The Case for Selective Use of Antipsychotics

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The Evidence for Our Current Use of Antipsychotics

Short-term Use

Antipsychotics reduce target symptoms of a disorder better than placebo in six-week trials.

Long-term Use

In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications.

Clinical Perceptions

The physician sees that the medications often work upon initial use, and sees that patients often relapse when they go off the medications.

The Relapse Literature

In a 1995 review of relapse studies, Patricia Gilbert reported:

- 53% of drug-withdrawn patients relapsed within 10 months.

- 16% of those maintained on antipsychotics relapsed within ten months.

Conclusion: "The efficacy of these medications in reducing the risk of psychotic relapse has been well documented."

Source: P. Gilbert, "Neuroleptic Withdrawal in Schizophrenic Patients," *Arch Gen Psychiatry 52 (1995):* 173-188.

Flaws in the Relapse Literature

A. In most of the relapse studies, the antipsychotics were abruptly withdrawn, a study design that increased the risk of relapse.

In a further review of the relapse studies, Ross Baldessarini at Harvard Medical School divided the drug-withdrawn cohorts into "abrupt-withdrawal" and "gradual withdrawal" groups. He found:

- The proportion of patients relapsing per month was "threefold greater after abrupt discontinuation of treatment" than with gradual withdrawal.

- In three gradual withdrawal studies (n = 58), only 32.5% relapsed within six months, and those who didn't relapse in that period had a good chance of remaining well indefinitely. "The later risk of relapsing was remarkably limited," Baldessarini and his colleagues wrote.

Source: R. Baldessarini. "Neuroleptic withdrawal in schizophrenic patients." *Arch Gen Psychiatry 52 (1995):* 189-191. A. Viguera. "Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment." *Arch Gen Psychiatry* 54 (1997):49-55.

B. The relapse studies do not provide evidence that antipsychotics are improving the long-term course of schizophrenia.

> "After fifty years of neuroleptics, are we able to answer the following simple question: Are neuroleptics effective in treating schizophrenia? [There is] no compelling evidence on the matter, when 'long-term' is considered."
>
> --Emmanuel Stip, *European Psychiatry* (2002)

Source: E. Stip. "Happy birthday neuroleptics! 50 years later: la folie du doute." *Eur Psychiatry* 17 (2002):115-9.

The Case For Selective Use of Antipsychotics

A review of the outcomes literature for antipsychotics reveals:

1. There is a subset of first-episode psychotic patients who, if treated with psychosocial care but without antipsychotics, can recover.

2. There is a significant percentage of schizophrenia patients who, once they become stable on antipsychotics, can then successfully withdraw from the medications.

3. There is evidence that, over the long-term, antipsychotics may induce changes in the brain that may make a person more biologically vulnerable to psychosis.

4. In 1992, a psychiatric district in northern Finland adopted a selective-use protocol for first episode patients, and it now has the best reported long-term outcomes in the developed world.

Schizophrenia Outcomes, 1945-1955

• At end of three years following hospitalization, 73 percent of first-episode patients admitted to Warren State Hospital from 1946 to 1950 were living in the community.

• At the end of six years following hospitalization, 70% of 216 first-episode patients admitted to Delaware State Hospital from 1948 to 1950 were living in the community.

• In studies of schizophrenia patients in England, where the disorder was more narrowly defined, after five years 33% enjoyed a complete recovery, and another 20 percent a social recovery, which meant they could support themselves and live independently.

Source: J Cole, *Psychopharmacology* (1959): 142, 386-7. R. Warner, Recovery from Schizophrenia (1985): 74.

Discharge Rates for Schizophrenia Patients in California, 1956-1957

In 1956:

- There were 673 patients newly hospitalized for schizophrenia.
- Of this group, 428 were treated without antipsychotics.
- Sixty-seven percent of the unmedicated patients were discharged within six months, and 88% at 18 months.

In 1957:

- There were 740 patients newly hospitalized for schizophrenia.
- Of this group, 384 were treated without antipsychotics.
- Seventy-one percent of the unmedicated patients were discharged within six months.

Source: L. Epstein. "An approach ot the effect of ataraxic drugs on hospital release rates." *Am J Psychiatry* 119 (1962):36-47.

A Retrospective Comparison of Outcomes in Pre-Drug and Drug Era

Relapse Rates Within Five Years of Discharge

1947 cohort: 55%
1967 cohort: 69%

Functional Outcomes

1947 cohort: 76% were successfully living in the community at end of five years

1967 cohort: They were much more "socially dependent"--on welfare and needing other forms of support--than the 1947 cohort.

Source: Bockoven, J. "Comparison of two five-year follow-up studies," *Am J Psychiatry* 132 (1975): 796-801.

Bockoven's Conclusion:

"Rather unexpectedly, these data suggest that psychotropic drugs may not be indispensable. Their extended use in aftercare may prolong the social dependency of many discharged patients."

Rappaport's Study: Three-Year Outcomes

Medication use (in hospital/after discharge)	Number of Patients	Severity of Illness (1= best outcome; 7 = worst outcome)	Rehospitalization
No meds/off	24	1.70	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.

Rappaport's 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. 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."

Loren Mosher's Soteria Project

Results:

At end of two years, the Soteria patients had "lower psychopathology scores, fewer [hospital] readmissions, and better global adjustment."

In terms of antipsychotic use, 42% had never been exposed to the drugs, 39% had used them temporarily, and 19% had used them regularly throughout the two-year followup.

Source: Bola, J. "Treatment of acute psychosis without neuroleptics." *J Nerv Ment Disease* 191 (2003):219-29.

Loren Mosher's Conclusion

"Contrary to popular views, minimal use of antipsychotic medications combined with specially designed psychosocial intervention for patients newly identified with schizophrenia spectrum disorder is not harmful but appears to be advantageous. We think the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined."

William Carpenter's In-House NIMH Study, 1977

- Compared 27 schizophrenia patients treated with psychotherapy and no antipsychotics to 22 patients treated with both psychotherapy and antipsychotics.

- Those treated without drugs were discharged sooner (108 days on average versus 126 days.)

- 35% of the group treated without drugs in the hospital relapsed within a year after discharge, versus 45% of the medicated group.

- The unmedicated group also suffered less from depression, blunted emotions, and retarded movements.

Source: Carpenter, W. "The treatment of acute schizophrenia without drugs." *Am J Psychiatry* 134 (1977):14-20.

