

Rethinking Antipsychotics:

Recovery Rates and Long-term Outcomes
for Unmedicated Patients with Schizophrenia
Spectrum Disorders

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Four Key “Evidence-Base” Questions

1. What were hospital discharge and stay-well rates for first-episode patients with functional psychotic disorders from 1945-1955, prior to the introduction of antipsychotics?
2. Did these discharge rates notably improve with the introduction of chlorpromazine?
3. Is there evidence that immediate use of neuroleptics in early episode schizophrenia produces a better outcome at one year?
4. In longer term studies, do medicated patients have better outcomes, or those that have stopped taking the drugs?

Discharge and Stay-well Rates for Schizophrenia-Spectrum Patients in U.S., 1945 - 1955

Discharge Rates

- At Warren State Hospital in Pennsylvania, 62% of first-episode psychotic patients admitted from 1946 to 1950 were discharged within 12 months.
- At Delaware State Hospital, 85% of 216 schizophrenia patients admitted between 1948 and 1950 were discharged by the end of five years.

Stay-Well Rates

- In the Warren State Hospital study, 73% were living in the community at the end of three years.
- In the Delaware Hospital study, 70% were living in the community six years or more after initial hospitalization.

Outcomes for First-Episode Patients with Functional Psychoses in Norway, 1948-1952

Outcomes at December 31, 1953.

N = 6315

Died in hospital	2.3%
Transferred to other care	9.3%
In hospital at end of study	15.8%
Discharged, but readmitted	9.4%
Discharged and not readmitted	63.2%

Source: Odegard, O. Pattern of discharge from Norwegian psychiatric hospitals before and after the introduction of the psychotropic drugs." *Am J Psychiatry* 120 (1964):772-78.

Did Discharge Rates for First-Episode Patients Improve After the Introduction of Chlorpromazine?

In the U.S., the California Department of Mental Hospital found that of 1,413 first-episode schizophrenia patients hospitalized in the state in 1956, the discharge rates at the end of 18 months were as follows:

- 88% for those treated without neuroleptics.
- 74% for those treated with neuroleptics.

The researchers concluded: The “drug-treated patients tend to have longer periods of hospitalization . . . The untreated patients consistently show a somewhat lower retention rate.”

Source: Epstein, L. “An approach to the effect of ataraxic drugs on hospital release rates.” *Am J of Psychiatry* 119 (1962):20-35.

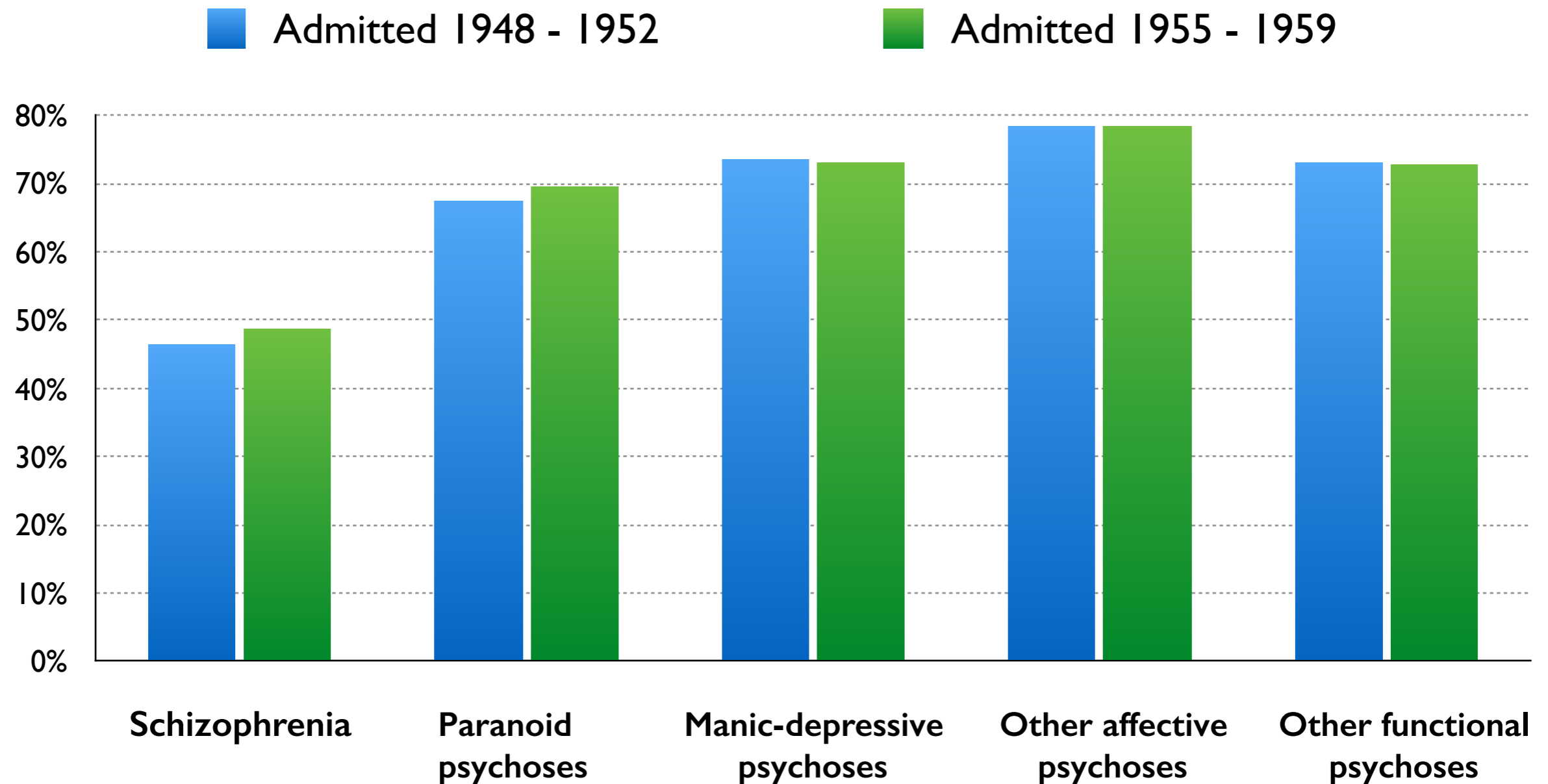
Outcomes for Functional Psychoses Patients in Norway After Introduction of Chlorpromazine

	1948-1952 (Outcomes at Dec. 31, 1953) N = 6315	1955-1959 (Outcomes at Dec. 31, 1960) N = 7000
Died in hospital	2.3%	1.6%
Transferred to other care	9.3%	9.0%
In hospital	15.8%	10.4%
Discharged, but readmitted during observation period	9.4%	12.3%
Discharged and not readmitted	63.2%	66.7%

Source: Odegard, O. "Pattern of discharge from Norwegian psychiatric hospitals before and after the introduction of the psychotropic drugs." *Am J Psychiatry* 120 (1964):772-78.

Outcomes for First-Episode Psychotic Patients in Norway by Diagnosis

Discharged and Not Readmitted



Source: Odegard, O. "Pattern of discharge from Norwegian psychiatric hospitals before and after the introduction of the psychotropic drugs." *Am J Psychiatry* 120 (1964):772-78.

Does Immediate Use of an Antipsychotic in Early Episode Schizophrenia Produce a Better Outcome in First Year of Treatment?

A Cochrane Review in 2011

The Cochrane investigators found only five studies, with a total of 998 patients, that compared initial antipsychotic use with placebo, milieu, or psychosocial treatment in patients experiencing early episode schizophrenia. The researchers excluded studies that assessed efficacy in drug-withdrawn patients who were then randomized to drug or placebo, as that design is flawed because the placebo group may be suffering withdrawal symptoms.

