Tapering antipsychotic medication: theory and practice

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Case study 1

- 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
- Titrated down to 5mg of olanzapine and 5mg of aripiprazole
- On reduction from 5mg to 2.5mg of olanzapine patient's AH increased, and he had distressing visual hallucinations of his wife and mother threatening him
- He increased to 5mg and these experiences returned to base line (some AH, some VH) 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, and returned to 5mg for 3 days before returning to 2.5mg on which he was stable
- Since then he has enrolled in an electrician course
- His wife described him as 'coming out of a fog', 'I have my husband back'
- (after the end of the trial, patient forgot to renew his script for three weeks, had increased symptoms, and returned to 10mg of olanzapine in order to stabilize them)

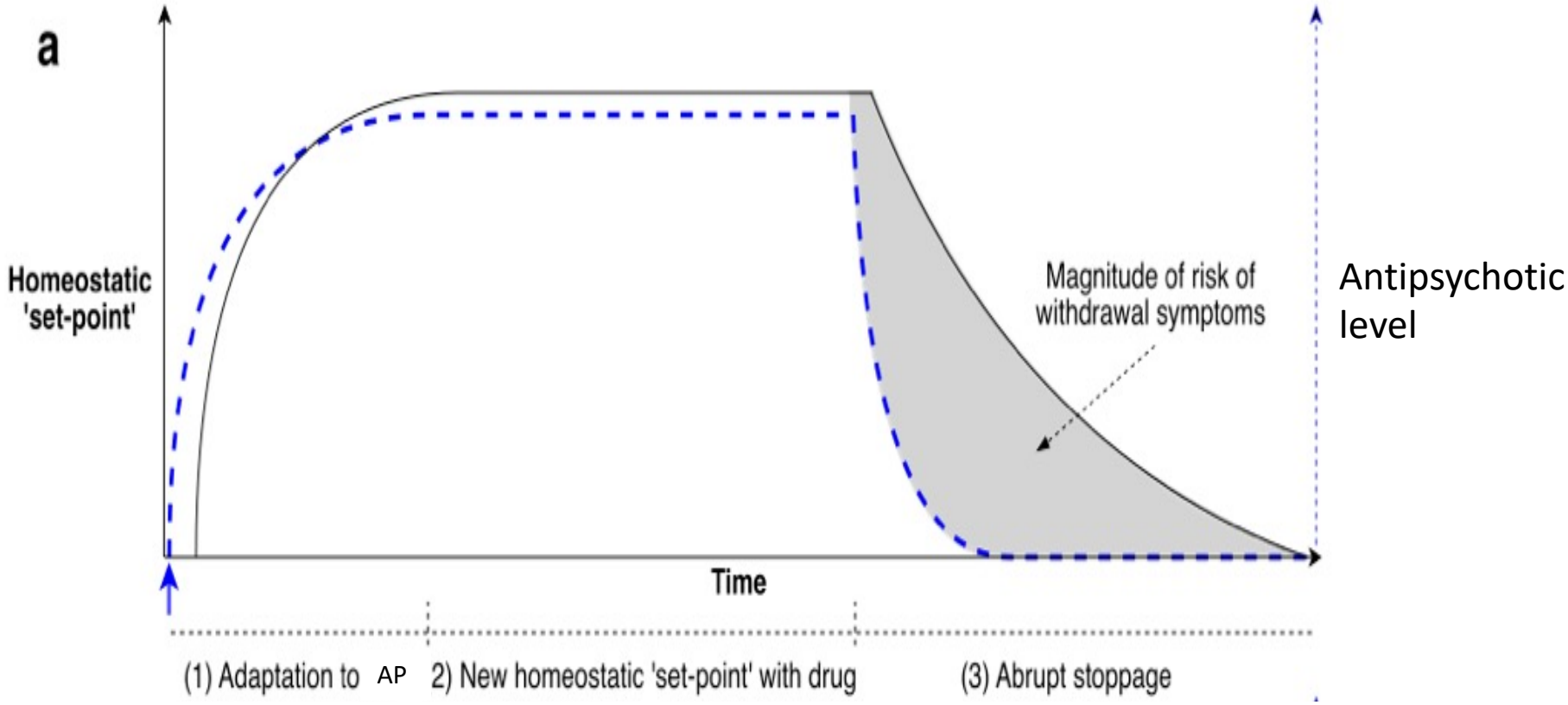
Key messages

- The way to stop antipsychotics to cause the most trouble for people is to do so abruptly or very quickly
- Stopping antipsychotics gradually is likely to cause much less destabilization to people – gradually might mean years for people who have been on these drugs long-term
- The way the drugs effect the brain suggests that we should reduce drug dose by smaller and smaller amounts (hyperbolic or proportionate tapers)
- The emergence of psychotic symptoms does not mean that the person needs the medication but may indicate that they need to reduce their dose more slowly (+/- pursue other means of managing their symptoms)

Withdrawal effects from antipsychotics

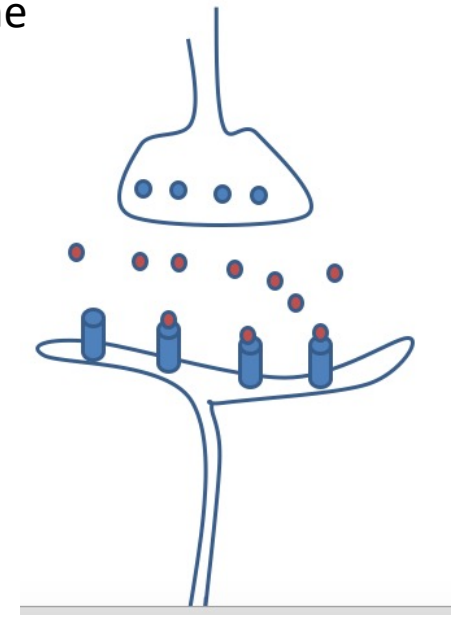
- Withdrawal effects “are a predictable aspect of the pharmacology of any drug that is eliminated more quickly than the time taken for established adaptations to the drug to resolve” (Reidenberg, 2011)
- The effects of antipsychotics can persist for months, years or decades after stopping them: clearest evidence is the persistence of tardive dyskinesia (Caroff, 2018)
- There are a variety of possible changes but most likely is up-regulation of post-synaptic dopamine receptors (in response to a dampened signal)

