

The Scientific Case Against Forced Drug Treatment

Robert Whitaker, Feb 2013

Antipsychotics: Mechanism of Action

A. Blockade of D2 receptors, thereby hindering dopaminergic pathways in the brain

B. Three main dopamine pathways in the brain

- Basal ganglia (control of motor movement)
- Limbic system (generates emotional responses)
- Frontal lobes (seat of self-consciousness)

Initial Impressions of Antipsychotics Within Psychiatry

Effect on basal ganglia: Thorazine can “metamorphose a highly mobile, flighty manic into a static, slow-motion shuffler.”

--Fritz Freyhan, 1955

Effect on limbic system: “Apathy, lack of initiative and loss of interest in surroundings are a common response in patients.”

--Irving Cohen, 1956

Effect on frontal lobes: “The drug produced an effect similar to frontal lobotomy.”

--N. William Winkelman, Jr. (1954)

The Long-Term Effects of Antipsychotics

- On psychotic symptoms
- On recovery rates
- On global outcomes
- On cognitive function
- On anxiety (and violence)
- Side Effects
- Mortality

The Evidence for Antipsychotics

Short-term Use

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In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications.

What's Missing From the Evidence Base?

A. It does not provide evidence that antipsychotics improve the long-term course of schizophrenia and other psychotic disorders, particularly in regard to functional outcomes.

B. The relapse studies may reflect risks associated with drug withdrawal, rather than just the return of the natural course of the disorder.

Assessing Long-Term Outcomes

“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.”

And:

“If we wish to base psychiatry on evidence-based medicine, we run a genuine risk in taking a close look at what has long been considered fact.”

--Emmanuel Stip, *European Psychiatry* (2002)

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.

The First Hint of a Paradox

NIMH's First Followup Study (1967):

At the end of one year, patients who were treated with placebo upon initial hospitalization “were less likely to be rehospitalized than those who received any of the three active phenothiazines.”

Source: Schooler, C. “One year after discharge.” *Am J of Psychiatry* 123 (1967):986-95.

Clinicians' Perceptions

- Patients were returning with great frequency, which was dubbed the “revolving door syndrome.”
- Relapse during drug administration “is greater in severity than when no drugs are given.”
- If patients relapse after quitting antipsychotics, symptoms tend to “persist and intensify.”

Source: Gardos, G. “Maintenance antipsychotic therapy: is the cure worse than the disease?” *American Journal of Psychiatry* 135 (1978): 1321-4.

Bockoven's 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

Results

- Those treated without drugs were discharged sooner than drug-treated patients in a comparison group.
- At the end of one year, only 35 percent of the non-medicated group 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.

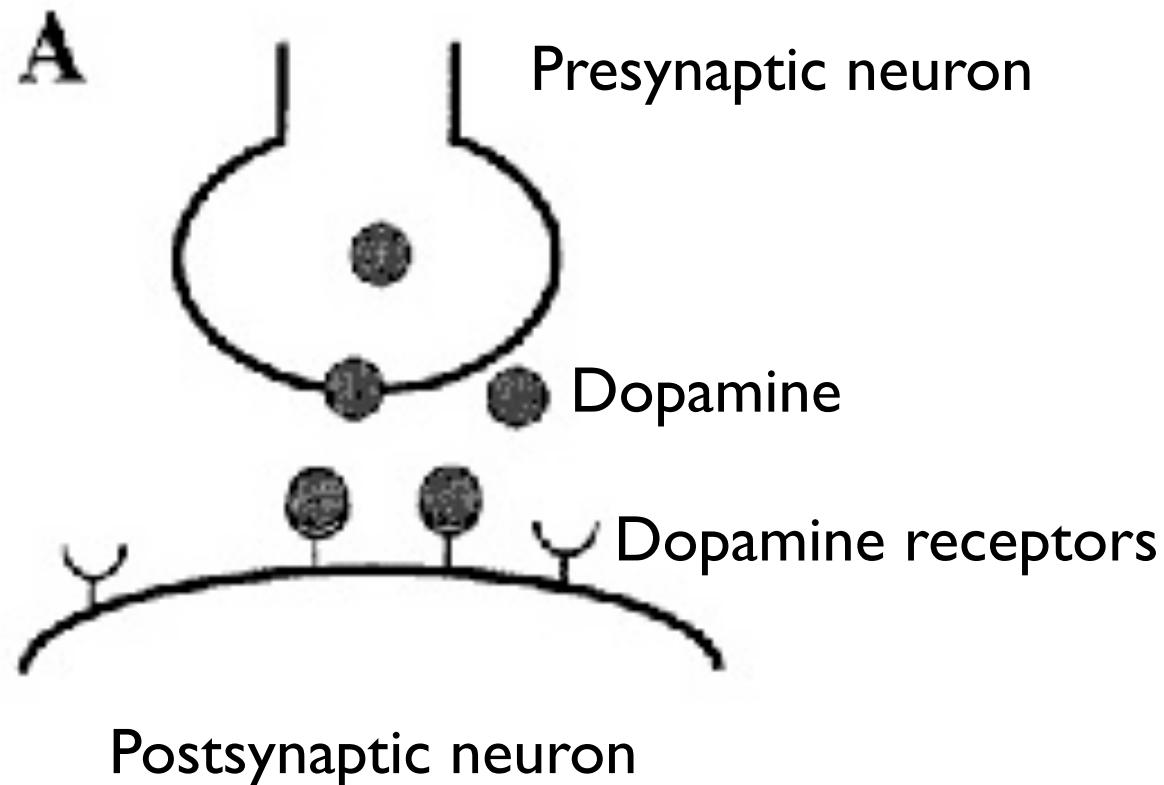
William Carpenter Raises a Question:

“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.”

