

# THE CASE AGAINST PSYCHIATRIC DRUGS

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## ABSTRACT

The conventional narrative in psychiatry tells of a psychopharmacological revolution that began with the arrival of chlorpromazine in asylum medicine in 1955. Today, psychiatric drugs are understood to be safe and effective treatments for a variety of disorders. However, a close review of the scientific literature, stretching over a span of 50 years, reveals a paradox: medications that are effective over the short term may increase the chronicity of a disorder over the long-term. A case study of antipsychotics best illustrates this paradox. The small number of researchers investigating this paradox are focusing on drug-induced “oppositional tolerance” as an explanation for the poor long-term outcomes of medicated patients.

**Keywords:** Psychiatric drugs; Psychiatry; Studies medicating.

## 1 INTRODUCTION

The conventional narrative in psychiatry, which drives care today, tells of how the arrival of chlorpromazine in asylum medicine in 1955 kicked off a psychopharmacological revolution, a great advance in care. This drug is remembered as the first antipsychotic, a name that tells of an antidote to psychosis, and shortly after chlorpromazine was introduced, new drugs described as “anti-anxiety” agents and “antidepressants” were brought to market.

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By the early 1960s, the revolution was in full sway, and soon researchers were hypothesizing that schizophrenia and depression were caused by chemical imbalances in the brain, which were put back into balance by the new medications.

The next step up this medical ladder of progress is understood to have occurred when a second generation of psychiatric drugs was brought to market, starting with Prozac's arrival in 1988. The public was informed that depression was due to a deficit in serotonin, and that this new drug, by blocking the normal reuptake of serotonin from the synaptic cleft, helped bring serotonin activity in the brain back into balance, and thus was like "insulin for diabetes." Soon atypical antipsychotics—risperidone, olanzapine, and others—were brought to market, and these drugs, much like the SSRIs, were said to be an advance on the old.

In 1999, U.S. Surgeon General David Satcher summarized this narrative of progress in a 458-page report titled *Mental Health*. Prior to the arrival of chlorpromazine, he wrote, psychiatry lacked treatments that could prevent "patients from becoming chronically ill." But today, he said, psychiatry had in its armament a "variety of treatments of well-documented efficacy for the array of clearly defined mental and behavioral disorders that occur across the life span."<sup>1</sup>

With this narrative fixed in the public mind, societal use of psychiatric medications in the United States, Europe and other developed countries has grown exponentially in the past three decades. Twenty percent of American adults now take a psychiatric drug on a daily basis, and more than five percent of all school-age children do.<sup>2</sup>

Given this narrative of progress, it could be expected that the introduction of these drugs and their widespread use would be a prescription for reducing the burden of mental illness in the United States and other developed countries. That is usually the case when effective medical treatments are discovered. However, in this instance, the opposite is the case. The burden of mental illness in the "developed world" has notably increased as this "psychopharmacological revolution" has unfolded, with this increase particularly dramatic since the arrival of Prozac and the second-generation psychiatric drugs.

In 1987, the year that Prozac was approved for marketing, there were 1.25 million adults in the United States receiving an SSI or SSDI payment due to a mental disorder. This produced a disability rate of 543 per 100,000 people. Since that time, the number of adults on government disability due to a mental disorder has risen to more than 4.5 million in 2014, a disability rate of 1,408 per 100,000. Thus, during the Prozac era, the disability rate has nearly tripled in the United States.<sup>3</sup>

The same sharp rise in disability due to mental disorders has occurred in country after country that has adopted widespread use of psychiatric drugs. Australia, New Zealand, Canada, United Kingdom, Iceland, Denmark, Sweden and numerous other countries have reported similar sharp rises in disability due to mental disorders.<sup>4</sup> All of which raises a question, which is the focus of this paper: Do these drugs help people stay well, or, for some paradoxical reason, do they worsen long-term outcomes and thus increase the risk that a person suffering from a psychiatric disorder will end up disabled by it?

## **1.1 Paradigm for Understanding Psychotropic Drugs**

The chemical imbalance theory of mental disorders tells of drugs that fix a known pathology, and in medicine, that is a prescription for an effective treatment. But as is now acknowledged by psychiatric researchers, the chemical imbalance theory never really panned out.

