipsychotics, they are at increased risk of relapse for some extended period, and there may be a much higher risk of suicide during that time as well.

In sum, Sohler's review provides support for this understanding of the research literature:

- Readmission rates increased following the introduction of chlorpromazine.
- In 60 years of antipsychotic use, there are only two studies in first episode patients that compared conventional antipsychotic treatment to care that minimized use of medications, and also followed the patients for at least two years while assessing their medication use (Rappaport and Mosher.) In both of those studies, the investigators concluded that long-term outcomes were better in the experimental arms. (The May study was not designed to assess the long-term effects of antipsychotics, but rather only the long-term effects of in-hospital treatment with the drugs.)
- In three longitudinal studies, the schizophrenia patients off medication had better long-term outcomes, particularly in functional domains.
- Once patients are exposed to antipsychotics, they are at increased risk of relapse following drug withdrawal, with this increased risk present throughout the first year. This risk may also put drug-withdrawn patients at increased risk of suicide.

CONCLUSION

This paper makes a case that antipsychotics, on the whole, worsen long-term outcomes. The drugs may provide a short-term benefit, and it is clear that once patients are on the medications, there is an increased risk of relapse, for some period of time, when discontinuing the medication. But there is also a long line of research that tells of treatment that may increase a person's biological vulnerability to psychosis and impair functioning over the long-term.

Sohler's review also reveals that there is an absence of research that tells of medications that improve functional outcomes over the long term. This absence, given the obvious desire by psychiatry to report such positive results, is compelling evidence on its own that these medications, when it comes to affecting aggregate outcomes, do more harm than good.

ENDNOTES

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