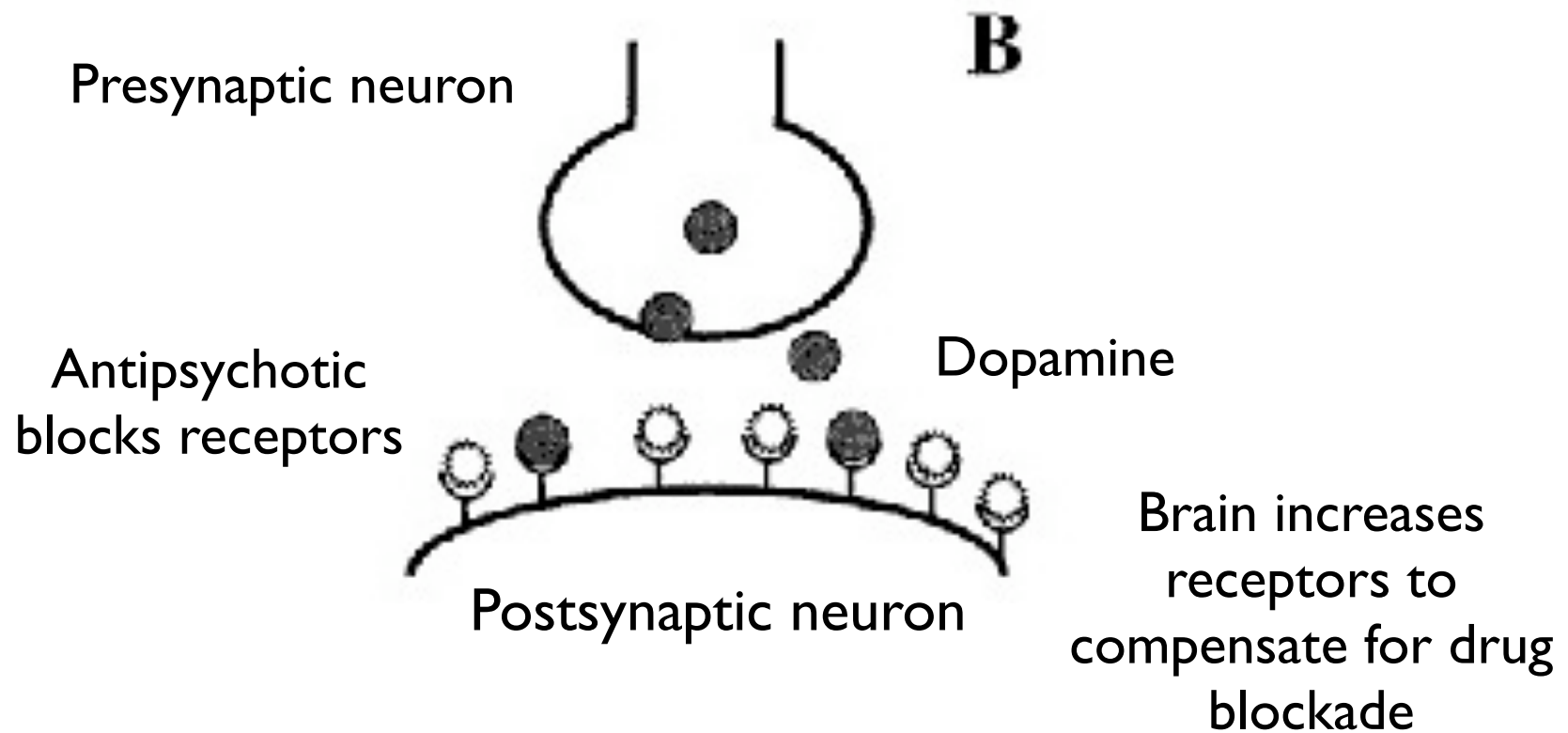
Source: Carpenter, W. “The treatment of acute schizophrenia without drugs.” *Am J Psychiatry* 134 (1977):14-20.

The Dopamine Supersensitivity Theory

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics



“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 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 psychosis, 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.

Animal Models of Psychosis and Drug-Induced Dopamine Supersensitivity

In 2005, Philip Seeman at the University of Toronto reported that agents that trigger psychotic-like behavior in animals -- amphetamines, angel dust, lesions to the hippocampus, gene-knockout manipulations -- all cause an increase in D2 receptors that have a “high” affinity for dopamine. These results “imply that there may be many pathways to psychosis, including multiple gene mutations, drug abuse, or brain injury, all of which may converge via D2 HIGH to elicit psychotic symptoms,” Seeman wrote.

Source: Seeman, P. “Dopamine supersensitivity correlates with D2 HIGH states, implying many paths to psychosis. *Proceedings of the Nat Acad of Science* 102 (2005): 3513-18. Samaha, A. “Breakthrough dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time.” *J Neuroscience* 27 (2007):2979-86.

Antipsychotics Increase the Density of D2 HIGH Receptors

In this same report, Seeman found that haloperidol and olanzapine both increased the density of D2 HIGH receptors, and thus cause the very biological abnormality that in animal models had been identified as a final pathway to psychosis.

Philip Seeman Tests His D2 High Theory

In rat studies, “we show that during ongoing treatment with clinically relevant doses, haloperidol and olanzapine progressively lose their efficacy . . . the loss of efficacy is linked to an increase in D2 receptor number and sensitivity. These results are the first to demonstrate that ‘breakthrough’ supersensitivity during ongoing antipsychotic treatment undermines treatment efficacy.”

Source: Samaha, A. “Breakthrough dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time.” *J Neuroscience* 27 (2007):2979-86.

Reviewing the Evidence for the Dopamine-Supersensitivity Theory

- Longer-term studies in the 1970s showed higher relapse rates for drug-exposed patients.
- A biological explanation for this paradoxical result was proposed and assessed in a study of schizophrenia patients.
- Animal models further refined understanding of drug-induced dopamine supersensitivity and researchers at University of Toronto concluded that this was why the medications failed over time.

Antipsychotics and Brain Volumes

MRI Study in Macaque Monkeys

- In macaque monkeys, treatment with either haloperidol or olanzapine for 17 to 27 months led to a “8-11% reduction in mean fresh brain weights” compared to controls.
- The differences (in brain weights and brain volumes) “were observed across all major brain regions, but appeared most robust in the frontal and parietal regions.”

Source: Dorph-Petersen. “The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation.” *Neuropsychopharmacology* (2005) 30: 1649-1661.

Nancy Andreasen's MRI Study

In 2003, Andreasen reported that schizophrenia was a “progressive neurodevelopmental disorder” characterized by “progressive reduction in frontal white matter volume.” This decline in brain volumes was seen in MRI imaging tests.

Source: Ho, B. “Progressive structural brain abnormalities and their relationship to clinical outcome.” *Arch Gen Psych* 60 (2003):585-94.

In 2003 and 2005, Andreasen reported that this brain shrinkage was associated with a worsening of negative symptoms, increased functional impairment, and, after five years, cognitive decline.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." *Arch Gen Psych* 60 (2003):585-94. Andreasen, N. "Longitudinal changes in neurocognition during the first decade of schizophrenia illness." *International Congress on Schizophrenia Research* (2005):348.

In 2011, Andreasen reported that this shrinkage was drug-related. Use of the old neuroleptics, the atypical antipsychotics, and clozapine were all “associated with smaller brain tissue volumes,” with decreases in both white and grey matter. The severity of illness and substance abuse had “minimal or no effect” on brain volumes.

Ho, B. “Long-term antipsychotic treatment and brain volumes.” *Arch Gen Psychiatry* 68 (2011):128-37.

