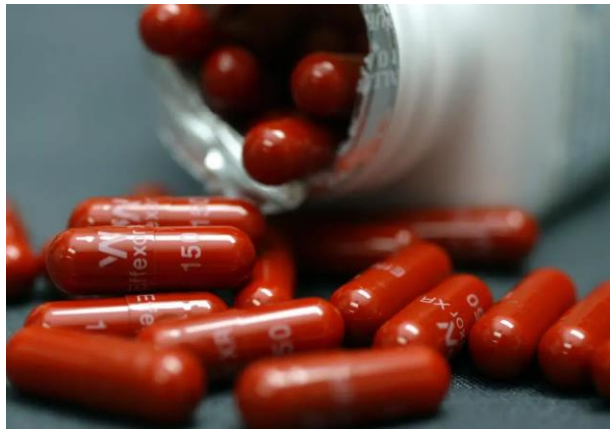
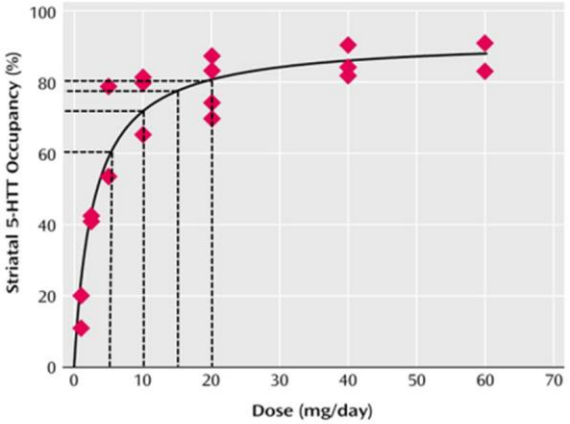




Deprescribing antipsychotics

Dr Mark Horowitz BA, BSc, MBBS, MSc, PhD (IoPPN, KCL)
Clinical Research Fellow in Psychiatry on RADAR trial (UCL, NELFT)
Psychiatry Trainee
m.horowitz@ucl.ac.uk

NELFT NHS
NHS Foundation Trust

UCL

Conflicts of interest

- I have no conflicts of interest

Stopping Antipsychotics

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
- Complained of a lack of motivation, sedation and weight gain on medication
- 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'
- *Why did he have more symptoms when dropping dose in one day versus over 6 months?*

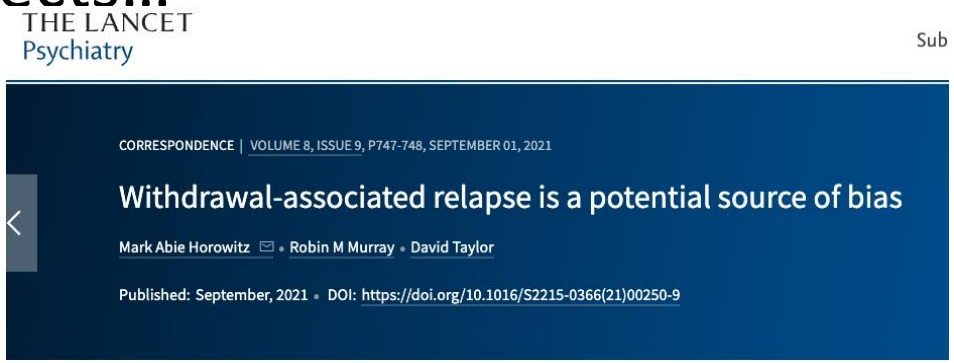
Why stop antipsychotics?

- Adverse effects:
  - Movement disorders, including tardive dyskinesia
  - Metabolic effects, possibly leading to earlier mortality
  - Reduced grey matter over time (initially interpreted as due to schizophrenia itself, increasing studies (including RCTs) find antipsychotics themselves cause volume reduction) (Fusar-Poli 2013, Dorph-Peterson 2005)
  - Negative effects on long-term recovery and functioning (Wunderink et al. 2013)
  - Subjective adverse effects –e.g. emotional blunting (Moncrieff 2009)
- Patient preference
  - In a meta-analysis of qualitative studies patients were largely positive about short term use but ambivalent about long-term use, particularly negative effects on functional and social recovery (Bjornestad et al 2019)

Why not stop antipsychotics?