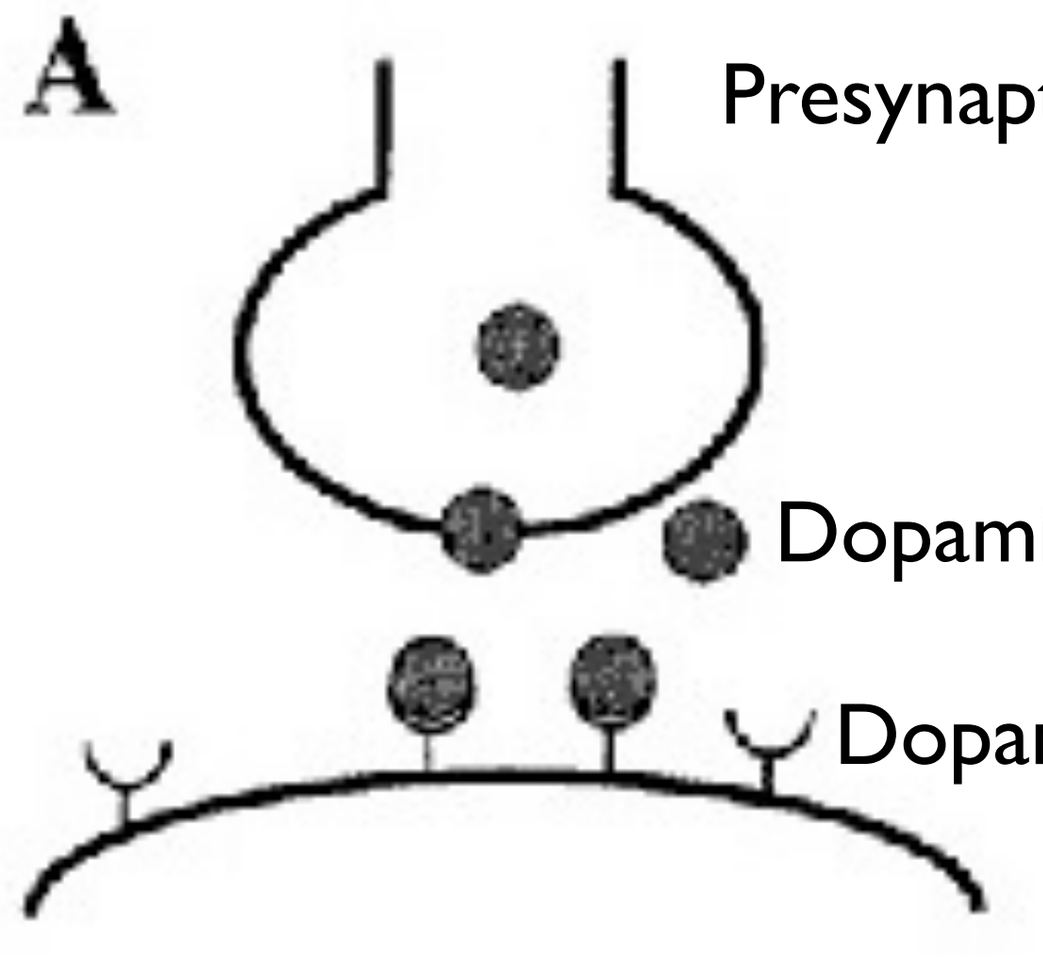
William Carpenter Raises a Question:

"There is no question that, once patients are placed on medication, they are less vulnerable to relapse if maintained on neuroleptics. But what if these patients had never been treated with drugs to begin with? . . . We raise the possibility that antipsychotic medication may make some schizophrenic patients more vulnerable to future relapse than would be the case in the normal course of the illness."

Source: Carpenter, W. "The treatment of acute schizophrenia without drugs." *Am J Psychiatry* 134 (1977):14-20.

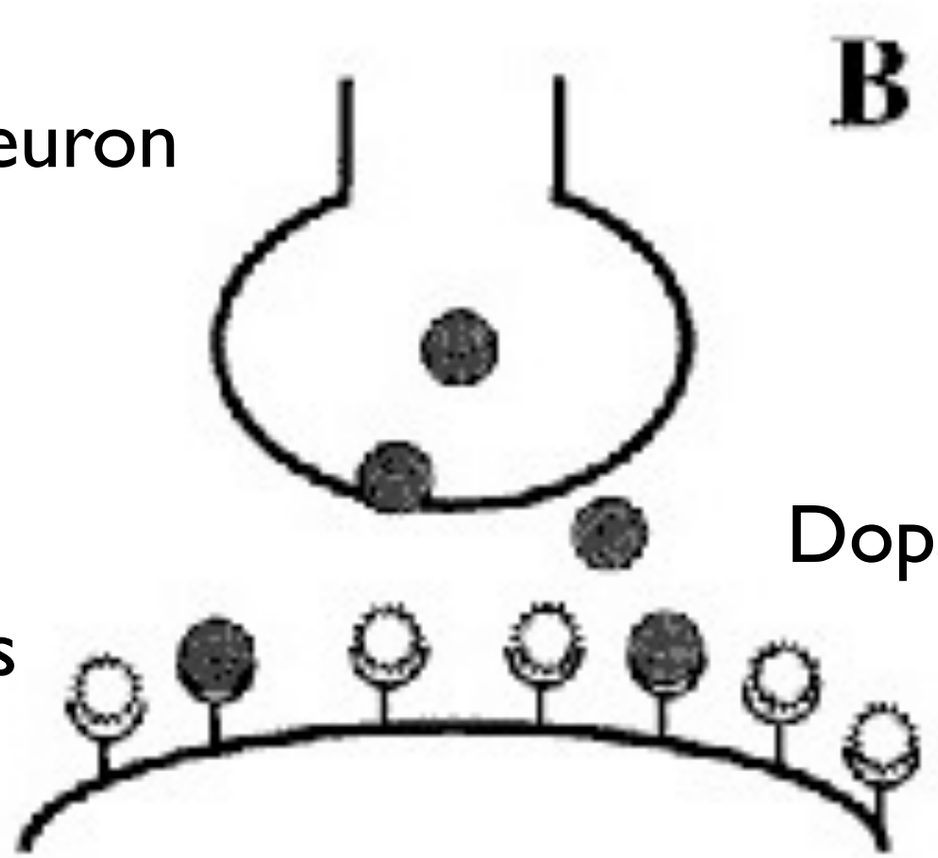
The Dopamine Supersensitivity Theory

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

Presynaptic neuron



Antipsychotic blocks receptors

Dopamine

Postsynaptic neuron

Brain increases receptors to compensate for drug blockade

The Consequences of Dopamine Supersensitivity

"Neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms . . . An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness."