Nancy Andreasen, former editor of the *American Journal of Psychiatry*, on antipsychotics:

“What exactly do these drugs do? They block basal ganglia activity. The prefrontal cortex doesn’t get the input it needs and is being shut down by drugs. That reduces psychotic symptoms. It also causes the prefrontal cortex to slowly atrophy.”

--*New York Times*, September 16, 2008

Summary of MRI Studies

- 1) Studies in monkeys found that antipsychotics shrink brain volumes.
- 2) Andreasen found that patients diagnosed with schizophrenia show a decline in brain volumes over time.
- 3) Andreasen found that this shrinkage was associated with increased negative symptoms, functional impairment and cognitive decline.
- 4) Andreasen determined that this shrinkage was associated with use of antipsychotics.

The Effect of Antipsychotics on Global Outcomes

- WHO Cross Cultural Studies
- Martin Harrow's Longitudinal Study

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 had a “considerably better course and outcome.”
- 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.

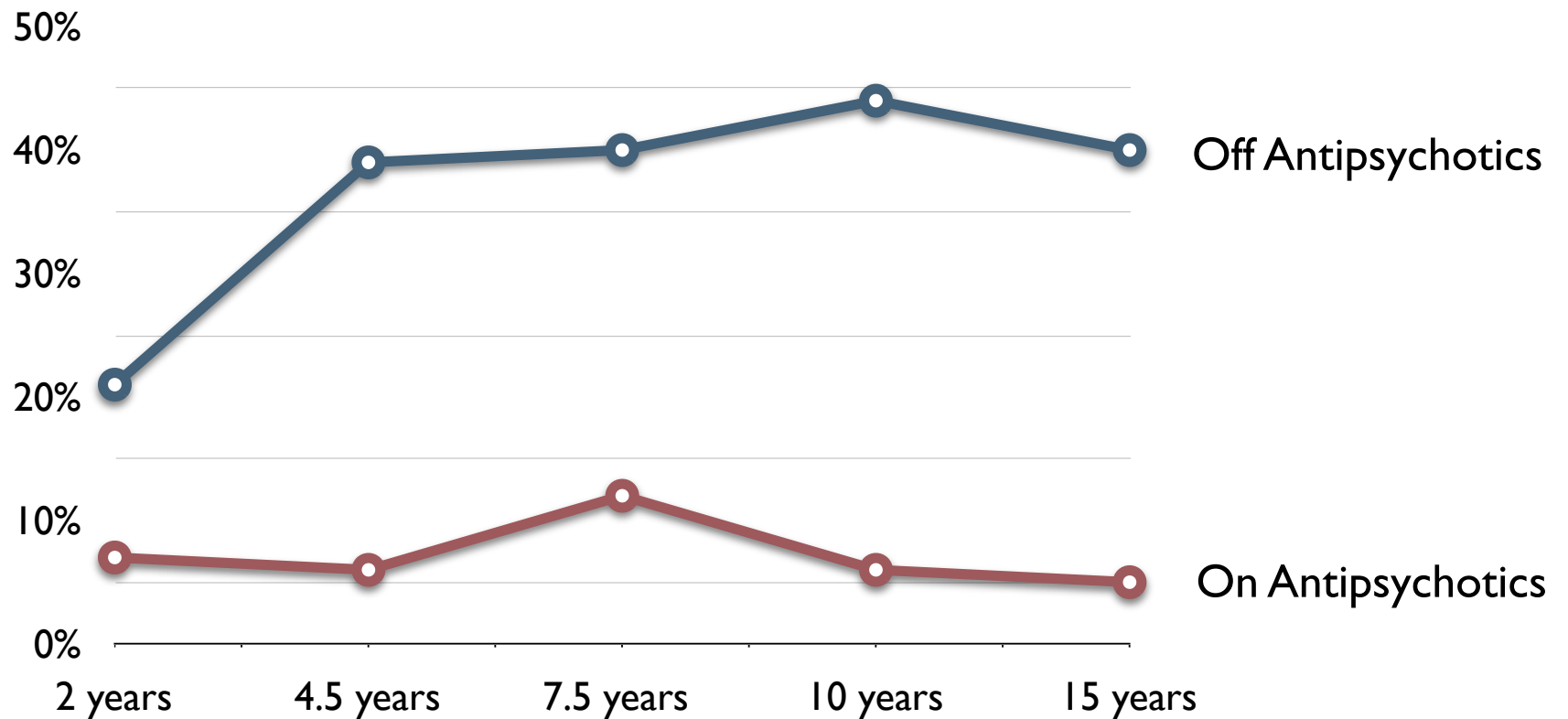
Martin Harrow's Long-Term Study of Psychotic Patients

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

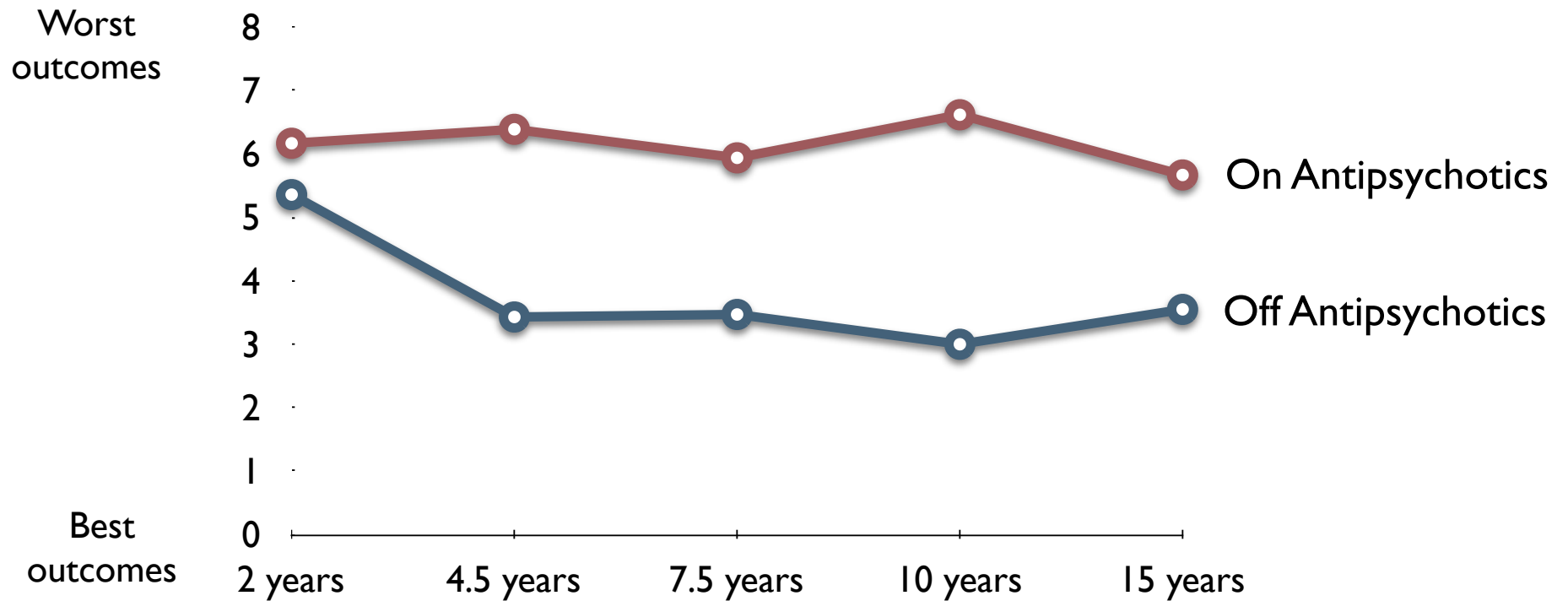
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Long-term Recovery Rates for Schizophrenia Patients