Conclusion: “With only a few studies meeting inclusion criteria, and with limited useable data in these studies, it is not possible to arrive at definitive conclusions. The preliminary pattern of evidence suggests that people with early episode schizophrenia treated with typical antipsychotic medications are less likely to leave the study early, but more likely to experience medication-related side effects. Data are too sparse to assess the effects of antipsychotic medication on outcomes in early episode schizophrenia.”

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.

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.”

Longer-Term Outcomes: Medicated vs. Unmedicated Patients

Bockoven's retrospective study (5 years)

Rappaport's randomized study (3 years)

Mosher's Soteria Project (2 years)

WHO's cross-cultural studies (2 and 5 years)

Harrow's prospective longitudinal study (15 to 20 years)

Wunderink's randomized study (7 years)

Danish longitudinal study (10 years)

Finnish birth cohort study (10 years)

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	1.7	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.

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

Design:

- Newly diagnosed schizophrenia-spectrum patients were randomized either to treatment as usual or to a residential home, Soteria, staffed by ordinary people.
- Those randomized to Soteria were not immediately put on antipsychotics (benzodiazepines were prescribed if necessary for restoring sleep.) Initiation of antipsychotics would begin if patients failed to improve, or deteriorated.
- Project ran from 1971 to 1983. N = 179.

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

Loren Mosher's Soteria Project

Results:

- At six weeks, “psychopathology in both groups had improved significantly, and similarly, and overall change was the same.”
- 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: Mosher, L. “The treatment of acute psychosis without neuroleptics: six-week psychopathology outcome data from the Soteria Project.” *Int J of Social Psychiatry* 41 (1995): 157-175. 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.”

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.

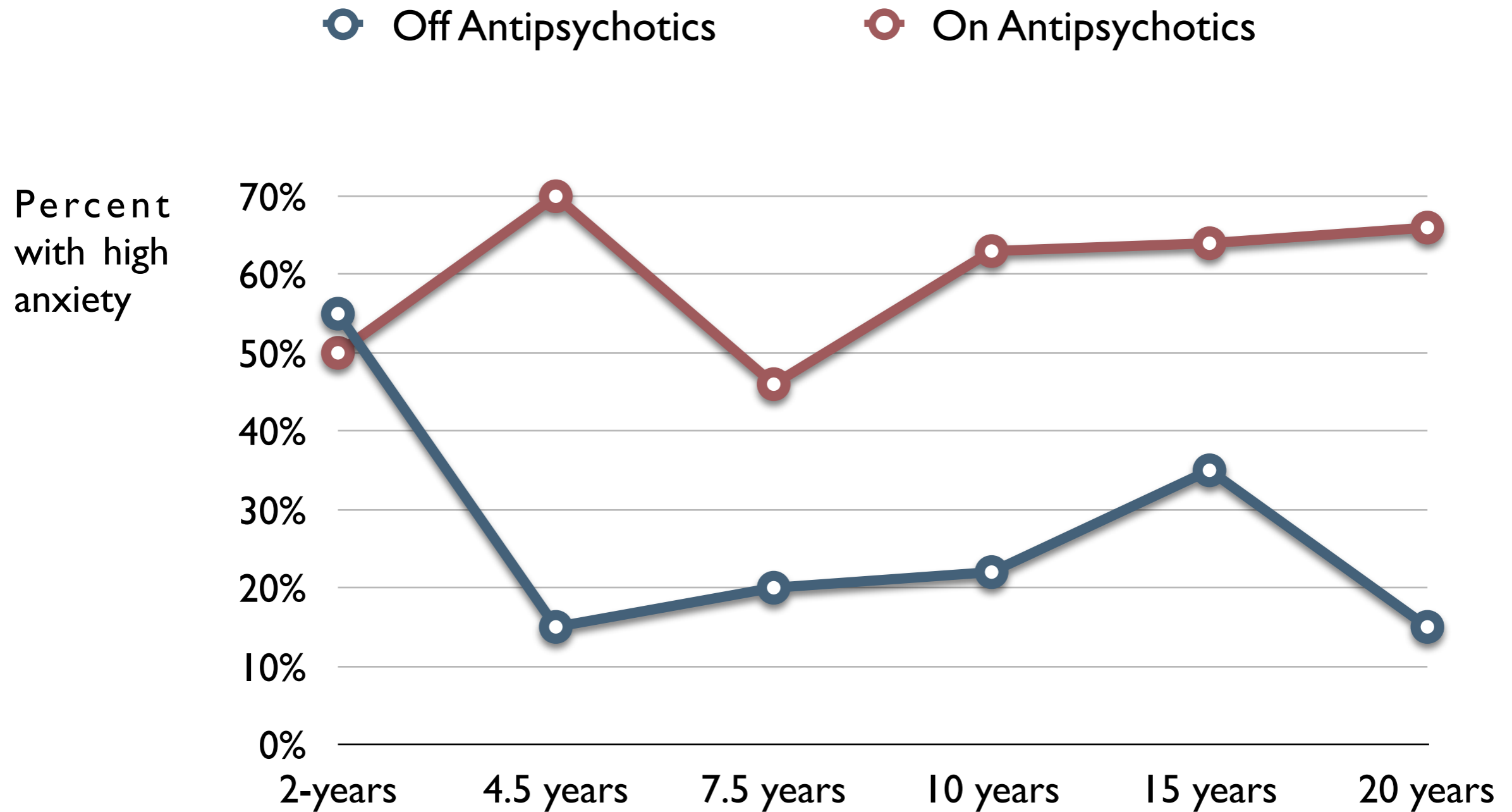
Source: Jablensky, A. “Schizophrenia, manifestations, incidence and course in different cultures.” *Psychological Medicine* 20, monograph (1992):1-95. See table on page 64 for medication usage. For followup, see Hopper, K. “Revisiting the developed versus developing country distinction in course and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

Martin Harrow's Long-Term Study of Psychotic Patients

200 patients enrolled. At 15 years, 145 were still in the study.

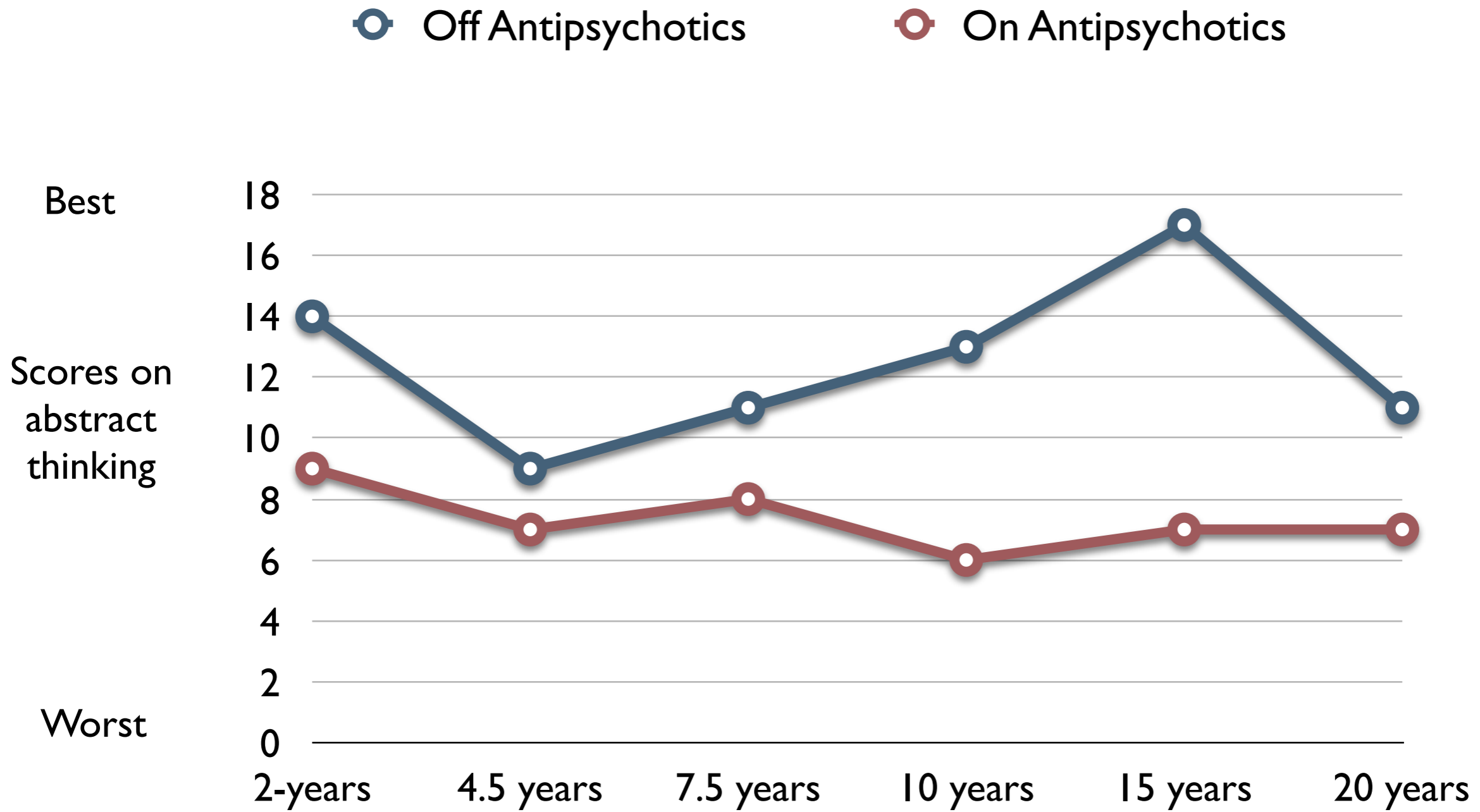
- 64 schizophrenia patients
- 81 patients with other psychotic disorders
 - 37 psychotic bipolar patients
 - 28 unipolar psychotic patients
 - 16 other milder psychotic disorders
- Median age of 22.9 years at index hospitalization
- Previous hospitalizations
 - 46% first hospitalization
 - 21% one previous hospitalization
 - 33% two or more previous hospitalizations

