Causation, Not Just Correlation: Increased Disability in the Age of Prozac

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The Case for Causation

• As prescriptions for antidepressants and other psychiatric drugs have risen, the number of people disabled by mental disorders, in country after country, has risen in lockstep (the correlative data).

• Psychiatric drugs are causative agents. They are expected to affect psychiatric and functional outcomes.

• Research studies reveal that antidepressants increase the risk that: (1) depression will run a chronic course; (2) a unipolar patient will convert to bipolar disorder; (3) a patient will become impaired and go on government disability.

• Studies have shown that benzodiazepines impair functioning in multiple domains when taken over the long-term.

• Research studies have found that antipsychotics appear to worsen functional outcomes over the long term.
Number on government disability due to mood disorders


Percent of population who used antidepressants in past month

United Kingdom, 1998-2014

Claims for sickness and disability benefits owing to mental illness in UK

Prescriptions for antidepressants in England

About two-thirds of the claims were for a depressive or anxiety disorder.


Australia, 1990-2011

Number on disability due to mental illness

Adults


Percent of population that used antidepressants

Denmark, 2000-2010

New cases of disability due to mental illness

Percent of population that used antidepressants


Iceland, 1996-2006

New cases of disability annually per 100,000 population

- Women
- Men

Percent of population that used antidepressants


Sweden, 2000-2010

Percent of new disability cases due to mental illness


Percent of population that used antidepressants

Psychotropic Drugs Create Abnormalities in Brain Function

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.”

Long-term Outcomes for Hospitalized Depressed Patients in the Pre-Antidepressant Era

- Emil Kraepelin, 1921. Sixty percent of 450 patients hospitalized for an initial bout of depression experienced but a single bout of the illness, and only 13% had three or more episodes in their lives.

- Horatio Pollock, New York State, 1931. In a long-term study of 2700 first-episode depressed patients, more than half never had another bout of depression that required hospitalization, and only 13% had three or more episodes.

- Gunnar Lundquist, Sweden, 1945. In an 18-year study of 216 patients, 49% had only a single episode, and another 21% had only one other episode.

Depression Was Understood to Be an Episodic Disorder

“Assurance can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course.”

--George Winokur, Washington University, *Manic Depressive Illness*, 1969
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.”

J.D. Van Scheyen, Dutch psychiatry, 1973:

After conducting a study of 94 depressed patients, he concluded that “long-term antidepressant medication, with or without ECT [electronconvulsive therapy], exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate and a decrease in cycle duration . . . Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?”
An Episodic Illness Turns Chronic in the Antidepressant Era

National Institute of Mental Health Panel on Mood Disorders, 1985:

“Improved approaches to the description and classification of [mood] disorders and new epidemiologic studies [have] demonstrated the recurrent and chronic nature of these illnesses, and the extent to which they represent a continual source of distress and dysfunction for affected individuals.”

The STAR*D Trial Confirms That Medicated Depression Runs a Chronic Course Today

One-Year Remission Rates in NIMH Study of Medicated Depression in “Real-World” Patients

• 126 patients were treated with antidepressants and given emotional and clinical support “specifically designed to maximize clinical outcomes.”

• Only 26% responded to antidepressants (50% reduction in symptoms).

• Only half of those who responded stayed better for a significant period of time.

• Only 6% remitted and then remained in remission at the end of one year.

“These findings reveal remarkably low response and remission rates.”

--John Rush, 2004
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
One-Year Recovery Rates in NIMH Study of Unmedicated Depression

“If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this.”

--Michael Posternak
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
Depression in the Netherlands

(Over the course of ten years)

- First episode treated with drug
- First episode treated without drug

N = 222

Five-Year Outcomes in Canada

Number of Weeks Depressed Each Year

<table>
<thead>
<tr>
<th>Number of Weeks</th>
<th>On Medication</th>
<th>Off Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>11</td>
</tr>
</tbody>
</table>

N = 9,508

These findings are consistent with Giovanni Fava’s hypothesis that “antidepressant treatment may lead to a deterioration in the long-term course of mood disorders.”

