

## Does Long-Term Treatment of Schizophrenia With Antipsychotic Medications Facilitate Recovery?

Martin Harrow\* and Thomas H. Jobe

Department of Psychiatry, University of Illinois College of Medicine, Chicago, IL

\*To whom correspondence should be addressed; 1601 W. Taylor (M/C 912), PI, Rm. 445, Chicago, IL 60612, US; tel: 312-996-3585, fax: 312-413-4503, e-mail: [Mharrow@psych.uic.edu](mailto:Mharrow@psych.uic.edu)

**Antipsychotic medications are viewed as cornerstones for both the short-term and long-term treatment of schizophrenia. However, evidence on long-term (10 or more years) efficacy of antipsychotics is mixed. Double-blind discontinuation studies indicate significantly more relapses in unmedicated schizophrenia patients in the first 6-10 months, but also present some potentially paradoxical features. These issues are discussed.**

*Key words:* psychosis/longitudinal studies/unmedicated patients/outcome

### Introduction

As a consequence of positive results from numerous short-term (1–2 years) studies, prolonged use of antipsychotic medications over a long period has become the current standard of care in the field. Thus, antipsychotic medications are viewed as the cornerstone of treatment, in both the short-term and the long-term treatments of patients with schizophrenia.<sup>1,2</sup>

American Psychiatric Association (APA) guidelines<sup>3</sup> suggest clinicians to consider antipsychotic discontinuation for schizophrenia patients who have been symptom free for a year or more. Nevertheless, many clinicians keep schizophrenia patients on antipsychotics indefinitely assuming that the medication is essential for continued stability.

Antipsychotics are also viewed by some as leading, over a prolonged period, to eventual recovery for some patients with schizophrenia. A comprehensive review from the World Psychiatric Association section on Pharmacopsychiatry notes “Antipsychotic treatment has a significant impact on the long-term course of schizophrenic illness and can significantly facilitate recovery.”<sup>4,p.31</sup>

Prolonged use of antipsychotic medications is viewed as a key factor in treatment for schizophrenia, but there is very little systematic evidence for the long-term benefits of antipsychotics. There is even some longitudinal data suggesting the opposite.

### Therapeutic Benefits: 3 Different Phases of Treatment

Therapeutics for schizophrenia can be considered in 3 different phases. The first is the period of acute and intense psychosis often found at the acute phase of hospitalization. The second is the 2- to 3-year period after the acute phase. The third is the period from 3 years onward. Only the first 2 of these periods have been investigated systematically in schizophrenia.

In addition to extensive acute phase studies, the potential improvement during the first 1–2 years has been studied even more frequently in double-blind, drug-placebo studies. These studies have produced positive results reviewed in the Schizophrenia Patient Outcomes Research Team project reports and many others, showing remission in some or many patients with schizophrenia.<sup>1,2</sup> The numerous short-term, double-blind studies, often regarded as proof of short-term and long-term efficacies of antipsychotics, provide some scientific rigor. However, they are imperfect because of the following reasons: (a) they are not precise as a model for *all* patients with schizophrenia because these studies do not include the 20%–40% of schizophrenia patients who have left our treatment systems<sup>5–7</sup> and are based only on the 60%–80% of patients in our treatment systems; (b) they often assess “remission” rather than complete recovery of symptoms,<sup>8</sup> with many patients with mild-moderate levels of psychotic symptoms viewed as “in remission”<sup>9</sup>; and (c) much of the short-term and long-term evidence on antipsychotics is based on discontinuation studies, which present complicated issues.

