Mad in America Science, Psychiatry and Community

Do Antipsychotics Worsen Long-term Schizophrenia Outcomes? Martin Harrow Explores the Question.

Robert Whitaker

March 26, 2013

Martin Harrow and Thomas Jobe have a new article coming out in Schizophrenia Bulletin that I wish would be read by everyone in our society with an interest in mental health. Harrow and Jobe, who conducted the best study of long-term schizophrenia outcomes that has ever been done, do not present new data in this article, but rather discuss the central question raised by their research: Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery? Or does it hinder it?

This is a paper that needs to be widely known. I wish every psychiatrist in the country would read it, and I wish that it would be widely discussed in the media too.

Now, Harrow's study produced findings that belied common wisdom. He and Jobe followed schizophrenia patients for 20 years, and those who got off antipsychotics, as a group, had much better outcomes. Over the long term, they were much more likely to be recovered, much more likely to work; they were much less likely to be experiencing psychotic symptoms; and they had better cognitive function and they were much less anxious. So how can you square that finding with research showing that when patients are withdrawn from antipsychotic medications, they relapse at a much higher rate? That is the evidence for long-term use of antipsychotics, and here is what Harrow and Jobe write: "We view the results from these discontinuation studies as involving a paradox."

Within six to 10 months following discontinuation, they write, 25% to 55% of schizophrenia patients withdrawn from their medications relapse. But, they note, "relapse rates are

considerably lower subsequently in discontinued schizophrenia patients who remain stable during these 6-10 months," and that "patients with schizophrenia not on antipsychotics for a prolonged period do not show this tendency to relapse when they remain unmedicated."

So the puzzle is this: Why is there such a high relapse rate in the immediate months following withdrawal, compared to the relapse rate when patients "remain unmedicated" after this initial discontinuation period?

The common perspective, they note, is that the high rate of relapse on discontinuation provides "evidence of the importance of antipsychotic medications in maintaining clinical stability by blocking dopamine receptors." But there is another perspective to consider:

"From an alternative perspective, the reduction in relapses and low relapse rate, after 6-10 months, could indicate a medicine-generated psychosis in the first 6-10 months, which then recedes. Using this perspective, the first 6-10 month increase in relapses after withdrawal may be influenced by biological conditions generated by the previous continuous use of antipsychotics, with this interacting with schizophrenia patients' underlying greater vulnerability to psychopathology. The discontinuation effect includes the potential of medication-generated buildup, prior to discontinuation, of supersensitive dopamine receptors, or the buildup of excess dopamine receptors, or supersensitive psychosis, as indicated by multiple studies by Seeman and others of dopamine-blocking agents using animal models."

This is key. Harrow and Jobe are stating that the high relapse rate that occurs in the drug-withdrawal studies may be an artifact of the patients having been on the drugs in the first place. The drugs induce a dopamine supersensitivity, which puts the patients at high risk of a "medicine-generated psychosis" upon drug withdrawal. And if this is so, then the entire evidence base for long-term use is based on a delusion: mistaking the high relapse rate for a sign that the "disease" is returning, when in truth it is related to prior drug exposure.

Next, Harrow and Jobe ask, what happens if people remain continuously on the drugs? "Well designed studies of dopamine blocking agents using animal models provide strong evidence that 'breakthrough supersensitivity during ongoing antipsychotic treatment undermines treatment efficacy,' " they write. In other words, even if people stay on the drugs, the drugs may stop working, and the reason is that the drugs make the patients more biologically vulnerable to psychosis.

This raises the next question: What do longitudinal studies tell us about outcomes for schizophrenia patients who, shortly after an acute episode, get off antipsychotics? These studies, they write, "could suggest that, long-term, schizophrenia patients with less or no antipsychotic use after the acute phase may show better outcomes and more periods of recovery."

