A Review of the Research Literature for Psychiatric Drug Withdrawal

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Research on Psychiatric Drug Withdrawal
Withdrawal in the Research Literature

1. The Disease Model.
   The drugs are treatments for a disease, and thus researchers study “relapse rates” when the drugs are withdrawn. The researchers are assessing the return of the illness in the absence of the treatment.

2. The Addiction Model
   Psychotropic drugs are understood to induce compensatory adaptations in the brain, and thus withdrawal is understood to be a process involving the brain seeking to renormalize its neurotransmitter pathways (and other functions.)

3. The Lived Experience Model
   Those who have sought to withdraw from their medications tell of their experiences, which may vary greatly from individual to individual.
The Disease Model

The Method
Researchers conduct randomized studies in patients who have stabilized on a drug (antipsychotic or antidepressant.) Patients are randomized either to placebo (withdrawal of the drug) or maintained on the drug, and then followed for a period of time.

The Outcome
Researchers assess whether the target symptom returns (psychosis, depression, etc.), and if so, the patient is said to have “relapsed.”

The Interpretation
The fact that placebo patients “relapse” more frequently is taken as evidence that the drugs provide a long-term benefit, as they reduce the likelihood that the disease will return.
In a 2012 review of 65 antipsychotic-withdrawal studies, here is how relapse was assessed:

The Psychiatrist Determines Who Has Relapsed

Leucht, S. “Maintenance treatment with antipsychotic drugs for schizophrenia.” Cochrane Database Review (2012), May 16.
The Patient Experience in The Relapse Studies

- In 54 of the 65 studies, the antipsychotic was abruptly withdrawn.

- Only 3 of the 65 studies even assessed the patients’ quality of life.

- Although “relapse” rates were lower in the drug-maintained group, 70% of this cohort either failed to improve or worsened during the study.

- In inpatient studies, only 5% of the drug-maintained patients were discharged.
The Addiction Model

- Psychiatric drugs perturb neurotransmitter systems, which cause changes in receptor densities.

- During the withdrawal process, these receptor densities must renormalize, which may take an extended period of time.

- Withdrawal symptoms vary by receptor type, and half-life of drug.
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

Presynaptic neuron

Antipsychotic blocks receptors

Dopamine

Postsynaptic neuron

Brain increases receptors to compensate for drug blockade
Return of Symptoms May be a Withdrawal Symptom

“Long-term use of drugs that suppress certain neurotransmitters is thought to cause a compensatory increase in the number and/or sensitivity of the relevant receptors (the concept of supersensitivity). When these receptors are no longer opposed by drugs there is an over-activity of the neurotransmitter or systems involved. This may result in the characteristic discontinuation syndromes, may cause rapid onset psychosis [antipsychotic withdrawal] and may act as a source of ‘pharmacodynamic stress’ which increases vulnerability to relapse.”

—Joanna Moncrieff

Moncrieff, J. “Why is it so difficult to stop drug treatment? It may be nothing to do with the original problem.” Medical Hypotheses 67 (2006):517-23.
## Expected Effects From a Drug’s Blockade of Receptors

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Adverse Events</th>
<th>Withdrawal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>EPS, weight gain, endocrine effects, akathisia, tardive dyskinesia, increased prolactin, sexual or reproductive system dysfunction</td>
<td>Psychosis, mania, agitation, akathisia, dyskinesia</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Weight gain, diabetes, increased appetite</td>
<td>EPS, akathisia, psychosis, decreased appetite</td>
</tr>
<tr>
<td>Histamine</td>
<td>Weight gain, diabetes, sedation</td>
<td>Agitation, insomnia, anxiety, EPS</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>Dry mouth, blurred vision, constipation, urinary retention, diabetes, memory problems, cognitive problems, tachycardia, hypertension</td>
<td>Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS, akathisia, diarrhea, nausea, vomiting, bradycardia, hypotension, syncope</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>Postural hypotension, dizziness, syncope</td>
<td>Tachycardia, hypertension, hypotension, dizziness</td>
</tr>
</tbody>
</table>

Gradual vs Abrupt Withdrawal

The understanding is that with gradual withdrawal, the receptors will more gradually return to normal densities, and that this will reduce the risk of relapse and the severity of withdrawal symptoms.
Relapse Rates Upon Withdrawal from Antipsychotics

Gradual = 3 weeks or longer, or stopping of depot injection

Relapse Rates Upon Withdrawal from Antidepressants

Rapid = 1 - 7 days
Gradual = 14 days or more

But Do Receptor Densities Always Renormalize?