Guy Chouinard and Barry Jones, McGill University

Source: Chouinard, G. "Neuroleptic-induced supersensitivity psychosis," *Am J Psychiatry* 135 (1978): 1409-10; and "Neuroleptic-induced supersensitivity psychosis," *Am J Psychiatry* 137 (1980): 16-20.

Study of Drug-Induced Tardive Psychosis

In 1982, Chouinard and Jones reported that 30% of the 216 schizophrenia outpatients they studied showed sign of tardive psychosis, which meant their psychosis was becoming chronic. When this happens, they wrote, "the illness appears worse" than ever before. "New schizophrenic symptoms of greater severity will appear."

Source: Chouinard, C. "Neuroleptic-induced supersensitivity psychos, the 'Hump Course,' and tardive dyskinesia." *J Clin Psychopharmacology* 2 (1982):143-44. Also, Chouinard, C. "Severe cases of neuroleptic-induced supersensitivity psychosis," *Schiz Res* 5 (1991):21-33.

WHO Cross-Cultural Studies, 1970s/1980s

• In both studies, which measured outcomes at the end of two years and five years, the patients in the three developing countries, India, Nigeria, and Colombia, had a "considerably better course and outcome" than in the U.S. and six other developed countries.

•The WHO researchers concluded that "being in a developed country was a strong predictor of not attaining a complete remission."

• They also found that "an exceptionally good social outcome characterized the patients" in developing countries.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." *Psychological Medicine* 20, monograph (1992):1-95.

WHO Findings, Continued

Medication usage:

16% of patients in the developing countries were regularly maintained on antipsychotics, versus 61% of the patients in rich countries.

15-year to 20-year followup:

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.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." Psychological Medicine 20, monograph (1992):1-95. See table on page 64 for medication usage. For followup, see Hopper, K. "Revisiting the developed versus developing country distinction in course and outcome in schizophrenia." *Schizophrenia Bulletin* 26 (2000):835-46.

The Vermont Longitudinal Study

Courtenay Harding conducted a 30-year followup of 269 schizophrenia patients released from the back wards of Vermont State Hospital in the 1950s.

In 1987, Harding reported that "at least 25% to 50% were completely off their medications, suffered no further signs and symptoms of schizophrenia, and were functioning well."

Harding concluded: It is a "myth" that schizophrenia "patients must be on medication all their lives. It may be a small percentage who need medication indefinitely."

Source: C. Harding. "The Vermont Longitudinal Study of Persons With Severe Mental Illness." *Am J Psychiatry* 144 (1987): 718-726. C. Harding. "Empirical correction of seven myths about schizophrenia with implications for treatment." *Acta Psychiatr Scand* 90, suppl 384 (1994):140-146.

Martin Harrow's Long-Term Study of Psychotic Patients

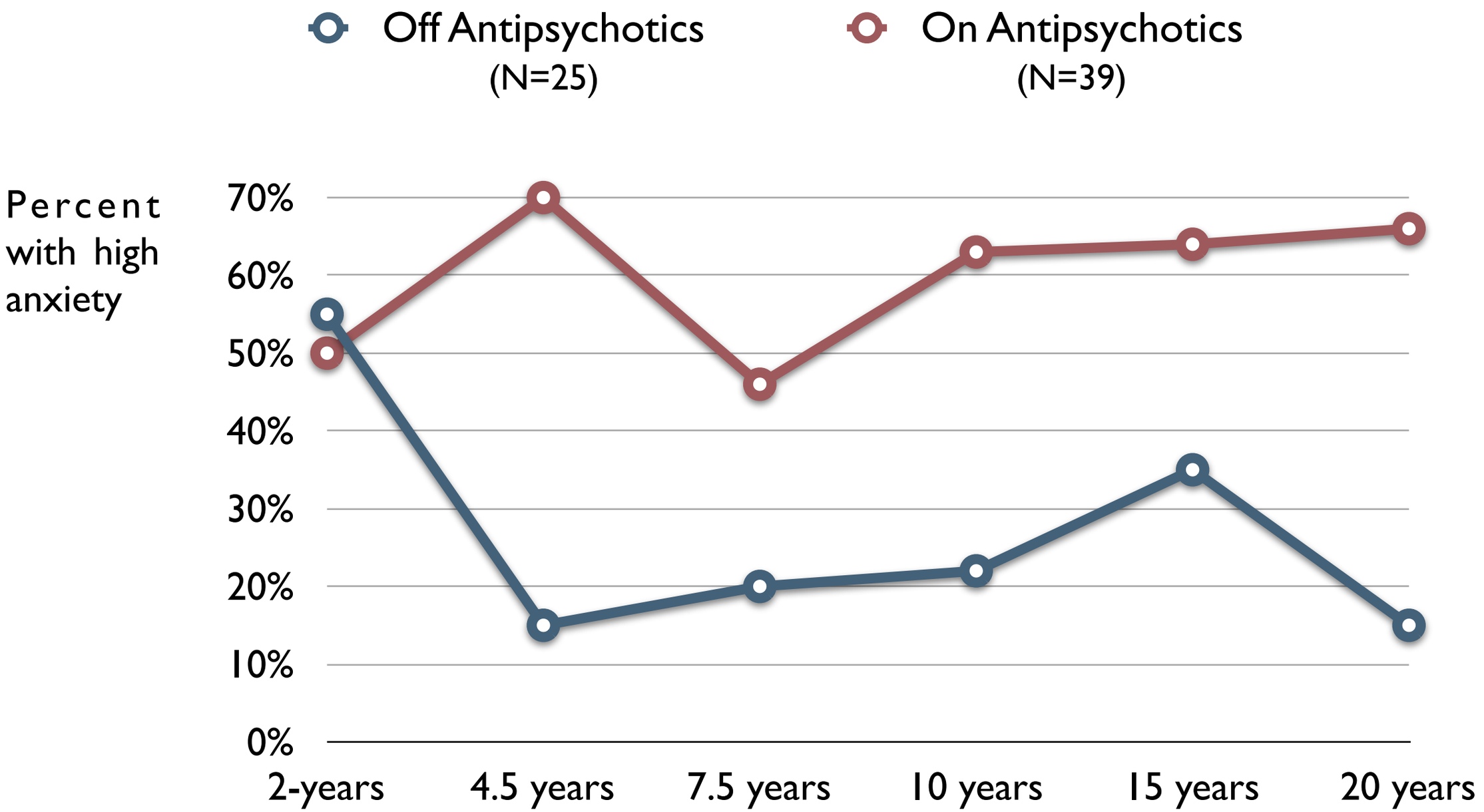
Patient Enrollment

- 64 schizophrenia patients
- 81 patients with other psychotic disorders
  - 37 psychotic bipolar patients
  - 28 unipolar psychotic patients
  - 16 other milder psychotic disorders