Anxiety Symptoms of Schizophrenia Patients



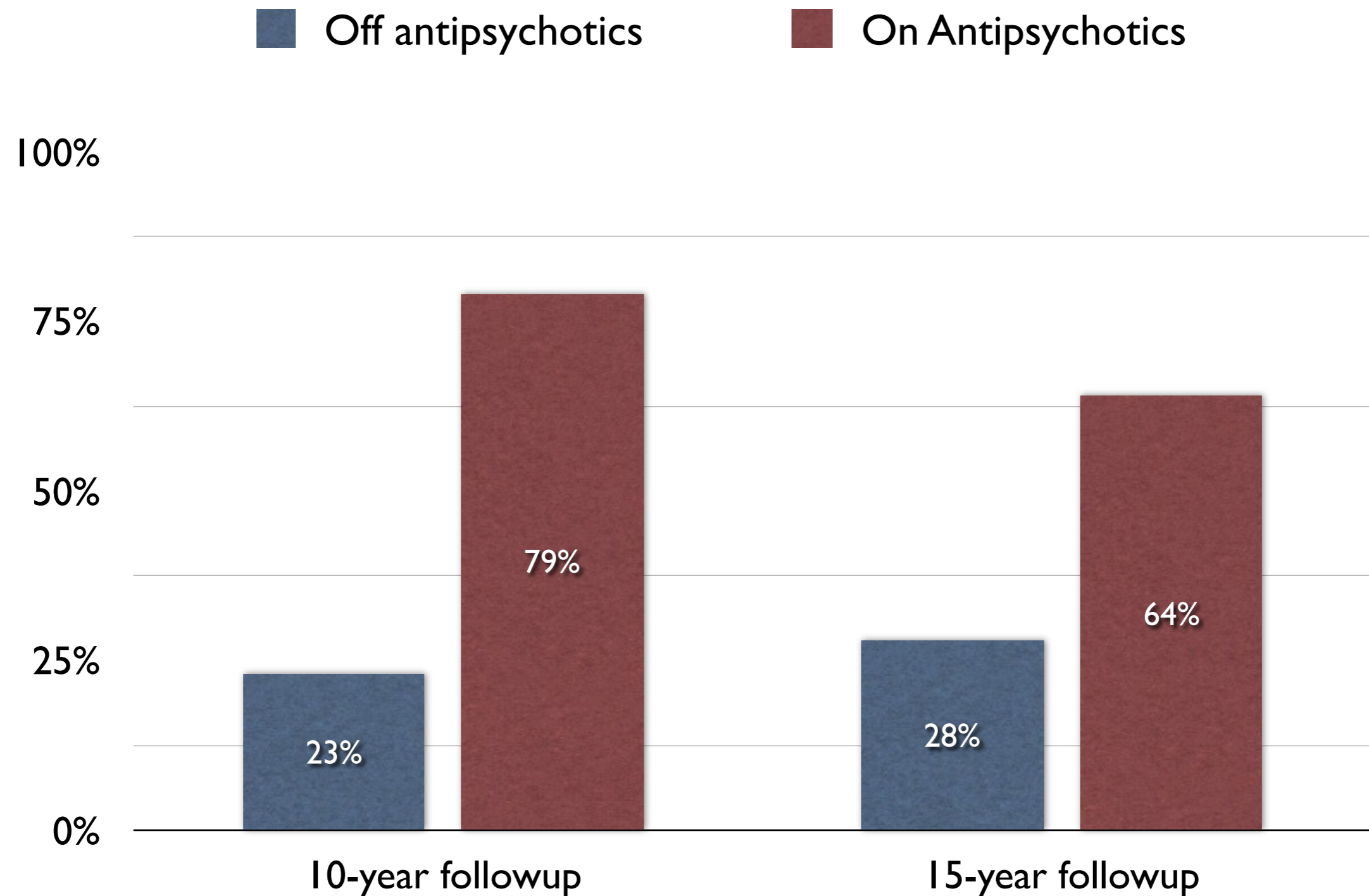
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study." *Psychological Medicine*, (2012):1-11.