Adaptation to drugs and withdrawal



Upregulation of dopamine receptors

Dopamine activity 100



Baseline

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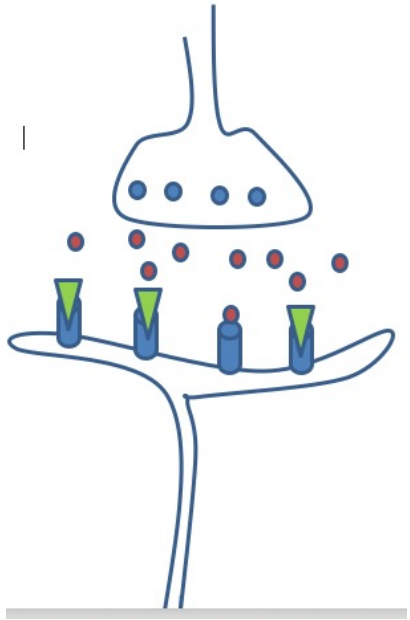
Dopamine activity 30



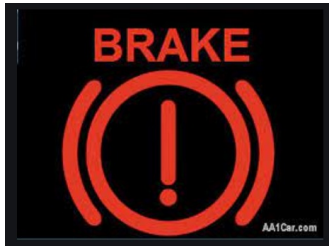
Antipsychotic blockade

presynaptic dopamine storage

Dopamine in synaptic cleft

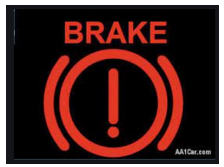
Post-synaptic dopamine receptor

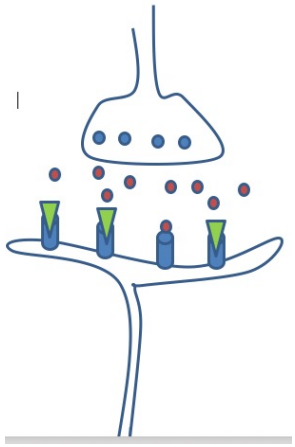
Antipsychotic occupying receptor and blocking dopamine



Upregulation of dopamine receptors

Dopamine activity 30





Antipsychotic blockade

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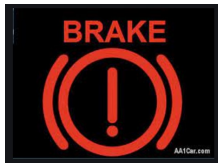
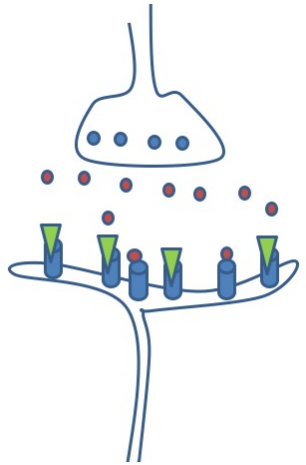
Dopamine activity 30-35



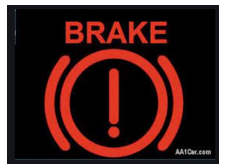


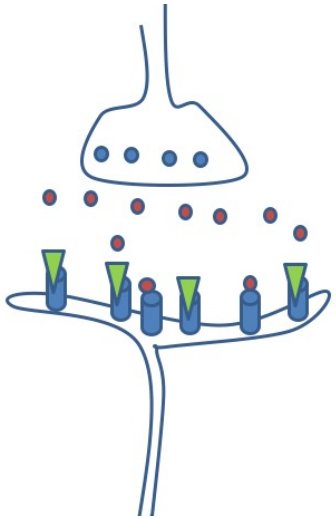
Up-regulation of dopamine receptors

- Chronic blockade of post-synaptic dopamine receptors leads to up-regulation to maintain homeostasis
- Can be seen in animals: occurs in 2 weeks of giving antipsychotics
- 9 months of haloperidol in rats leads to a 2-3-fold increase in D2 receptors; stay increased for at least a year in human equivalent time (Joyce, 2001)
- 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

Dopamine activity 30-35





Up-regulation of dopamine receptors

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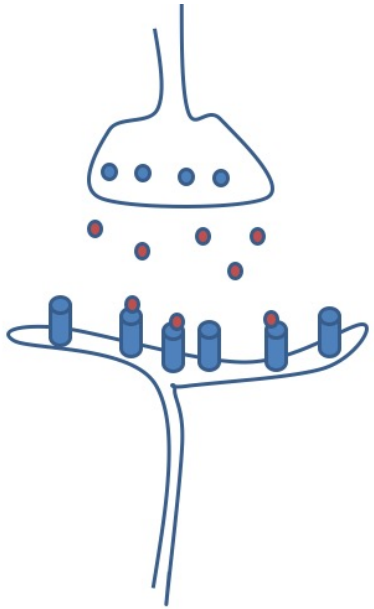
Dopamine activity 150 or ?more



Abrupt stopping of antipsychotics leads to rebound of dopamine activity on up-regulated receptors

- 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

Antipsychotic withdrawal symptoms

- Depending on the receptor targets of the drug
- Meta-analysis finds that 53% of people experience withdrawal symptoms after abrupt cessation of antipsychotics (Brandt et al., 2020)
- Symptoms:
  - Insomnia (most common)
  - Movement disorders (eg withdrawal dyskinesia)
  - Dizziness
  - Anxiety/ depressed mood
  - Probably includes psychotic symptoms
- Probably most severe for clozapine (including anti-cholinergic effects)

People without psychotic disorders who have experienced psychotic symptoms on stopping antipsychotics

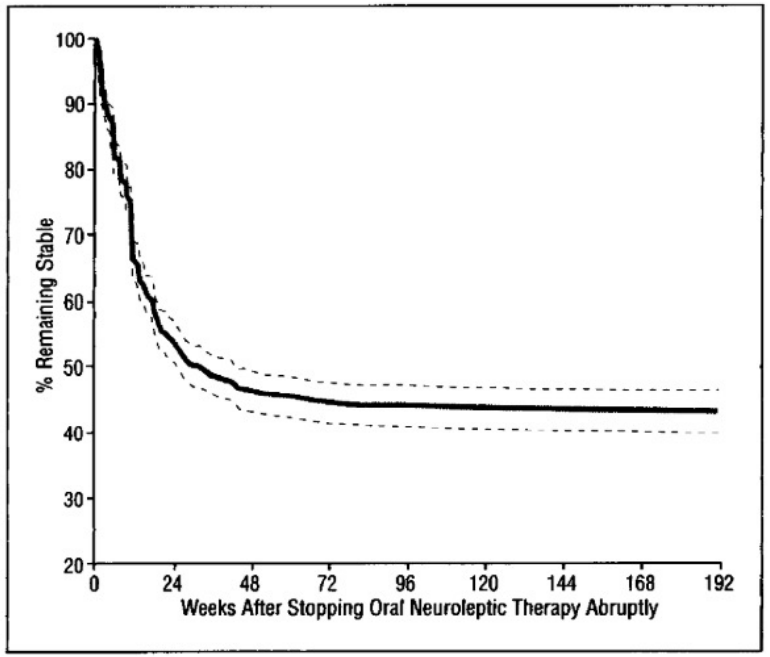
- People who were given antipsychotics or dopamine antagonists (domperidone, ziprasidone, metoclopramide) for reasons other than psychosis (Horowitz et al., 2021)
- E.g. nausea (metoclopramide) or difficulties with lactation (domperidone)
- No psychotic disorder
- On abrupt cessation of the antipsychotic or dopamine antagonist they developed psychotic symptoms including cardinal symptoms like
  - auditory hallucinations,
  - Persecutory, nihilistic and Capgras delusions
- In one female lawyer with no MH history after stopping domperidone after 10 months of use, she 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

