The Case for Psychiatric Drug Withdrawal

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The Problem With Psychiatric Drugs

• The drugs create abnormalities in brain function. They do not fix chemical imbalances, but instead create them.

• Over the long-term, psychiatric drugs increase the chronicity of psychiatric disorders, and impair functioning. They lower long-term recovery rates.
The Chemical Imbalance Theory of Mental Disorders

• Arose from understanding of how drugs act on brain (1960s-1970s)

• Investigations of dopamine theory of schizophrenia and serotonin theory of depression started in 1970s
Findings re the Chemical Imbalance Theory of Mental Disorders

A. Serotonin Theory of Depression

“Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression.” --NIMH, 1984.

“There is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no real monoamine deficit.”--Stephen Stahl, Essential Psychopharmacology, 2000
B. Dopamine Theory of Schizophrenia

“There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia.” Stephen Hyman, Molecular Psychiatry, 2002

C. Chemical Imbalance Theory of Mental Disorders (in general)

“We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them.” Kenneth Kendler, Psychological Medicine, 2005.

“In truth, the chemical imbalance notion was always a kind of urban legend, never a theory seriously propounded by well-informed psychiatrists.” Ronald Pies, July 11, 2011 in Psychiatric Times.
Stephen Hyman, former director of the NIMH, 1996:

• 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.”

Dopamine function before exposure to antipsychotics

Presynaptic neuron

Dopamine

Dopamine receptors

Postsynaptic neuron
Dopamine function after exposure to antipsychotics

Brain increases receptors to compensate for drug blockade

Antipsychotic blocks receptors

Presynaptic neuron

Postsynaptic neuron

Dopamine

B
The “Chemical Imbalance” Paradox

• Investigators have not found that a characteristic “chemical imbalance” is the biological cause of any major mental disorder.

• Investigators have found that psychiatric drugs induce compensatory changes in the brain that create a “chemical imbalance” in the brain, and of the type hypothesized to cause the mental disorder in the first place.
The Possible Consequences of “Oppositional Tolerance” With All Psychiatric Drugs

“Continued drug treatment may induce processes that are the opposite of what the medication originally produced.” This may “cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible.”

-Rif El-Mallakh, University of Louisville, 2011

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

Psychotic Symptoms of Schizophrenia Patients

Source: Harrow M. “Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis?” Psychological Medicine, (2014): doi:10.1017/S0033291714000610
Cognitive Function of Schizophrenia Patients

Long-term Recovery Rates for Schizophrenia Patients

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

--Martin Harrow, American Psychiatric Association annual meeting, 2008
Global Adjustment of “Other Psychotic” Patients

Global Adjustment of All Psychotic Patients

“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
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.

Long-Term Recovery Rates (at 7 Years)

- Drug reduction/discontinuation: 40%
- Drug maintenance: 18%
Outcomes By Antipsychotic Use

Discontinued/Low Dose
- N = 34

Standard Dose
- N = 69

- Symptom Remission: 85% (Discontinued/Low Dose), 59% (Standard Dose)
- Functional Remission: 56% (Discontinued/Low Dose), 22% (Standard Dose)
- Full Recovery: 53% (Discontinued/Low Dose), 17% (Standard Dose)
Wunderink’s Conclusion

“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.”
Clinical Perceptions in Early Years of Antidepressant Use

- H.P. Hoheisel, German physician, 1966: Exposure to antidepressants appeared to be “shortening the intervals” between depressive episodes.

- Nikola Schipkowensky, Bulgarian psychiatrist, 1970: The antidepressants were inducing “a change to a more chronic course.”

The APA Acknowledges Change in Course of Depression in Modern Era

American Psychiatric Association’s Textbook of Psychiatry, 1999:

It used to be believed that “most patients would eventually recover from a major depressive episode. However, more extensive studies have disproved this assumption.” It was now known that “depression is a highly recurrent and pernicious disorder.”
One-Year Outcomes in WHO Screening Study for Depression

WHO Study: Medicated Patients Stop Getting Better After Three Months

Severity of symptoms on GHQ scale

Real World Outcomes in Minnesota: Few Patients in Recovery At End of Year

Source: MN Community Measures, Annual Health Care Quality Report (2010-2014)

Number of patients
2010 = 29,199
2011 = 65,307
2012 = 80,067
2013 = 86,147
Five-Year Outcomes in Canada

Number of Weeks Depressed Each Year

On Medication

Off Medication

N = 9,508

Six-Year Outcomes in NIMH Study of Untreated Depression

Do Antidepressants Worsen the Long-term Course of Depression?

“Antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression . . . Use of antidepressant drugs may propel the illness to a more malignant and treatment unresponsive course.”

--Giovanni Fava, *Psychotherapy and Psychosomatics*, 1995
The Problem With Antidepressants: Drug-Induced “Oppositional Tolerance”

“When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible.”

Giovanni Fava, 2011

Tardive Dysphoria

“A chronic and treatment-resistant depressive state is proposed to occur in individuals who are exposed to potent antagonists of serotonin reuptake pumps (i.e. SSRIs) for prolonged time periods. Due to the delay in the onset of this chronic depressive state, it is labeled tardive dysphoria. Tardive dysphoria manifests as a chronic dysphoric state that is initially transiently relieved by -- but ultimately becomes unresponsive to -- antidepressant medication. Serotonergic antidepressants may be of particular importance in the development of tardive dysphoria.”

-- Rif El-Mallakh, 2011

Adverse Effects of Long-term Benzodiazepine Use

- Cognitive impairment
- Increased depression and anxiety
- Functional impairments
- Physical decline

In a 2007 survey of 4,425 long-term benzodiazepine users, French researchers found that 75% were “markedly ill to extremely ill . . . a great majority of the patients had significant symptomatology, in particular major depressive episodes and generalized anxiety disorder, often with marked severity and disability.”

Research Questions

• Does the brain renormalize upon drug withdrawal? Do presynaptic release of neurotransmitters and post-synaptic receptor densities normalize? If so, how long does this take?

• How often do long-term users of antipsychotics, antidepressants, and benzodiazepines, upon drug withdrawal, exhibit evidence of brain impairments that do not renormalize: tardive dyskinesia, post SSRI sexual dysfunction (PSSD), and protracted withdrawal symptoms?

• Are their drug-tapering protocols that can help renormalization?
• How can withdrawal symptoms be distinguished from “return of the disorder” symptoms?

• What tapering speeds produce the best results? Can tapering protocols be developed? Or must discontinuation efforts be individualized?

• What protocols can be developed for withdrawing from multiple psychiatric drugs?
A Final Question

Why hasn’t the medical community addressed this issue before?