### Long-Term Treatment With Antipsychotic Medications and the Discontinuation Paradox

Part of the evidence leading to optimism about the long-term treatment of schizophrenia with antipsychotic medications is based on the results of

short-term discontinuation studies. We view the results from these discontinuation studies as involving a paradox. Discontinuation after prolonged use of antipsychotics presents a striking paradox because (a) within the first 6–10 months after discontinuation, 25%–55% of schizophrenia patients discontinued from antipsychotics relapse.<sup>1,10</sup> (b) In contrast, relapse rates are considerably lower subsequently in discontinued schizophrenia patients who remain stable during these 6–10 months.<sup>10,11</sup> Many investigators have emphasized this disparity.<sup>10,11</sup> (c) In addition, patients with schizophrenia not on antipsychotics for a prolonged period do not show this tendency to relapse when they remain unmedicated.<sup>6,12</sup>

Fitting this paradox on the high initial rates of relapse, withdrawal studies by Viguera and Baldessarini<sup>10</sup> and others indicate that when vulnerable patients are treated with antipsychotics for a prolonged period, this increases their chances of relapsing if they subsequently discontinue.<sup>11</sup> Expressed differently, they may “experience relapse rates that are temporarily greater than predicted in the ordinary course of the illness”<sup>13</sup>; “the increased incidence of relapse following drug withdrawal is concentrated in the first few months and trails off thereafter”<sup>11</sup>; or, as Gilbert, in her classic literature summary, noted “risk was nonlinearly distributed over time and ... much of the excess risk after stopping treatment arose early.”<sup>1</sup>

From one perspective, the high rate of relapse on discontinuation could (a) provide evidence of the importance of antipsychotic medications in maintaining clinical stability by blocking dopamine receptors. This important outlook is assumed by most in the field. From an alternate perspective, (b) 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<sup>14</sup> and others<sup>13</sup> of dopamine-blocking agents using animal models.

Well-designed studies of dopamine-blocking agents using animal models provide strong evidence that “break-through supersensitivity during ongoing antipsychotic treatment undermines treatment efficacy.”<sup>14</sup> There also could be other undiscovered genetic and epigenetic pathways toward dopamine receptor resistance. Regardless of which outlook is correct, while discontinuation is important, it may be a problem for some, but not all, schizophrenia patients. It would be important to determine which types of patients are vulnerable to antipsychotic

discontinuation effects. While such mechanisms involve 1 possible explanation of the discontinuation paradox, this is far from proven.

Standard double-blind studies to determine whether some or many medicated and unmedicated schizophrenia patients do well on a longitudinal basis are not possible when considerable length (10 or more years) is involved. As Leucht, reviewing double-blind studies, notes “... nothing is known about the effects of antipsychotic drugs compared to placebo after three years.”<sup>15</sup> Other research designs of matched medicated and unmedicated samples of schizophrenia patients are needed. One research design to study potential discontinuation effects further involves testing and comparing for subsequent relapses 3 matched samples. (a) One sample would involve assessing schizophrenia patients who have been on antipsychotics for at least a 1- to 2-year period who are not being withdrawn from antipsychotics. (b) The second would involve assessing a matched sample of patients who have been on antipsychotics for a 1- to 2-year period and have then been gradually withdrawn from antipsychotics. (c) The third would involve assessing a matched unmedicated schizophrenia sample of patients who have not been on antipsychotics for a year or longer, to avoid potential discontinuation effects. This study design would throw further light on the discontinuation paradox and on the efficacy of long-term antipsychotic treatment.

### Evidence From Longitudinal Studies

In contrast to optimistic views from short-term studies, a series of longitudinal studies of samples of schizophrenia patients in the United States, Canada, and other countries raise considerable questions on optimistic expectations about long-term antipsychotic treatment. Even prior to the longitudinal period, a major review by Leucht, Davis, and colleagues has raised questions about long-term efficacy, noting “The meta-regression suggested that antipsychotic drugs might lose their effectiveness with time.”<sup>16</sup> Other longitudinal studies 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.