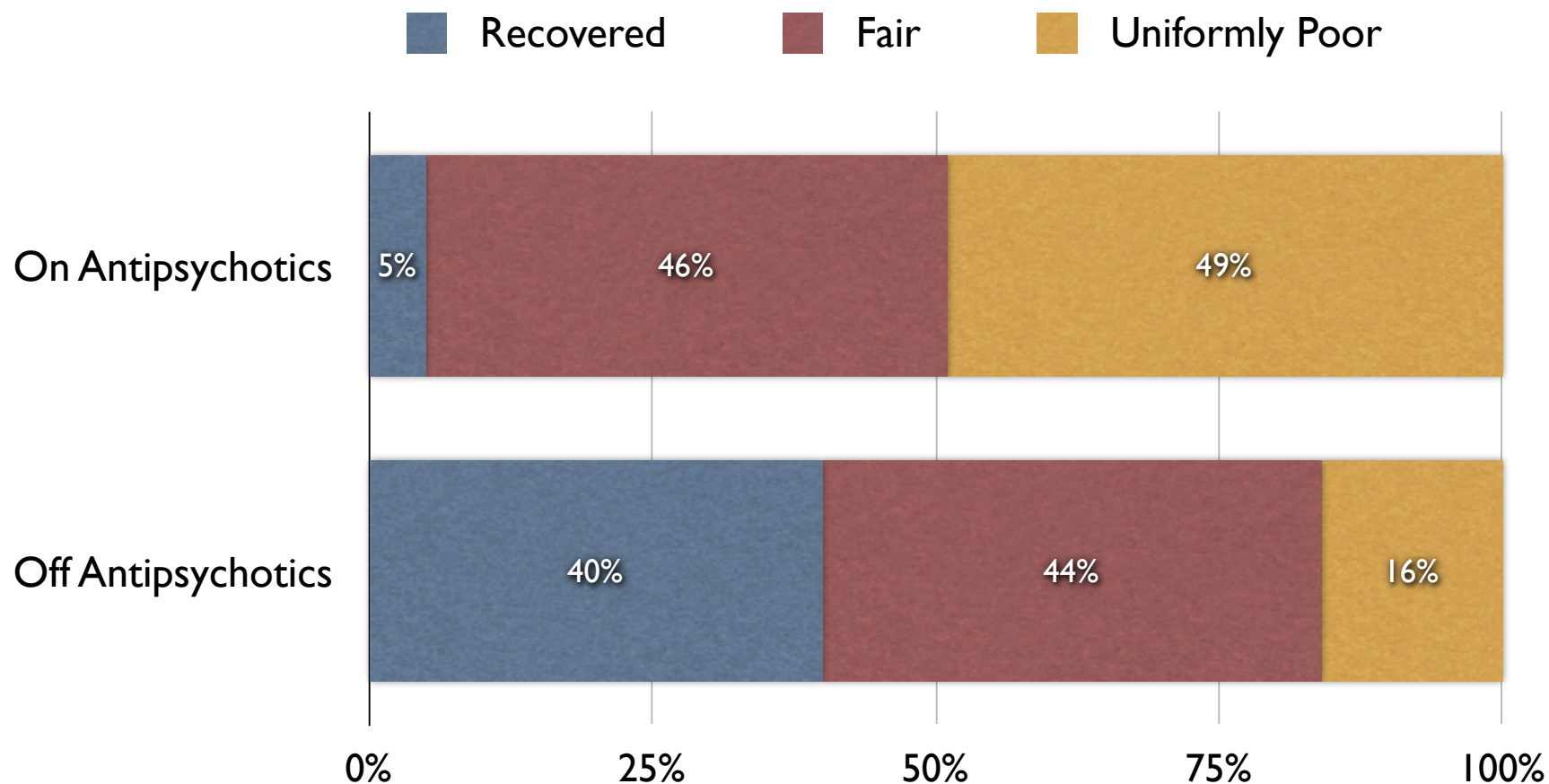
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Global Adjustment of Schizophrenia Patients



