The right way and the wrong way to stop psychiatric medications 2: antipsychotics and benzodiazepines

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Conflicts of interest

• I have no conflicts of interest
Tapering antipsychotics
Case study – Mr X

• Mr X, 29 year old man, on olanzapine 15 mg, aripiprazole 15mg, diagnosis of schizophrenia, residual auditory (and some visual) hallucinations

• Not employed or in education for the period since FEP (8 years), 2 admissions – lacked motivation and drive

• Titrated down to 5mg of olanzapine and 5mg of aripiprazole

• On reduction from 5mg to 2.5mg of olanzapine patient’s auditory hallucinations increased, and he had distressing visual hallucinations

• He increased to 5mg and these experiences returned to base line within two weeks
Case study 1 – cont’d

- 3 months later he reduced his olanzapine to 3.75mg (making ¾ of a 5mg tablet with a pill cutter) with no noticeable effect
- 3 months later further reduction from 3.75mg to 2.5mg – he had some mild exacerbation of symptoms which lasted for a few days – he remained stable on this dose
- Since then he has enrolled in an electrician course
- His wife described him as ‘coming out of a fog’, ‘I have my husband back’
- He reported that he preferred to have slightly more symptoms but be able to work to support his family
Withdrawal effects from antipsychotics

• Withdrawal effects “are a predictable aspect of the pharmacology of any drug that is eliminated more quickly than the time taken for established adaptations to the drug to resolve” (Reidenberg, 2011)

• The effects of antipsychotics can persist for months, years or decades after stopping them: clearest evidence is the persistence of tardive dyskinesia (Caroff, 2018)
Fig. 1. Symptoms of the antipsychotic withdrawal syndrome, adapted from Chouinard et al.²⁵
People without psychotic disorders who have experienced psychotic symptoms on stopping antipsychotics

- People who were given antipsychotics or dopamine antagonists (domperidone, ziprasidone, metoclopramide) for reasons other than psychosis (Horowitz et al., 2021)
- E.g. nausea (metoclopramide) or difficulties with lactation (domperidone)
- No psychotic disorder
- On abrupt cessation of the antipsychotic or dopamine antagonist they developed psychotic symptoms including cardinal symptoms like
  - auditory hallucinations,
  - Persecutory, nihilistic and Capgras delusions
- One female lawyer with no MH history stopping domperidone after 10 months of use developed psychotic symptoms that lasted 10 months
- In some cases patients had to be re-started on the antipsychotic to manage symptoms and then tapered off them more slowly
-Attributed to dopaminergic hypersensitivity
Relapses cluster close to cessation point, suggesting withdrawal effects are likely

- Data from an earlier meta-analysis of discontinuation studies
- Patients on antipsychotics abruptly stopped – most relapses occur in the first 6 weeks (and almost all by 24 weeks) (Viguera et al., 1999)

- Patients treated with placebo have relapses evenly spread over time (Johnstone and Geddes, 1994)
Rate of tapering might be causally related to relapse

<table>
<thead>
<tr>
<th>Duration of tapering period</th>
<th>0 (abrupt)</th>
<th>1-2 weeks</th>
<th>3-10 weeks</th>
<th>&gt;10 weeks</th>
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<td>Relapse rate (confidence interval)</td>
<td>77% (56-98%)</td>
<td>57% (35-80%)</td>
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<td>31% (26-36%)</td>
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<td>Number of cohorts</td>
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<td>12</td>
<td>7</td>
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- Systematic review and meta-analysis of dose reduction and discontinuation of antipsychotics (Bogers et al., 2020, Schizophrenia Bulletin Open)
- 46 cohorts (1677 patients)
- The slower the tapering period the lower the chance of relapse
Upregulation of dopamine receptors

- Dopamine activity 100 (Baseline)
- Dopamine activity 30 (Antipsychotic blockade)

- Presynaptic dopamine storage
- Dopamine in synaptic cleft
- Post-synaptic dopamine receptor
- Antipsychotic occupying receptor and blocking dopamine

With thanks to Dr John Cookson for the diagrams
Upregulation of dopamine receptors

- Chronic blockade of post-synaptic dopamine receptors leads to up-regulation to maintain homeostasis.
Most likely mechanism: up-regulation of dopaminergic receptors

