Antipsychotic Medications and their Long Term Effects: What the Defense Team Needs to Know.

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Chemical Imbalance = Mental Illness? Poll of Audience

D2 Dopamine Decrease =
Symptom Improvement =
Chemical Imbalance?

Why Is This Important?
We Want To Help

- Antipsychotics are increasingly being used as the standard of care for many psychiatric diagnosis, and as a first line of defense for treatment.

- Mental health experts often discuss the need for antipsychotic medications, and make opinions about their need, use, and safety.

- Are those opinions supported by the peer reviewed evidence?

- Does our treatment really help people over the long term and they are happy with the treatment.

- Treatment for just Schizophrenia accounts for approximately 30 percent of the 104 billion spent on mental health in the United States. (Coffey, 2005)

Goals Today

1. Provide summary of the narrative and ideological underpinnings for usage.
2. Provide ALL the short term studies assessing medication naive patients compared to other treatments for psychosis.
3. Provide All the long term studies assessing effectiveness of antipsychotic medication for psychosis, compared to minimal and or short term use, no use at all, or stopping their usage.
4. Provide not only controlled studies, but a host of other studies using a different design (e.g. brain scans, animal studies, epidemiological studies, cross cultural, etc…), and learn what these medications do to outcomes and brain functioning.
5. Provide peer reviewed research as to what these medications do to overall biological health to the patient, including mortality.

The Evidence for Antipsychotics

Short-term Use:

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

Adams, (2005). “Chlorpromazine for Schizophrenia: A Cochrane systematic review of 50 years of randomized controlled trials.” BMC Medicine, 3:15.

Cole, J, et al. (1964). “Phenothiazine treatment in acute schizophrenia.” Archives of General Psychiatry, 10:246-61.

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In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications.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, attorneys and judges see that the medications often work upon initial use, and they see that patients often relapse when they go off the medications.

The Common Wisdom

The introduction of chlorpromazine [Thorazine] into asylum medicine in 1955:

“initiated a revolution in psychiatry, comparable to the introduction of penicillin in general medicine. ”

--Edward Shorter, A History of Psychiatry

The narrative given is that prior to antipsychotics, mental patients did not get out of hospitals

What's Missing From The Evidence Base? Are There Studies To Fill What's Missing?

A. Evidence of Short Term Methodologically Sound Studies.

B. Evidence on the Long Term Course Schizophrenia with Medication, particularly in regard to functional outcomes and spectrum disorders.

B. Acknowledgement that the Relapse Studies Reflect Risks Associated with Drug Withdrawal Effects, rather than the return of the natural course of the disorder.

C. Physicians today no longer have clinical experience with the long-term course of schizophrenia patients off medication.

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

A Cochrane Review in 2011

Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care.
They investigate the effects of interventions for prevention, treatment and rehabilitation.

The researchers excluded studies that assess efficacy in drug-withdrawn patients who were then randomized to drug or placebo, as that design is flawed because the placebo group is not a placebo group, but really a Drug Withdrawal Group, who really are suffering abrupt withdrawal symptoms. We all know it is a really bad idea to abrupt remove the drug. There are hundreds of studies where they take them off, then randomly assign.

The investigators found only FIVE studies (in over 50 years available), with a total of 998 patients, that compared initial antipsychotic use with placebo, milieu, or psychological treatment in patients experiencing early episode schizophrenia.

Bola J, Kao D, Soydan H, Adams CE. Antipsychotic medication for early episode schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD006374. DOI: 10.1002/14651858.CD006374.pub2

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.

What they are Saying:

After 50+ years of research, we do not have evidence to say that immediate antipsychotic medication intervention for schizophrenia actually improve outcomes for people after one year.

Recognition: Evidence For Long-term Use of Antipsychotics is Lacking

"After fifty years of neuroleptics, are we able to answer the following simple question: Are neuroleptics [Antipsychotics] 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). [Underline Added]

Dr. Stip was the holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal. His research had received funding from CIHR, Lundbeck Canada Inc. and Otsuka Canada Pharmaceutical Inc. He has served on the advisory boards and been a lecturer for Lundbeck Canada Inc, Otsuka Canada Pharmaceutical Inc, and Janssen.

What Have We Forgotten or Missed?

What is the natural course of the disorder?

What is the range of outcomes for people so diagnosed?

Does therapy improve on the “natural” long-term recovery rate?

What does the scientific literature reveal?

Do Antipsychotics Do More Harm Than Good?

Investigators from Columbia University and City College of New York:

“Recently, Robert Whitaker [Dr. Toby Watson] advanced a troubling interpretation of the evidence base for long-term use of antipsychotic medication. He reviewed a number of epidemiological and clinical studies and concluded that antipsychotic medications are an iatrogenic cause of chronicity in schizophrenia, and that these medications may lead to the deterioration of patients’ health and well-being over time. His explanation rested on the notion that antipsychotic medication may induce a hypersensitivity to dopamine. We were concerned by Whitaker’s findings and wondered whether a systematic appraisal of published literature would produce the same results.”

Source: N. Sohler. Weighing the evidence for harm from long-term treatment with antipsychotic medications: A systematic review. Am Journal of Orthopsychiatry, Vol 86, 2016, 477-485

They Concluded…

We found the published data to be inadequate to test this hypothesis.

BUT

By extension, these data were also inadequate to conclusively evaluate whether long-term antipsychotic medication treatment results in better outcomes on average. We conclude that careful reappraisal of existing data is useful to ensure standard of care treatment strategies are indeed evidence-based. In the case of long-term use of antipsychotic medications, new data may be needed to establish a sufficient evidence base to understand its benefit/risk balance for patients with schizophrenia.

NIMH: Schizophrenia Outcomes in the Decade Before Antipsychotics (1945-1955)

- At end of three years following hospitalization, 73% 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% had a social recovery, meaning they could support themselves and live independently.

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

Not cherry picked data, but in 1956 NIMH convened a meeting and reviewed data above. The conventional narrative that patients did not get out of hospitals and did not get well was not supported by the data.

Question Then Became: Did the arrival of antipsychotics lower hospitalization and increase discharge rates?

The Revolving Door Appears

• A British study of 100 schizophrenia patients found that those treated in 1956/57, had, if anything, a "higher rate of readmission" in the three years following discharge than those treated in 1952/53, prior to the introduction of the phenothiazines.

• A Norwegian study of hospital admission and discharge records in 1948/52 and in 1955/1959 determined that while there may have been a slight improvement in discharge rates after chlorpromazine arrived in asylum medicine, [BUT] the total number of readmissions "increased 41.6%," which the researchers described as "characteristic of the drug period."

• In a study of 221 first-episode schizophrenia patients admitted into Scottish hospitals from 1949 to 1957, with patients followed for three years, there was no difference in the percentage that suffered a single "attack" (about 70% of all patients in both the pre-drug and post-drug eras), but among all discharged patients, there was an "increased relapse frequency" following the introduction of chlorpromazine [Thorazine].

Source: Pritchard, M. "Prognosis of schizophrenia before and after pharmacotherapy: II. Three- year follow-up." Br J Psychiatry 113 (1967):1353-59. 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. McWalter, H. "Outcomes of treatment of schizophrenia in a north-east Scottish mental hospital. Am J Psychiatry 118 (1961):529-533.

The First Hint of a Paradox

NIMH's First Follow up Controlled Study (1967):

At the end of one year, those 6 week 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."

(thioridazine (Mellaril), fluphenazine (Prolixin), chlorpromazine (Thorazine)

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

1967 NIMH Schooler Conclusion

However, in spite of this finding, which the researchers wrote: "was so unexpected," the NIMH investigators stated that they "were unprepared to recommend placebo as treatment of choice."

In other words, the NIMH researchers decided they wouldn't develop treatment guidelines based on their own research, which found that placebo patients did better than the drug-treated patients. (Page 991)

A Retrospective Comparison of Outcomes: Pre-Drug Vs Drug Era

Relapse Rates Within Five Years of Discharge:

1947 cohort: 55%

1967 cohort: 69%

Functional Outcomes

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

1967 cohort: 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.

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. "

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

Beginning Worries

- 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?” Am J P sychiatry 135 (1978): 1321-4.

NIMH Concerned: 3 Studies Funded

In the 1970s, the NIMH conducts three studies

- Compare antipsychotic treatment with “environmental” care that minimizes use of the drugs.
- Conclusions?

NIMH #1 Study: William Carpenter

Compared:

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

Results:

- No Drug Group Discharged Sooner (108 day average versus 126 days.)
- 45% medicated group relapsed within a year after discharge, compared to
- 35% no medication relapsed within a year after discharge.
- The no medication group reported less depression, blunted emotions, and retarded movements.

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

NIMH Carpender Study

"Patients reported experiencing more anguish with our treatment approach, whereas they felt a greater sense of frustration and of being 'frozen in the psychosis' in settings emphasizing drug treatment . . . insofar as the psychotic break contains potential for helping the patient alter pathological conflicts within himself and establish a more adaptive equilibrium with his environment, our present-day practice of immediate and massive pharmacological intervention may be exacting a price in terms of producing 'recovered' patients with greater rigidity of character structure who are less able to cope with subsequent life stresses." --William Carpenter

Underlined added

William Carpenter: Question Raised!

"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. Thus, as with tardive dyskinesia, we may have a situation where neuroleptics increase the risk for subsequent illness but must be maintained to prevent this risk from becoming manifest." (bold - underline added)

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

NIMH #2: Loren Mosher "Soteria Project"

Head of NIMH Schizophrenia Studies

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.

19% had used them regularly throughout the two year follow up.