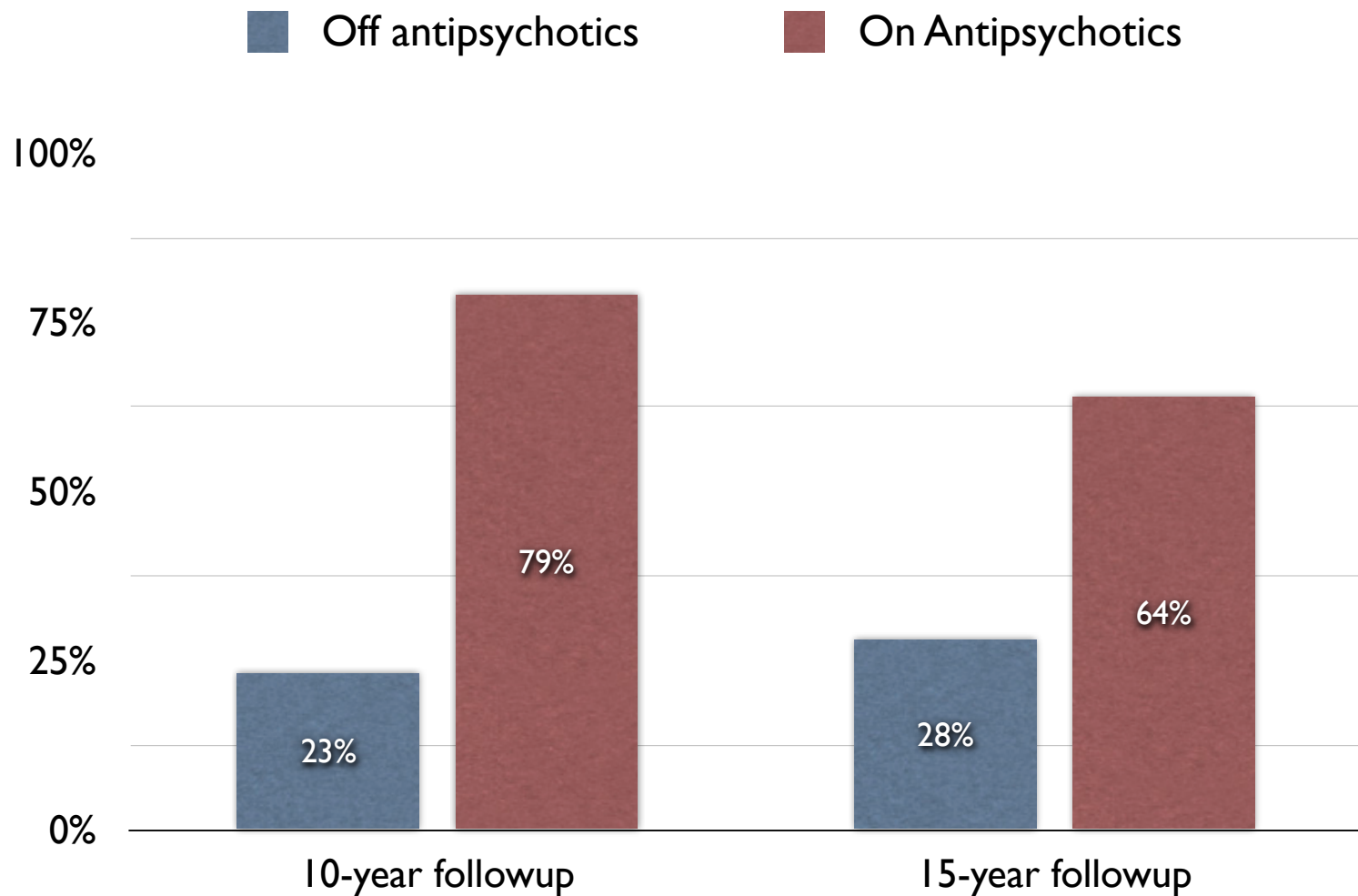
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Spectrum of Outcomes in Harrow's Study



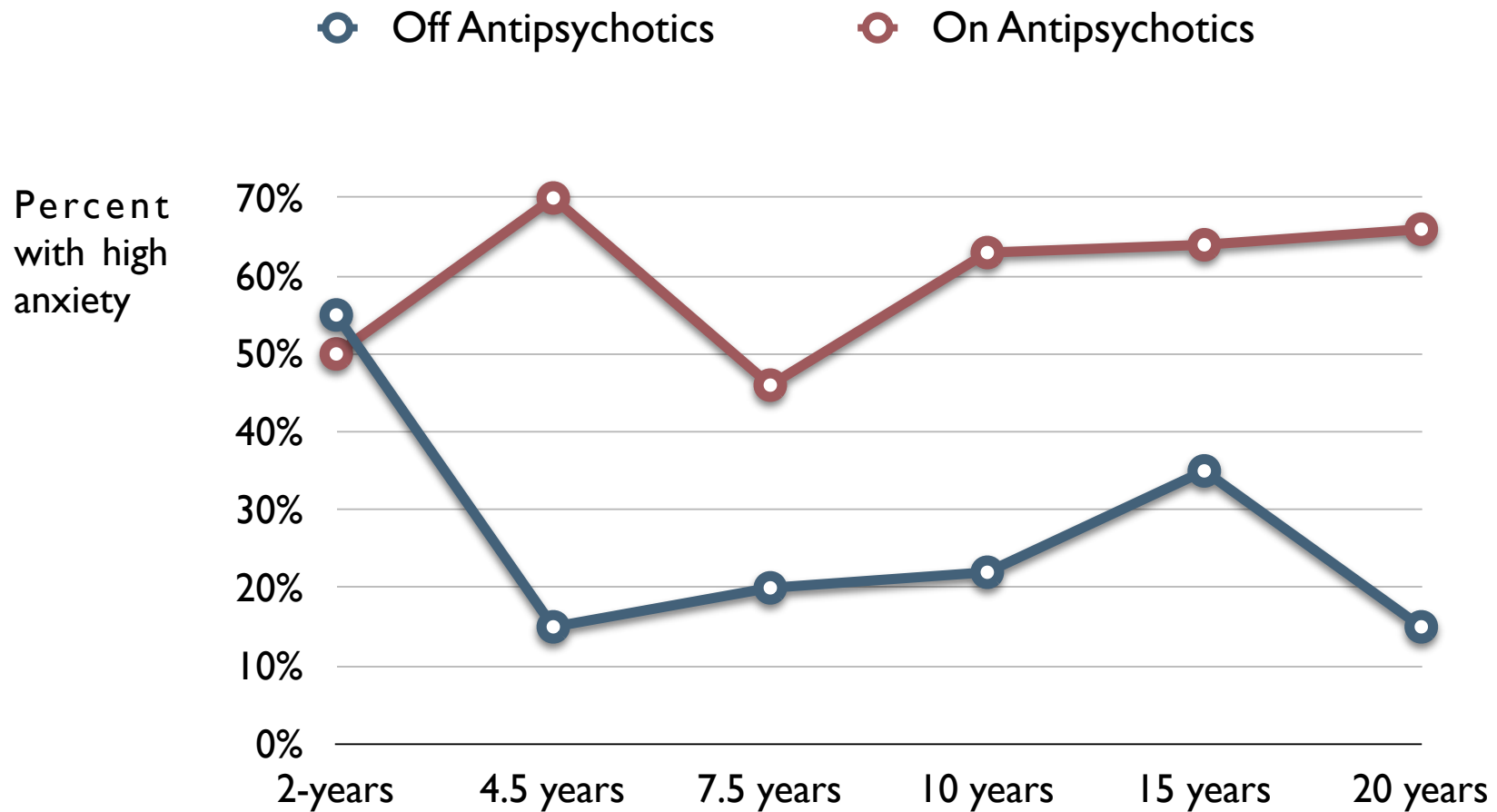
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Psychotic Symptoms in Schizophrenia Patients Over the Long Term