Patients without psychosis who develop psychotic symptoms on abrupt stopping of antipsychotics

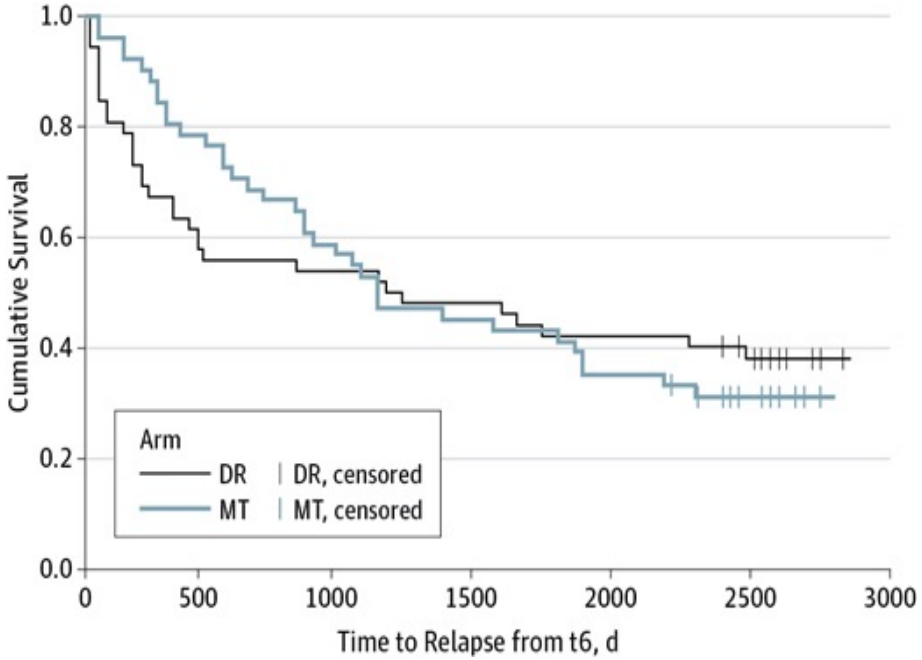
Kent and Wilber [50]	Woman with no psychiatric history	Resperine (dopamine depleting agent) for hypertension for 20 years	Euphoric, visual hallucinations, hyperactivity, and pressured speech Only extinguished by recommencement of reserpine
Witschy et al[51]	26 M BPAD with brief DIP and no other psychotic symptoms	Fluphenazine for acute drug-induced psychosis	Paranoia, disconnected thoughts, and sense of personal disintegration Distinct from any previous experience Extinguished on recommencement of fluphenazine (did not reoccur when medication was tapered over several months)
Steiner et al[52]	5 pts with BPAD with no psychotic symptoms	First-generation antipsychotics used as mood stabilisers for 2–8 years	Paranoid delusions, auditory, and visual hallucinations Irritability, insomnia, dysphoria, and poor concentration None of these symptoms had been present prior to AP use
Lu et al[47]	2 men with no psychiatric history	Metoclopramide for gastro-intestinal complaints for 3–6 months	Auditory hallucinations, persecutory delusions, ideas of reference, 12h and 3 days after abrupt cessation
Roy-Desruisseaux et al[44]	Elderly woman, with dementia but no mental health history	Domperidone for gastroesophageal reflux disorder for 10 years	Capgras and persecutory delusions, disorganized thought form, suicidal (no evidence of delirium) Responded to risperidone
Jacob et al[45]	17 F with depression and emotional dysregulation but no history of psychotic symptoms	Ziprasidone for emotional dysregulation for 2 years	Pt experienced visual and tactile ("bugs crawling" on her) hallucinations after she ran out of her prescription. Symptoms resolved within 24 h of recommencing ziprasidone
Bastiampillai et al[53]	28 M with moderate intellectual impairment but no history of psychotic symptoms	Thioridazine for behavioural management for 15 years	When thioridazine was switched to risperidone, pt experienced persecutory delusions and auditory hallucinations for the first time in his life
Seeman[46]	Woman, lawyer, no psychiatric history	Domperidone for breast milk stimulation for 10 months	Akathisia, severe anxiety, depression, nihilistic delusions ("putrefying inside"); cognitive and memory problems Disorganized in behavior, amotivated, suicidal

Horowitz et al. 2021, Schizophrenia Bulletin

Relapses cluster close to cessation point, suggesting withdrawal effects



Patients on antipsychotics abruptly stopped – most relapses occur in 24 weeks (Viguera et al., 1999)



Patients who are stopped off their medication more gradually have relapses more 'evenly spread' over time (closer to natural history of the disorder in all likelihood)

Rate of tapering might be causally related to relapse

Duration of tapering period	0 (abrupt)	1-2 weeks	3-10 weeks	>10 weeks
Relapse rate (confidence interval)	77% (56-98%)	57% (35-80%)	47% (28-67%)	31% (26-36%)
Number of cohorts	14	12	7	10

- 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

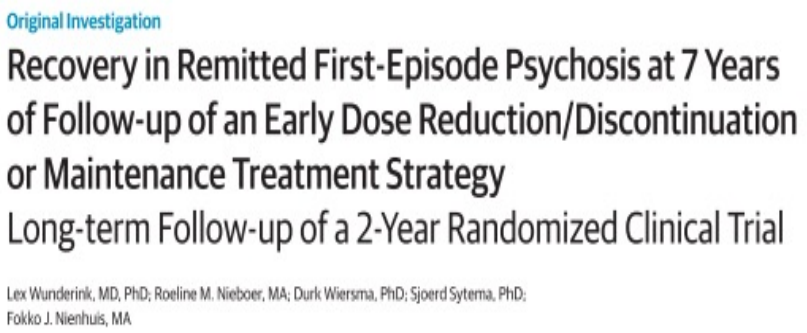
Randomised trial

Wunderink et al., 2007, 2013 - Dutch first episode study.