Cognitive Function of Schizophrenia Patients



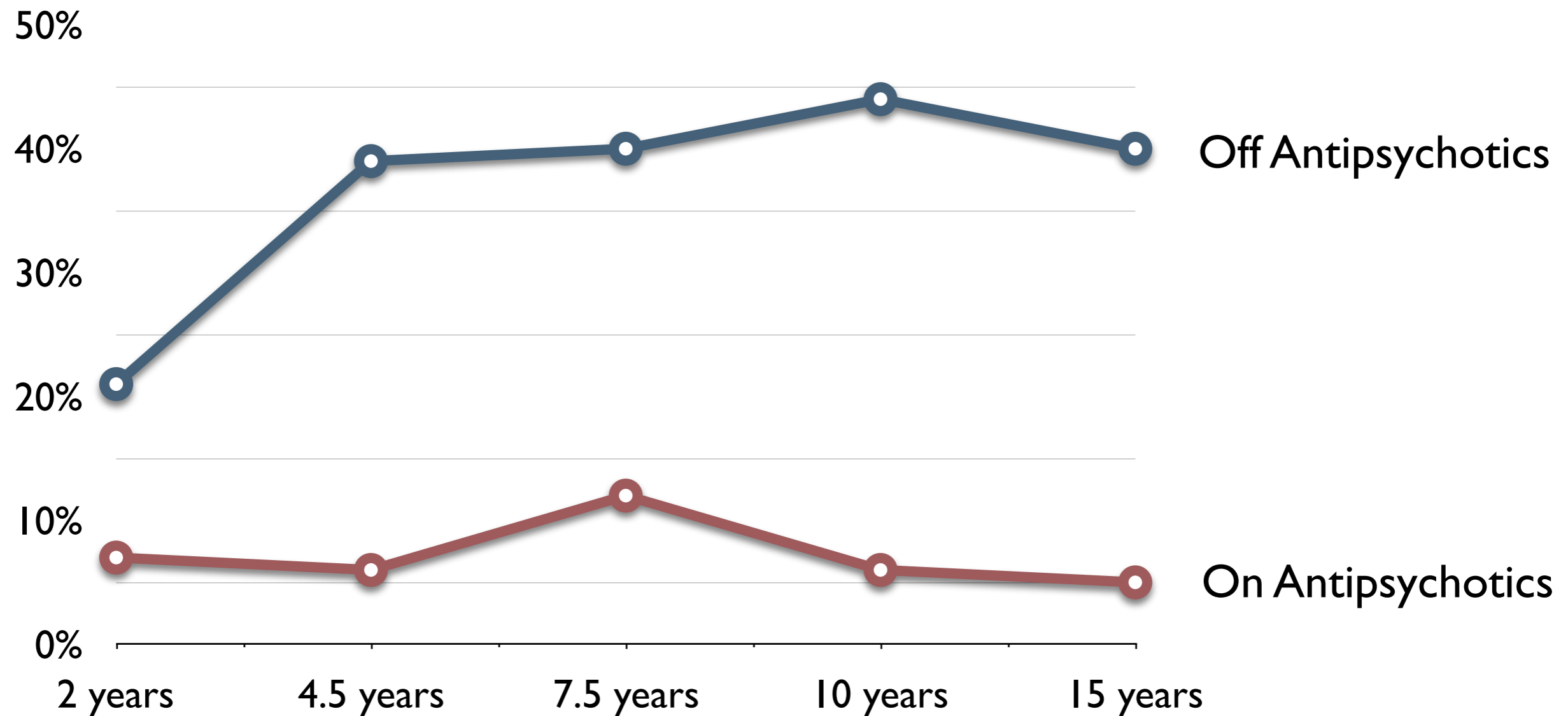
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study." *Psychological Medicine*, (2012):1-11.

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



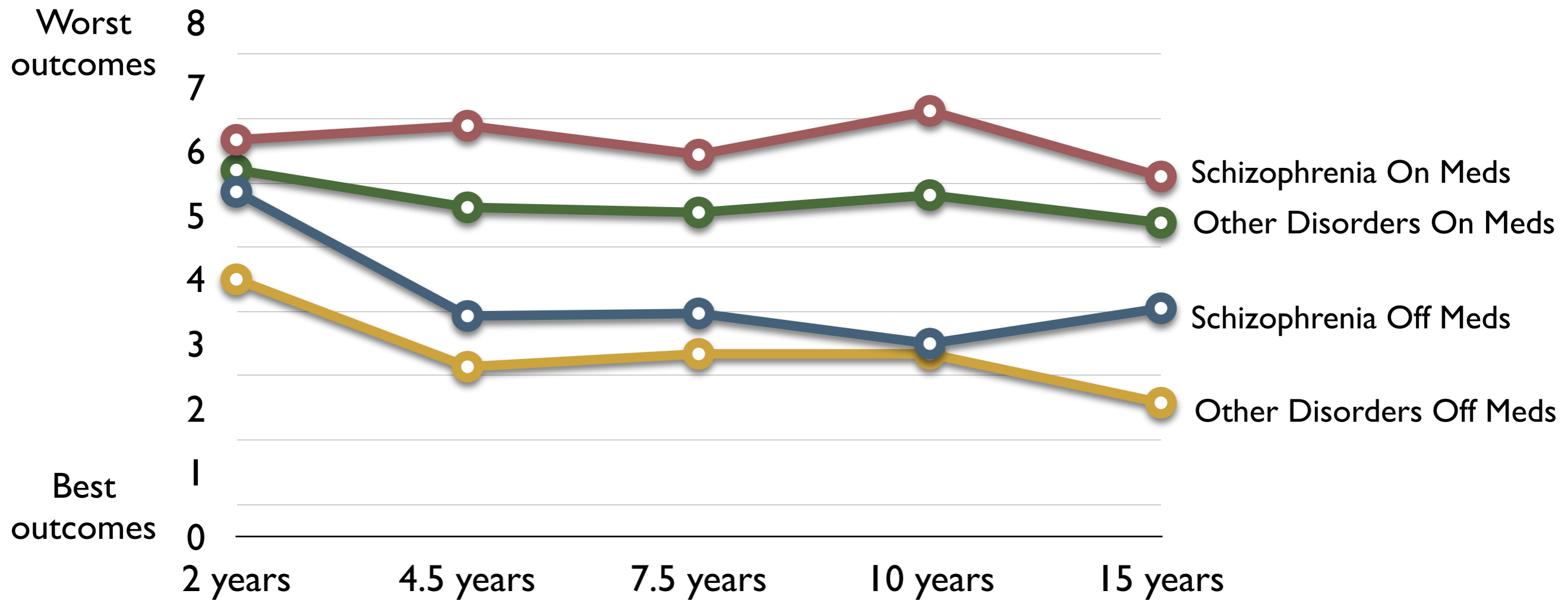
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

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.

Global Adjustment of All Psychotic Patients



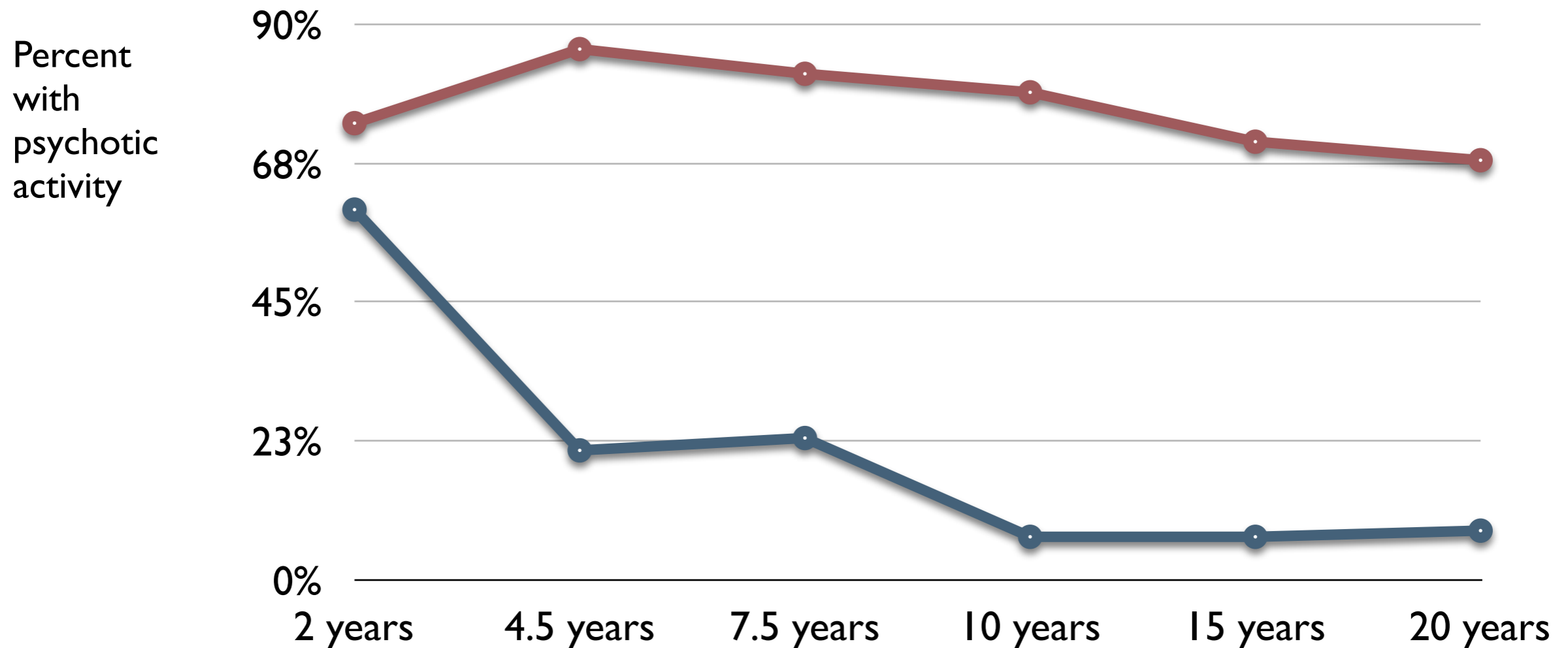
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