- In PET/SPECT scanning of humans on antipsychotics D2/D3 receptor availability increased only in those subjects who have been exposed to antipsychotics and not to drug-naïve people (Howes et al., 2012) (about 30% in one study (Silvestri et al, 2000))
Stopping antipsychotics

• Abrupt stopping can lead to a surge in dopaminergic signaling: where physiological levels of dopamine act on up-regulated receptors

• This may cause similar effects to dopamine agonists (i.e. overactivity of dopamine), including psychotic symptoms

• Analogous to abrupt cessation of beta blockers which can cause adrenergic rebound – increased blood pressure, heart rate, and even myocardial infarction
Tapering antipsychotics

Dopamine activity 30-35

Up-regulation of dopamine receptors

→ Small reduction in blockade

→ Slow adaptation to less blockade
Rate of tapering might be causally related to relapse

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Pharmacology of antipsychotics

Relationship between dose and effect on symptoms (Leucht et al., 2020)
Tapering antipsychotics

- Reduction from 0.25mg of haloperidol to 0mg is greater than the reduction from 10mg to 2mg of haloperidol
Hyperbolic tapering of antipsychotics

- Reduction from 0.08mg of haloperidol has more of an effect as reduction from 4 mg to 2mg.

<table>
<thead>
<tr>
<th>Haloperidol dose (mg)</th>
<th>D2 occupancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.8</td>
<td>90</td>
</tr>
<tr>
<td>4.4</td>
<td>80</td>
</tr>
<tr>
<td>2.1</td>
<td>70</td>
</tr>
<tr>
<td>1.2</td>
<td>60</td>
</tr>
<tr>
<td>0.78</td>
<td>50</td>
</tr>
<tr>
<td>0.50</td>
<td>40</td>
</tr>
<tr>
<td>0.32</td>
<td>30</td>
</tr>
<tr>
<td>0.18</td>
<td>20</td>
</tr>
<tr>
<td>0.08</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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</table>
Pharmacologically rational reduction regimens (Horowitz et al., 2021)

<table>
<thead>
<tr>
<th>Steps</th>
<th>Haloperidol (mg)</th>
<th>Risperidone (mg)</th>
<th>Olanzapine (mg)</th>
<th>Clozapine (mg)</th>
<th>Quetiapine (mg)</th>
<th>Amisulpride (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>4.0</td>
<td>7.5</td>
<td>300</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>2.5</td>
<td>5.9</td>
<td>210</td>
<td>240</td>
<td>270</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>1.7</td>
<td>4.6</td>
<td>150</td>
<td>200</td>
<td>190</td>
</tr>
<tr>
<td>4</td>
<td>0.85</td>
<td>1.2</td>
<td>3.6</td>
<td>110</td>
<td>160</td>
<td>140</td>
</tr>
<tr>
<td>5</td>
<td>0.6</td>
<td>0.85</td>
<td>2.7</td>
<td>80</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
<td>0.6</td>
<td>2</td>
<td>55</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>0.25</td>
<td>0.4</td>
<td>1.4</td>
<td>40</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>0.15</td>
<td>0.25</td>
<td>0.9</td>
<td>25</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>0.05</td>
<td>0.1</td>
<td>0.4</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- 10 equally spaced steps (in terms of effect on D2 receptors) from therapeutically minimum doses to 0.
- Note how small final doses are – will require liquid versions of medication
- Such reductions might be made every 3 months, depending on how long the patient has been on the drug, and how they tolerate the process
Resolution of tardive dyskinesia following cessation of antipsychotics and its relationship to period of follow up.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Recovery (%)</th>
<th>Period of follow up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulson (1968)</td>
<td>33</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hershon et al. (1972)</td>
<td>23</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Edwards (1970)</td>
<td>19</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Crane (1970)</td>
<td>39</td>
<td>8</td>
<td>6-24</td>
</tr>
<tr>
<td>Itoh and Yagi (1979)</td>
<td>19</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Degwitz (1969)</td>
<td>273</td>
<td>19</td>
<td>7-10</td>
</tr>
<tr>
<td>Uhrbrand and Faurbye (1960)</td>
<td>17</td>
<td>35</td>
<td>4-22</td>
</tr>
<tr>
<td>Yagi et al. (1976)</td>
<td>19</td>
<td>53</td>
<td>12-24</td>
</tr>
<tr>
<td>Jeste et al. (1979)</td>
<td>21</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>Itoh and Yagi (1979)</td>
<td>14</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Quitkin et al. (1977)</td>
<td>12</td>
<td>92</td>
<td>1-24</td>
</tr>
</tbody>
</table>

- Dopaminergic hypersensitivity thought to underlie withdrawal effects, also responsible for tardive dyskinesia
- Tardive dyskinesia can improve over months or years following antipsychotic cessation, suggesting this is the time period taken for dopaminergic hypersensitivity to resolve
Time period for tapering?