Source: Bola, J. "Treatment of acute psychosis without neuroleptics." J Nerv Ment Disease 191 (2003):219-29.
Mosher LR and Menn AZ. Soteria: An Alternative to Hospitalization for Schizophrenia. In JH Masserman (Ed), Current Psychiatric Therapies, (Vol. XIV). New York: Grune and Stratton, Inc., pp. 287-296, 1974.
Menn AZ and Mosher LR. The Soteria Project. An Alternative to Hospitalization for Schizophrenics: Some Clinical Aspects. In J Jorstad and E Ugelstad (Eds), Schizophrenia 75. Oslo, Norway: Universitetsforlaget, pp. 347-372, 1976.
Mosher LR and Menn AZ. Dinosaur or Astronaut? One-Year Follow-Up Data from the Soteria Project. In M Greenblatt and RD Budson (Eds), "A Symposium: Follow-up of Community Care". American Journal of Psychiatry, 133:8, 919-920, 1976.

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.”

NIMH #3: Rappaport Three-Year Outcomes

U.C. San Francisco, n=80, Agnews State Hosp, Only 27% of the drug-free patients relapsed in the three years following discharge, compared to 62% of the medicated group. Most notably... only 8% rehosp.

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." Antipsychotic medication may make some "patients more vulnerable to future relapse than would be the case in the natural course of the illness." Underline added.

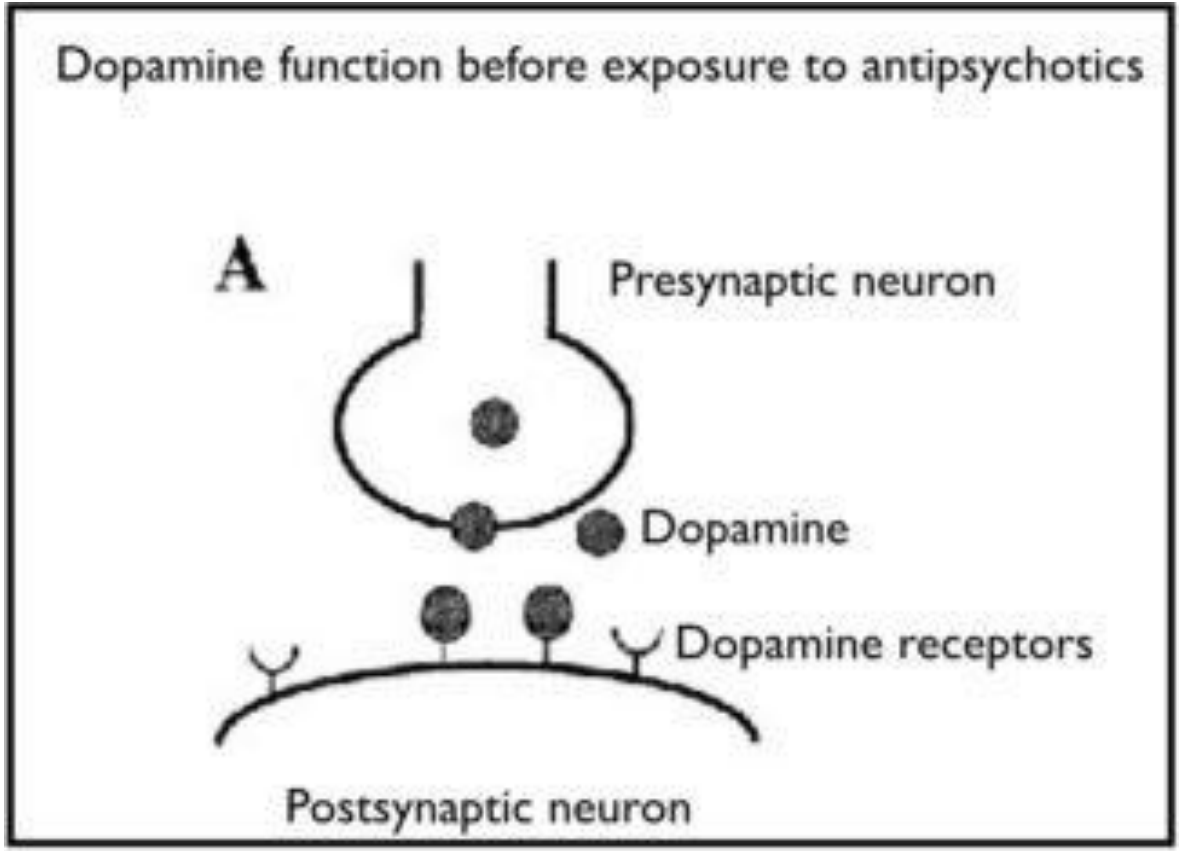
Why Greater Relapse?

In the 1970s, two neuro researcher physicians at McGill University, Guy Chouinard and Barry Jones, offered a biological explanation for why this is so.

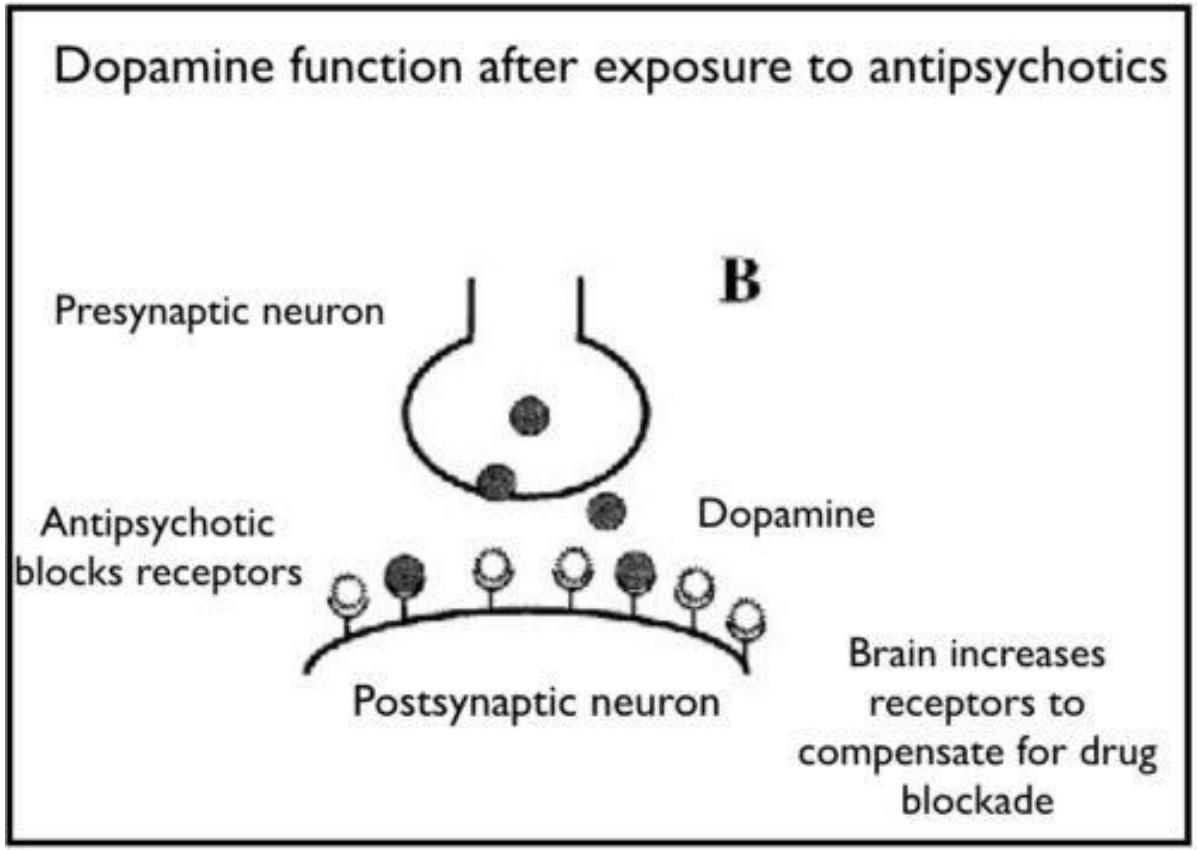
The brain responds to neuroleptics and their blocking of dopamine receptors as though they are a pathological insult. To compensate, dopaminergic brain cells increase the density of their D2 receptors by 40% to 90%.

Silvestri S, Seeman MV, Negrete JC et al. (2000). "Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study". Psychopharmacology, 152: 174–80. doi:10.1007/s002130000532. PMID 11057521.

Dopamine Supersensitivity



Dopamine Supersensitivity



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

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 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.

Psychotropic Drugs Create Abnormalities in Brain Function
Stephen Hyman, past director of the NIMH

- Psychiatric medications “create perturbations in neurotransmitter functions.”

- In response, the brain goes through a series of compensatory adaptations in order “to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu.”

- The “chronic administration” of the drugs then cause “substantial and long lasting alterations in neural function.”

- After a few weeks, the person’s brain is now functioning in a manner that is “qualitatively as well as quantitatively different from the normal state.”

Hyman, S. “Initiation and adaptation: A paradigm for understanding psychotropic drug action.” Am J Psychiatry 153 (1996):151-61.

What Does the Other Evidence Show?

- Animal scan (PET) studies
- MRI scan studies
- UK first-episode study
- Cross-cultural study
- Longitudinal studies
- Randomized tapering study
- Medication compliance study
- Quebec epidemiological study

Animal Models

Question: Does Induced Psychosis Lead To Dopamine Supersensitivity?

In 2005, Philip Seeman at the University of Toronto reported that agents that trigger psychotic-like behavior in animals include: amphetamines, angel dust (PCP), lesions to the hippocampus, gene knockout manipulations, AND all cause an increase in D2 receptors (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,"

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 Density of D2 HIGH Receptors

Seeman found:

Haloperidol and olanzapine [Zyprexa] both increased the density of D2 HIGH receptors.... thus, they cause the very biological abnormality that in animal models had been identified as a final pathway to psychosis.

Seeman Tests:
Efficiency Reduction D2 High Theory

In rat studies, “we show that during ongoing treatment with clinically relevant doses, haloperidol and olanzapine [Zyprexa] 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.

MRI Macaque Monkey Study

Finding:

- In macaque monkeys, treatment with either haloperidol or olanzapine [Zyprexa] 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.

MRI Schizophrenia Study

Gur: Department of Psychiatry, University of Pennsylvania School of Medicine

Patients:

96 schizophrenia patients, 21 neuroleptic naive & 75 previously treated.