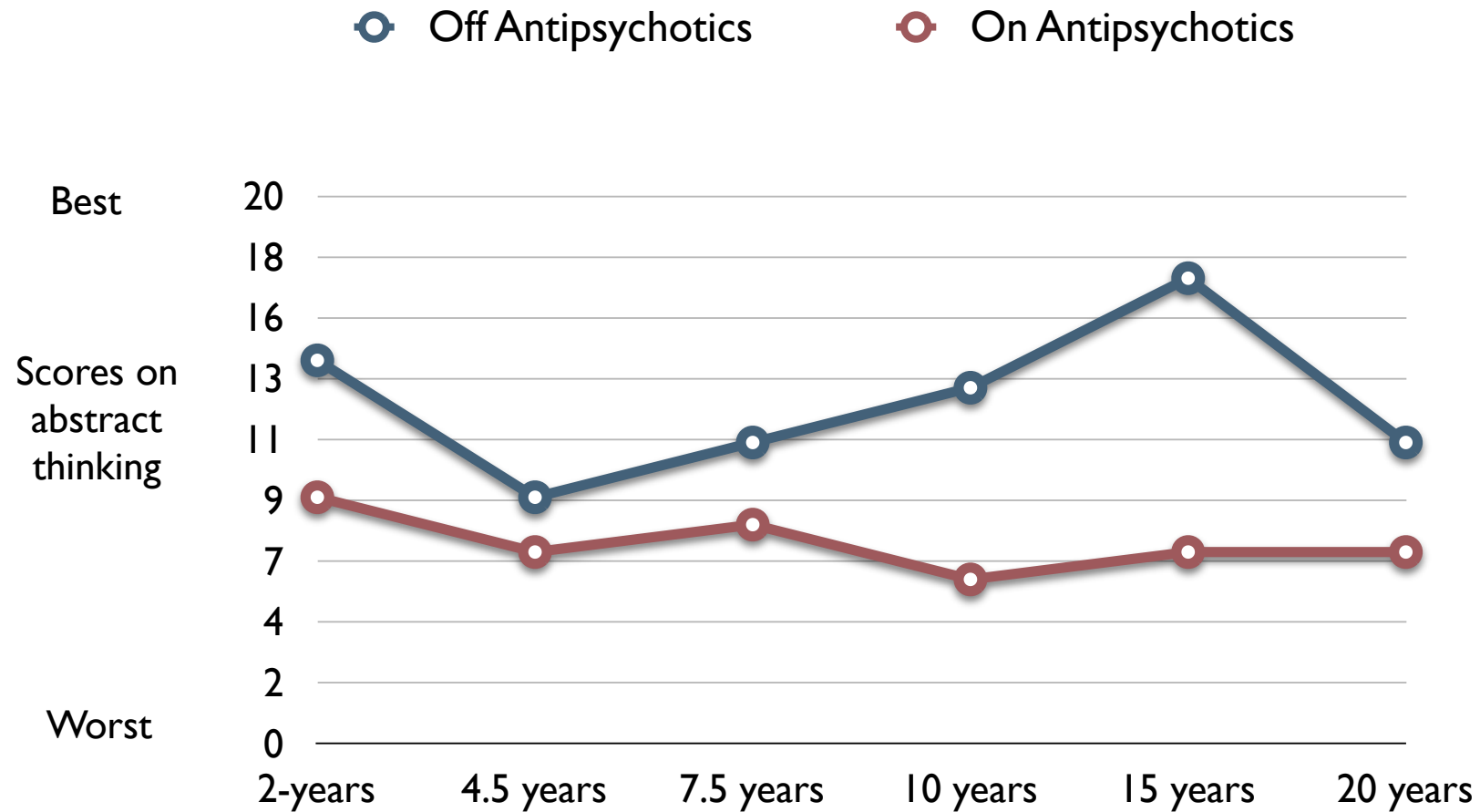
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." *Journal of Nervous and Mental Disease* 195 (2007):406-14.

Anxiety Symptoms of Schizophrenia Patients



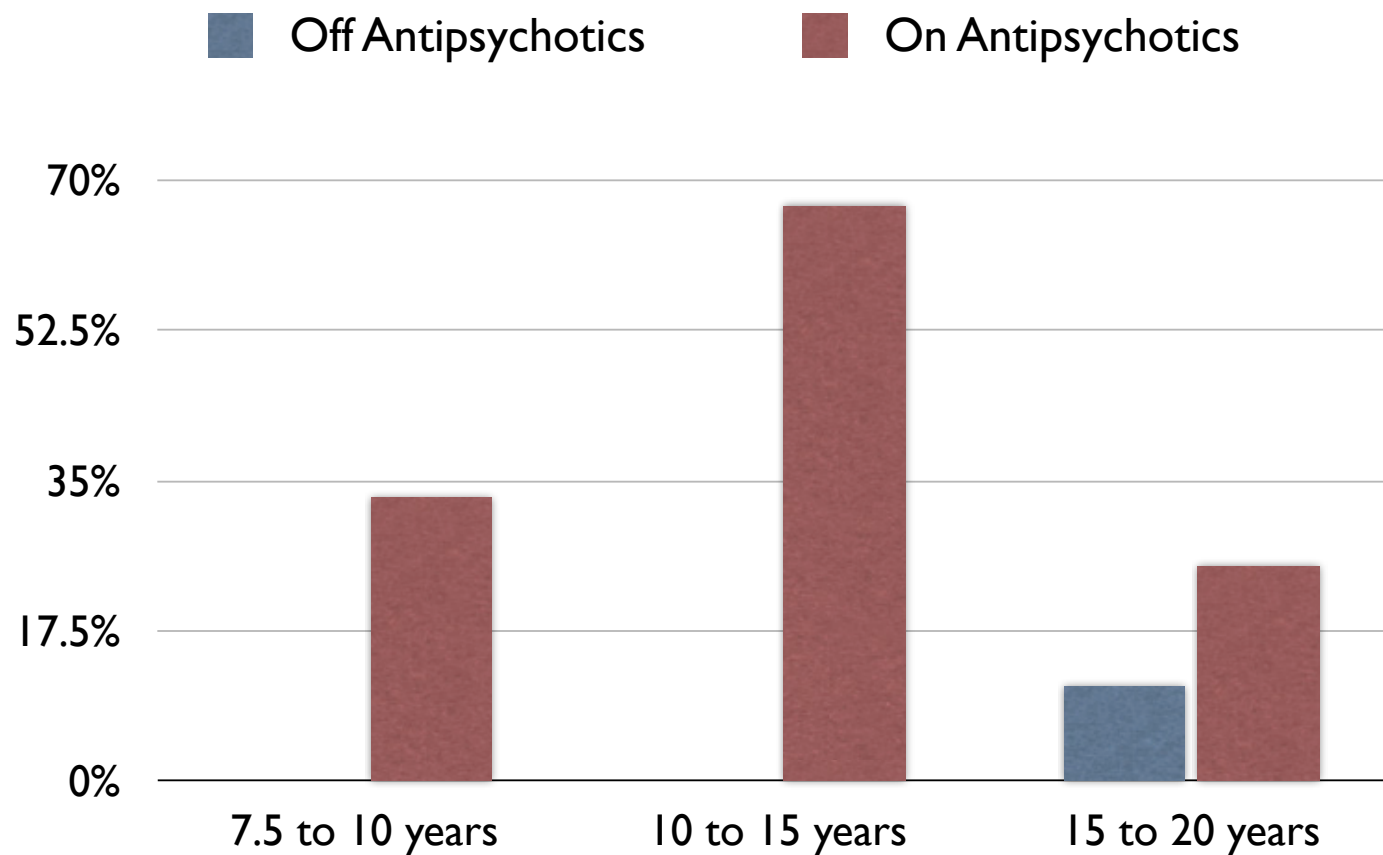
Source: Harrow M. "Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study." *Psychological Medicine*, (2012):1-11.