- RCT of gradual, flexible antipsychotic discontinuation vs maintenance (18-month FU):
  - 22% discontinued successfully
  - 46% never discontinued
  - 32% stopped and re-started
- 7-year follow-up

Guided Discontinuation Versus Maintenance Treatment in Remitted First-Episode Psychosis: Relapse Rates and Functional Outcome

Lex Wunderink, M.D., Ph.D.; Fokko J. Nienhuis, M.A.; Sjoerd Sytema, Ph.D.; Cees J. Slooff, M.D., Ph.D.; Rikus Knegtering, M.D., Ph.D.; and Durk Wiersma, Ph.D.



Original Investigation

Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy

Long-term Follow-up of a 2-Year Randomized Clinical Trial

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

18 month follow up

No differences in global social functioning

Discontinuation group showed:

- Higher relapse rates (43% vs 21%, p = .01)
- No difference in hospitalisation
- Trend towards higher rates of work (35% vs 17%, p=0.06)

Wunderink et al, 2007

Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Characteristic	No. (%)		
	DR (n = 52)	MT (n = 51)	Total Sample (n = 103)
Recovery	21 (40.4)	9 (17.6)	30 (29.1)
Remission			
Symptomatic	36 (69.2)	34 (66.7)	70 (68.0)
Functional	24 (46.2)	10 (19.6)	34 (33.0)

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.

Wunderink et al, 2013

7 year follow-up

- DR = dose reduction/

discontinuation
- MT = maintenanc e treatment

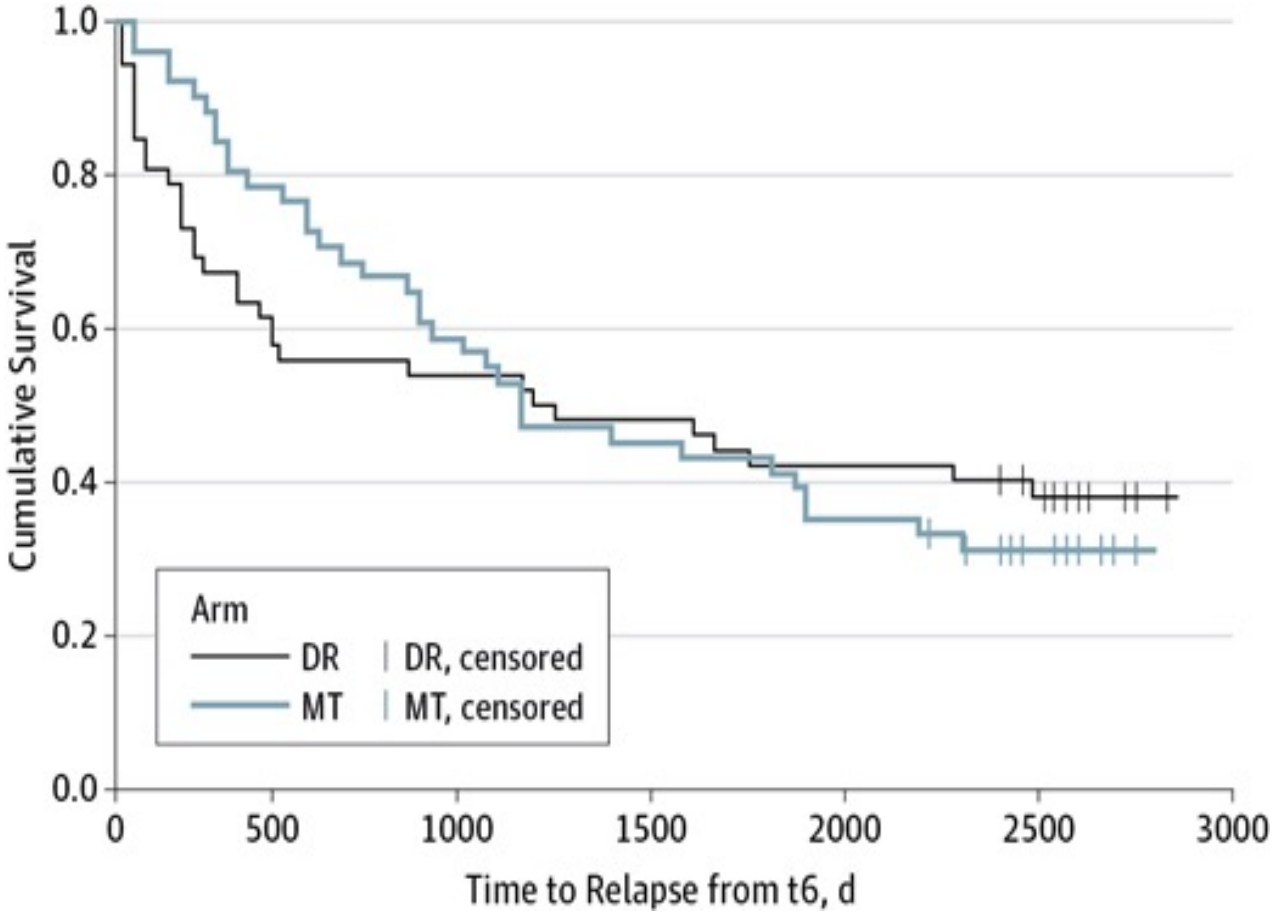


Figure 1. Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18-months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT)

Wunderink et al, 2013

Other research trials

- RADAR trial running in 19 NHS sites in England, due to report next year
- In Australia: the Reduce trial
- In Denmark: the TAILOR trial
- In Holland: the HAMLETT trial
- An antipsychotic reduction trial in Taiwan
- An antipsychotic reduction trial in Germany

Evidence for the benefits of long-term treatment with antipsychotics

Leucht et al, 2012.