“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

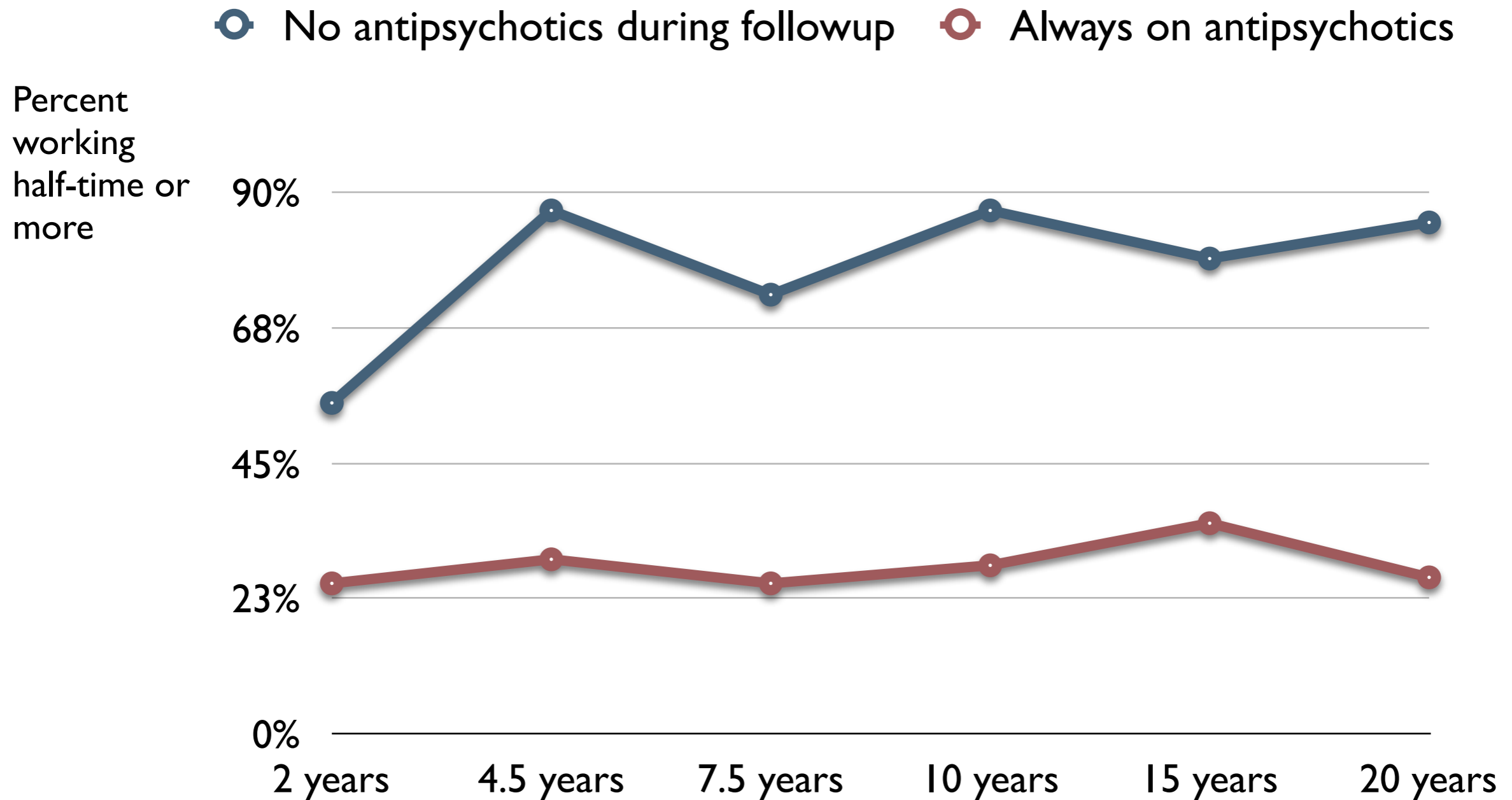
Psychotic Symptoms of Schizophrenia Patients

- No antipsychotics during followup (n = 15)
- Always on antipsychotics (n = 25)



Source: Harrow M. "Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis?" *Psychological Medicine*, (2014):doi:10.1017/S0033291714000610

Work History of Schizophrenia Patients



Source: M. Harrow. "Pharmacological Treatment for Psychosis: Emerging Perspectives." Presentation in Syracuse, NY, October 2, 2014.

“Is very long-term treatment with antipsychotic medication undesirable?”

--Martin Harrow, 2012

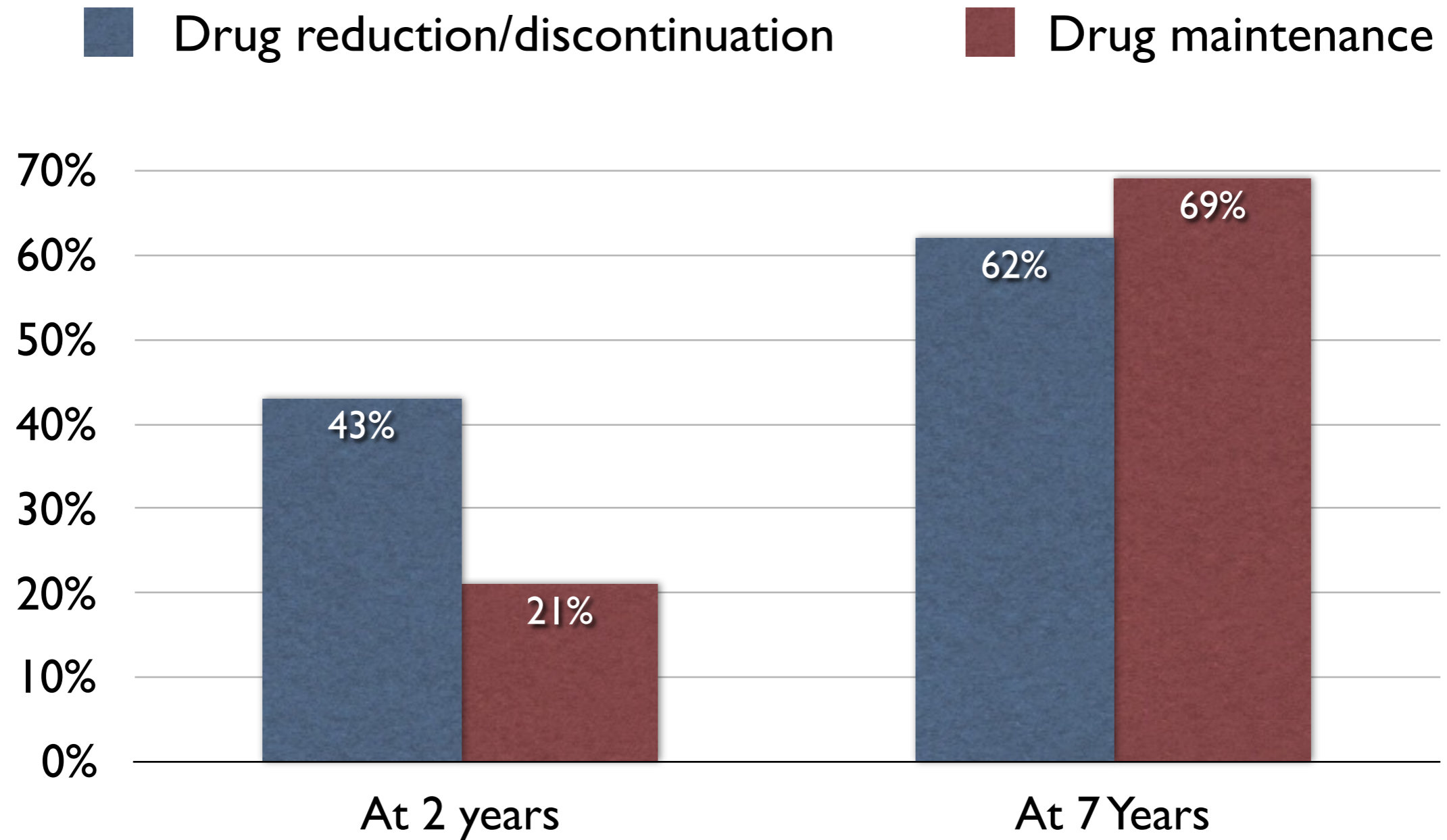
Lex Wunderink's Randomized Study of Long-term Outcomes

Study Design

- 128 stabilized first-episode psychotic patients who had been stable for six months on antipsychotics. (103 patients were still in the study at the end of seven years.)
- Randomized either to a dose reduction/discontinuation treatment, or to standard antipsychotic treatment.