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.

Relapse Rates Once Patients Are Stable



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

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 longitudinal study." *Psychological Medicine*, (2012):1-11.

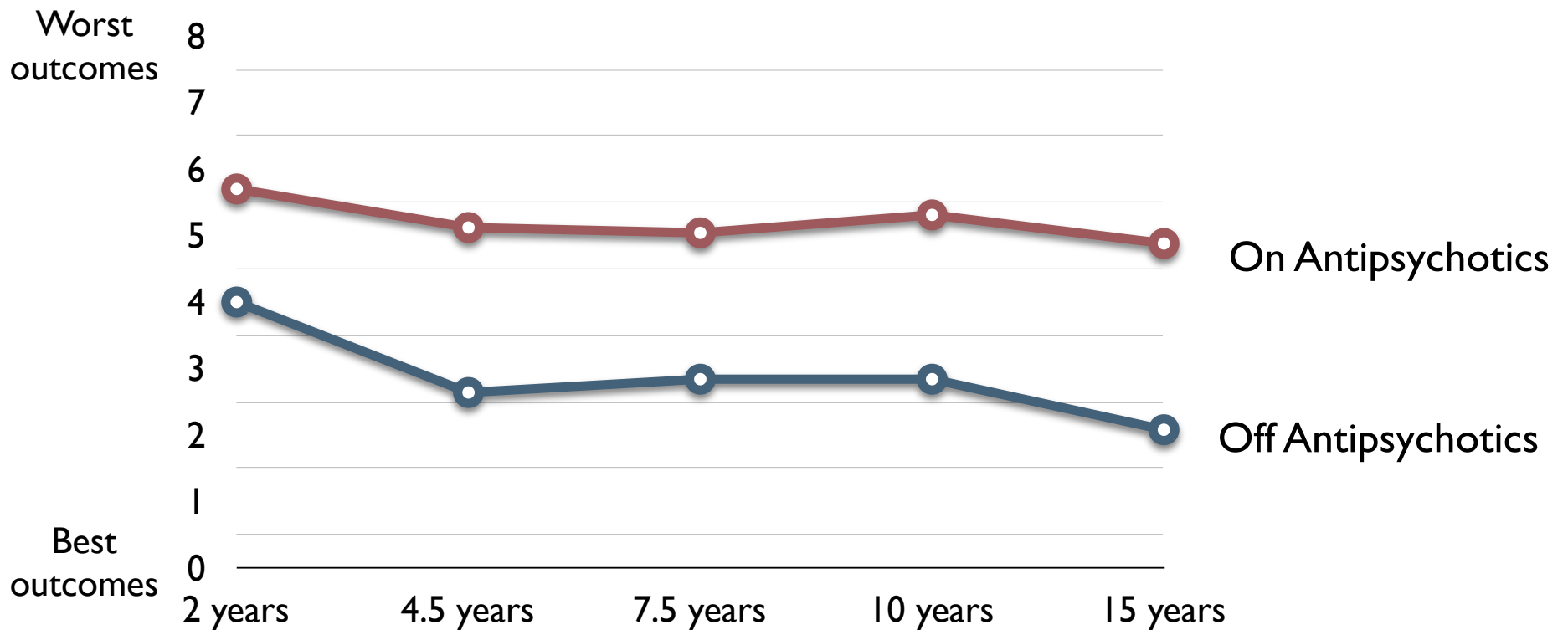
“I conclude that patients with schizophrenia not on antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics.”

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

“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.”

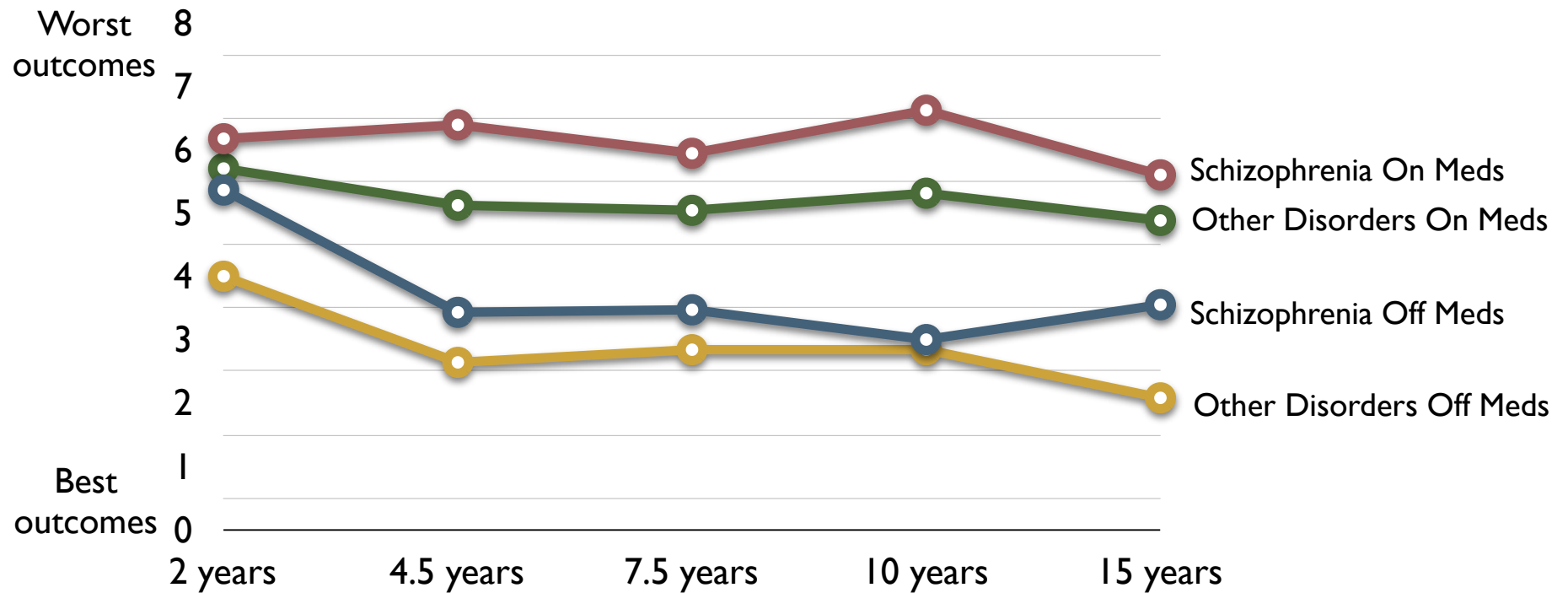
Martin Harrow, page 411.