- Median age of 22.9 years at index hospitalization
- Previous hospitalization
  - 46% first hospitalization
  - 21% one previous hospitalization
  - 33% two or more previous hospitalizations

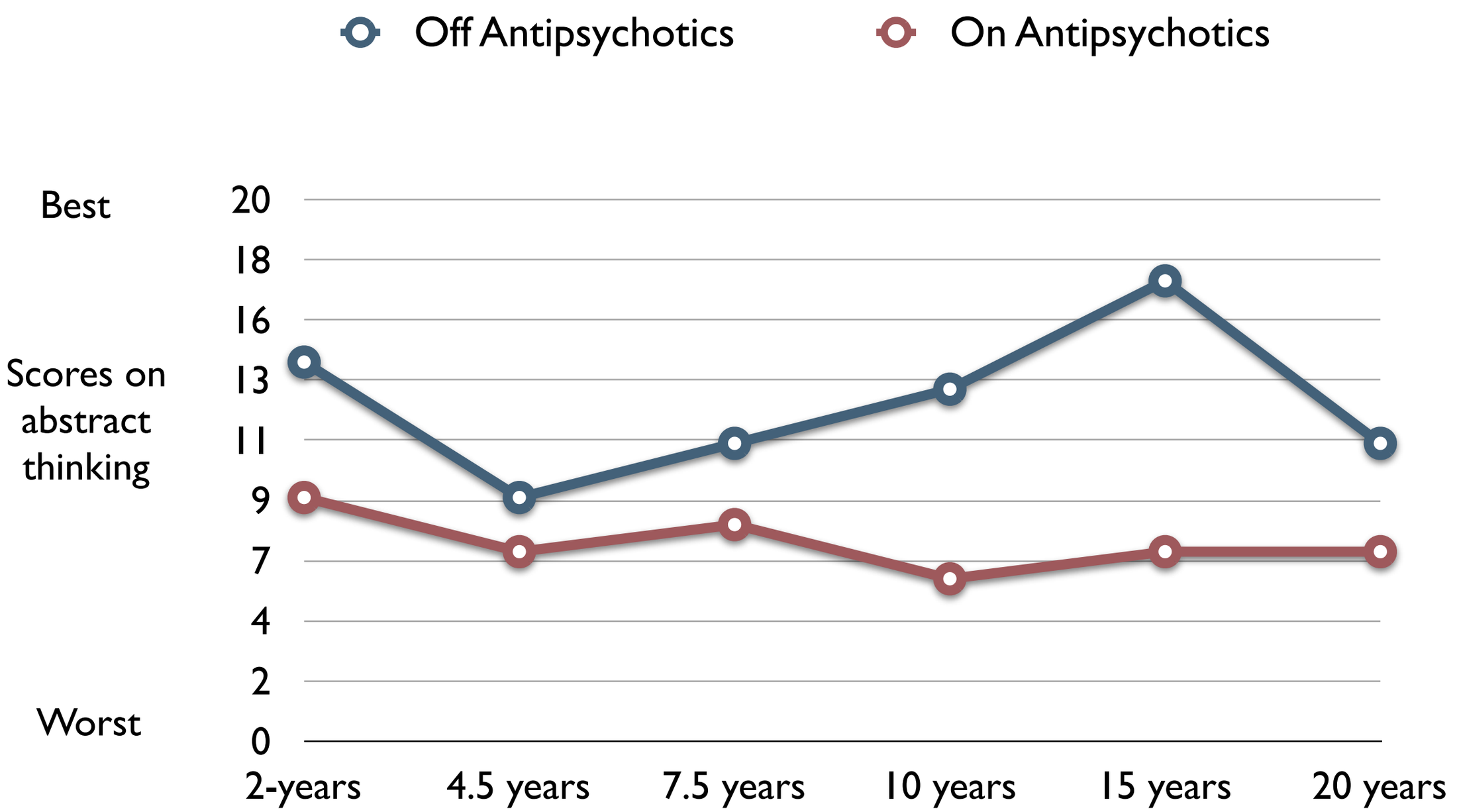
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Anxiety Symptoms of Schizophrenia Patients



Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Cognitive Function of Schizophrenia Patients