Wunderink, L. "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy." *JAMA Psychiatry*, published online, July 3, 2013.

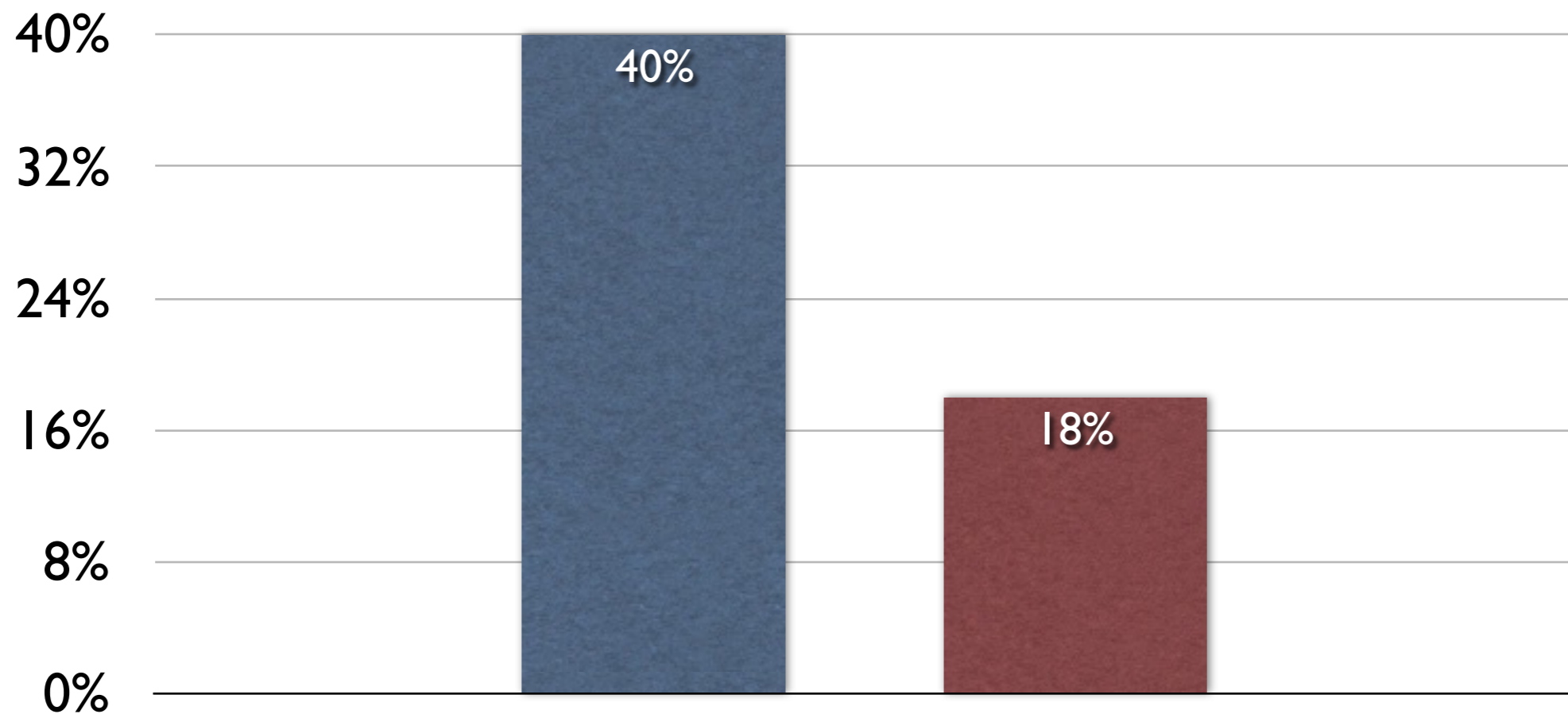
Relapse Rates



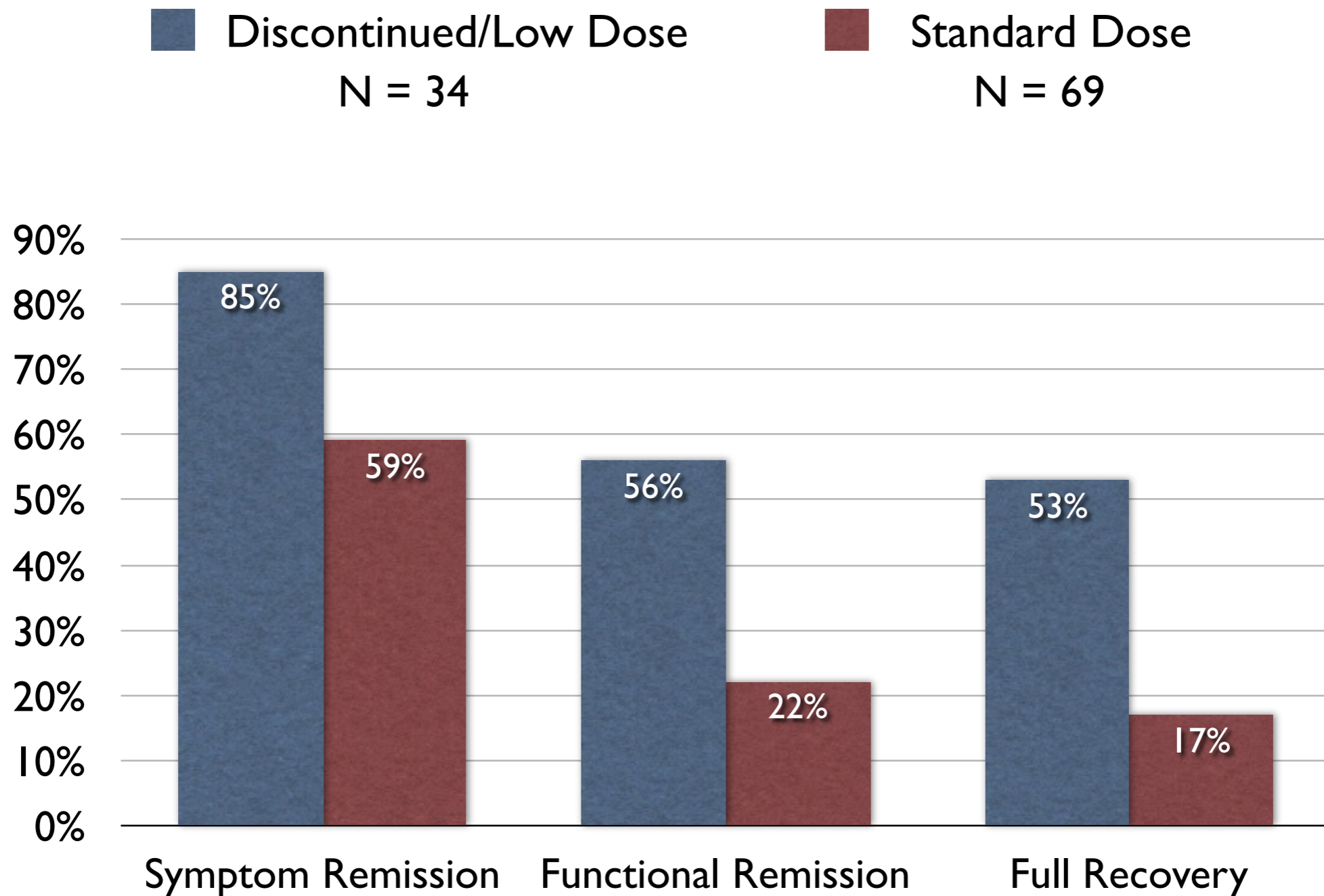
Wunderink, L. "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy." *JAMA Psychiatry*, published online, July 3, 2013.