• Tapering over months or years may be required
• Likely to be related to duration of treatment: patients treated for only a few weeks or months likely to be able to taper much more rapidly than patients treated for years
• One study showed that most patients could reduce their dose of antipsychotic by 25% every 6 months (calculated on the last dose, following a near-hyperbolic pattern) (Liu and Takeuchi, 2020)
• Another pilot study found that patients could reduce their dose by 42% over 6 months with no extra relapses (Huhn et al., 2020)
Practical advice

• Titrating rate of taper to patient’s ability to tolerate
• The appearance of psychotic symptoms especially if mild may not indicate that the patient cannot reduce (or stop) their medication but might indicate that the patient needs to taper more gradually
• If psychotic symptoms are exacerbated and the degree of risk is not concerning, then holding a dose for a longer period of time or a small updose to stabilize before starting to reduce more gradually might be helpful
• Further psychosocial supports (eg increased contact) might be helpful during this period
• Tapering at a rate of about 25% of the most recent dose (so that the size of reductions become smaller and smaller) every 3 months may be tolerable (equivalent to about 10% of the most recent dose every month)
Relapse prevention properties of antipsychotics

• Leucht et al, 2012
• Meta-analysis: 65 RCTs, total n = 6493 patients
• Relapse - maintenance treatment: 22%
• Relapse - antipsychotic discontinuation: 57%
• Core of NICE guidance
• Average period over which oral antipsychotics were stopped in these meta-analysis was stopped was 4 weeks (abruptly for depot)
• Withdrawal-related effects might have increased relapses in the discontinuation arm, exaggerating the relapse prevention properties of antipsychotics
Tapering benzodiazepines
Protracted, disabling withdrawal symptoms from benzodiazepines

• People coming off benzodiazepines can also experience disabling symptoms, including neurological, gastrointestinal, psychiatric symptoms which can last for years.
• Such patients are often told that their symptoms could not be caused by a drug they are no longer taking, leading to stigma, isolation and financial problems for these people who are denied benefits or labelled ‘malingers’ or told it is ‘in their head’ or a return of their underlying condition
• However, protracted withdrawal symptoms from benzodiazepine have been observed for 30 years and is well-characterized, including many neurological symptoms not present in anxiety (eg electric shock sensations, muscle tremors and pain)
Going from 1mg to 0mg of diazepam causes as big a reduction in effect on the brain as going from 100mg to 75mg. So reductions have to get smaller and smaller as you go down to lower doses. People often need weeks between doses.
Slow tapering of benzodiazepines

• Protracted withdrawal symptoms are most likely if drugs are stopped abruptly or too quickly
• Many patients can only tolerate reductions of 10% of their last dose a month or even slower (such regimes closely follow the hyperbolic pattern of benzodiazepine effects)
• The best pace is the pace that the patient can tolerate - imposing regimes tends to backfire
• The process takes many months or years and some people may need to go down to doses as small as 0.1mg of diazepam equivalent
NICE guidance on tapering benzodiazepines

**Suggested withdrawal schedule for diazepam**

- From diazepam 40 mg per day or less:
  - Reduce dose by 2–4 mg every 1–2 weeks until reaching 20 mg per day, then
  - Reduce dose by 1–2 mg every 1–2 weeks until reaching 10 mg per day, then
  - Reduce dose by 1 mg every 1–2 weeks until reaching 5 mg per day, then
  - Reduce dose by 0.5–1 mg every 1–2 weeks until completely stopped.
- Estimated total withdrawal time:
  - From diazepam 40 mg per day: 30–60 weeks.
  - From diazepam 20 mg per day: 20–40 weeks.
Thanks for listening

• Questions?

• Email: M.horowitz@ucl.ac.uk
Selected bibliography - Antipsychotics