The case of TD

• Antipsychotics are known to cause tardive dyskinesia (TD.) The severity of this disorder has been found to associated with the increase of dopamine (D2) receptors (drug-induced dopamine supersensitivity.)

• Yet, in adults, TD regularly persists after the offending antipsychotic is withdrawn. Studies have found that D2 receptor levels remain abnormally high in such patients.
The case of PSSD

- SSRIs are known to cause sexual dysfunction or impairment in a high percentage of users of the drugs.

- In a significant percentage of patients, some degree of sexual dysfunction persists after drug withdrawal (PSSD).

- While the cause of PSSD is still unknown, one thought is that the down-regulation of serotonergic receptors persists “even after removal of the SSRI.”
**Protracted benzodiazepine withdrawal syndromes**

- Benzodiazepines induce a down-regulation of GABA receptors in the brain.

- GABA inhibits neural activity, and thus upon withdrawal, there is a deficiency in this “brake” upon normal neuronal activity.

- The fact that some long-term users of benzodiazepines suffer “protracted (withdrawal) symptoms” is probably “due to the failure of the (GABA) receptors to return to their normal state.” — Heather Ashton
One Hypothesis Re Protracted Withdrawal Syndromes

• A psychiatric drug acts as an acute stressor, which induces a compensatory adaptation.

• The change in receptor densities shows that there has been a change in the expression of the gene that codes for the receptor protein. The neuron’s production of the protein has been “reset.”

• When a drug is gradually withdrawn, there is no stressor that induces the cell to reset its production of the receptor protein.
The Big Worry

“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

Flaws with the Addiction Model

• Psychiatric drugs act on more than one receptor type.

• There are feedback loops in the brain that cause perturbations in one neurotransmitter system to cause changes in other neurotransmitter systems (such as the feedback loop between dopaminergic and serotonergic activity.)

• In the same class of drugs, individual drugs may have different binding profiles and varying half-lives, which lead to varying withdrawal symptoms.

• In the current era, patients often take several classes of psychiatric drugs, and there is no model that explains the physiology of brain changes caused by polypharmacy, or the possible renormalization of neurotransmitter systems following withdrawal from multiple drugs.
The Disease Model versus Addiction Model: Return of Illness or Withdrawal Symptoms?

In a 2012 review of 65 antipsychotic-withdrawal studies, here is how relapse was assessed:

Leucht, S. “Maintenance treatment with antipsychotic drugs for schizophrenia.” Cochrane Database Review (2012), May 16.
A Proposed Model for Distinguishing Relapse from Withdrawal Symptoms

*Withdrawal symptoms*

- New symptoms common to withdrawal of CNS drugs.
- New symptoms common to withdrawal by receptor type.
- Rebound: return of original symptoms at greater intensity than original symptoms.
- Persistent post withdrawal disorders: Return of original symptoms at greater intensity or emergence of symptoms of new mental disorders.

*Relapse/recurrence*

- Same episode returns; symptoms similar to original episode.
## Withdrawal from Antidepressants

<table>
<thead>
<tr>
<th>Withdrawal Symptoms</th>
<th>Relapse</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>New symptoms common to CNS drugs: nausea, headaches, sleep disturbances, anxiety, decreased concentration, agitation, dysphoria, aggression, depression. Symptoms appear within 36 to 96 hours, but may occur later. Last up to six weeks.</td>
<td>Same episode returns within 24 hours to six weeks.</td>
<td>New episode (following at least partial response to treatment.) Episode returns after six months or more.</td>
</tr>
<tr>
<td>Specific serotonin-related new symptoms: flu-like symptoms, dizziness, tachycardia, diarrhea, electric shock sensations, confusion, premature ejaculations. Symptoms appear within 36 to 96 hours, may last up to six weeks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebound: Return of original symptoms at greater intensity: anxiety, psychic anxiety, somatic anxiety, panic, agitation, insomnia, depression, dysphoria, obsessions, compulsions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent post withdrawal disorders. Return of original symptoms at greater intensity and/or with additional symptoms. Appearance of symptoms related to emerging new mental disorders. Symptoms appear 24 hours to six weeks. May last several months or more.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of Studies That Sought to Promote Successful Withdrawal from Antidepressants or Antipsychotics
Users’ Accounts of Withdrawal
Why and How People Decide to Stop Taking Psych Drugs