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.

Side Effects

Physical

Rigidity, akathisia, acute dystonias, Parkinson's symptoms, impotence, dulled facial features, slowed movements, sedation, insomnia, lethargy, neuroleptic malignant syndrome, weight gain, metabolic dysfunction, diabetes, cardiac problems, gastrointestinal problems, hormonal abnormalities (lactation in boys), disfiguring facial hair growth (in women), skin rashes, seizures, respiratory depression, eye disorders, and brain shrinkage.

Emotional/Mental

Confusion, disorientation, depression, inner agitation, anxiety, apathy, emotional indifference, social isolation, cognitive slowing, withdrawal psychosis, behavioral toxicity, and violence.

Akathisia and Behavioral Toxicity

Drug-induced akathisia--an extreme inner agitation--has been linked to both suicide and violence.

- In one study, 79% of mentally ill patients who tried to kill themselves suffered from akathisia. Another researchers documented 30 cases of akathisia-linked suicides. “They appeared to be driven to find some kind of relief.”
- A 1990 study determined that 50% of all fights on a psychiatric ward were linked to akathisia. Case reports tell of patients suffering from “violent urges to assault anyone near” once injected with Haldol.
- Researchers studying this link concluded that Haldol could produce a “marked increase in violent behavior,” which they dubbed drug-induced “behavioral toxicity.”
- A 1987 study determined that 75% of patients treated with a Haldol injection experienced akathisia.
- In Harrow’s study, 60% to 70% suffered from “high anxiety,” which Harrow speculated was linked to akathisia.

Akathisia/Violence Sources

Shear, "Suicide Association with Akathisia and Depot Fluphenazine Treatment," *J Clin Psychopharmacology* 3 (1983):235-6.

Van Putten, "Phenothiazine-induced Decompensation," *Arch Gen Psychiatry* 30 (1974):102-5.

Van Putten, "The Many Faces of Akathisia," *Comprehensive Psychiatry* 16 (1975):43-6.

Van Putten, "Behavioral Toxicity of Antipsychotic Drugs," *J Clin Psychiatry* 48 (1987):13-19.

Drake, "Suicide Attempts Associated with Akathisia," *Amer J Psychiatry* 142 (1985):499-501.

Schulte, "Homicide and Suicide Association with Akathisia and Haloperidol," *Amer J of Forensic Psychiatry* 6 (1985):3-7.

Shaw, "A Case of Suicidal and Homicidal Ideation and Akathisia in a Double-Blind Neuroleptic Crossover Study," *J Clin Psychopharmacology* 6 (1986):196-7.

Herrera, "High-potency Neuroleptics and Violence in Schizophrenia," *J of Nerv and Ment Disease* 176 (1988): 558-561.

Galynker, "Akathisia as Violence," *J of Clin Psychiatry* 58 (1997):31-32.

Tardive Dyskinesia

Symptoms: Repetitious motor movements, such as rolling of tongue, clenching of jaw, and jerky, spasmodic movements of the arms, legs, fingers, toes, torso, neck, and larynx.

Severe TD: Said to resemble “known neurological diseases, such as Huntington’s disease, dystonia musculorum deformans, and postencephalitic brain damage.”

Risk: As assessed by Yale investigators, 2010 study.

- Older neuroleptics: 5.6% year.
- Atypicals: 5.9% per year
- Combination of new and old: 9.6% per year

Source: Woods, “Incidence of Tardive dyskinesia with atypical versus conventional antipsychotic medications.” *Journal of Clinical Psychiatry* 71 (2010):463-74.

Marker for Global Decline: TD patients show impairments in learning, memory, and a variety of other intellectual tasks. TD may warn of a “larval dementia.”

Early Death

- Those with serious mental disorders are now dying 15 to 25 years earlier than normal.
- Problem of early death has become more pronounced in past 15 years.
- Patients are dying from cardiovascular ailments, respiratory problems, metabolic illnesses, diabetes, and kidney failure.
- Studies have found that number of neuroleptics taken and dosage are associated with higher risk of early death.

Sources: Colton, "Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states." *Preventing Chronic Disease* 3, (April 2006.) Saha, "A systematic review of mortality in schizophrenia." *Arch Gen Psych* 64 (2007):1123-1131. Appleby, "Sudden unexplained death in psychiatric in-patients," *Brit J of Psychiatry* 176 (2000):405-6. Joukamaa, "Schizophrenia, neuroleptic medication, and mortality." *Brit J of Psychiatry* 188 (2006):122-27.

Summary of Scientific Case Against Forced Treatment

Over the short-term, antipsychotics cause a host of physical, emotional and mental side effects.

Over the long-term, antipsychotics:

- Shrink the brain
- Worsen global outcomes
- Worsen psychotic symptoms
- Lower recovery rates
- Impair cognitive function
- Increase anxiety, which is associated with violence and suicide.
- Frequently cause tardive dyskinesia, a permanent form of brain damage
- Are associated with early death

The Alaskan Precedent

In *Myers v. Alaska Psychiatric Institute*, the Supreme Court of the State of Alaska summed up the plaintiff's argument in this way:

“Myers argues that the right to refuse forced medication is fundamental and that API cannot abridge this right without first showing that medication would advance a compelling state interest and that no less intrusive alternative is available. She further contends that our state's constitutional liberty and privacy guarantees require that courts authorizing the administration of psychotropic medications must find, first, that the requested course of medication is in the patient's best interests; and second, that the patient would presently consent to the treatment if capable of making an informed decision.”

The Court's Discussion re Meds

“Because psychotropic medication can have profound and lasting negative effects on a patient’s mind and body, we now similarly hold that Alaska’s statutory provisions permitting nonconsensual treatment with psychotropic medications implicate fundamental liberty and privacy interests.”

The Court's Decision

“We hold that in future non-emergency cases a court may not permit a treatment facility to administer psychotropic drugs unless the court . . . expressly finds by clear and convincing evidence that the proposed treatment is in the patient's best interests and that no less intrusive alternative is available.”