--Scott Patten
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

Antidepressants Lessen the Long-Term Benefits of Exercise

<table>
<thead>
<tr>
<th>Treatment during first 16 weeks</th>
<th>Percentage of patients in remission at end of 16 weeks</th>
<th>Percentage of patients who relapsed in following six months</th>
<th>Percentage of all patients depressed at end of ten months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoloft alone</td>
<td>69%</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Zoloft plus exercise</td>
<td>66%</td>
<td>31%</td>
<td>55%</td>
</tr>
<tr>
<td>Exercise alone</td>
<td>60%</td>
<td>8%</td>
<td>30%</td>
</tr>
</tbody>
</table>

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

Putting the Hypothesis to the Test

Three-month relapse rate after initial remission: placebo vs. SSRI-withdrawn patients

“The more antidepressants perturb monamine levels in the brain, the more the brain appears to push back, which increases the risk of relapse when the drug is discontinued . . . antidepressant use appears to increase [biological] susceptibility to depression.”

--Paul Andrews, 2012
Two-Year Relapse Rates for Remitted Patients in the Netherlands

“Continued antidepressant treatment may oppose the initial acute effects of [the] antidepressant . . . neurobiological mechanism(s) may be involved in increasing vulnerability” to relapse.

--C. Bockting, 2008
“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

Summing up the Evidence That Antidepressants Increase the Chronicity of Depression

- Depression has changed from an episodic illness to a chronic one during the antidepressant era.

- In naturalistic studies, unmedicated patients have better long-term outcomes than medicated patients.

- Investigators have proposed a biological explanation for why antidepressants worsen the long-term course of depression.
Antidepressants Increase the Risk that a Unipolar Patient will Convert to a Bipolar Diagnosis

1956: First case report of antidepressant-induced mania is published

1985: Swiss investigators tracking change in the patient mix at Burgholzli psychiatric hospital report that the percentage with manic symptoms jumped dramatically following the introduction of antidepressants. “Bipolar disorders increased; more patients were admitted with frequent episodes.”

1993: An American Psychiatric Association guide to depression warns: “All antidepressant treatments, including ECT, may provoke manic or hypomanic episodes.”
Yale Investigators Quantify the Risk of Conversion to a Bipolar Diagnosis with Antidepressant Use

Study design: Yale Investigators analyzed the records of 87,920 patients, ages 0 to 29, initially diagnosed with an anxiety or non-bipolar mood disorder from 1997-2001. The median follow-up time was 41 weeks. They reported on the number of patients who converted to a bipolar diagnosis according to whether they were “exposed” to an antidepressant.

<table>
<thead>
<tr>
<th>Age</th>
<th>Not Exposed</th>
<th>Exposed</th>
<th>NNH</th>
</tr>
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<tbody>
<tr>
<td>15-19</td>
<td>698 (4.8%)</td>
<td>1093 (10.9%)</td>
<td>16</td>
</tr>
<tr>
<td>20-24</td>
<td>390 (4.3%)</td>
<td>591 (7.6%)</td>
<td>31</td>
</tr>
<tr>
<td>25-29</td>
<td>333 (2.7%)</td>
<td>587 (6.2%)</td>
<td>29</td>
</tr>
<tr>
<td>15-29</td>
<td>1421 (4.1%)</td>
<td>2271 (8.3%)</td>
<td>23</td>
</tr>
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</table>

### Increase in Bipolar Diagnoses in United States, 1994 to 2003

**Number of office-based visits with a diagnosis of bipolar disorder**

<table>
<thead>
<tr>
<th></th>
<th>1994-1995</th>
<th>2002-2003</th>
<th>Increase in rate</th>
</tr>
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<tbody>
<tr>
<td>Youth (0-19 years)</td>
<td>25 per 100,000</td>
<td>1003 per 100,000</td>
<td>40-fold increase</td>
</tr>
<tr>
<td>20 years and older</td>
<td>905 per 100,000</td>
<td>1,679 per 100,000</td>
<td>85% increase</td>
</tr>
</tbody>
</table>

In a survey of members of the Depressive and Manic-Depressive Association, 60 percent of those with a bipolar diagnosis had initially fallen ill with major depression and had turned bipolar after exposure to an antidepressant.