Findings:

- Previous drug treatment = larger subcortical volumes (basal ganglia), dose related.
- Larger volumes = mildly linked to greater severity for negative & positive symptoms.

Conclusion:

"Increased subcortical volumes in treated schizophrenia patients seem to be medication-induced hypertrophy. This hypertrophy could reflect structural adaptation to receptor blockade."

Source: R. Gur. "Subcortical Volumes in Neuroleptic Naive and Treated Patients With Schizophrenia." American Journal of Psychiatry 155 (1998):1711-1717.

Gur Summary:

In other words...

The antipsychotic medication caused morphological changes in the brain that are associated with a worsening of the very symptoms the drugs are supposed to alleviate.

This is analogous to what happens in tardive dyskinesia (TD),
whereby dopaminergic (DA) receptors in the nigro neostriatal pathway are up-regulated (i.e. the DA receptors become more numerous and sensitive) secondary to chronic DA antipsychotic blockade, thereby causing the random purposeless movement seen in TD.

Dopaminergic receptors in the mesolimbic pathway, thought to mediate the positive symptomatology (e.g. voices and delusions), become more sensitized and numerous (e.g. up-regulated).

When the person removes the neuroleptic-Dopaminergic blocking agent (e.g. drug), particularly abruptly, it 'unmasks' the now up-regulated Dopaminergic receptors, resulting in a 'tardive' or 'rebound' or 'supersensitivity' psychosis.

The "oppositional tolerance" is created by the continuation of the drug treatment,
and is producing...

Drug-induced Oppositional Tolerance:

"..the opposite of what the medication originally produced."

...and may cause

"... a worsening of the illness,[which] continues for a period of time after discontinuation of the medication, and may not be reversible."

-Rif El-Mallakh, University of Louisville, 2011
Board Cert Psychiatry-NIMH Researcher

Source: El-Mallakh, R. "Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. Medical Hypotheses 76 (2011): 769-773.

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:
Past 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

More Brain Imaging Evidence: Antipsychotics Cause Brain Damage-Shrinkage

In a 2012 review of 43 brain-imaging studies of first-episode psychosis, European researchers determined that a loss of gray matter volume was "significantly more severe in medicated patients. "

Source: J. Radua. "Multimodal meta-analysis of structural and functional changes in first episode psychosis and the effects of antipsychotic medications." Neuroscience and Biobehavioral Review, in press as of 9/04/2012.

A German Perspective on Drug-Induced Brain Shrinkage

“The findings indicate that there is evidence for grey and white matter volume changes of the frontal brain, which cannot be explained by the severity of the disease alone but are also very likely a manifestation of long-term effects of antipsychotics . . . Considering the contribution of antipsychotics to the changes in brain structure, which seem to depend on cumulative dosage and can exert adverse effects on neurocognition, negative and positive symptoms and psychosocial functioning, the guidelines for antipsychotic long-term drug treatment should be reconsidered.”

Source: Aderhold, V. “HeinzFrontale Hirnvolumenminderung durch Antipsychotika? Der Nervenarzt. May, 2014

U.K. First Episode Study, 1990

- 253 first-episode schizophrenia patients.
- In patients who had been ill less than one year, patient treated with placebo had significantly better "occupational outcome" at two years.

Conclusion: The present finding may be considered as a stronger indication [then even an earlier study] of the possible social cost of maintenance neuroleptic medication."

Source: E.C. Johnstone. "Further investigation of the predictor of outcome following first schizophrenia episodes." Br J of Psychiatry 157 (1990):182-89.

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.

•Concluded:

"being in a developed country was a strong predictor of not attaining a complete remission."

but…

"an exceptionally good social outcome characterized the patients" in developing countries.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." Psychological

WHO Findings - Continued

Medication usage:

- 16% regularly maintained on drugs in developing countries
- 61% of in rich developed countries maintained antipsychotics

15-year to 20-year follow up:

- 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.

Longitudinal Study: Martin Harrow

Baseline

n = 200 psychotic patients tracked from the 1980s

Median age: 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

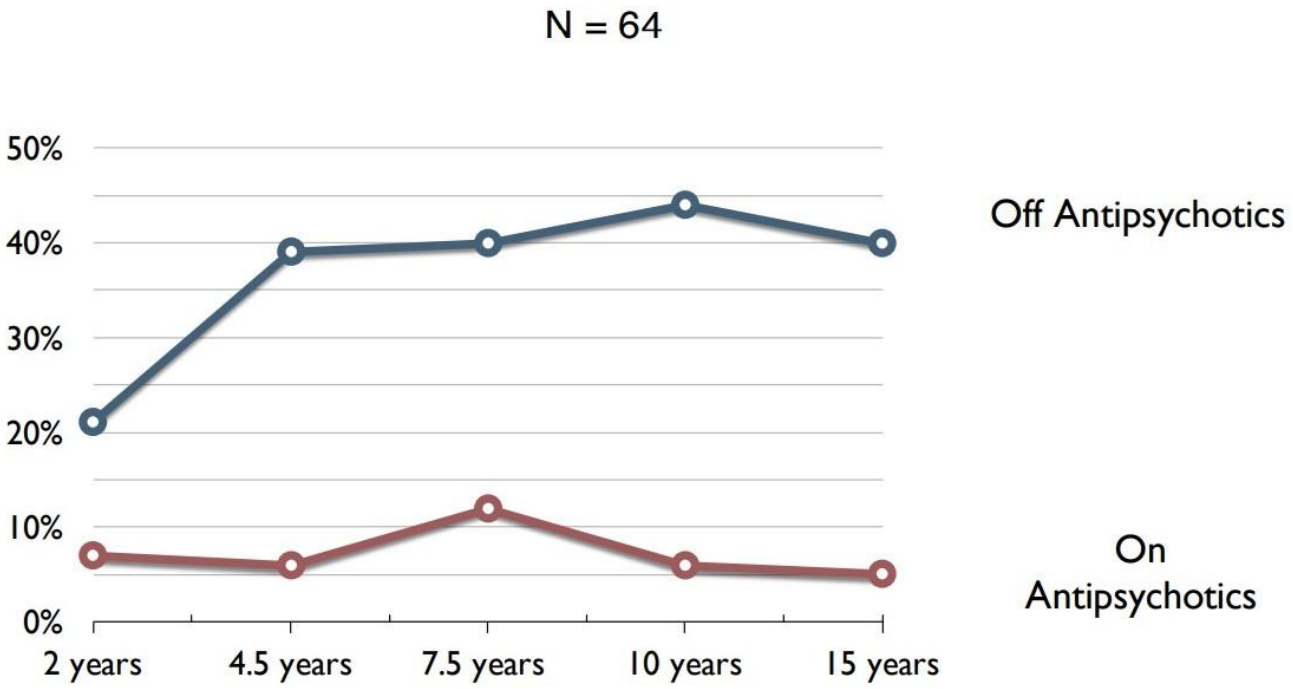
Patient Composition at 15 Years

145 patients still in study (77%)

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

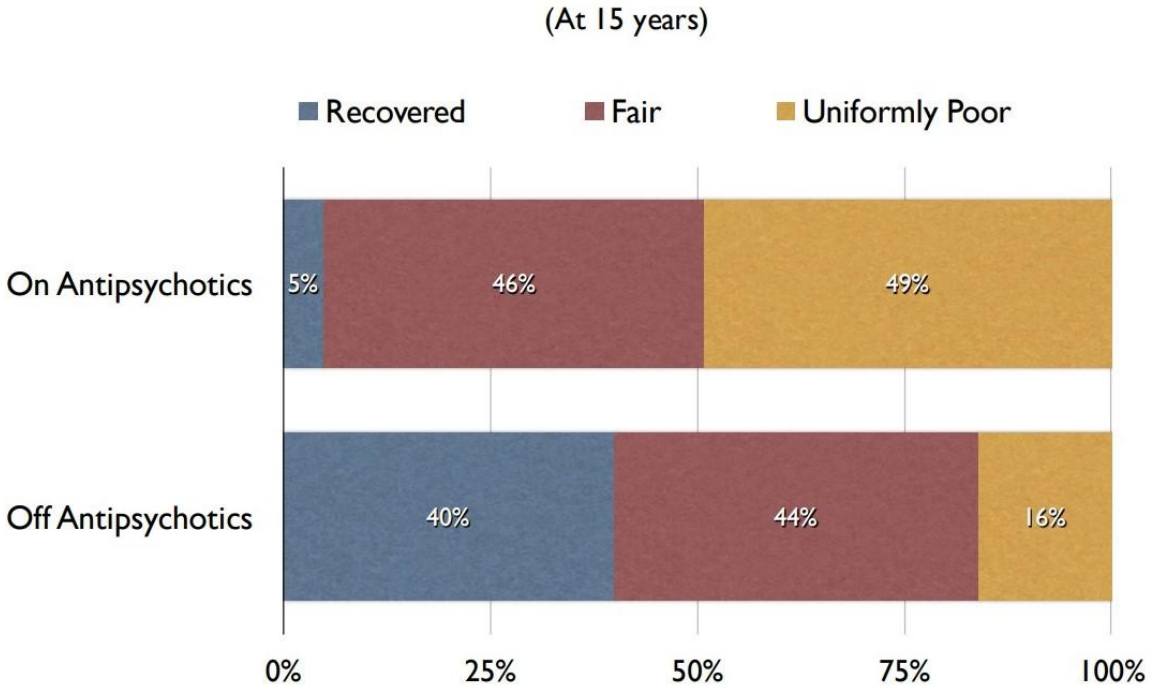
Source: Harrow M. “Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications.” J of Nervous and Mental Disease 195 (2007):406-14.