Our own research (the Chicago Followup Study) on a sample of schizophrenia patients who were treated continuously with antipsychotics over 15-year and 20-year periods have shown considerable psychopathology and few sustained periods of recovery.<sup>5,6,17</sup> Our data from the Chicago Followup Study show some continuously medicated schizophrenia patients with a low level of psychotic symptoms, but for most schizophrenia patients continuously on antipsychotics for prolonged periods, the psychotic symptoms were frequent and, while not intense, were at least of moderate severity, usually with some disruption of functioning.<sup>5,6</sup> Other important studies have shown similar findings, noting the lack

of complete recovery in the short-term treatment of schizophrenia.<sup>18</sup> In addition, in our longitudinal studies, the sample of schizophrenia patients who were untreated for many years showed significantly better outcomes than did those on antipsychotics.<sup>5,6,17</sup> Many patients who left treatment for multiyear periods and had favorable outcomes were good prognostic schizophrenia patients,<sup>5</sup> giving some confirmation to earlier views about the importance of prognostic factors.<sup>19</sup> However, some patients treated for many years with antipsychotics also were good prognostic schizophrenia patients who did not show favorable outcomes, suggesting early prognostic status is one important, but not the only, influence on long-term outcome. In regard to recovery, remission, and stable long-term courses, greater focus is needed to differentiate patients who are stable and symptom free from patients who are stable with persistent symptoms of psychosis.

Other longitudinal studies have found similar results. This includes important longitudinal studies such as the Vermont studies of C. Harding<sup>20,21</sup> and the Chestnut Lodge Study.<sup>22</sup> In Canada, the Alberta Hospital Studies of Bland (1978) found similar results. Overseas the longitudinal studies of M. Bleuler (1978) led to his commenting about relapses for many schizophrenia patients treated with antipsychotics. The important World Health Organization (WHO) Study and the Determinants of Outcome of Severe Mental Disorders (DOSMED) Study by Edgerton and Cohen found better outcomes in many developing countries where only a small percentage of schizophrenia patients were treated with antipsychotics.<sup>12</sup>

Other evidence, also from longitudinal studies, suggest that long-term outcome for schizophrenia in the modern era is not much better than it was 60–80 years ago.<sup>23,24</sup> In regard to relapses, our own evidence indicates that many schizophrenia patients who have not been treated with antipsychotic medications for prolonged periods show a low rate of relapse over the next 5-year period.<sup>6</sup>

We have noted above 2 possible alternate factors responsible for the discontinuation paradox. One is the relatively high rate of relapses in the discontinuation paradox may be due to the previous importance of antipsychotics in blocking dopamine receptors. The second alternative view is that the relatively high rate of relapses in the discontinuation paradox may be due to medicine-generated buildup, prior to discontinuation, of an excess of dopamine receptors, or the prior buildup of supersensitive dopamine receptors, or supersensitive psychosis.<sup>11,14</sup> Possibly both alternatives are true but for different subgroups of schizophrenia patients.

Because there is considerable outcome heterogeneity in schizophrenia patients regardless of treatment employed, a more directed research agenda involving subgrouping according to response to treatment is needed. As noted by APA,<sup>3</sup> there are benefits for early acute schizophrenia patients treated with antipsychotics (potential symptom

reduction or “remission”) with the possibility that many patients stay in long-term remission. However, research is required distinguishing which types and what percentage of schizophrenia patients stay in remission with long-term antipsychotic treatment and whether some or many of them achieve complete recovery. Overall discussion of the risk-benefit profiles for different subgroups of schizophrenia patients in different stages of illness seems warranted.

At present, valid individual criteria and outcome predictors are lacking that would allow us to distinguish between schizophrenia patients who need extended long-term antipsychotic treatment and those who could be withdrawn after 1–2 years. Intensified research is needed on the benefits and risks associated with long-term antipsychotic treatment.

### Some Issues About Antipsychotic Medications

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. To name a few, the development of insulin resistance in diabetes over time, beta-adrenergic resistance over time in asthma, the development of tamoxifen resistance in breast cancer over time, steroid resistance over time in autoimmune diseases, antibiotic resistance in chronic infection, and many other medical drug treatments in long-term situations. Some developments of treatment resistance are currently thought to be related to receptor transformation and resistance from interaction with the genome either by direct feed-back cascades or by epigenetic effects.