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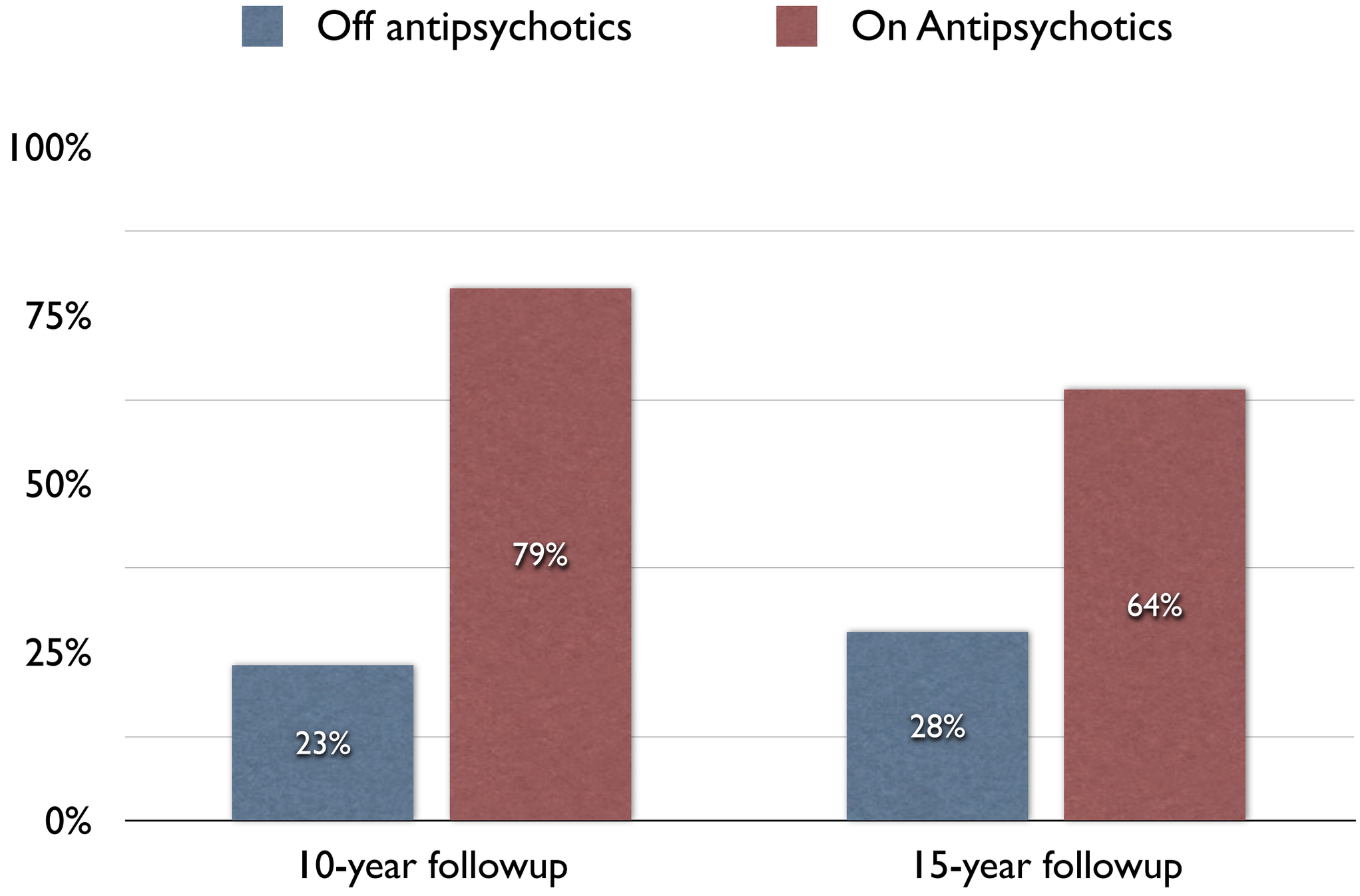
Psychotic Symptoms in Schizophrenia Patients Over the Long Term



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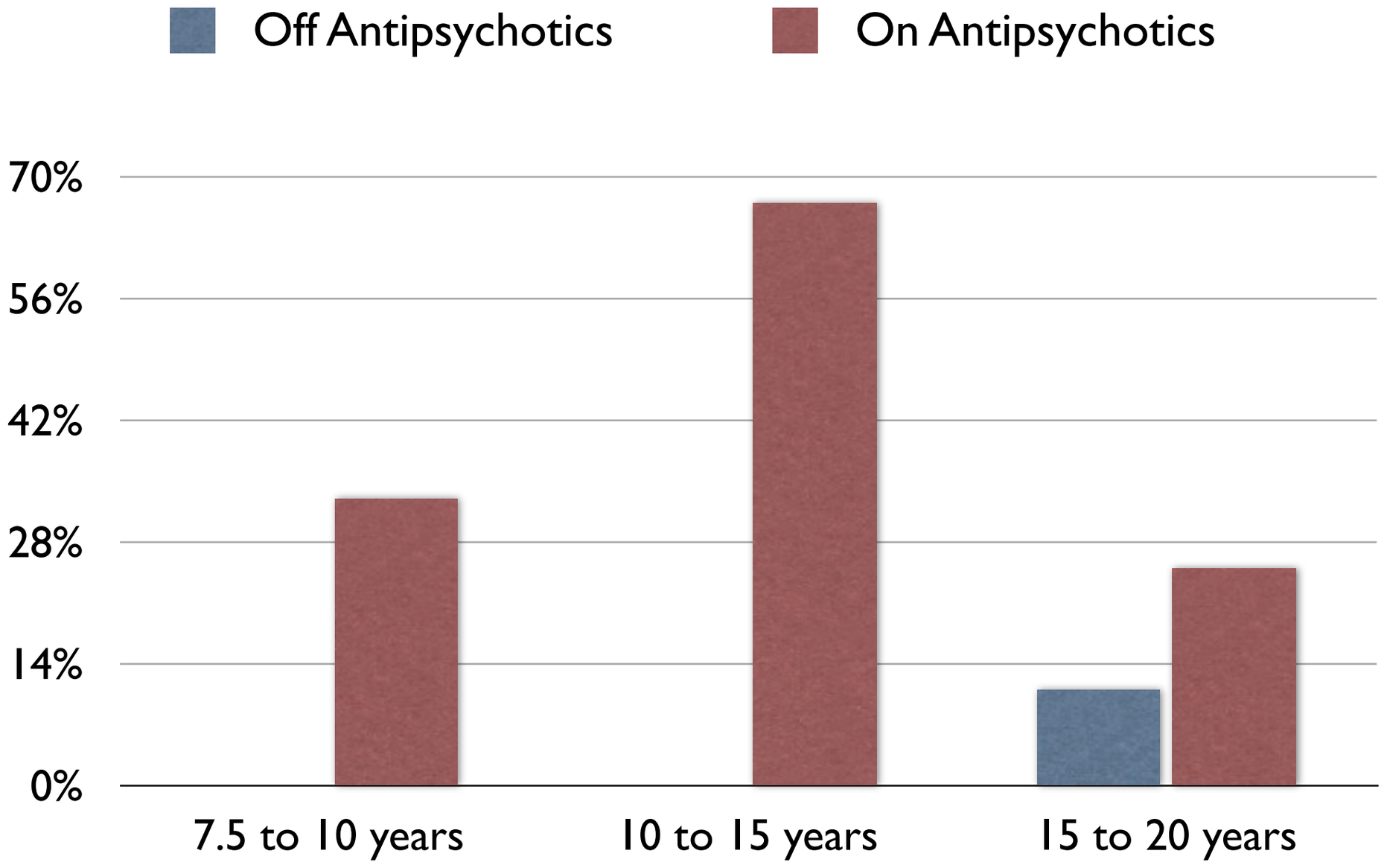
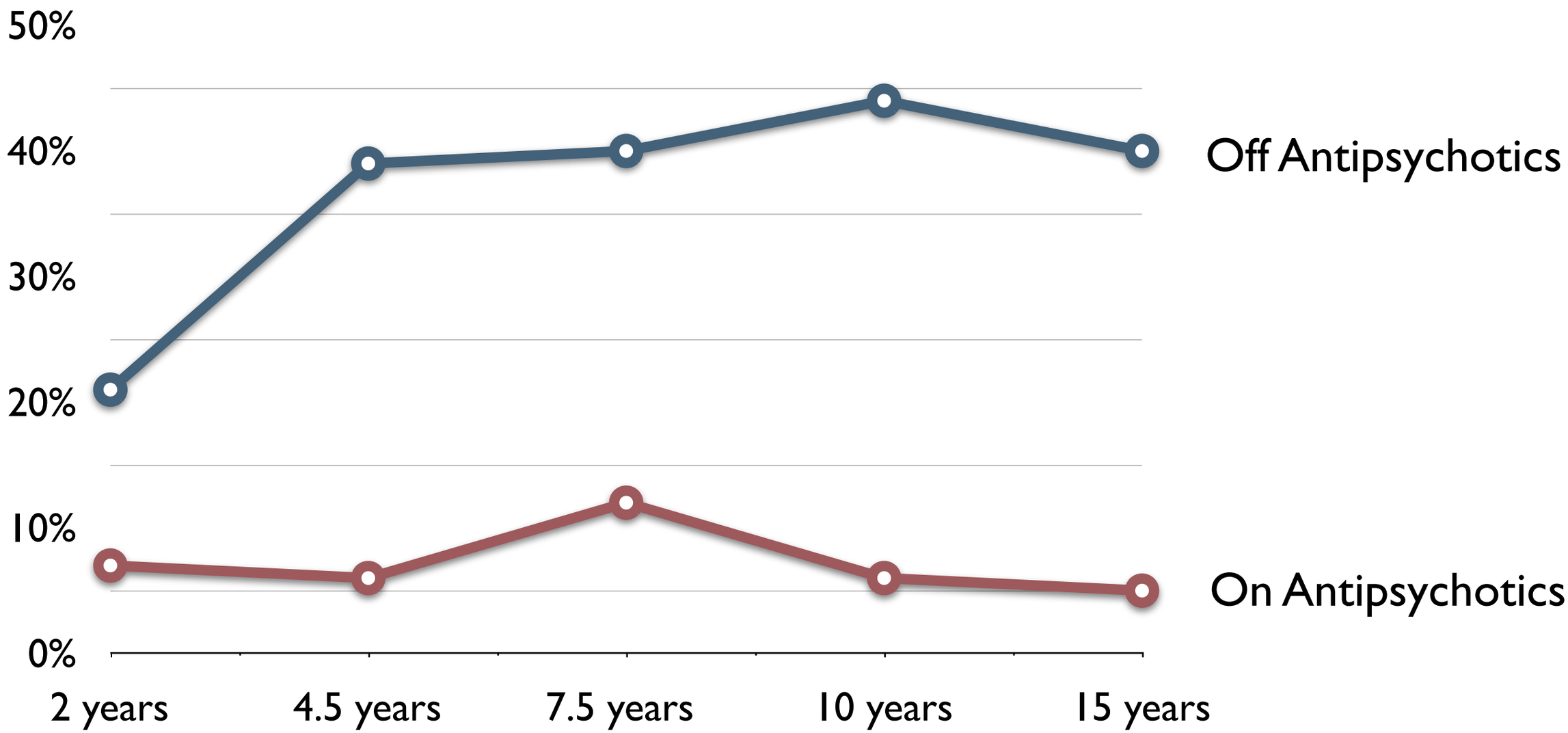
Relapse Rates Once Patients Are Stable



Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Long-term Recovery Rates for Schizophrenia Patients



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

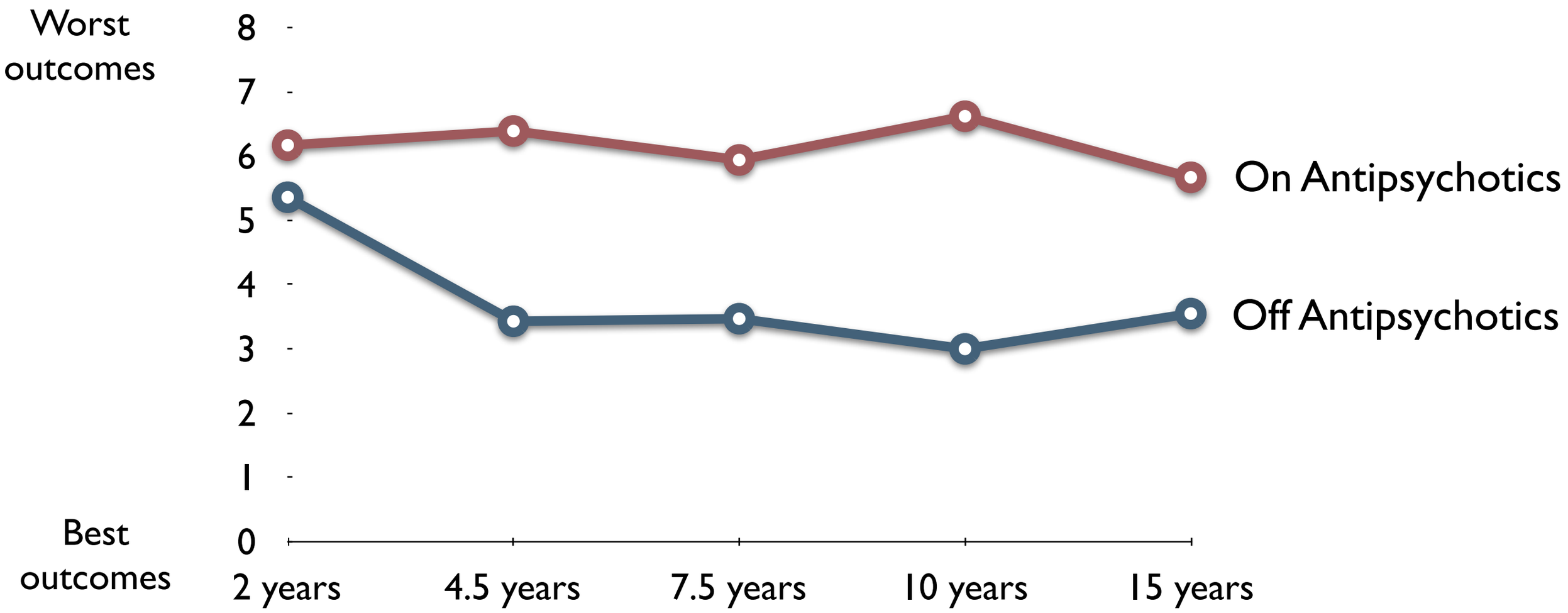
More on Recovery Rates

Medication compliant patients throughout 20 years: 17% had one period of recovery.