Recovery Rates ?
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 Schizophrenia
15 Year 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 follow up.” [underline added]

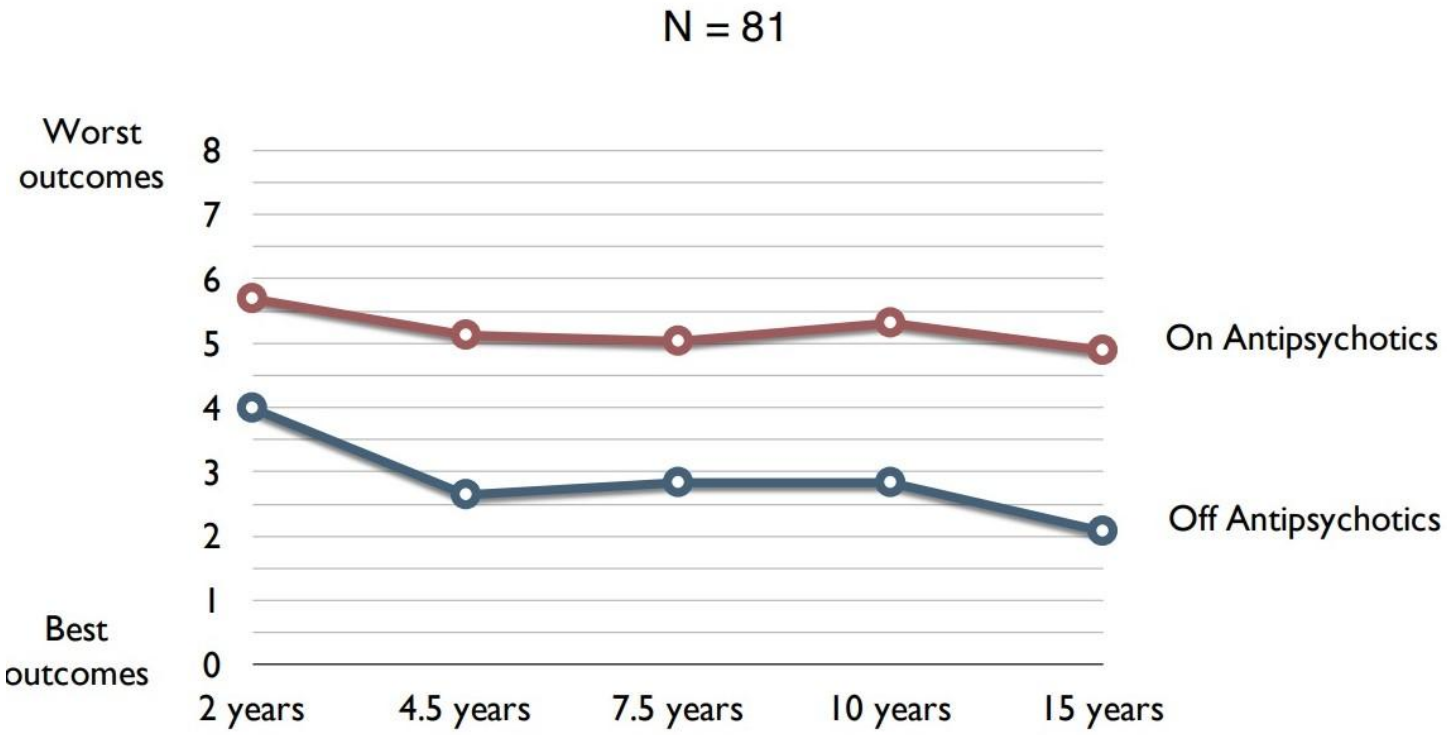
Martin Harrow, page 411.

Harrow Conclusion：

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

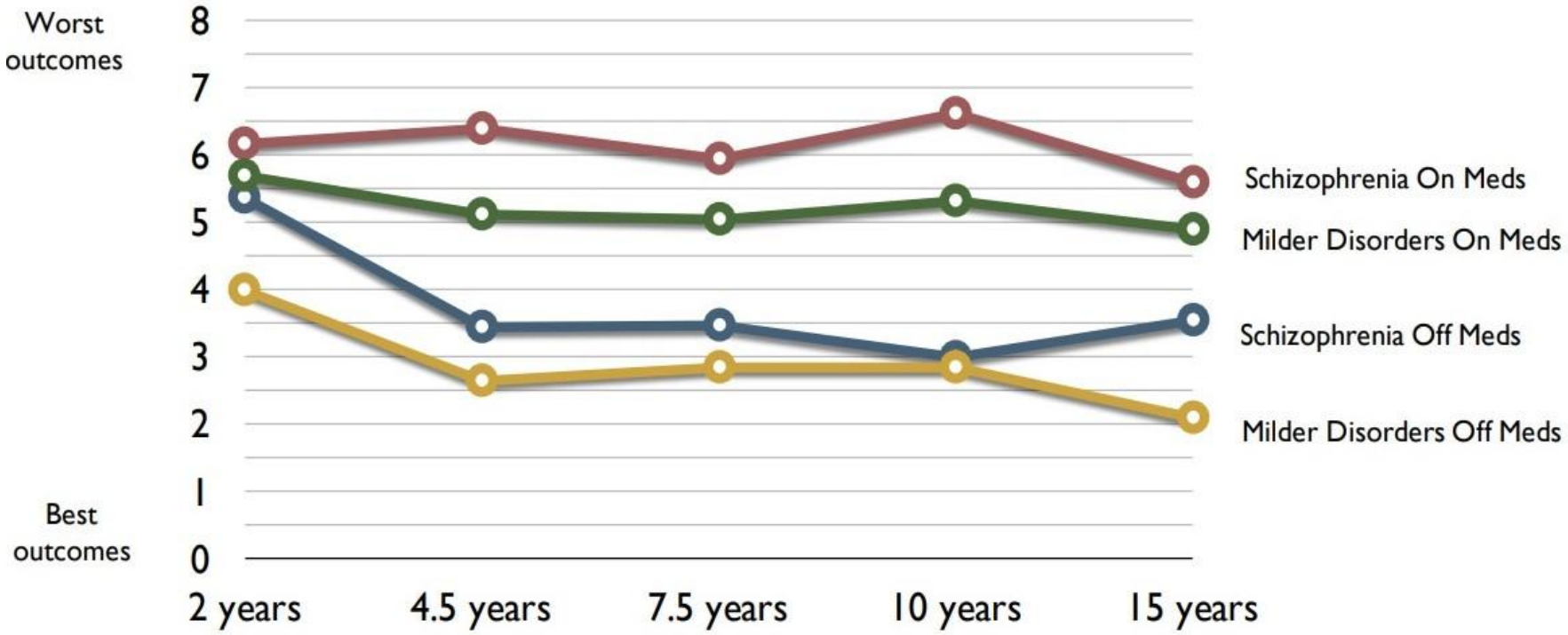
--Martin Harrow, American Psychiatric Association annual meeting, 2008

Global Adjustment of "Other Psychotic" Patients



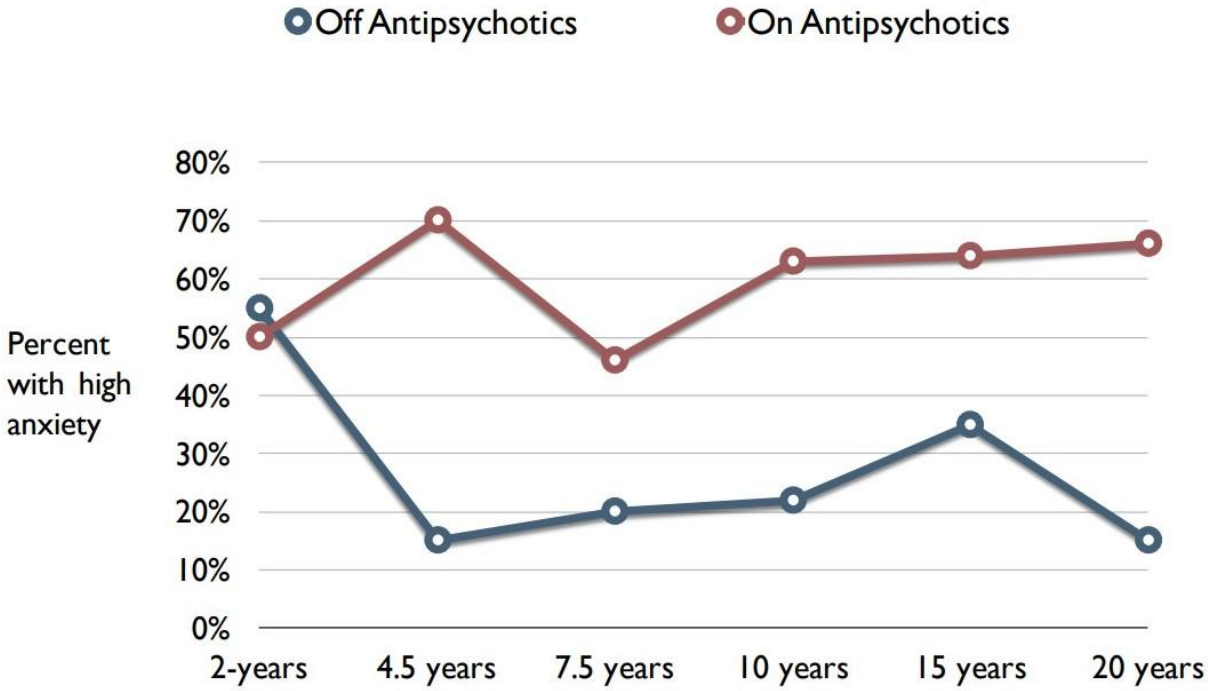
Source: Harrow M. "Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications." Journal of Nervous and Mental Disease 195 (2007):406-14.