The chemical imbalance theory of mental disorders arose in the 1960s from an understanding of how the first-generation antipsychotics and antidepressants acted on the brain. Chlorpromazine and other antipsychotics were found to block dopamine receptors in the brain, and this led researchers to hypothesize that schizophrenia was due to too much dopamine activity in the brain. In a similar vein, tricyclics and monoamine oxidase inhibitors were found to block the normal removal of monoamines from the synaptic cleft between neurons, which increased monoamine activity, and thus depression was hypothesized to be due to a deficit in monoamines. However, when researchers

investigated whether schizophrenia patients had overactive dopamine systems as a matter of course, or whether depressed patients had a monoamine deficit, they did not find this to be so.

This can be seen most clearly in the case of the low-monoamine theory of depression. Serotonin is a monoamine, and as early as 1984, investigators at the National Institute of Mental Health (NIMH) announced that they weren't finding that patients with depression, prior to being medicated, had low serotonin levels.<sup>5</sup> After Prozac came to market, researchers redoubled their studies of serotonergic activity in depressed patients, but again and again, they didn't find that there was a deficiency with this neurotransmitter. In his 2000 textbook *Essential Psychopharmacology*, Stephen Stahl summed up the research findings in this way: "There is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no real monoamine deficit."<sup>6</sup>

The dopamine hyperactivity hypothesis of schizophrenia has had a more complicated history. Researchers are still studying whether the dopaminergic system might shift into a "high" state during the onset of a psychotic episode, but by the early 1990s, they were reporting that they had failed to find that schizophrenia patients, prior to being medicated, had overly active dopamine systems. Their presynaptic neurons did not release abnormally high amounts of dopamine, and their postsynaptic neurons did not have an abnormally high number of dopamine receptors. As Eric Nestler wrote in a 2002 textbook, *Molecular Psychiatry*: "There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia."<sup>7</sup>

Studies of other psychiatric disorders also failed to find that they were due to a simple chemical imbalance, which could then be corrected by a drug. In 2005, Kenneth Kendler, co-editor in chief of *Psychological Medicine*, penned what could be described as a succinct epitaph for the chemical imbalance theory of mental disorders: "We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them."<sup>8</sup>

But this is not the end of this scientific story. Research into the chemical imbalance theory of mental disorders did bear fruit in one way: it helped flesh out an understanding of how the brain is changed by a psychiatric drug. And what the researchers found is that a psychiatric drug, in essence, creates the very chemical imbalance hypothesized to cause the disorder in the first place.

For instance, an antipsychotic blocks a particular dopamine receptor subtype, known as the D2 receptor. This blockade acts as a brake on dopamine transmission. But the brain, with its many feedback mechanisms, then tries to compensate for this blockade by increasing its dopaminergic activity. The presynaptic neurons release more dopamine than normal into the synaptic cleft, while the postsynaptic neurons increase the density of their D2 receptors. The first compensatory response—the increased release of dopamine—appears to burn out after a time, but the second one, the increase in dopamine receptors, remains. The brain is now understood to be “supersensitive” to dopamine, which is the very pathology hypothesized to cause schizophrenia.

Research into the low-serotonin theory of depression led to the same startling conclusion. Antidepressants up serotonin activity in the brain, and in response, the brain dials down its serotonergic activity. The presynaptic neurons put out less serotonin than normal (a compensatory response that may cease after a time), while the postsynaptic neurons decrease the density of receptors for serotonin. An SSRI ultimately drives the brain into a subserotonergic state.