Those off antipsychotics by year two who then remained off throughout next 18 years: 87% had two or more sustained periods of recovery.

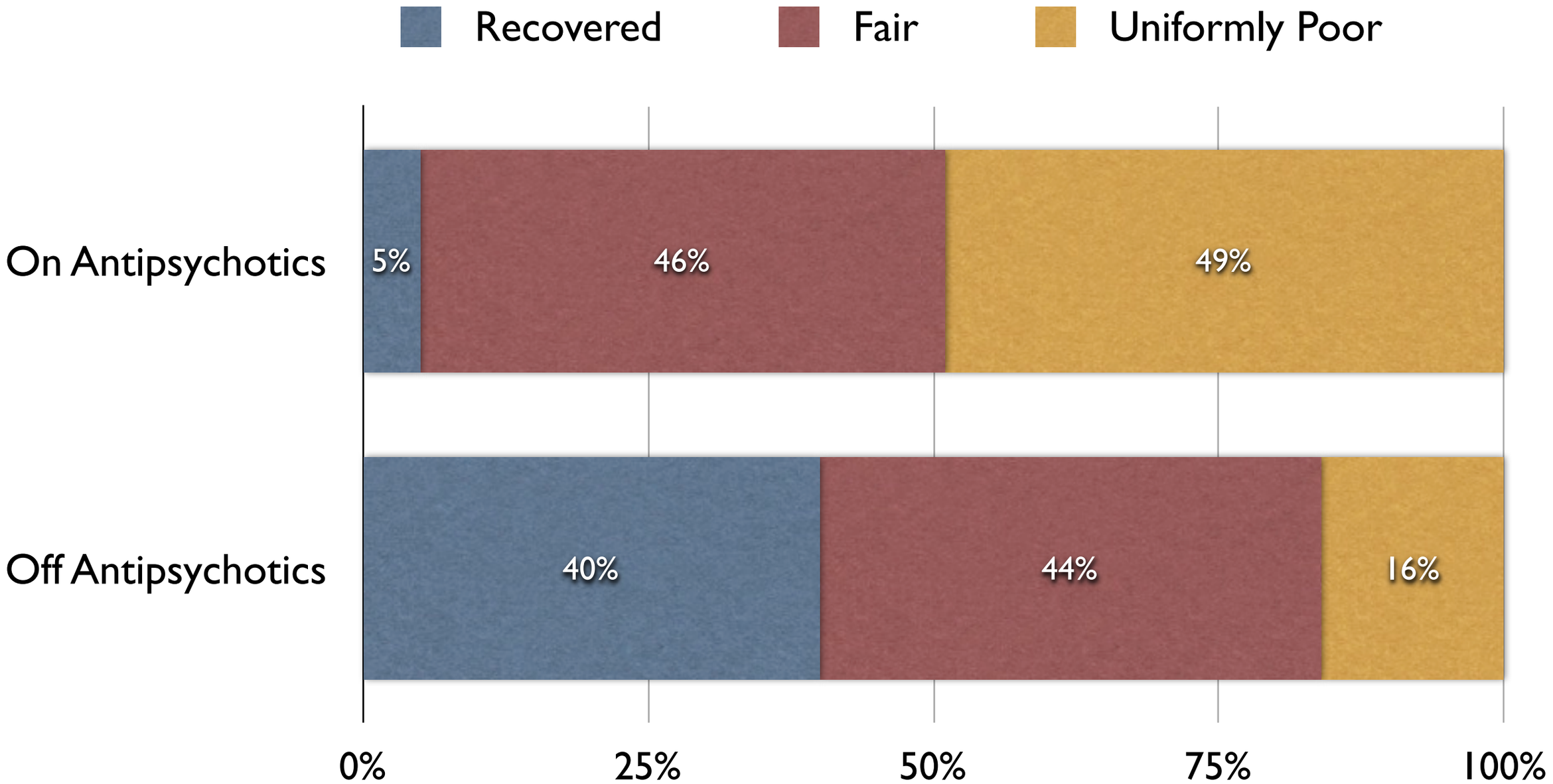
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longtitudinal study." *Psychological Medicine*, (2012):1-11.

Global Adjustment of Schizophrenia Patients



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

Spectrum of Outcomes in Harrow's Study



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

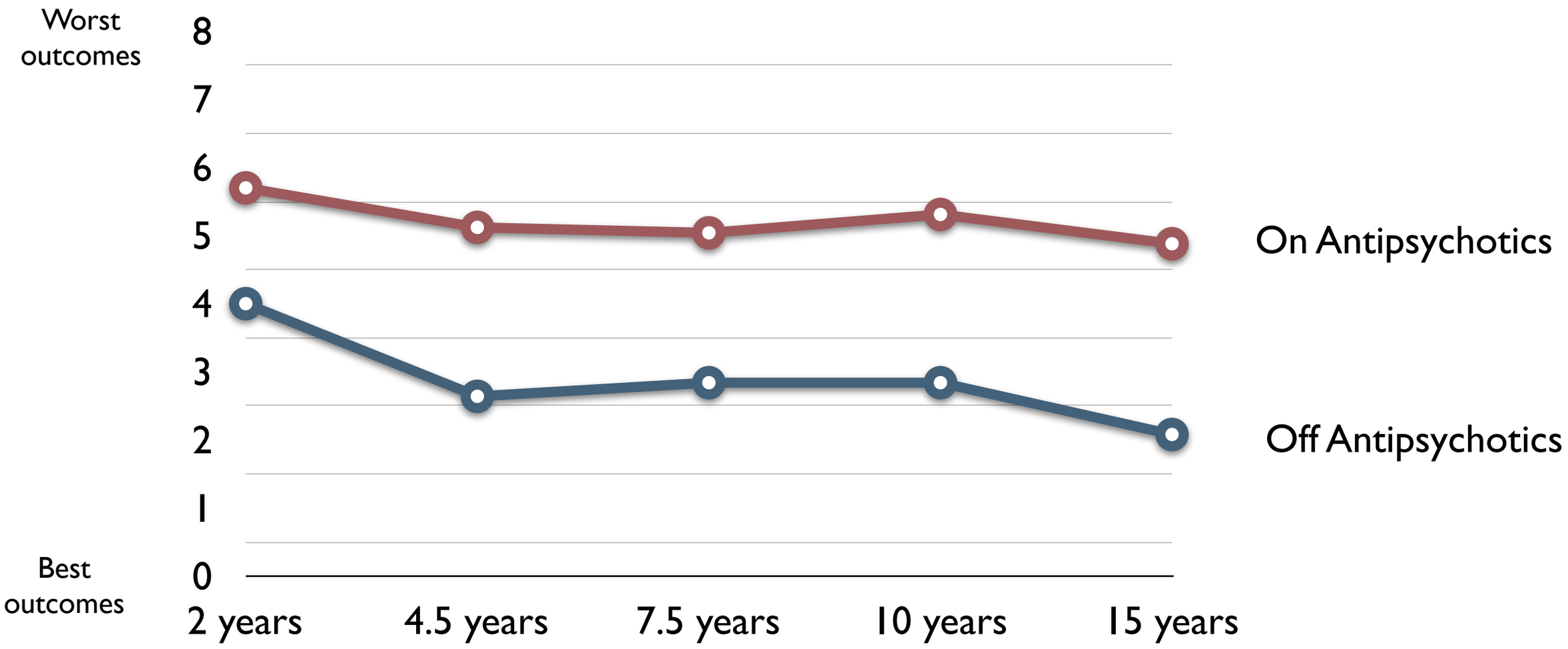
"In addition, global outcome for the group of patients with schizophrenia who were on antipsychotics was compared with the off-medication schizophrenia patients with similar prognostic status. Starting with the 4.5-year follow-up and extending to the 15-year follow-up, the off-medication subgroup tended to show better global outcomes at each followup."