In their own research they write, those who stayed continuously on antipsychotics over 15-year and 20-year periods experienced "considerable psychopathology and few sustained periods of recovery." While some continuously medicated patients had a low level of psychotic symptoms, for most patients so treated "the psychotic symptoms were frequent and, while not intense, were at least of moderate severity, usually with some disruption of functioning." In contrast, the schizophrenia patients "who were untreated for many years showed significantly better outcomes than those on antipsychotics."

Now, when Harrow and Jobe reported their 15-year outcomes, Harrow and Jobe noted that it was the good prognosis patients who were most likely to go off, and so many readers took that as the explanation for the better outcomes for those who got off the drugs: the difference in outcomes could be explained by a difference in prognostic status. But in their 15-year paper, Harrow and Jobe also observed that the good prognosis patients who got off antipsychotics did better than the good prognosis patients who stayed on, and that the bad prognosis patients who got off the drugs did better than those who stayed on. And in their new paper, in the *Schizophrenia Bulletin*, they directly address this fact:

"Many patients who left treatment for multiyear periods and had favorable outcomes were good prognostic schizophrenia patients, giving some confirmation to earlier views about the importance of prognostic factors. However, some patients treated for many years with antipsychotics also were good prognostic patients who did not show favorable outcomes."

Furthermore, they note, other longitudinal studies have "found similar results." They cite studies by Courtney Harding, the Chestnut Lodge study, the Alberta Hospital Studies in Canada, and those of M. Bleuler in Europe. Finally, Harrow and Jobe note that in the studies by the World Health Organization, researchers "found better outcomes in many developing countries where only a small percentage of schizophrenia patients were treated with antipsychotics."

Thus, in this review, they sum up the big puzzle regarding the evidence base for antipsychotics. Do they show efficacy over the short term? Yes. Do patients withdrawn from the drugs relapse at higher rates than those maintained on the medications? Yes. But is there evidence that over the long term, the drugs may worsen outcomes? Yes.

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

The conclusion they draw is a straightforward one: our current paradigm for treating schizophrenia, which emphasizes continual lifelong use of antipsychotics, needs to be fundamentally rethought.

"Overall, the longitudinal studies cited do not provide conclusive proof of a causal relationship between being off medications and being psychosis free. They do clearly indicate that not all schizophrenia patients need continuous antipsychotics for a prolonged period, providing extensive evidence of samples of medication-free schizophrenia patients with favorable outcomes . . . The longitudinal studies indicate the importance of further research on how many schizophrenia patients profit from continuous administration of antipsychotics over a prolonged period, what factors identify and separate schizophrenia patients who do not need prolonged antipsychotic treatment, and whether or not prolonged use of antipsychotics is harmful for some or many patients."

This is a manifesto for change, and much to my amazement, it will be published in the *Schizophrenia Bulletin*. This is a mainstream journal, and its editors surely wouldn't publish this discussion unless they knew that the scientific evidence warranted it.

This is a hopeful moment, and an opportunity to be seized. I would urge Madinamerica readers to help seize that opportunity. We can ask those who prescribe antipsychotics and providers of service to read this article in *Schizophrenia Bulletin* and consider its implications. I hope that E. Fuller Torrey will read it, and that other prominent defenders of the common wisdom will read it too. I hope that Thomas Insel, director of the National Institute of Mental Health, will read it and blog about it. In this way, perhaps this article can trigger a serious discussion, *within mainstream psychiatry*, about the wealth of evidence showing that our current paradigm of care, regarding the use of antipsychotics, needs to be fundamentally rethought. And that it needs to be rethought with this question in mind: we need to assess, as Harrow and Jobe wrote, whether "prolonged use of antipsychotics is harmful for some or many patients."

That is a societal discussion we have needed to have for a long, long time.

This entry was posted in Antipsychotics, Blogs, Featured Blogs, Schizophrenia/Psychotic Disorders by Robert Whitaker. Bookmark the permalink.

http://understandingpsychosisexploringalternatives.files.wordpress.com/2011/12/intar-2011-toronto-robert-whitaker-anatomy-of-an-epidemic-2.pdf