This adaptive process provides a model for understanding the long-term effects of psychiatric drugs on brain physiology. In 1996, Stephen Hyman, who was director of the NIMH at that time, wrote a paper titled “Initiation and Adaptation: A Paradigm for Understanding Psychotropic Drug Action,” which detailed this process. Psychotropic drugs perturb neurotransmitter function in the brain. The brain then goes through a series of compensatory adaptations in an effort to maintain a homeostatic equilibrium, e.g., the normal functioning of its neurotransmitter pathways. At the end of this process, Hyman wrote, the brain is functioning in a manner that is both “qualitatively as well as quantitatively different from the normal state.”<sup>9</sup>

In short, the conventional narrative of a “psychopharmacological revolution” told of drugs that fixed a known pathology. But science was revealing a very different story, of pathologies that remained unknown, and of drugs that perturbed normal neurotransmitter function and induced abnormalities in brain function. With that scientific understanding in mind, it becomes easier to understand why long-term use of the drugs might be problematic.

## **2 A METHOD FOR ASSESSING LONG-TERM EFFECTS**

Psychiatric drugs are approved for sale in the United States and other countries because, in industry-funded trials, they reduce a target symptom—psychosis, depression, etc.—better than placebo. This is understood to be evidence of their short-term efficacy. There is, however, no societal standard for assessing their long-term merits. To do that, it is necessary to put together a *history* of research, which consists of studies of many types.

The foil for such an inquiry necessarily begins with trying to flesh out the “natural course” of the disorder being treated. For any treatment to provide a long-term benefit, it must improve on the natural recovery rate. For instance, if 60% percent of patients with a disorder naturally recover with time, then the recovery rate for treated patients needs to be higher than that in order to conclude that the treatment is effective over the long term. If only 40% of patients treated for such a disorder recover, then the treatment has lowered the recovery rate (from 60% to 40%), and thus it can be concluded that the treatment, on the whole, is doing more harm than good over the long term.

Once that “natural” recovery rate is fleshed out (to the best degree that is possible), then the hope is that a narrative of science can be put together from a close review of the research literature that tells a coherent and convincing story of the drugs’ long-term effects. In the case of psychiatric drugs, there is fifty years of research to be reviewed.

There is not enough space in this article to do such a review for more than one class of psychiatric drugs. But if only one class of drugs is to be reviewed,

antipsychotics are the best choice. They are the best studied class of psychiatric medications, and, according to the conventional narrative, these drugs are an essential treatment for schizophrenia patients, which means that if there is going to be evidence of long-term efficacy for any class of psychiatric drugs, then it should be for the antipsychotics. As such, a case study of antipsychotics provides the best way to put the conventional narrative to test.

### **3 A CASE STUDY**

Although schizophrenia is often described as a chronic deteriorating disease, a conception that is attributed to Emil Kraepelin, studies of first-episode schizophrenia patients from 1945 to 1955 in the United States belied that understanding. More than fifty percent of the patients were discharged within 12 months, and at the end of five years or so, two-thirds or so were successfully living within the community. Only a small percentage of the initial cohorts—20 percent or so—were continually hospitalized.<sup>10, 11</sup> During this same period, longer-term outcome studies in England, where the diagnosis of schizophrenia was being more narrowly defined, produced similar findings. Thirty-three percent of the patients enjoyed a “complete recovery,” and another 20 percent a “social recovery,” which meant they could support themselves and live independently.<sup>12</sup>

The evidence for the long-term use of antipsychotics comes from relapse studies. Once chlorpromazine was introduced, there were studies that found that newly hospitalized patients did better on the medication than on placebo for the first six weeks. Then, starting in the 1960s, the NIMH funded a number of drug-withdrawal studies. Patients who had stabilized well on the medication were either maintained on the drug or withdrawn from it (usually abruptly), and with great regularity the withdrawn group relapsed at a higher rate over the next months than the drug-maintained group.<sup>13</sup> This became the evidence for maintaining patients on antipsychotics indefinitely, as the treatment was seen as lowering the risk that the “disease” would return.