Long-Term Recovery Rates (at 7 Years)

■ Drug reduction/discontinuation ■ Drug maintenance



Outcomes By Antipsychotic Use



Wunderink's Conclusions

I. Antipsychotics may worsen functional outcomes:

“Antipsychotic postsynaptic blockade of the dopamine signaling system, particularly of the mesocortical and mesolimbic tracts, not only might prevent and redress psychotic derangements but also might compromise important mental functions, such as alertness, curiosity, drive, and activity levels, and aspects of executive functional capacity to some extent.”

2. The previous methods to assess outcomes were flawed:

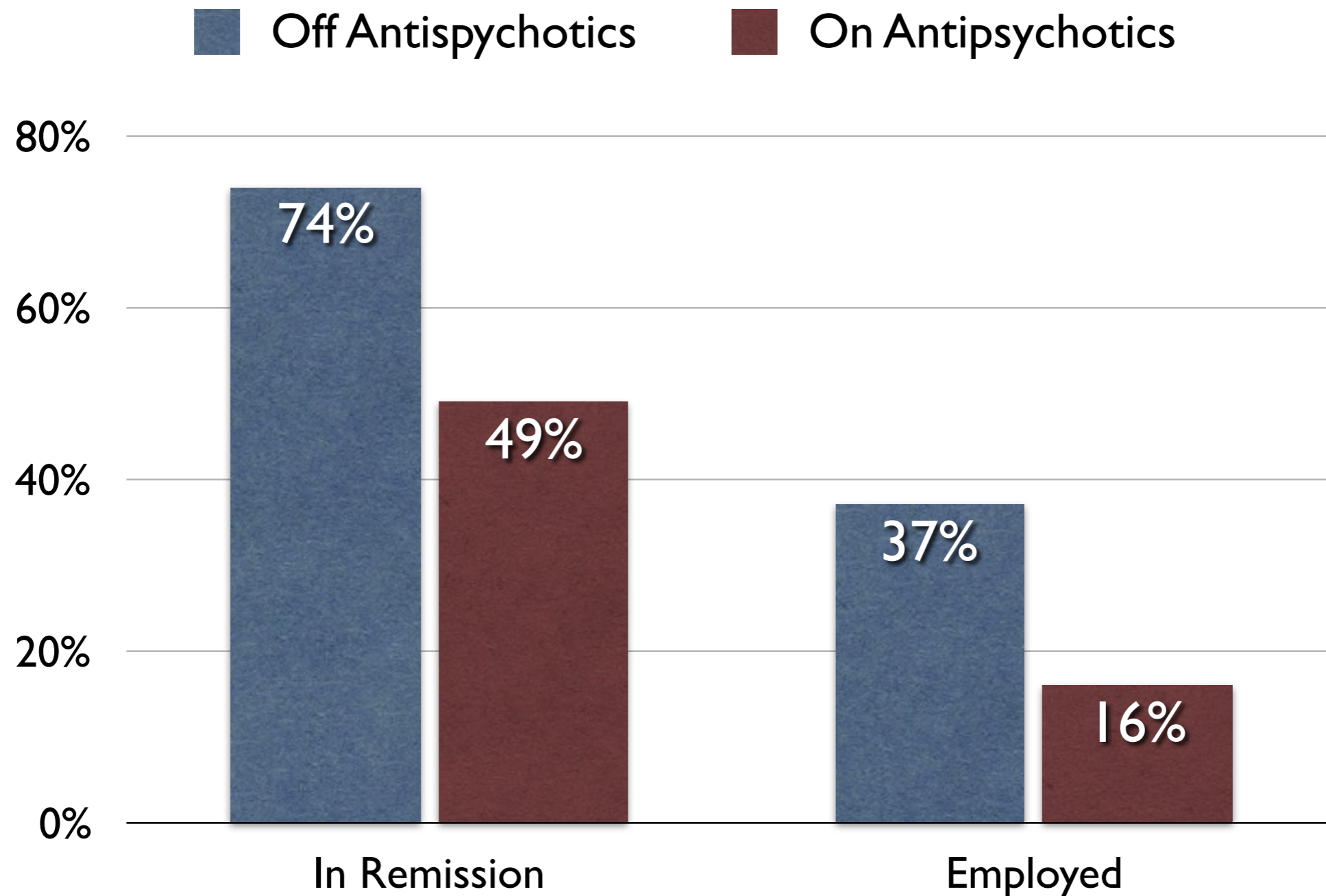
“The results of this study lead to the following conclusions: schizophrenia treatment strategy trials should include recovery or functional remission rates as their primary outcome and should also include long-term follow-up for more than 2 years, even up to 7 years or longer. In the present study, short-term drawbacks, such as higher relapse rates, were leveled out in the long term, and benefits that were not evident in short-term evaluation, such as functional gains, only appeared in long-term monitoring.”

Long-term Outcomes in Denmark's Opus Study

Study Design

- Initial cohort of 496 first-episode schizophrenia spectrum patients diagnosed between 1998-2000. At time of recruitment, patients had been on antipsychotics less than 12 weeks.
- At 10 years, there were 303 patients still in the study. There were 121 who were “non-compliant” and had stopped taking antipsychotics.
- There were no differences at baseline for the off-med and on-med groups at 10 years, including baseline pathology scores, premorbid social functioning, or duration of untreated psychosis.

Outcomes at 10 Years in Opus Study



Wils, R. "Antipsychotic medication and remission of psychotic symptoms after a first-episode psychosis." *Schizophrenia Research*. DOI: <http://dx.doi.org/10.1016/j.schres.2016.10.030>