Global Adjustment of All Psychotic Patients



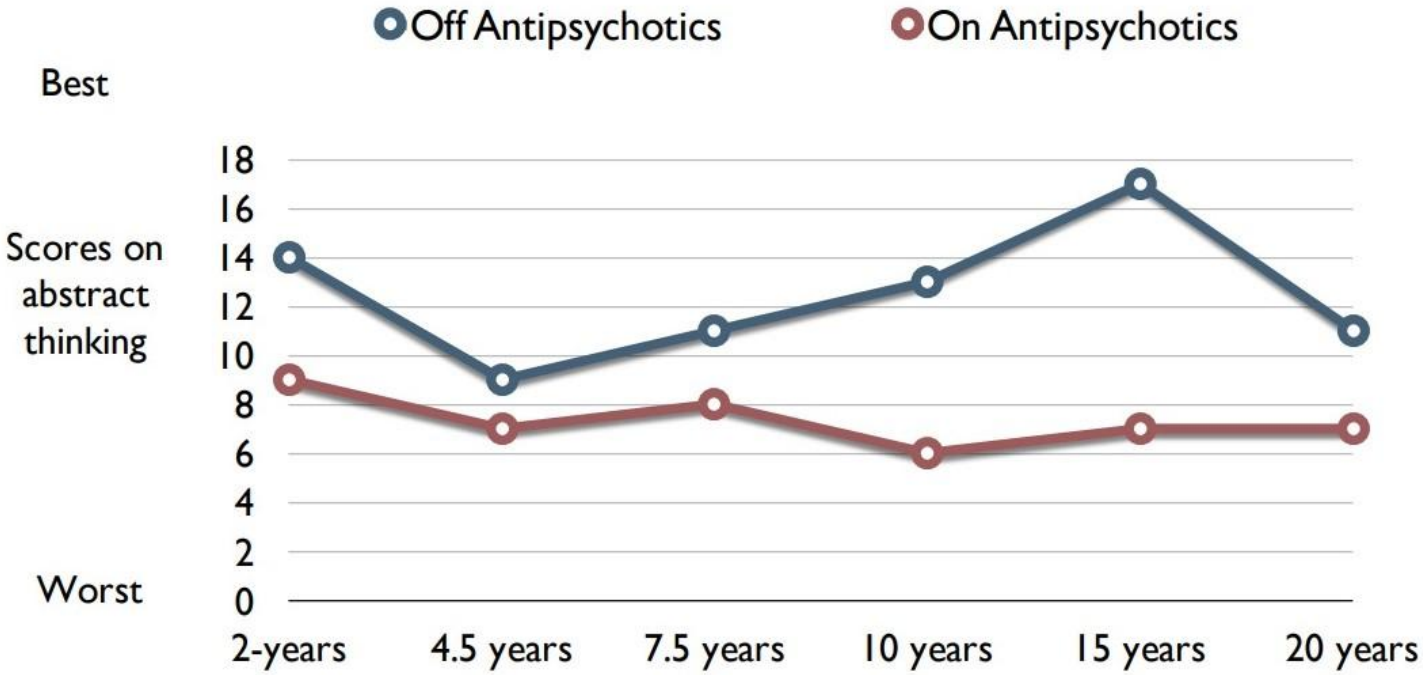
Source: Harrow M. “Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications.” Journal of Nervous and Mental Disease 195 (2007):406-14.

Anxiety Symptoms of Schizophrenia Patients



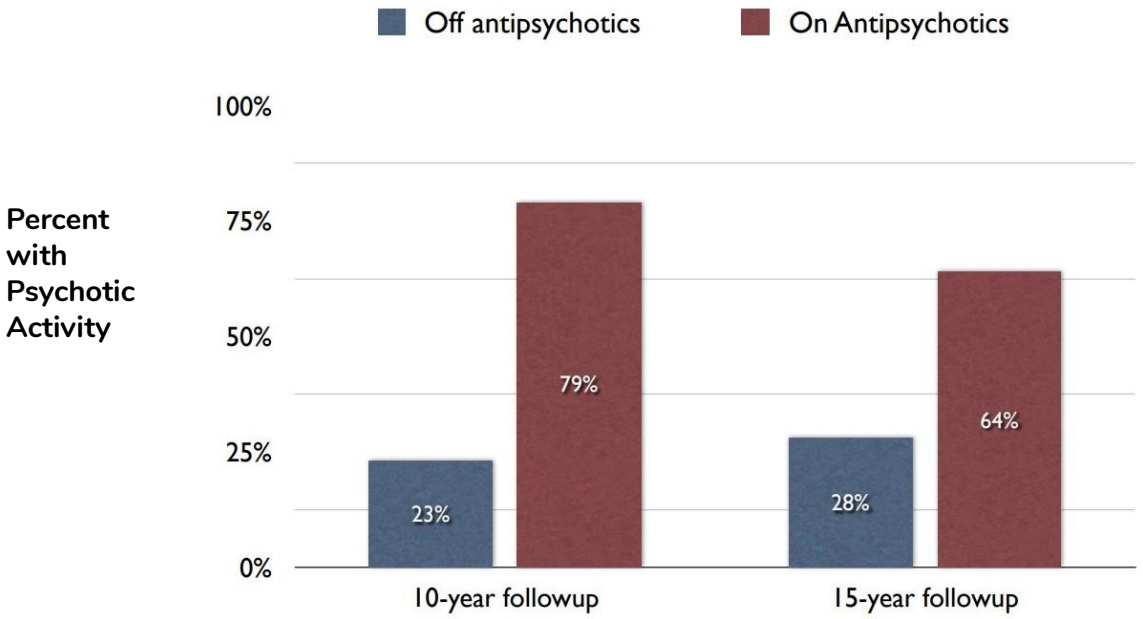
Source: Harrow M. “Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study.” Psychological Medicine, (2012):1-11.

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.

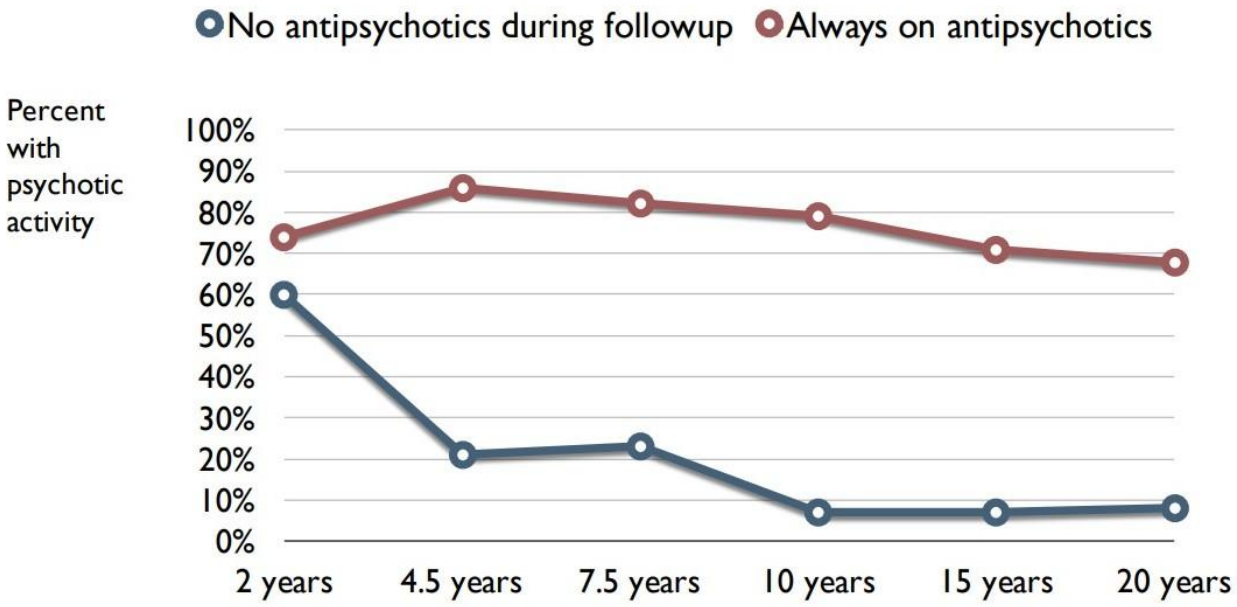
Psychotic Symptoms in Schizophrenia Patients Over the Long Term



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.

Psychotic Symptoms of Schizophrenia Patients

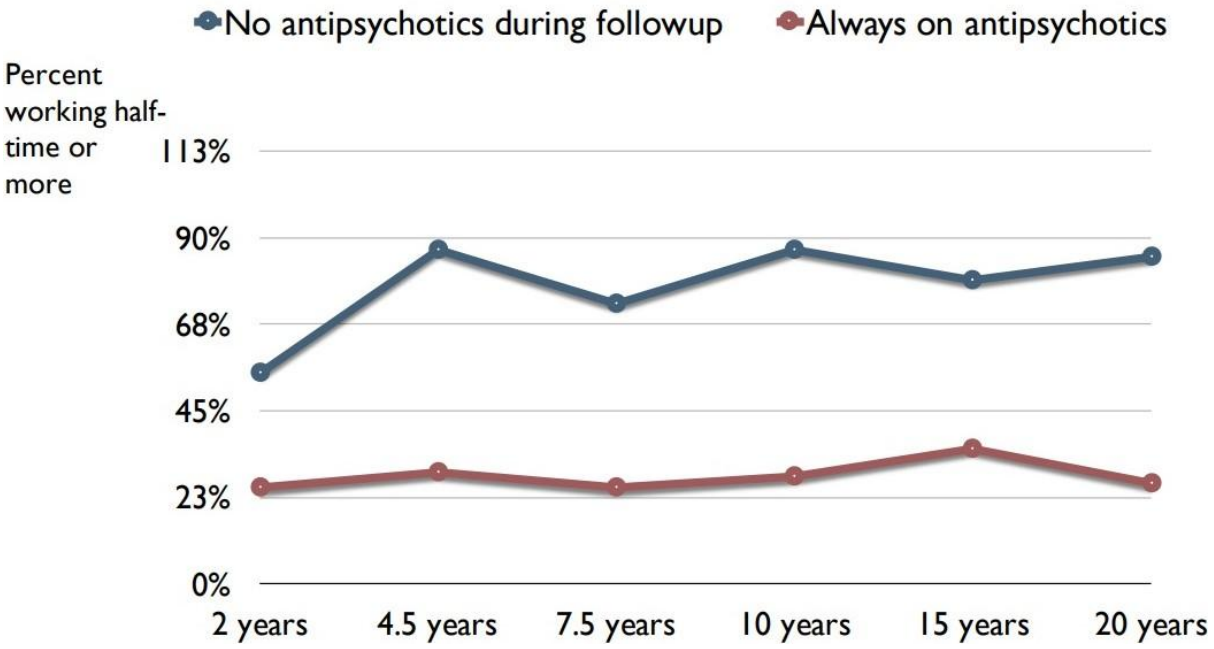
(Subset analysis of schizophrenia patients)



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

(Subset analysis of schizophrenia patients)



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

How Can This Be True?