- Meta-analysis: 65 RCTs, total n = 6493 patients
- Relapse - maintenance treatment: 22%
- Relapse - antipsychotic discontinuation: 57%

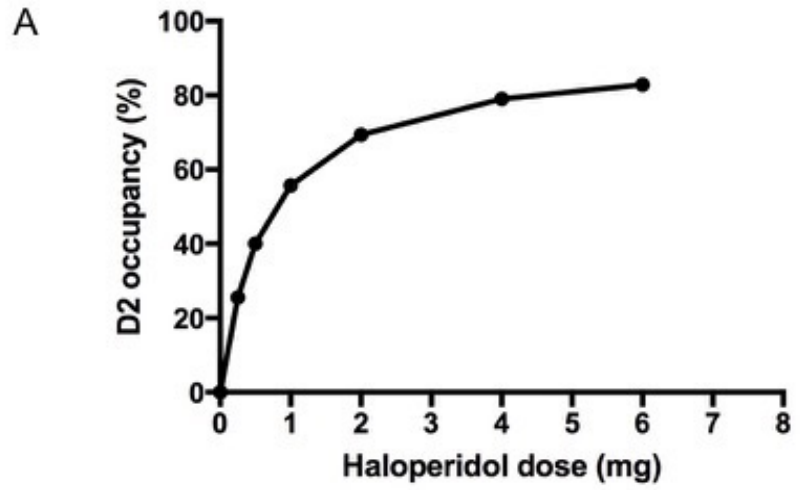
Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

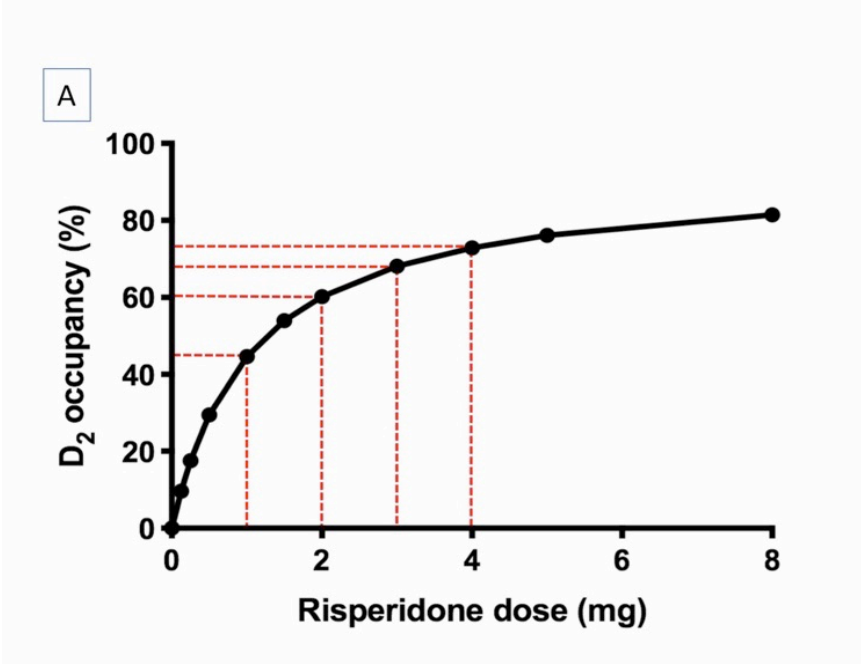
Stefan Leucht, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

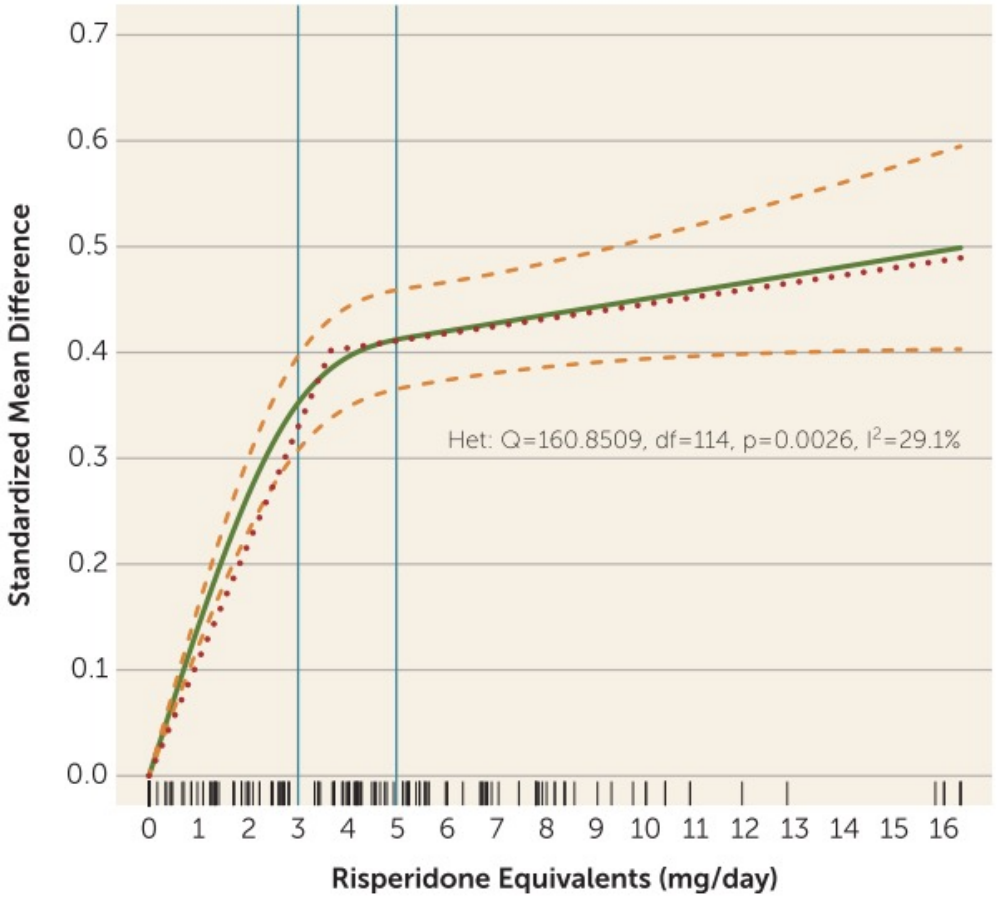
Limitations of antipsychotic maintenance studies

- Evidence consists of antipsychotic *discontinuation* studies, which are confounded by adverse effects of discontinuation (including psychosis and probably discontinuation-induced relapse)
- Average period antipsychotics were stopped in these studies – 4 weeks (or depot stopped abruptly)