### Conclusions

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.<sup>6,12,22</sup> Is it at least a moderate-sized number of schizophrenia patients who do well, longitudinally, without medications? This important issue needs longitudinal research for more precise answers. 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.

The above-cited longitudinal results from many different countries and different types of schizophrenia patients provide data bearing on issues about long-term treatment. Discussions by Whitaker, Moncrieff, and others question long-term antipsychotic treatment.<sup>25-27</sup> These disparate views, research by WHO and DOSMED in developing countries,<sup>12</sup> and our own longitudinal studies<sup>5-7</sup> should be considered as prompts for further long-term outcome research on this important issue.

### Funding

National Institute of Mental Health (MH-26341, MH-068688); Foundation for Excellence in Mental Health Care (to Dr Harrow).

### Acknowledgments

The authors wish to acknowledge Robert Faull for his help in conceptual analyses. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

### References

1. Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry*. 1995;52:173-188.
2. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60:553-564.
3. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161:1-56.
4. Tandon R, Belmaker RH, Gattaz WF, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res*. 2008;100:20-38.
5. Harrow M, Jobe TH. Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: a 15-year multifollow-up study. *J Nerv Ment Dis*. 2007;195:406-414.
6. Harrow M, Jobe TH, Faull RN. Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. *Psychol Med*. 2012;42:2145-2155.
7. Jobe T, Harrow M. Schizophrenia course, long-term outcome, recovery, and prognosis. *Curr Dir Psychol Sci*. 2010;19:220-225.
8. Silverstein SM, Bellack AS. A scientific agenda for the concept of recovery as it applies to schizophrenia. *Clin Psychol Rev*. 2008;28:1108-1124.
9. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162:441-449.
10. Viguera AC, Baldessarini RJ, Hegarty JD, van Kammen DP, Tohen M. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Arch Gen Psychiatry*. 1997;54:49-55.
11. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (super-sensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand*. 2006;114:3-13.
12. Jablensky A, Sartorius N. What did the WHO studies really find? *Schizophr Bull*. 2008;34:253-255.
13. Tranter R, Healy D. Neuroleptic discontinuation syndromes. *J Psychopharmacol*. 1998;12:401-406.
14. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci*. 2007;27:2979-2986.
15. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2012;5:CD008016.
16. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379:2063-2071.
17. Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. *Schizophr Bull*. 2005;31:723-734.
18. Ventura J, Subotnik KL, Guzik LH, et al. Remission and recovery during the first outpatient year of the early course of schizophrenia. *Schizophr Res*. 2011;132:18-23.
19. Carpenter WT Jr, Stephens JH. Prognosis as the critical variable in classification of the functional psychoses. *J Nerv Ment Dis*. 1982;170:688-691.
20. Harding CM, Brooks GW, Ashikaga T, Strauss JS, Breier A. The Vermont longitudinal study of persons with severe mental illness, II: Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *Am J Psychiatry*. 1987;144:727-735.
21. Harding CM, Zahniser JH. Empirical correction of seven myths about schizophrenia with implications for treatment. *Acta Psychiatr Scand Suppl*. 1994;384:140-146.
22. Fenton WS, McGlashan TH. Sustained remission in drug-free schizophrenic patients. *Am J Psychiatry*. 1987;144:1306-1309.
23. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry*. 1994;151:1409-1416.
24. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia [published online ahead of print November 20, 2012]. *Schizophr Bull*. doi:10.1093/schbul/sbs130.
25. Whitaker R. *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America*. New York, NY: Broadway Books; 2011.
26. Whitaker R. *Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill*. New York, NY: Basic Books; 2010.
27. Moncrieff J. *The Myth of the Chemical Cure: A Critique of Psychiatric Drug Treatment*. Basingstoke, UK: Palgrave Macmillan; 2009.