“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.” --Martin Harrow, 2013

Wunderink's Randomized Study of Long-term Outcomes

Dutch Study: Neuroleptic or Atypical could be causing the worsening of outcomes?

Study Design

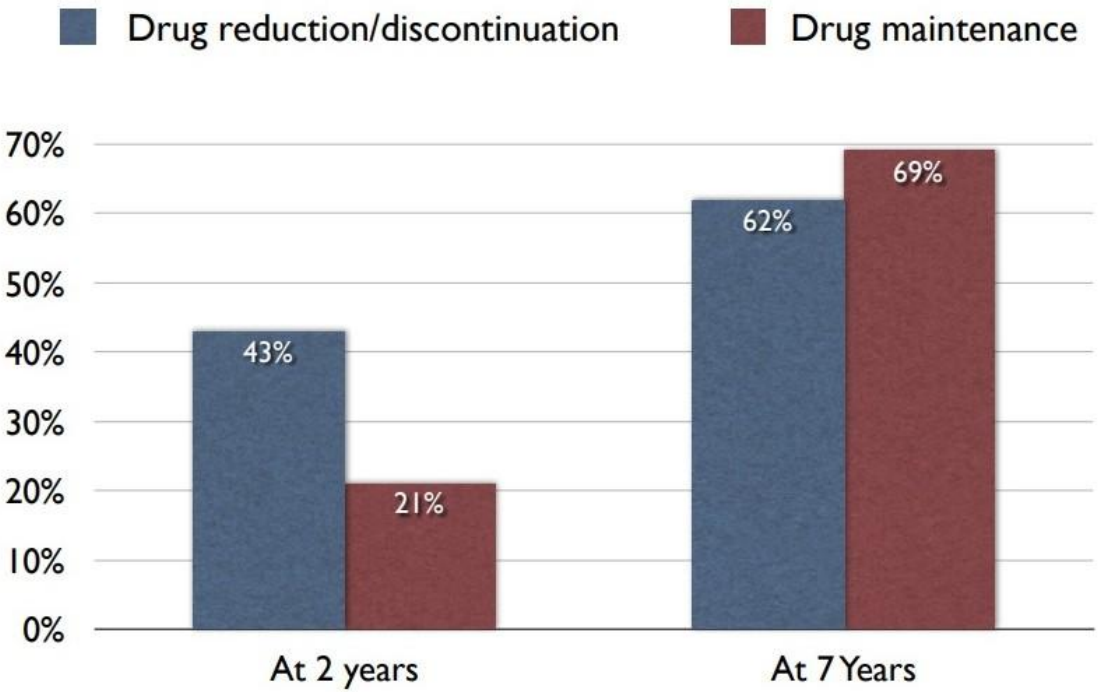
- 128 stabilized first-episode psychotic patients who had been stable for six months on antipsychotics. (103 patients were still in the study at the end of seven years.)

- Randomized either to a dose reduction-discontinuation treatment, or

- Randomized to standard antipsychotic treatment.

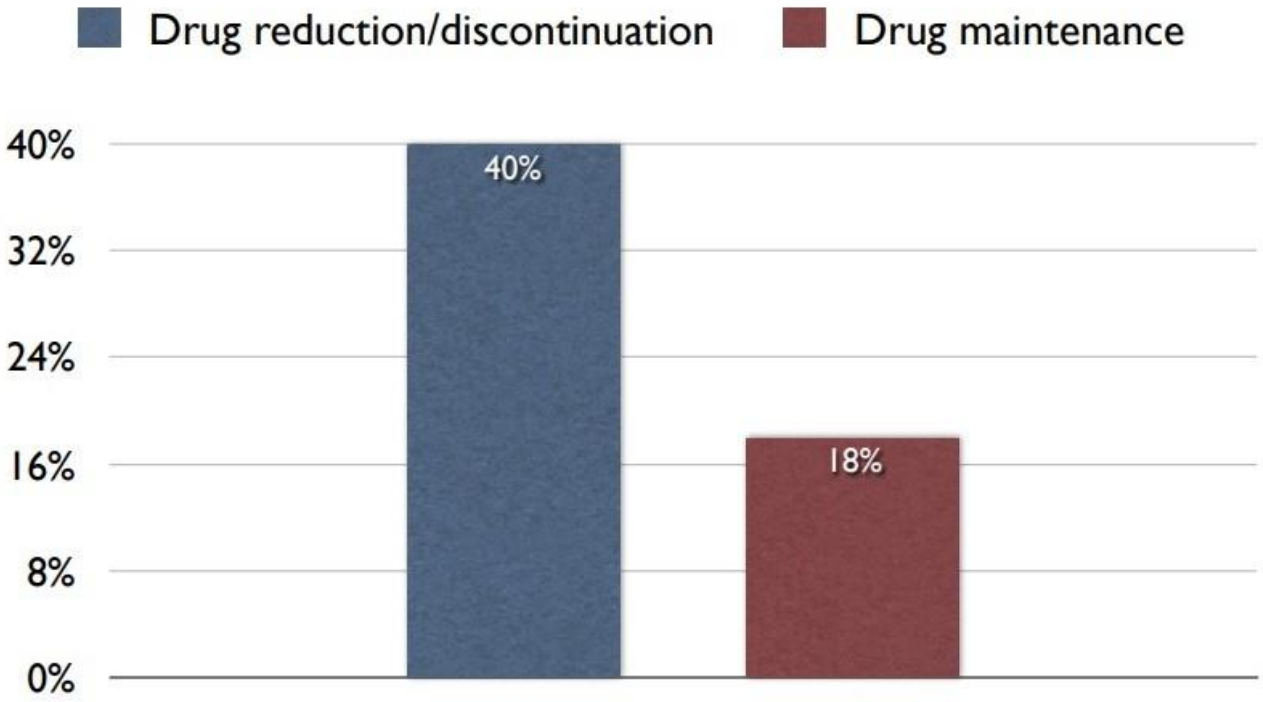
L. Wunderink. "Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy." JAMA Psychiatry, pub online, July 3, 2013.

Relapse Rates



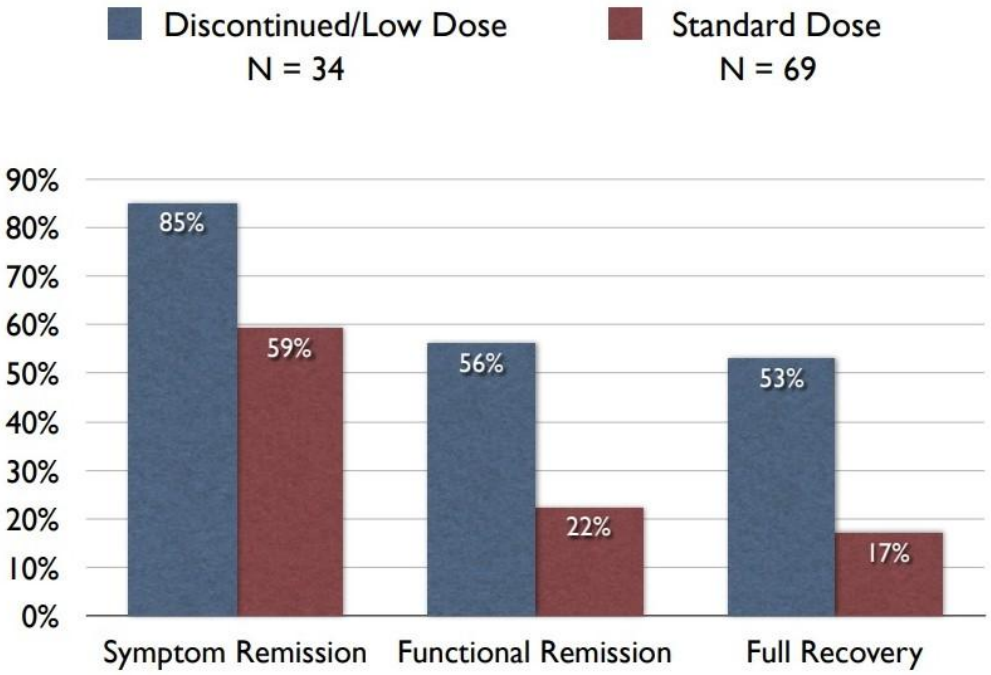
L. Wunderink. “Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation of maintenance treatment strategy.” JAMA Psychiatry, pub online, July 3, 2013.

Long-Term
Recovery Rate



7 Year Outcomes By Antipsychotic Use

When data from the patients who took themselves off the drugs (N=34), regardless of which group, were assessed to those who were regularly maintained on antipsychotic medications (N=69), the symptomatic remission rate for all patients who stopped all medications was 85% (compared to 59%), the functional remission was 56% versus 22%, and the full recovery rate was 60% versus 17%.



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

Wunderick's study indicates antipsychotics *lower* long-term recovery due to "antipsychotic postsynaptic blockage of the dopamine signaling system, particularly the mesocortical and mesolimbic tracts… compromising important mental functions, such as alertness, curiosity, drive, and activity levels and aspects of executive functional capacity…"

Wunderink, L, Nieboer, R. et al, "Recovery in Remitted First Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation of an Early Dose Reduction/Discontinuation of Maintenance Treatment Strategy: Long-term Follow-up of a 2 Year Randomized Clinical Trial", JAMA Psychiatry. 2013, Online July 3, 2013. http://archpsyc.jamanetwork.com/article.aspx?articleid=1707650

Medication Compliant - NonCompliant Effects on Outcomes

- 81 first episode patients in Australia
- 41 randomized to specialized relapse prevention programing therapy, expected to increase medication compliance.
- Specialized therapy increased drug compliance over 30 months.
- **Outcome:**

Increase in medication compliance = “decreases in psychosocial functioning and increases in negative symptoms.”