Pharmacology of antipsychotics

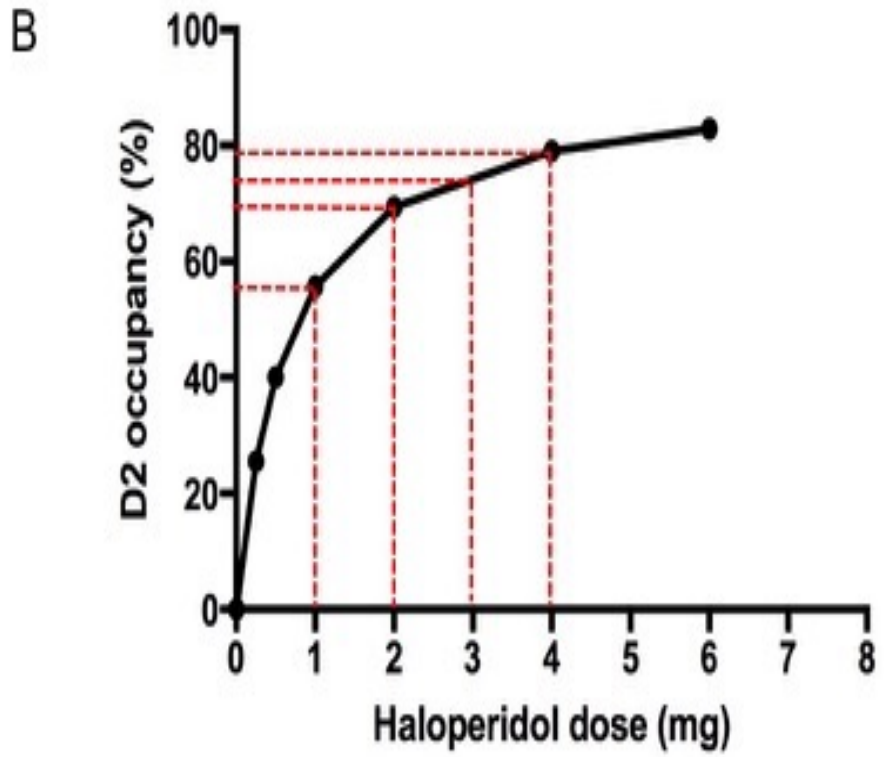






Relationship between dose and effect on symptoms (Leucht et al., 2020)

Tapering antipsychotics



Haloperidol dose (mg)	D2 occupancy (%)
10	86.3
8	85.0
6	82.9
4	79.0
3	75.5
2	69.4
1	55.7
0.5	40.0
0.25	25.5
0	0

Reduction from 0.25mg of haloperidol to 0mg is greater than the reduction rom 10mg to 2mg of haloperidol

Hyperbolic tapering of antipsychotics

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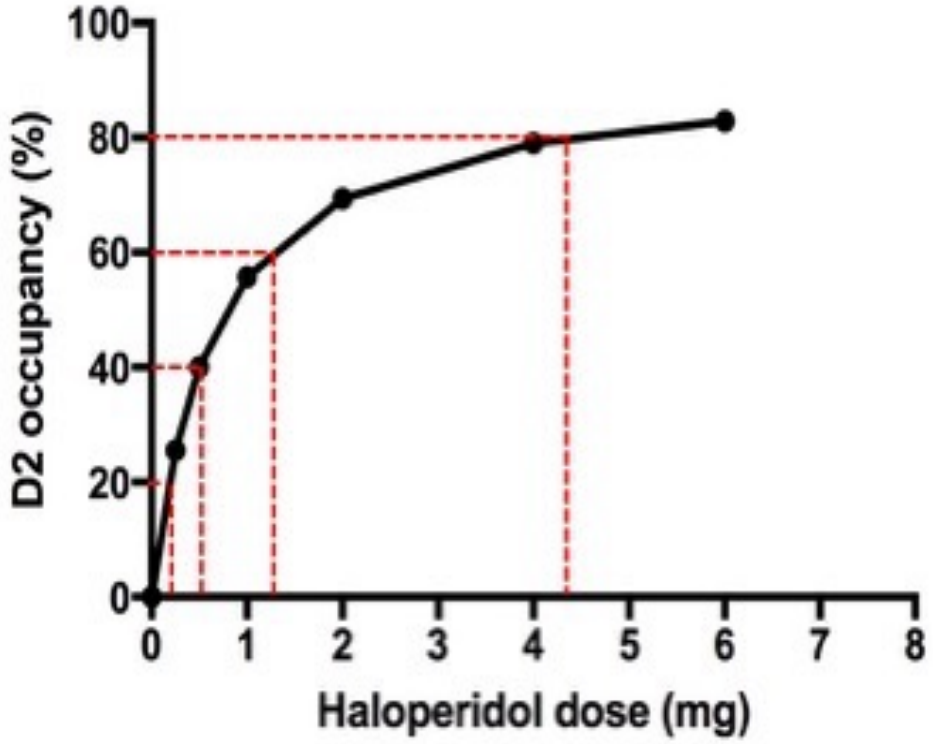


Haloperidol dose (mg)	D2 occupancy (%)
30.8	90
4.4	80
2.1	70
1.2	60
0.78	50
0.50	40
0.32	30
0.18	20
0.08	10
0	0

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

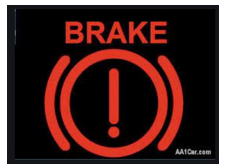
Pharmacologically rational reduction regimens

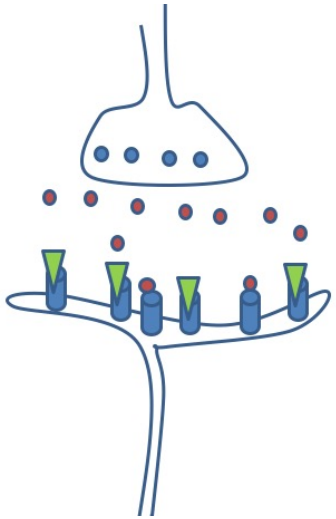
Steps	Haloperidol (mg)	Risperidone (mg)	Olanzapine (mg)	Clozapine (mg)	Quetiapine (mg)	Amisulpride (mg)
1	4.0	4.0	7.5	300	300	400
2	2.0	2.5	5.9	210	240	270
3	1.3	1.7	4.6	150	200	190
4	0.85	1.2	3.6	110	160	140
5	0.6	0.85	2.7	80	120	95
6	0.4	0.6	2	55	90	70
7	0.25	0.4	1.4	40	65	45
8	0.15	0.25	0.9	25	40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

10 equally spaced steps (in terms of effect on D2 receptors) from therapeutically minimum doses to 0. Note how small final doses are