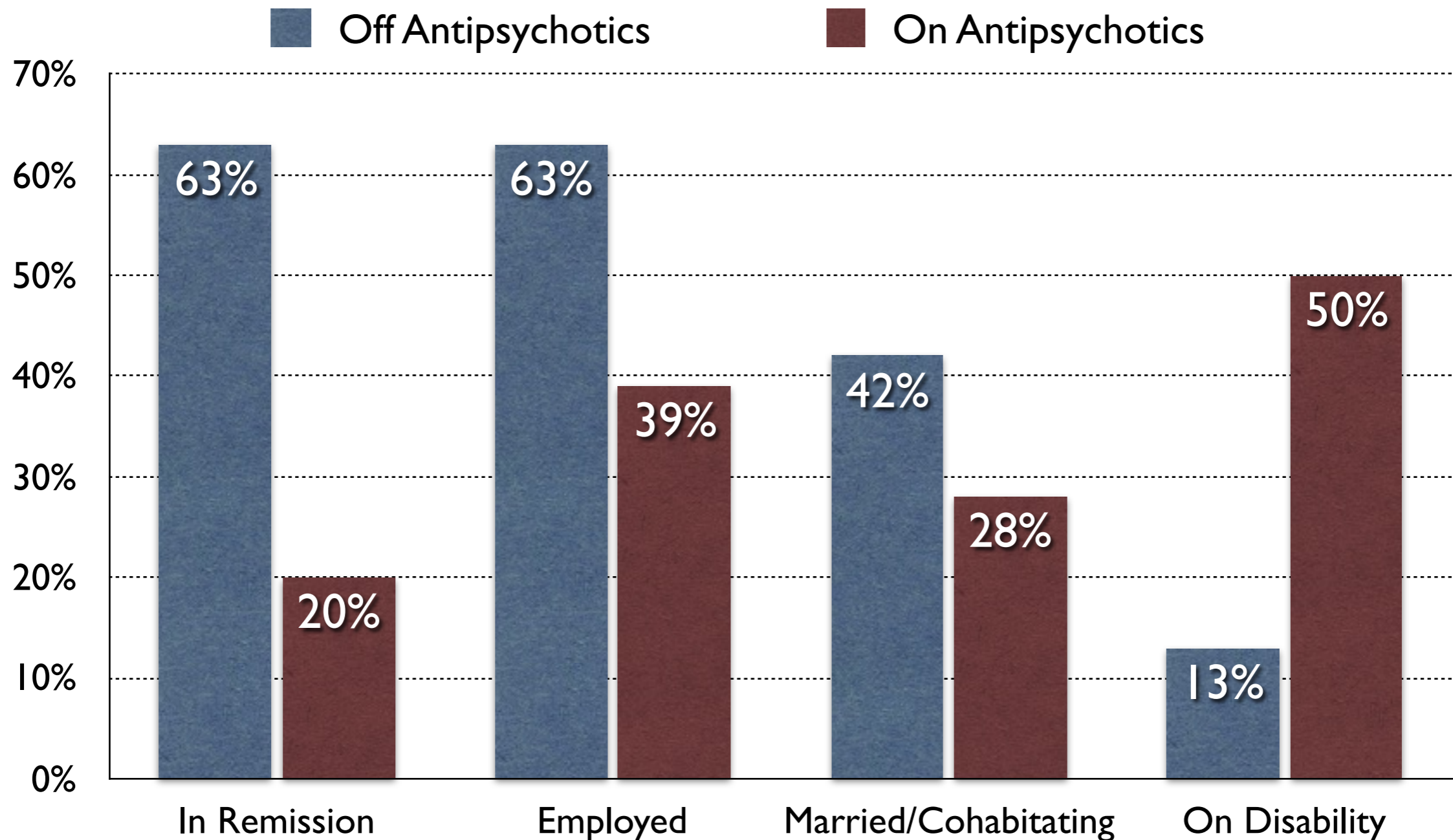
Finnish Birth Cohort Study

Study Design

- This study evaluated 70 individuals diagnosed with schizophrenia spectrum disorders who had been born in Northern Finland in 1966, and were now 34 years old.
- The median time of illness for the 70 patients was 10 years.
- There were 46 taking antipsychotics, and 24 who were off the drugs (and had been for at least three months).
- The group was then followed for another 8.7 years.

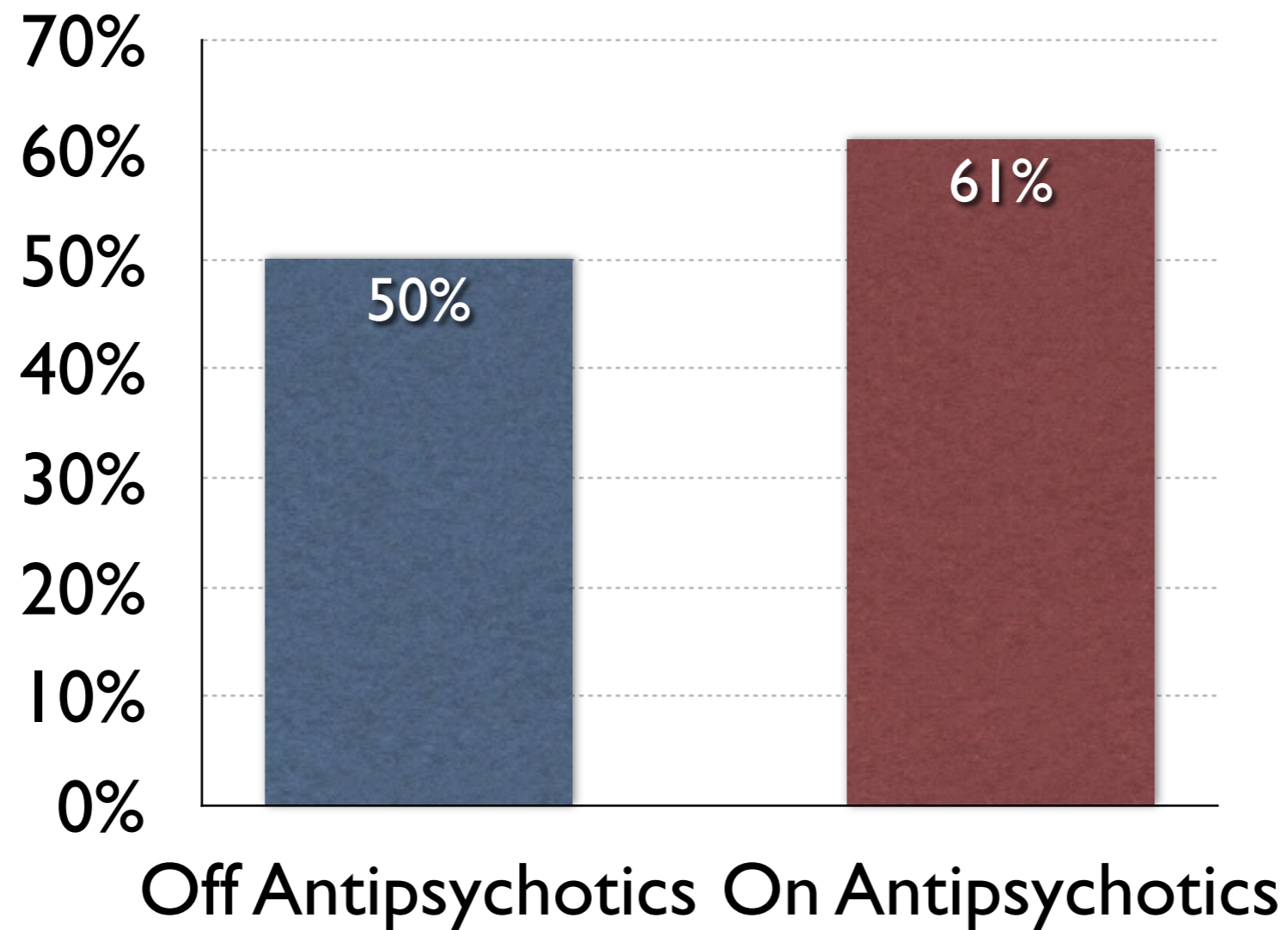
Moilanen, J. "Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication – A 10-year follow-up of the Northern Finland 1966 Birth Cohort study ." *European Psychiatry* 28 (2013):53-58.

Outcomes at Age 34 in Birth Cohort Study



Moilanen, J. "Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication – A 10-year follow-up of the Northern Finland 1966 Birth Cohort study ." *European Psychiatry* 28 (2013):53-58.

Hospitalization Rates During Nine-Year Followup



Moilanen, J. "Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication – A 10-year follow-up of the Northern Finland 1966 Birth Cohort study ." *European Psychiatry* 28 (2013):53-58.

Summarizing The Evidence to Four Key Questions

1. In Norway and the United States, prior to the introduction of antipsychotics, more than 60% of first-episode schizophrenia spectrum patients would be discharged (with most discharged within two years.) At longer-term followups, two-thirds or more of the first-episode cohort would be living in the community.
2. In Norway and the United States, comparative studies of outcomes before and after the introduction of drugs did not find a significant difference in discharge rates.
3. A 2011 Cochrane Review of the research literature did not find compelling evidence that initial use of antipsychotics produced a superior outcome during the first year compared to placebo or psychosocial care.
4. In longer term studies of different designs, those off medication, as a group, have superior outcomes: they are more likely to be in remission, employed and in “recovery.”

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