Martin Harrow, page 411.

"I conclude that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics."

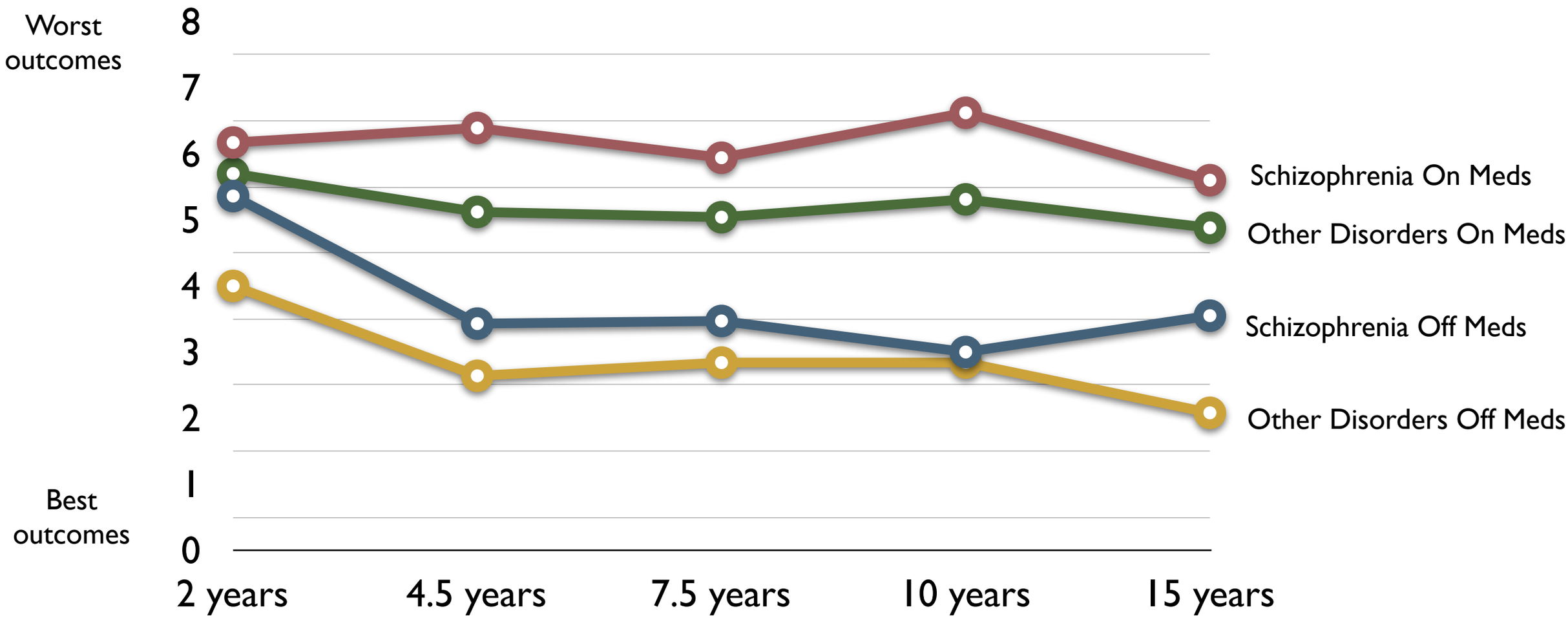
--Martin Harrow, American Psychiatric Association annual meeting, 2008

Global Adjustment of "Other Psychotic" Patients



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

Global Adjustment of All Psychotic Patients



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

"How unique 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."

--Martin Harrow, 2013

A Call to Rethink Antipsychotics

"It is time to reappraise the assumption that antipsychotics must always be the first line of treatment for people with psychosis. This is not a wild cry from the distant outback, but a considered opinion by influential researchers . . . [there is] an increasing body of evidence that the adverse effects of [antipsychotic] treatment are, to put it simply, not worth the candle."

--Peter Tyrer, Editor

British Journal of Psychiatry, August 2012

Outcomes with Selective Use Of Antipsychotics

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.

What Percentage of First-Episode Psychotic Patients Could Recover Without Exposure to Antipsychotics?

1945-55: More than 70% of first-episode patients discharged within 18 months.

1956-57: 67% of hospitalized patients discharged within six months.

Rappaport (1978): 58% (24 of 41) still off medication and doing well at end of three years.

Mosher (1970s): 42% never exposed to antipsychotics at end of two years.

Western Lapland (1990-2005): 67% recovered without use of antipsychotics.

What Percentage of Schizophrenia Patients Might Not Need Maintenance Treatment?

1945-55: 70% of first-episode patients living in community at 5 years.

Bockoven: 76% living in community at five years.

Rappaport: 51% of patients (41 of 80) at three years.

Mosher: 81% at end of two years.

Baldessarini: 68% stable after six months.

Harding: 25% to 50% at 30 years.

Harrow: 33% (21 of 64) in recovery or doing okay at 15 years.

Western Lapland: 80% at five years.