Abrupt stopping antipsychotics

Dopamine activity 30-35





Up-regulation of dopamine receptors

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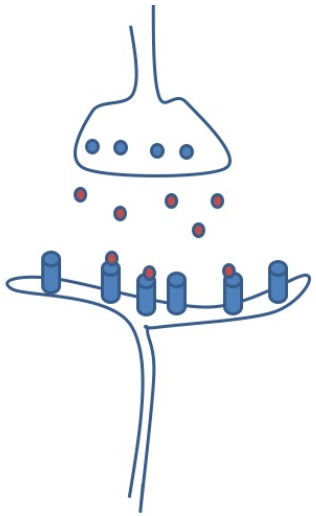
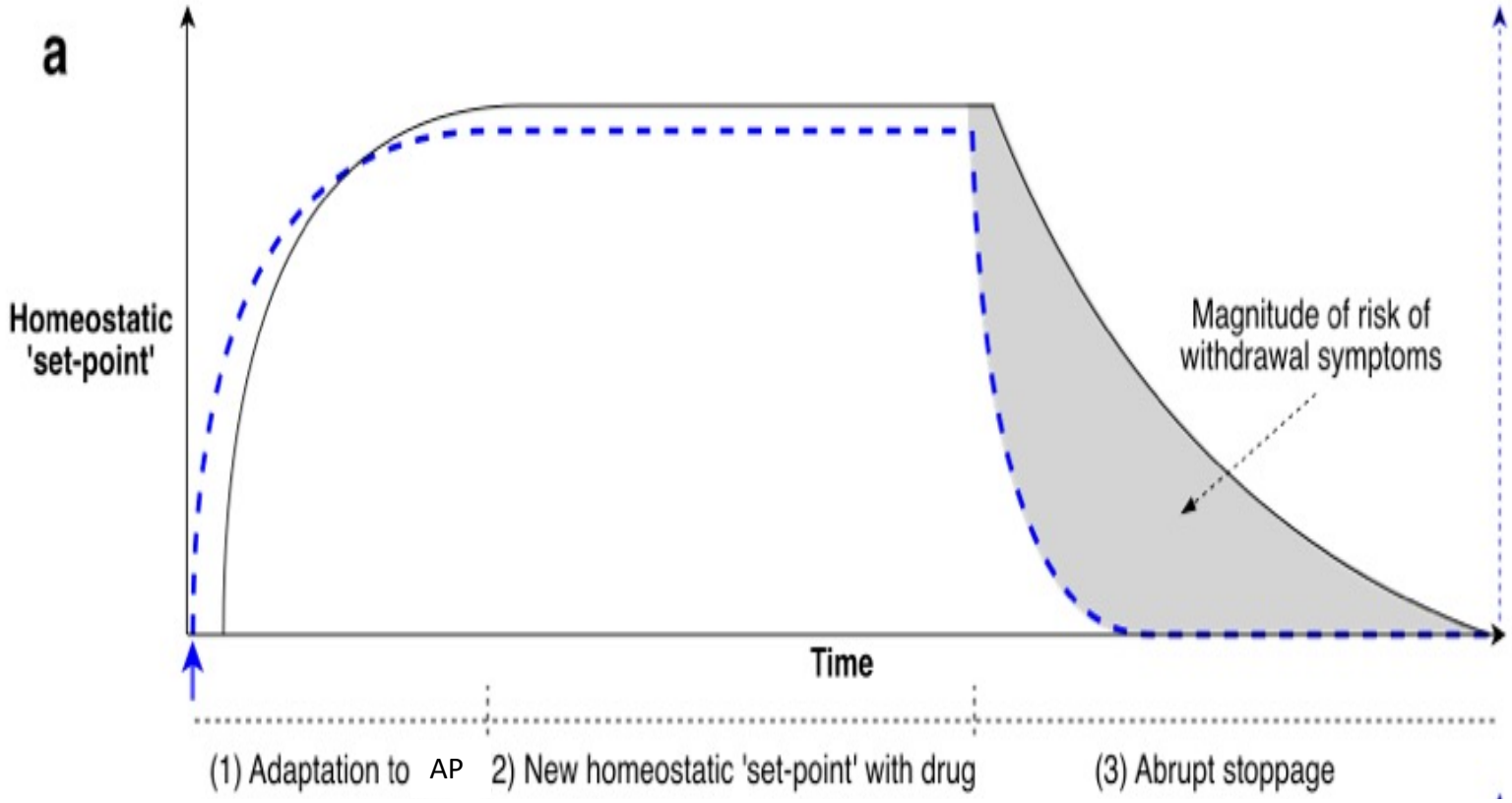
Dopamine activity 150 or ?more



Abrupt stopping of antipsychotics leads to rebound of dopamine activity on up-regulated receptors

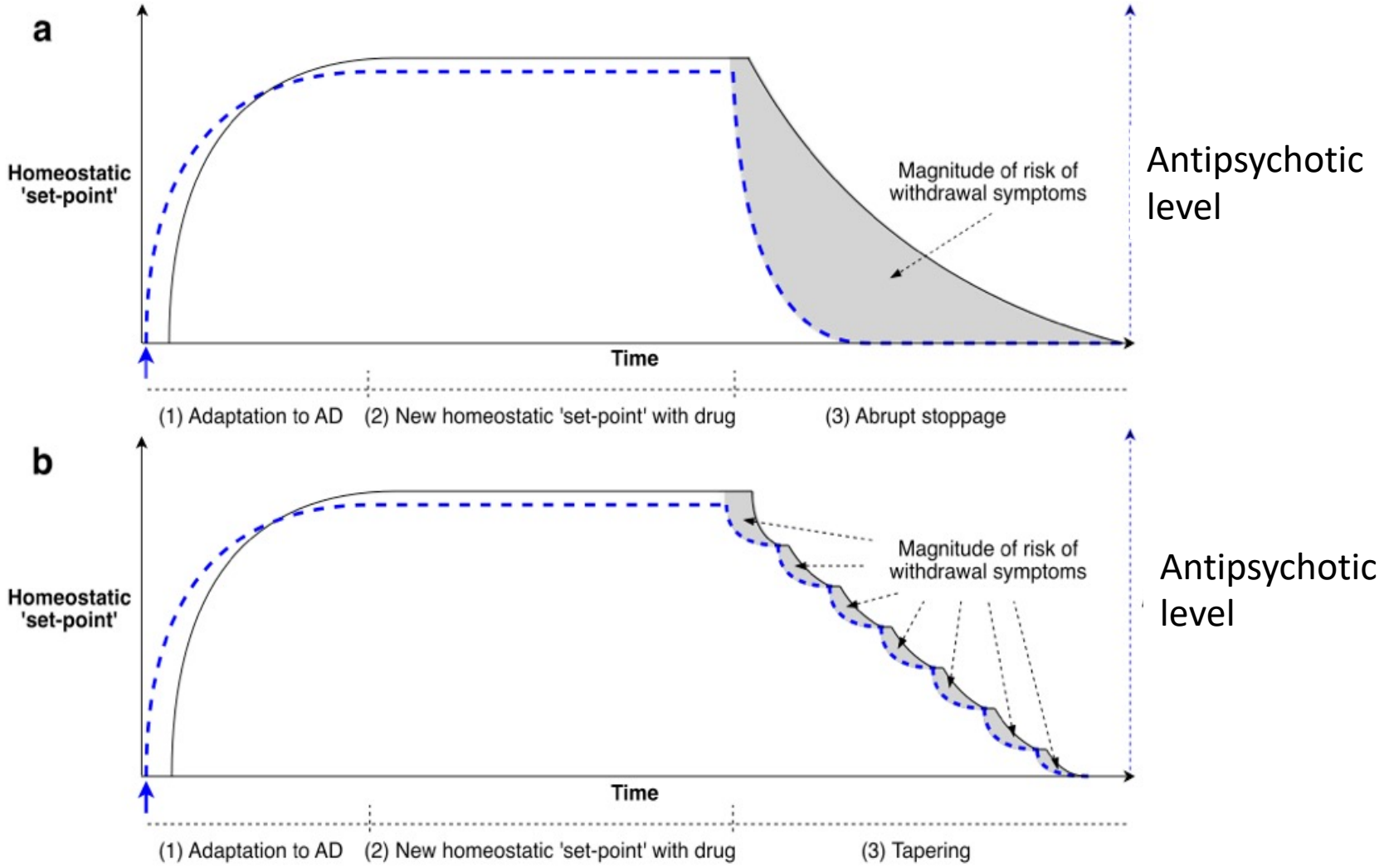
- Most likely method to cause withdrawal effects or relapse