A common reason often listed by psychiatry

• the patient lacks “insight” into his or her illness

What a survey of users’ found:

• they start taking the medication during a “major emotional crisis”

• the questioning of medications involves multiple steps:
  — the person experiences “losses generated” by taking the medication
  — questions the authenticity of their “self” on medication
  — feels their psychiatrist only cares about whether they are taking the medication
  — perception of “payoff matrix” changes; negative consequences seen as outweighing benefits

• there is a period of questioning: to “adhere or not to adhere”

• there is a gradual “resolving” of the conflict as the person becomes more determined and certain of his or her decision to stop, which is often keep “secret” from others

• they come to see this as a “personal issue,” of whether the meds are good for “them,” and making the choice to stop “contributes to their restoration of self”

Experiencing Antipsychotic Discontinuation: A Survey of Australian Consumers

• Survey of 98 “consumers”, 88 of whom reported stopping an antipsychotic at least once.

• This (2014) study represents the “first investigation of Australian consumer perspectives on their antipsychotic discontinuation experiences.

Prescriber communications

• Nearly half of the sample (47%) reported they were not sure if their prescriber had given them any information about the proposed length of their antipsychotic treatment. Of those who did recall the topic being raised, 73% said they were told they would need to take an antipsychotic indefinitely or for life.

• Over half of the sample (56%) reported that they couldn’t recall being given any information about what might happen if they discontinued their antipsychotic abruptly.

• Only 10 people reported that they were informed about the possibility of discontinuation symptoms others than relapse.
Reasons for stopping antipsychotic

• Didn’t like adverse effects (54%)

• Didn’t like idea of being on them long term (43%)

• Felt better and didn’t need them (35%)

• The drug(s) were not useful (19%)

• Advised to come off them by doctor (19%)
Length of time on antipsychotics before last discontinuation attempt

N = 88
Speed of discontinuation

N = 88

- Abruptly: 40%
- <1 month: 15%
- 1-6 months: 25%
- 6+ months: 10%
- Not reported: 0%
Domains of reported discontinuation symptoms

- Emotional: 55%
- Sleep: 50%
- Cognitive: 45%
- Psychotic: 40%
- Physical: 35%
Most common specific withdrawal symptoms

Difficulty falling asleep or staying asleep
Mood changes
Increase in anxiety/agitation
Increase in hallucinations/delusions/unusual beliefs
Difficulty concentrating/completing tasks
Increases in paranoia
Headaches
Memory loss
Nightmares
Nausea and vomiting
Most Helpful People

<table>
<thead>
<tr>
<th>Role</th>
<th>Number of Times Named</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiater</td>
<td>29</td>
</tr>
<tr>
<td>Friend</td>
<td>24</td>
</tr>
<tr>
<td>Counselor</td>
<td>19</td>
</tr>
<tr>
<td>Family</td>
<td>18</td>
</tr>
<tr>
<td>Nobody</td>
<td>18</td>
</tr>
<tr>
<td>Nurse</td>
<td>5</td>
</tr>
</tbody>
</table>
Helpful Activities

Number of times named

<table>
<thead>
<tr>
<th>Activity</th>
<th>Number of times named</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>50</td>
</tr>
<tr>
<td>Relaxation</td>
<td>30</td>
</tr>
<tr>
<td>Creative activities</td>
<td>30</td>
</tr>
<tr>
<td>Reading</td>
<td>20</td>
</tr>
<tr>
<td>Nothing</td>
<td>10</td>
</tr>
</tbody>
</table>
Outcomes at time of survey

N = 88

- No antipsychotic use
- On antipsychotic
- No disclosure

- No antipsychotic use: 20%
- On antipsychotic: 50%
- No disclosure: 30%
Discontinuing Psychiatric Medications: A U.S. Survey

• Web survey of 250 people over age 18 with a diagnosis of a major mental disorder. All had taken one or more psychiatric medications for more than nine months in past five years, and had attempted to discontinue one or two of these medications.