However, there are obvious flaws with this evidence for long-term use. The first was that the design of the studies—abrupt withdrawal of the medication—was flawed, as it is now well understood that abrupt withdrawal increases the risk of relapse. The high relapse rate may have been, at least in part, a drug withdrawal effect, as opposed to being due to the “return of the disease.” In addition, the relapse studies didn’t provide any information about how well the patients were functioning over the long term. Were they working? Were they socially engaged? In 2002, Emmanuel Stip, a professor of psychiatry at the Université de Montréal, reviewed this literature and concluded that there was “no compelling evidence” that neuroleptics were effective, “when ‘long-term’ is considered.”<sup>14</sup>

While the relapse literature doesn’t reveal whether antipsychotics provide a long-term benefit, there is a body of research that can be traced that does help answer that question. This review begins with a pivotal study conducted in 1961. That year, the NIMH conducted its first well-controlled study of antipsychotics as a treatment for schizophrenia. The study was conducted at nine hospitals, and patients were randomized either to an antipsychotic or to placebo, and at the end of six weeks, the drug-treated patients were doing better. However, many in the placebo group had also improved, and at the end of one year, the researchers reported that the drug-treated patients had been rehospitalized at a higher rate than those in the placebo group.<sup>15</sup> Thus, at this very earliest moment in the research literature, there is the hint of a paradox: could a drug treatment that was effective over the short-term paradoxically increase the chronicity of the disorder over the long term?

With the antipsychotics now being regularly used, psychiatrists began talking about a “revolving door syndrome.” Their patients may have been getting better faster, but they were returning to the hospitals in droves. At least a few clinicians also reported that when patients relapsed after exposure to an antipsychotic, the relapse was more severe than on placebo.

Such concerns led the NIMH to fund four studies during the 1970s that revisited the long-term efficacy of antipsychotics. The first was a retrospective



study by Samuel Bockoven. He compared five-year outcomes for psychotic patients admitted to Boston Psychopathic Hospital in 1947 to five-year outcomes for a similar group of patients admitted in 1967, and found that the relapse rate for the 1947 cohort was slightly lower (55% compared to 69%.) Even more important, the 1947 cohort had substantially better functional outcomes. Those treated in 1967 with antipsychotics were much more “socially dependent”—on welfare and other forms of social support.<sup>16</sup>

In two of the other three studies funded by the NIMH, investigators compared conventional drug treatment with experimental forms of care that involved psychosocial care and no immediate use of antipsychotics, with drug treatment then reserved for those who didn’t do well in the initial phase. In each case, the researchers found that the experimental arms produced better outcomes at the end of two to three years, including lower relapse rates and improved social functioning. In particular, those patients who were able to recover from their psychotic break without going on an antipsychotic had superior long-term outcomes.<sup>17,18</sup>

The fourth study, led by William Carpenter, was conducted at NIH’s own research facility, and at the end of one year, the unmedicated patients had relapsed at a lower rate, and also suffered less from depression, blunted emotions, and retarded movements. This led Carpenter to raise a haunting 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 natural course of the illness.”<sup>19</sup>

Two Canadian physicians, Guy Chouinard and Barry Jones, then stepped forward with a biological explanation for why that might be so. Chlorpromazine

and other antipsychotics blocked dopamine receptors in the brain. In response to this blockade, the brain increased the density of its dopamine receptors. This “dopamine supersensitivity,” they wrote, could lead “to both dyskinesic symptoms 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.”<sup>20</sup>

With their work, Chouinard and Jones had presented a picture of how neuroleptics, over time, acted as a trap. The drugs’ initial blockade of dopamine receptors helped reduced symptoms over the short term. However, the brain’s compensatory response to the drugs produced a dopamine supersensitivity that made patients particularly vulnerable to relapse when the drugs were withdrawn, and yet, if patients stayed on the drugs indefinitely, the dopamine supersensitivity increased the risk the patients would become chronically psychotic. In 1982, Chouinard and Jones reported that thirty percent of 216 schizophrenia outpatients they studied showed signs of such drug-induced tardive psychosis. When this sets in, they wrote, “new schizophrenic symptoms or original symptoms of greater severity will appear.”<sup>21</sup>

This presented psychiatry with a moment of truth. If Chouinard and Jones were correct, the field needed to rethink its use of antipsychotics. However, within a fairly short time, this “dopamine supersensitivity” worry was cast aside, with several leading figures in American psychiatry characterizing it as a false alarm. But thirty years have passed since that worry arose, and so this question can now be raised again: What does research during this period—research of several different types—reveal? Is there reason to conclude that antipsychotics worsen long-term outcomes (in the aggregate), or not?