Compliance Conclusion:

“This is consistent with previous research showing an association between better vocational functioning at 2-year follow-up and placebo treatment compared with antipsychotic medication in a first-episode schizophrenia sample.”

J. Gleeson. “A randomized controlled trial of relapse prevention therapy for first-episode psychosis patients.” Schizophrenia Bulletin 39 (2013):436-48.

Side Effects or Just Negative Effects?

a) Tardive dyskinesia. The most visible sign of tardive dyskinesia is a rhythmic movement of the tongue, which is the result of permanent damage to the basal ganglia, which controls motor movement. People suffering from tardive dyskinesia may have trouble walking, sitting still, eating, and speaking. In addition, people with tardive dyskinesia show accelerated cognitive decline. NIMH researcher George Crane said that tardive dyskinesia resembles “in every respect known neurological diseases, such as Huntington’s disease, dystonia musculorum deformans, and postencephalitic brain damage.” (Crane, 1973). Tardive dyskinesia appears in *five percent* of patients treated with standard neuroleptics *in one year*, with the percentage so afflicted increasing an *additional five percent with each additional year of exposure*(Correll, 2004). The risk of developing this possible life threatening effect from the neuroleptic or atypical medication increases with higher doses and longer duration. (Crimson, 2011).

Akathisia. In the 1960s and 1970s, patients treated with antipsychotics regularly complained that these drugs, rather than serve as tranquilizers, could induce an excruciating inner restlessness and anxiety, the pain so severe that they “just wanted to jump out of their skins.” Starting in the 1970s, a handful of researchers began publishing case reports about this phenomenon, which they dubbed “akathisia”, and concluded that it led to an increased risk of suicide and violence. This side effect, years after first being noted, has been linked to assaultive, murderous behavior and is a cause of suicide.[,,,,] In their case reports, researchers described how patients treated with these drugs, seeking to escape from this misery, had jumped from buildings, hung themselves, and stabbed themselves. In one study, 79% of mentally ill people who had tried to kill themselves were found to have been suffering from akathisia.

(Shear, 1982; Van Putten, 1987; Van putten, 1975; Herrera, 1998)

Emotional impairment. Many patients describe feeling like “zombies” on the medications. In 1979, UCLA psychiatrist Theodore van Putten reported that most patients on antipsychotics were spending their lives in “virtual solitude, either staring vacantly at television, or wandering aimlessly around the neighborhood, sometimes stopping for a nap on a lawn or a park bench… they are bland, passive, lack initiative, have blunted affect, make short, laconic replies to direct questions, and do not volunteer symptoms…there is a lack not only of interaction and initiative, but of any activity whatsoever. (Van Putten, 1979). The quality of life on conventional neuroleptics, researchers agreed, is “very poor.” (Weiden, 1996).

Cognitive impairment. Various studies have found that neuroleptics reduce one's capacity to learn and retain information. As Duke University scientist Richard Keefe said in 1999, these drugs may "actually prevent adequate learning effects and worsen motor skills, memory function, and executive abilities, such as problem solving and performance assessment." (Keefe, 1999)

Other side effects of standard neuroleptics include a vast array of negative effects on a striking number of physical systems. These include drowsiness, dizziness, nausea, vomiting, diarrhea, constipation, heartburn, dry mouth, increased saliva production, increased appetite, weight gain, stomach pain, anxiety, agitation, restlessness, difficulty falling asleep or staying asleep, decreased sexual interest or ability, vision problems, muscle or joint pain, dry or discolored skin, difficulty urinating, muscle stiffness, confusion, fast or irregular pulse, sweating, unusual and uncontrollable movements of the face or body, faintness, seizures, Parkinsonian symptoms such as slow movements or shuffling walk, hives, itching, difficulty breathing or swallowing, gynecomastia in male children, painful erection of penis lasting for hours. Additionally, an increased incidence of blindness, fatal blood clots, arrhythmia, heat stroke, swollen breasts, leaking breasts, obesity, sexual dysfunction, skin rashes and seizures, and early death. (Arana, 2000; Waddington, 1998; Joukamaa, 2006)

Suicide: Schizophrenia patients now commit suicide at 20 times the rate they did prior to the use of neuroleptics, and when researcher's completed the largest study ever done to address suicide in psychotic patients, they concluded that the 10% lifetime rate of suicide is incorrect, noting it is approximately 4%, and that psychiatric medications appears to be a causal factor for suicide (Healy, 2006). When researchers compared typical hospital treatment with neuroleptic or atypical medications against non-psychiatric psychological interventions over an 11 month period, pure psychological interventions were less likely to produce suicides (3 suicides compared to none in the pure psycho-social treatment group). (Healy, 2006; Deikman, 1979).

Death: During a 17 year follow up study that involved 99 people diagnosed with psychosis, 39 of the patients died; however, when researchers accounted for age, gender, somatic diseases, blood pressure, cholesterol, body mass index, smoking, exercise, alcohol, education and other premature death factors, the relative risk was 2.50 *times greater* (95% confidence level) *if the patient took just one neuroleptic at baseline, and this relative risk increased to nearly 700% if they took 3 antipsychotics at some point over the term.*(Joukamaa, 2006)

In October of 2006, the National Association of State Mental Health Program Directors noted that with the impact of psychiatric medications:

"...with time and experience, the second generation antipsychotic medication have become more highly associated with weight gain, diabetes, dyslipidemia, insulin resistance and metabolic syndrome...", all factors leading to premature death.(Parks, 2006) They noted some medications also reduce the ability to feel physical pain, a natural safety mechanism. Antipsychotic medications may "increase caloric intake or reduce the activity level" of patients, which additionally negatively impacts overall general medical conditioning.

Early Death by 20 Years(Davies, 2007)

Newer antipsychotics may not clamp down on dopamine transmission quite as powerfully as the old standard neuroleptics, but they also block a number of other neurotransmitter systems, most notably serotonin and glutamate. As a result, they may cause a broader range of physical ailments, with diabetes and metabolic dysfunction particularly common for patients treated with Zyprexa.

Researcher Waddington in 1998 followed 88 patients over a 10 year period and noted that 39 of them died, however, he discovered that of those who died, it was caused by taking two or more neuroleptic or atypicals over time and the patient was later so burdened with chronic physical illnesses, it replaced the “psychiatric disorder as the primary focus of medical care.” He concluded that the final pathway to death for the psychiatric treated patient was “global medical decline” and or respiratory illness following medication usage.

J. Waddington, "Mortality in Schizophrenia," British Journal of Psychiatry, 173 (1998), 325-329.

A few years later in 1991, researchers surveyed 49 cases of sudden death and indicated that in 46 of the 49 cases of sudden death reported, the psychiatric medications were indicative of the cause.

Mehtonen OP; Aranko K; M¨alkonen L; Vapaatalo H. Acta Psychiatr Scand, 84(1):58-64 1991 Jul.

In a 2003 Irish study, 25 of 72 patients (35%) died over a period of 7.5 years, leading the researchers to conclude that the risk of death for schizophrenics had “doubled” since the introduction of the atypical antipsychotics.

Morgan, M, et al. “Prospective analysis of premature morbidity in schizophrenia in relation to health service engagement." Psychiatry Research 117 (2003):127-35.

In 2014, Gerhard et al, studied over 136,000 people 65 years old and older, all who had first contact with antipsychotic medication, and estimated the comparative mortality risk between differing antipsychotic medications. *Over the six month assessment period, they found a positive causal* dose-response increase mortality effect (i.e. the higher the dosing of a psychiatric mediation, the more likely a patient would die within six months) and noted that significant variation in mortality affects survival rates for those patients taking these medications. (Gerhard, 2014).

Gerhard et al also noted prior meta-analysis research of 15 clinical trials, and found a 50% increase in mortality for patients taking newer antipsychotic medications. Subsequent observational studies found similar mortality risks for first generation antipsychotic medications, whereby the United Kingdom and the United States drug regulatory bodies started issuing warnings about the increased mortality for using antipsychotic medications.

Gerhard T, et al. Comparative mortality risks of antipsychotic medications in community-dwelling older adults. BJP, Jul 2014, 205 (1) 44-51; DOI: 10.1192/bjp.bp.112.122499.

Finally, in 2016, Parkinson disease researchers at the VA Center for Clinical Management Research (n=7,900) noted patients who took typical and atypical antipsychotic medications (Thorazine, Haldol, Risperdal, Zyprexa, Seroquel):
were twice as likely to die over six months, compared to no antipsychotic medications. They reviewed 17 placebo-controlled studies and found similar results where antipsychotics carried approximately twice the increase in mortality (demented elderly).

Although the authors noted:
antipsychotics can worsen Parkinson's disease and that as many as 60% of patients can develop psychosis and 80% can develop dementia at some point prior to death, which coincides with prior noted researcher's indicating using antipsychotic medications can cause patients to develop prolonged psychosis.

Newer Medications Does Not Mean Safer

In 2000, a team of English researchers led by John Geddes at the University of Oxford reviewed results from 52 studies, involving 12,649 patients. They concluded: “There is no clear evidence that atypicals are more effective or are better tolerated than conventional antipsychotics.” The English researchers noted that Janssen, Eli Lilly and other manufacturers of atypicals had used various ruses in their clinical trials to make their new drugs look better than the old ones. In particular, the drug companies had used “excessive doses of the comparator drug.”

Geddes, J. (2000). Atypical antipsychotics in the treatment of schizophrenia. British Medical Journal, 321:1371-76.

Newer Medications Does Not Mean Safer

In 2005, a National Institute of Mental Health study found that were “no significant differences” between the old drugs and the atypicals in terms of their efficacy or how well patients tolerated them. Seventy-five percent of the 1432 patients in the study were unable to stay on antipsychotics owing to the drugs’ “inefficacy or intolerable side effects,” or for other reasons.