Fred Goodwin, former director of the National Institute of Mental Health, 2005:

“If you create iatrogenically a bipolar patient, that patient is likely to have recurrences of bipolar illness even if the offending antidepressant is discontinued. The evidence shows that once a patient has had a manic episode, he or she is more likely to have another one, even without the antidepressant stimulation.”
Experts Recognize the Decline in Bipolar Outcomes

Carlos Zarate, head of NIMH Mood Disorders Program, 2000:

“In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment.”


“Prognosis for bipolar disorder was once considered relatively favorable, but contemporary findings suggest that disability and poor outcomes are prevalent, despite major therapeutic advances.”

Fred Goodwin, 2008

“The illness has been altered. Today we have a lot more rapid cycling than we described in the first edition [of his book, Manic Depressive Illness], a lot more mixed states than we described in the first edition, a lot more lithium resistance, and a lot more lithium treatment failure than we described in the first edition. The illness is not what Kraepelin described any more.”
Canadian Study of Risk of Long-term Disability for Depressed Workers

N = 1,281

Six-Year Outcomes in NIMH Study of Untreated Depression

Same Prevalence + More Treatment = Soaring Numbers of Adults Disabled by Affective Disorders in U.S.

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<thead>
<tr>
<th></th>
<th>1991</th>
<th>2002</th>
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<tbody>
<tr>
<td>U.S. adult population</td>
<td>188 million</td>
<td>214 million</td>
</tr>
<tr>
<td>Prevalance of anxiety, mood and</td>
<td>29.4%</td>
<td>30.5%</td>
</tr>
<tr>
<td>substance disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with anxiety, mood and</td>
<td>55.3 million</td>
<td>65.3 million</td>
</tr>
<tr>
<td>substance disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage treated for those disorders</td>
<td>20.3%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Number treated for those disorders</td>
<td>11.2 million</td>
<td>21.4 million</td>
</tr>
<tr>
<td>Number on disability due to affective disorders</td>
<td>292,000</td>
<td>940,000</td>
</tr>
<tr>
<td>Percentage with those disorders on</td>
<td>1 of 188</td>
<td>1 of 69</td>
</tr>
<tr>
<td>disability</td>
<td></td>
<td></td>
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The Burden of Bipolar Illness on Society Today

• In 1955, there were 12,750 adults hospitalized with bipolar illness in the United States. Today there are nearly six million adults in the United States with this diagnosis.

• According to the Johns Hopkins School of Public Health, 83 percent of people diagnosed with bipolar are “severely impaired” in some facet of their lives. (5 million adults.)

• Bipolar illness is now said to be the sixth leading cause of medical-related disability in the world.
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.”

Long-term Recovery Rates for Schizophrenia Patients

Work History of Schizophrenia 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
Drug-induced Oppositional Tolerance: A Universal Problem?

“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

The Evidence All Fits Together

• Correlative data across different cultures

• A robust body of evidence that antidepressants increase the chronicity of depression

• Studies find that patients medicated for depression are more likely to end up disabled by the disorder

• Robust evidence that antidepressants increase the risk that a unipolar patient will switch to bipolar disorder

• Evidence that the prevalence of bipolar disorder has notably increased during the Prozac era, and so too the burden of disability due to bipolar illness

• Evidence that long-term benzodiazepine use leads to impairment in many domains

• Long-term studies of psychotic patients show patients maintained on antipsychotics have much lower recovery rates

• Researchers have proposed a biological explanation for why psychiatric drugs would have these harmful long-term effects