Stopping abruptly



Tapering

- ‘Taking your foot off the break slowly’
- Allows the system to re-adapt to lower levels of blockade more gradually so less chance of rebound or ‘overshoot’



Time period?

- Tardive dyskinesia can persist for months or years following antipsychotic cessation, suggesting this is the time period dopaminergic hypersensitivity can persist
- One study found that reductions of 25% of the most recent dose (charting out a hyperbola very similar to that suggested by the occupancy curve) every 6 months tolerable to most patients (Liu and Takeuchi, 2020).
- Another study found that a 42% dose reduction over 6 months caused no difference in relapse rate from maintenance patients (Huhn et al., 2020)

Tapering rate

- Overall, it seems reasonable to suggest 25-50% dose reductions (of the most recent dose) every 3-6 months.
- This is equivalent to about a reduction of D2 occupancy of 5 to 10 percentage points every 3-6 months
- Or 2-3 percentage points of D2 occupancy each month (equivalent to about a 10% reduction in dose every month, so that the reductions get smaller each month)
- The most important thing is to titrate it to the tolerability of the patient – if they experience insomnia, slight worsening of psychotic symptoms, the rate should be slowed down or a slight updose
- The experience of psychotic symptoms (if risk is manageable) are not necessarily a sign that a patient required life-long antipsychotics but might indicate that they simply need to make reductions more gradally (smaller amounts spread out at greater intervals)

Example tapering regimes

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

- E.g. making these reductions every 2-4 months (depending on how long patients have been on the medication), or even smaller reductions every 1-2 months

Practical aspects - 1

- Wide variability in patient's ability to tolerate reductions – ?unknown determinants (?age, ?length of Tx , medication)
- Some patients experience a temporary increase in symptoms following a reduction that resolves over time – sometimes that period of time is weeks or months (?may correspond to time for down-regulation of receptors)
- Patients with better social supports can tolerate this exacerbation of symptoms better (although sometimes social supports do not tolerate), other may need increased attention from services or short-term prescription of z-drug/promethazine for sleep, others may not be able to tolerate this at all

Practical aspects - 2

- If a reduction has caused an exacerbation of symptoms often returning to previous dose at which they were stable in the reduction can resolve symptoms (over weeks, but sometimes months)
- Often these patients can tolerate further reductions in their dose subsequently – but with smaller reductions spaced out over greater time periods

Case study 2

- Mrs Y, 65 year old lady, with schizophrenia, long-term risperidone depot 25mg fortnightly
- She was reduced slowly to 0.5mg of risperidone over about 12 months without any increase in symptoms
- She then had her risperidone ceased from 0.5mg (Nov 2018)
- In April 2019 her behavior became disorganized (throwing out possessions) and delusional, family called CRT (6 months off medication)
- HTT involved, risperidone 1mg re-commenced
- Family upset, worried, HTT recommended increase to 2mg of risperidone and/or re-commencement of her risperidone depot

Case study 2 – cont'd

- Patient was strongly opposed to either an increase in dose or depot, willing to continue 1mg risp
- As her risks were minimal (throwing out clothes, angry at parked cars), she maintained 1mg risp (although HTT continued to advocate for at least 2mg)
- Her symptoms did not resolve over 4-6 weeks and HTT decided to impose a depot, with family in agreement – as family about to go overseas for 6 weeks
- Patient sabotaged depot appt, and went overseas, on 1mg risp/day
- On return from trip – about 4 months after re-commencement of 1mg risp she was close enough to baseline (as when on depot) that she was continued on 1mg of risp
- Patient appreciative of less side effects, family grateful that she was not put back on depot as patient had complained about this for years+ side effects

Case study 3

- Mr Z, 49 year old man, schizophrenia, residual tactile and auditory hallucinations. Only weekly activity – going food shopping.
- On melperone, very similar to clozapine, with strong anticholinergic properties
- Reduced from 300mg to 275mg without incident
- Reduced from 275mg to 250mg – partial insomnia from 2nd day afterward to 5th day associated with an increase in auditory hallucinations (distressing). He persisted with the reduced dose – by 6th day after dose he was sleeping normally with baseline level of AH
- Did not want to reduce from 250 to 225, so we reduced his dose to 237.5mg (by splitting a 25mg tablet with a tablet cutter): he experienced partial insomnia from 2nd to 4th day after reduction, associated with an increased in auditory hallucinations and tactile hallucinations. I had increased phone contact with him during this period

Case study 3 – cont'd

- He has reduced from 237.5mg to 225mg to 212.5mg. On each occasion he has 2-4 days of insomnia and an increase in auditory hallucinations that have resolved by a week after the reduction.
- I usually call him on the 2nd and 4th day for a few minutes to support him through the reduction
- He has increased his daily activities in the year of the trial – before Lockdown he had arranged to attend a day group three times a week, was visiting his sister once/week, and had re-connected with an old friend
- This improvement in his energy, and feeling better ("clearer in my head") motivated him to persevere through the unpleasant withdrawal symptoms (?cholinergic effects) that occurred whenever he reduced his dose

Questions?

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Thank you for listening

- Questions?

- My email for any further questions:

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