Lieberman, J, et al. (2005). Effectiveness of antipsychotic drugs in patients with schizophrenia. The New England Journal of Medicine 353:1209-1233.

Newer Medications Does Not Mean Safer

In 2007, a study by the British government found that schizophrenia patients had better “quality of life” on the old drugs than on the new ones. This finding was quite startling given that researchers had previously determined that patients medicated with the old drugs had a “very poor” quality of life.

Davies, L, et al. (2007). Cost-effectiveness of first- v. second-generation antipsychotic drugs. The British Journal of Psychiatry, 191:14-22.

These drugs *are not like* “insulin for diabetes.”

They do not serve as a corrective to a known biological abnormality.

Instead, standard antipsychotics work by powerfully blocking dopamine transmission in the brain.

Specifically, these drugs block 70% to 90% of D2 dopamine receptors. This thwarting of normal dopamine transmission is what causes the drugs to be so problematic in terms of their side effects.

Wysong, P., (2000). PET Brain Scans Best to Determine Schizophrenics’ drug dosages, In the Washington Post, April 12, 2000, Vol. 36, Issue 14.

Few Dopamine Blocking Effects

Blocking effects can often be seen at certain levels of blockage:

- prolactin elevations begin at 72% blockade
- extrapyramidal motor disturbances and akathisia > 78%
- clinically significant dysphoric reactions (listless, dejected) > 70%
- cognitive impairments > 70%
- aggravation of depression, neuroleptic induced “negative” symptoms,, also known as neuroleptic-induced-deficit syndrome > 70% (NIDS)

Today's Overall Conclusion: 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

Remember that 1st Slide?

D2 Dopamine Decrease =
Symptom Improvement =
Chemical Imbalance?

Dr. William Wirshing, professor at UCLA and a leading psychiatric researcher, publicly announced: “We have been lying to the public about the chemical imbalance theory of mental illness”,

Dr. Ronald Pies, editor-in-chief emeritus of the Psychiatric Times indicated: “In truth, the ‘chemical imbalance’ notion was always a kind of urban legend- never a theory seriously propounded by well-informed psychiatrists.”

AND, in Aug. 2019, he again stated

What Do You Do When Proven Wrong? Never Admit You Believe It

...“Like the legendary Count Dracula, who could be killed only by driving a stake through his heart, some myths seem almost immortal. For more than 8 years now, I have tried to drive a stake through the heart of two myths regarding the so-called “chemical imbalance theory”—but with only limited success...

And, yes, there are really two myths to debunk. The first holds that mental illnesses (psychiatric disorders) in general are caused by “a chemical imbalance” in the brain—the so-called “chemical imbalance theory.” The second myth holds that “Psychiatry” as a profession endorsed the first myth…”

Dr Pies is Professor in the psychiatry departments of SUNY Upstate Medical University, Syracuse, NY and Tufts University School of Medicine, Boston. He was Editor in Chief of Psychiatric Times *(2007 2010).*

Solutions

The Opportunity:

The research literature is telling us that psychiatric disorders, including more severe ones, may be, in the majority of cases, episodic in nature, rather than chronic illnesses.

The Solution:

Confronting treatment protocols that are not consistent with the long term research on outcomes, the harm caused by the medications, and finding experts to report the research evidence to the courts, and to create treatment protocols that provide psychosocial care and use psychiatric drugs in a selective manner that minimizes initial exposure and their long-term use.

Open Dialog Approach:
A Model for Selective Use of Antipsychotics

The practice in Western Lapland, Finland (since 1992)

• First-episode patients are not immediately put on antipsychotics. Instead, they are treated with intensive psychosocial care, and benzodiazepines on an as-needed basis, to help people sleep.

• As long as patients are getting better, antipsychotics are not used. If, after several weeks, they are not improving, then low doses of an antipsychotic are prescribed.

• After the medicated patients are stabilized, there is an effort-- after six months or so--to gradually withdraw them from the medication.

Outcomes with Selective Use Of Antipsychotics

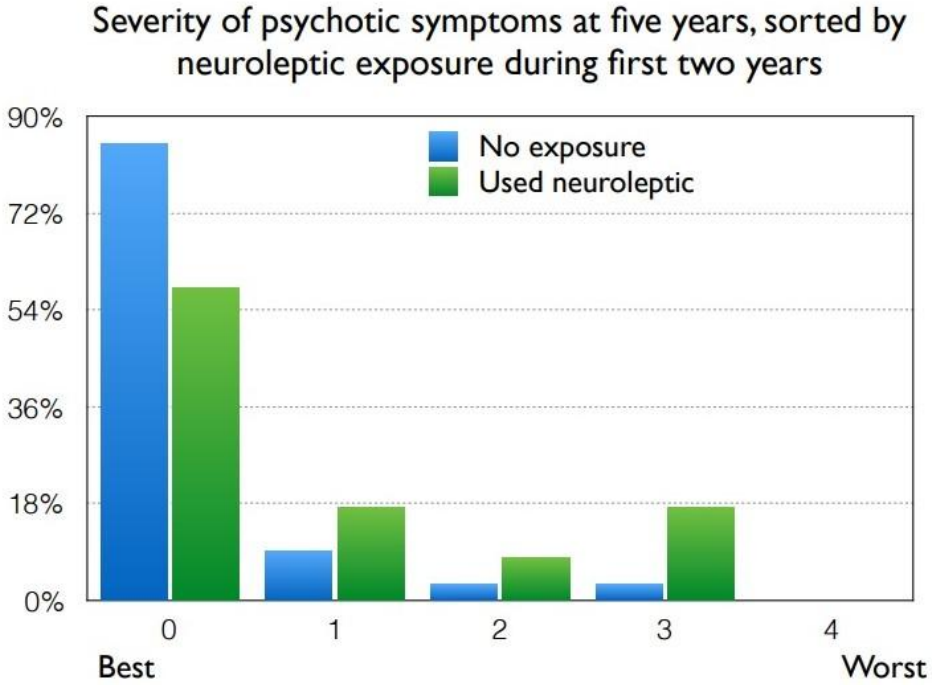
5 Year Outcomes for First Episode Psychotic Patients Treated With Open Dialog Approach

Patients: N=75 (Schizophrenia = 30 & Other Psychosis = 45)

Antipsychotic Usage	
Never Exposed =	67%
Occasional Use During 5 Years =	33%
Ongoing Use at End of 5 Years =	20%
Psychotic Symptoms	
Never Relapsed at 5 Years =	67%
Asymptomatic at End of 5 Years =	79%-82%
Functional Outcome at 5 Years	
Working or In School =	86%-73%
Unemployed =	7%
On Disability =	20%

Seikkula, J., Aaltonen, J., Alakare, B., Haarakangas, K., & Lehtinen, K. (2006). Five-year experience of first-episode nonaffective psychosis in open-dialogue approach: Treatment principles, follow-up outcomes, and two case studies.

Best Outcomes Are in Never-Exposed Patients



Presentation by Jaakko Seikkula on “Open Dialogue Research,” in Gothenburg, Sweden, Oct. 15, 2016.

On importance of using neuroleptics in a selective fashion:

“I am confident of this idea. There are patients who may be living in a quite peculiar way, and they may have psychotic ideas, but they still can hang on to an active life. But if they are medicated, because of the sedative action of the drugs, they lose this ‘grip on life,’ and that is so important. They become passive, and they no longer take care of themselves.”

--Jaakko Seikkula

1950s-1960s Vermont State Hospital

In 1994, Courtenay Harding at Boston University reported on the long-term outcomes of 82 chronic psychotic patients discharged from Vermont State Hospital in the late 1950s and early 1960's.

She found that one-third of this cohort had recovered completely and were asymptomatic, and that all who did shared one characteristic: *They had all stopped taking antipsychotic medication.*

The notion that psychotic people needed to stay on antipsychotics all their lives was a "myth," Harding said.

Harding, C. (1994). Empirical correction of seven myths about schizophrenia with implications for treatment. Acta Psychiatrica Scandinavica, 90(384):140-6.

NIMH: RAISE - NAVIGATE

Hofstra North Shore-LIJ School of Medicine

In 2015, NIMH funded a 2 year study with 404 subjects.

First episodic psychotic patients from 21 states.

The Recovery After an Initial Schizophrenia Episode-RAISE study w/ the NAVIGATE program.

1) reducing dosing of antipsychotic medications by 20-50%,
2) providing individual psychotherapy and family therapy,
3) providing psychoeducation and
4) providing employment-education programming)

RAISE Results

RAISE group:

- had significantly less psychotic and depressive symptoms.
- greater improvement in quality of life. (10 versus 16 on 126 point scale)
- less likely to be re- hospitalized for psychiatric reasons.
- significantly more likely to be working and going to school.

The effects were more pronounced for shorter duration of psychosis before intervention.

Dr. Kane, lead researcher, stated:

> In order to minimize the "bad effects of the drugs those in the new treatment group received the lowest doses possible- up to 50% less than what is prescribed in standard treatments."

Danish OPUS-Schizophrenia Study

2017: 10 year follow-up study of 303 1st episode schizophrenia spectrum patients, aged 18-45.

The OPUS-cohort was a randomized clinical trial for intensive early intervention.

121 patients off all medications Versus 182 taking antipsychotic medications:

74% of the Off-Medication group were in remission (90 of 121), compared to...

49% of the On-Medication group were in remission (90 of 182) via drug suppression.

Staying off medication was the biggest factor for symptom remission, in addition to: being female, having higher functioning prior to onset, having vocational/ educational/ employment.

There was no positive relationship for age of onset, high school completion and premorbid IQ;

The longer the duration prior to some treatment, the worse the outcome.

Conclusion: Off-Medication group was able to function higher, had fewer negative symptoms and was able to be employed a significantly higher rate.

Wils, R. S., Gotfredsen, D. R., Hjorthøj, C., Austin, S. F., Albert, N., Secher, R. G., … & Nordentoft, M. (2016). Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis. *Schizophrenia Research*.(Abstract)