Here are the relevant studies to be found.

### **3.1 Cross-cultural studies**

In two cross-cultural studies, one five years in length and the other two years in length, the World Health Organization twice found that patients in three

“developing” countries—India, Nigeria, and Colombia—had much better outcomes than in the U.S. and other “developed” countries. The WHO also found that in the poor countries, only 16% of schizophrenia patients were regularly maintained on antipsychotic drugs, versus 61% of the patients in the rich countries. Thus, in these cross-cultural studies, better outcomes were associated with lower use of the drugs on a long-term basis.<sup>22</sup>

### **3.2 MRI studies**

With the advent of MRI technology, researchers were able to measure brain volumes in schizophrenia patients. In a series of studies from 1994 to 1998, investigators reported that antipsychotics caused basal ganglion structures and the thalamus to swell, and the frontal lobes to shrink, with these changes in volumes “dose related.” In 1998, Raquel Gur concluded that the swelling of the basal ganglia and thalamus was “associated with greater severity of both negative and positive symptoms.”<sup>23</sup>

Next, Nancy Andreasen, long-time editor in chief of the *American Journal of Psychiatry*, reported that schizophrenia patients suffered from a shrinkage of the frontal lobes over the long term, and that this shrinkage was associated with a worsening of negative symptoms and functional impairment, and after five years, a decline in cognitive function.<sup>24,25</sup> Initially, she attributed this shrinkage to the disease, but subsequently concluded that the “more drugs you’ve been given, the more brain tissue you lose.”<sup>26</sup>

Numerous other studies have concluded that antipsychotic use is associated with shrinkage of brain volumes. In a summary review of this literature, German investigators concluded that that these “changes in brain structure” could “exert adverse effects neurocognition, negative and positive symptoms and psychosocial functioning.”<sup>27</sup> This MRI research tells of an iatrogenic process: The drugs cause changes in brain volumes associated with a worsening of symptoms and functional impairment.

### **3.3 Longitudinal Studies**

In the late 1970s, Martin Harrow, a psychologist at the University of Illinois, began a long-term study of 200 patients diagnosed with schizophrenia and other psychotic disorders. Forty-six percent were first-episode patients, and the median age upon enrollment in the study was 22.9 years, which meant that Harrow could track the long-term course of their lives starting from the onset of their illness, or shortly thereafter. All patients were treated conventionally in the hospital and discharged, and then Harrow periodically assessed how well they were doing over the next 20 years. Were they symptomatic? In recovery? Employed? Were they taking psychiatric medications? He managed to keep 77% of the patients in his study throughout the first fifteen years, meaning that relatively few were lost to follow-up.

At the end of year two, there was little difference between the schizophrenia patients on medication and those who had stopped taking an antipsychotic. But over the next two and a half years, the outcomes for the two groups diverged in dramatic ways. The medicated group, on the whole, did not get better during this period. At the end of 4.5 years, only six percent were in recovery and few were working. In contrast, as a group those off medication improved markedly during this period—psychotic symptoms and feelings of anxiety lessened notably—and by the end of 4.5 years, 39 percent were in recovery, and more than 60 percent were working.<sup>28</sup> This stark difference in outcomes remained throughout the study, leading Harrow to conclude, when he presented his findings at the 2008 meeting of the American Psychiatric Association, “that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics.”

This was true for the patients with milder psychotic disorders as well in Harrow’s study. Most notably, schizophrenia patients off medication had better long-term outcomes than those with milder psychotic disorders who stayed on antipsychotics throughout the study. As Harrow presented his results, he also observed that those who were medication compliant throughout the study were much more likely to have continuing psychotic symptoms than those who got off the medication by year two and stayed off of it, leading him to revisit the

dopamine supersensitivity theory. This could explain why the medicated patients had such poor long-term outcomes, he said.