• Diagnoses
  — 64% major depressive disorder
  — 41% bipolar disorder
  — 20% schizophrenia or other psychotic disorder

Total lifetime exposure to psychiatric medication

- < five years
- 5-9 years
- >9 years
Class of psychiatric medication used before discontinuation

(For this study, max of 2 drugs)
Perceptions of medications before discontinuation

- Helpful: 40%
- Somewhat helpful: 50%
- Not helpful: 10%
Provider support for discontinuation

- Collaborative: 60%
- Against prescriber's advice: 40%
- Didn't tell prescriber: 20%
## Reasons for discontinuing psychiatric medications

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term effects</td>
<td>74</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>73</td>
</tr>
<tr>
<td>Wanted to know who I am</td>
<td>48</td>
</tr>
<tr>
<td>Learned about alternative approach</td>
<td>34</td>
</tr>
<tr>
<td>Felt better</td>
<td>34</td>
</tr>
<tr>
<td>Drug not useful</td>
<td>29</td>
</tr>
<tr>
<td>Drug did not work anymore</td>
<td>23</td>
</tr>
<tr>
<td>Short term use intended</td>
<td>13</td>
</tr>
<tr>
<td>Concerned about reproductive health</td>
<td>13</td>
</tr>
<tr>
<td>Advised to discontinue by prescriber</td>
<td>8</td>
</tr>
<tr>
<td>Advised to discontinue by health care provider</td>
<td>5</td>
</tr>
<tr>
<td>No access to medications</td>
<td>4</td>
</tr>
<tr>
<td>Advised by someone in personal life</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>29%</td>
</tr>
</tbody>
</table>
Speed of discontinuation

- Abruptly: 10%
- <1 month: 30%
- 1-6 months: 40%
- 6+ months: 50%
## Withdrawal experiences

<table>
<thead>
<tr>
<th>Effects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disruptions</td>
<td>80</td>
</tr>
<tr>
<td>Increased anxiety</td>
<td>76</td>
</tr>
<tr>
<td>Difficulty with emotions</td>
<td>73</td>
</tr>
<tr>
<td>Sadness, tearfulness</td>
<td>70</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69</td>
</tr>
<tr>
<td>Difficulty with thinking</td>
<td>64</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>62</td>
</tr>
<tr>
<td>Difficulty with memory or concentration</td>
<td>61</td>
</tr>
<tr>
<td>Neurological symptoms (brain zaps, for example)</td>
<td>61</td>
</tr>
<tr>
<td>Diarrhea or constipation</td>
<td>47</td>
</tr>
<tr>
<td>Thoughts of suicide</td>
<td>44</td>
</tr>
<tr>
<td>Thoughts of self-harm</td>
<td>36</td>
</tr>
<tr>
<td>Psychosis</td>
<td>22%</td>
</tr>
</tbody>
</table>
Overall severity of withdrawal effects

- Severe: 50%
- Medium: 20%
- Low: 10%
## Self-care coping strategies

<table>
<thead>
<tr>
<th>Helpful practices used during discontinuation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-education about withdrawal</td>
<td>76</td>
</tr>
<tr>
<td>Outdoor activities</td>
<td>74</td>
</tr>
<tr>
<td>Getting sleep</td>
<td>67</td>
</tr>
<tr>
<td>Expressing feelings</td>
<td>67</td>
</tr>
<tr>
<td>Being with pets or animals</td>
<td>67%</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>64</td>
</tr>
</tbody>
</table>
Outcomes

• 54% met their goal of completing discontinuing one or more medications.

• 82% of this group were satisfied or very satisfied with their decision to discontinue the medications.

• 46% either discontinued one medication but not the other; or remained on the same dose or higher.

• 50% of this group were satisfied or very satisfied with their decision to try to discontinue their medications.
Developing a Research Agenda

The disease model

In the absence of disease markers, which could be used to assess a return of the disease, should the relapse studies, which so often involved abrupt withdrawal of the drug, be seen as flawed and an invalid measurement of whether psychiatric drugs reduce symptoms over the long term?
The addiction model

- Do receptor densities renormalize? What is the speed at which this occurs?
- Is there renormalization of other domains (metabolic function, hormonal function, etc.)
- How does patient age and length of drug exposure affect renormalization/recovery processes?
- How does speed of drug withdrawal impact recovery processes?
- How does exposure to polypharmacy complicate recovery processes?
- Are there treatments that can promote recovery processes and lessen withdrawal symptoms?
The user-oriented model

- What are informational sources that can promote informed choices about whether to try a tapering/discontinuing effort?
- What are self-care strategies that can help lessen withdrawal symptoms: exercise, diet, sleep, and so forth?
- What are the social supports—support from providers, family, friends and peers—that can help people cope with withdrawal symptoms?
Psychiatry has developed informed protocols for drug discontinuation