“How unique among medical treatments is it that the apparent efficacy of antipsychotics could diminish over time or become ineffective or harmful? .. . There are many examples for other medications of similar long-term effects, with this often occurring as the body readjusts, biologically, to the medications.”<sup>29</sup>

Harrow’s findings directly challenged the conventional narrative about antipsychotic drugs, and in response, defenders of that narrative argued that his findings could be dismissed because his was not a randomized study. In 2013, Lex Wunderink from the Netherlands filled in this gap. In his study, psychotic patients who had stabilized on an antipsychotic were either maintained on the drug or withdrawn from it (or tapered down to a low dose). At the end of seven years, the withdrawn/low-dose group had a much higher recovery rate (40 percent versus 18 percent.) Antipsychotics, Wunderink concluded, “might compromise important mental functions, such as alertness, curiosity, drive, and activity levels, and aspects of executive functional capacity to some extent.”<sup>30</sup>

Such is the narrative of science related to the long-term effects of antipsychotics that can be dug out from the research literature. The evidence that antipsychotics, on the whole, worsen the long-term course of psychotic disorders showed up early in the study of these drugs, and then appeared again and again, in studies of many types, and across a span of fifty years. That is what makes it such a compelling narrative: there is a consistency in the results, both across time and across different types of studies.

#### **4 OPPOSITIONAL TOLERANCE: A UNIVERSAL PROBLEM?**

A similar case, although not quite as robust in scope, can be put together related to the long-term effects of antidepressants. Prior to the antidepressant era, depression was understood to be an episodic disorder. But once

antidepressants began to be commonly used, at least a few psychiatrists began to worry that the drugs were causing a “chronification” of the disease, and numerous studies have since found that depression runs a much more chronic course today than it did before the advent of the drugs. In addition, long-term studies conducted during the past 20 years have regularly found that the unmedicated patients have better outcomes. These findings have led to the worry, first expressed by Giovanni Fava in 1994, that antidepressants induce a biological change in the brain that increases a person’s biological vulnerability to depression.<sup>31</sup>

In a review of this question, Rif El-Mallakh, an expert in mood disorders from the University of Louisville School of Medicine, concluded that SSRI antidepressants could induce a chronic depressive state he called tardive dysphoria. “Continued drug treatment may induce processes that are the opposite of what the medication originally produced,” he wrote. This may “cause a worsening of the illness, continue for a period of time after discontinuation of the medicine, and may not be reversible.”<sup>32</sup>

This problem of oppositional tolerance is likely a universal one with long-term use of psychiatric drugs. The drugs induce compensatory adaptations in the brain that are the opposite of their intended effect. Long-term outcome studies of other psychiatric disorders provide additional reason to worry that this might be so. Over the long-term, benzodiazepine users are likely to experience an increase in anxiety symptoms. Long-term outcomes for bipolar patients have notably deteriorated in the last forty years. Studies of stimulants as a treatment for ADHD have failed to find that the treatment provides a long-term benefit.

This is the case to be made against psychiatric drugs. They may provide a benefit over placebo in reducing target symptoms over the short term. However, they are not antidotes to a known pathology. Instead, they work by perturbing normal neurotransmitter function, which ultimately causes the brain to begin working in an abnormal manner. And, as the research literature reveals again

and again, this is not a process that, on the whole, produces beneficial long-term outcomes.

There may be many factors that have contributed to the rise in disability rates due to mental illness in the United States and other developed countries in the past 30 years. However, as this review reveals, this is also an outcome predicted by the scientific literature. Widespread use of drugs that induce abnormalities in brain function could be expected to have such an effect.

## REFERENCES

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- <sup>1</sup>U.S. Department of Health and Human Services, *Mental Health: A Report of the Surgeon General*(1999), 3, 78.
- <sup>2</sup> Medco. "America's State of Mind." November 2011.
- <sup>3</sup> Social Security Administration, annual statistical reports on the SSI and SSDI programs, 1987-2014.
- <sup>4</sup> R. Whitaker. *Anatomy of an Epidemic* (New York: Crown, 2014 edition):363-4.
- <sup>5</sup> J. Maas, "Pretreatment neurotransmitter metabolite levels and response to tricyclic antidepressant drugs," *Am J Psychiatry* 141 (1984):1159-71.
- <sup>6</sup> As cited by J. Lacasse, "Serotonin and depression: a disconnect between the advertisements and the scientific literature." *PLoS Med* 2 (2005):1211-16.
- <sup>7</sup> E. Nestler. *Molecular Neuropharmacology* (New York: McGraw Hill, 2002):392.
- <sup>8</sup> As cited by Lacasse, *ibid*.
- <sup>9</sup> S. Hyman, "Initiation and adaptation: A paradigm for understanding psychotropic drug action," *Am J Psychiatry* 153 (1996):151-61.
- <sup>10</sup> J. Cole, editor, *Psychopharmacology* (Washington, DC: National Academy of Sciences, 1959): 142, 386-7.
- <sup>11</sup> N. Lehrman, "Follow-up of brief and prolonged psychiatric hospitalization," *Comprehensive Psychiatry* 2 (1961):227-40.
- <sup>12</sup> R. Warner, *Recovery from Schizophrenia* (Boston: Routledge&Kegan Paul, 1985), 74.
- <sup>13</sup> P. Gilbert, "Neuroleptic withdrawal in schizophrenia patients," *Arch Gen Psychiatry* 52 (1995):173-88.
- <sup>14</sup> E. Stip, "Happy birthday neuroleptics!" *Eur Psychiatry* 17 (2002):115-9.
- <sup>15</sup> N. Schooler, "One year after discharge," *Am J of Psychiatry* 123 (1967):986-95.
- <sup>16</sup> J. Bockoven, "Comparison of two five-year follow-up studies," *Am J of Psychiatry* 132 (1975):796-801.
- <sup>17</sup> M. Rappaport, "Are there schizophrenics for whom drugs may be unnecessary or contraindicated?" *IntPharmacopsychiatry* 13 (1978):100-11.
- <sup>18</sup> S. Mathews, "A non-neuroleptic treatment for schizophrenia," *Schizophrenia Bulletin* 5 (1979):322-32.
- <sup>19</sup> W. Carpenter, "The treatment of acute schizophrenia without neuroleptics," *Am J of Psychiatry* 134 (1977):322-32.
- <sup>20</sup> G. Chouinard, "Neuroleptic-induced supersensitivity psychosis," *Am J of Psychiatry* 135 (1978):1409-10.

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- <sup>21</sup> G. Chouinard, "Severe cases of neuroleptic-induced supersensitivity psychosis," *Schizophrenia Research* 5 (1991):21-33.
- <sup>22</sup> A. Jablensky, "Schizophrenia: manifestations, incidence and course in different cultures," *Psychological Med* 20, monograph, (1992):1-95. See table on page 64 for medication usage by developed and developing countries.
- <sup>23</sup> R. Gur, "Subcortical MRI volumes in neuroleptic-naïve and treated patients with schizophrenia," *Am J of Psychiatry* 155 (1998):1711-17.
- <sup>24</sup> B. Ho. "Progressive structural brain abnormalities and their relationship to clinical outcome," *Arch Gen Psychiatry* 60 (2003):585-94.
- <sup>25</sup> N. Andreasen, "Longitudinal changes in neurocognition during the first decade of schizophrenia illness," *International Congress on Schizophrenia Research* (2005):348.
- <sup>26</sup> C. Dreifus, "Using imaging to look at changes in the brain," *New York Times*, September 16, 2008.
- <sup>27</sup> V. Aderhold. "Heinzfrontale Hirnvolumenminderung durch Antipsychotika?" *Der Nervenarzt*. May, 2014
- <sup>28</sup> M. Harrow, "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications," *J Nerv Ment Disease* 195 (2007):406-14.
- <sup>29</sup> M. Harrow, "Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery?" *Schizophrenia Bulletin* 39 (2013):962-5.
- <sup>30</sup> L. Wunderink, "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy," *JAMA Psychiatry* 70 (2013): 913-20.
- <sup>31</sup> See R. Whitaker. *Anatomy of an Epidemic* (New York: Crown, 2014 edition):148-71; 373-6.
- <sup>32</sup> R. El-Mallakh, "Tardive dysphoria: the role of long-term antidepressant use in inducing chronic depression." *Medical Hypotheses* 76 (2011):769-73.