- Beneficial effects:
  - Acute symptom control
  - Prevention of relapse in the future (evidence may be confounded, see later) (Leucht et al, 2012)
- When patients stop antipsychotics there is a greater chance of relapse

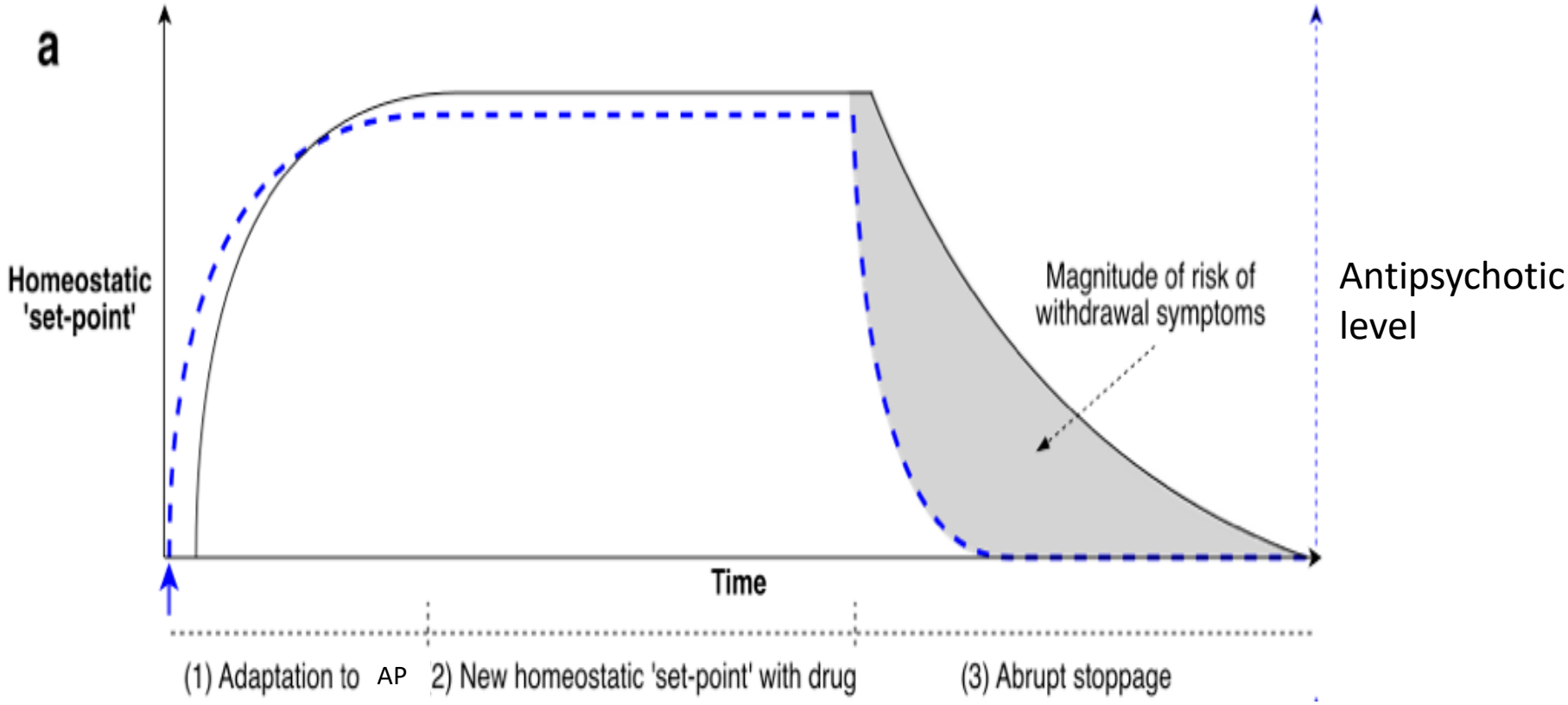
- But we need to consider withdrawal effects…



Withdrawal effects from antipsychotics

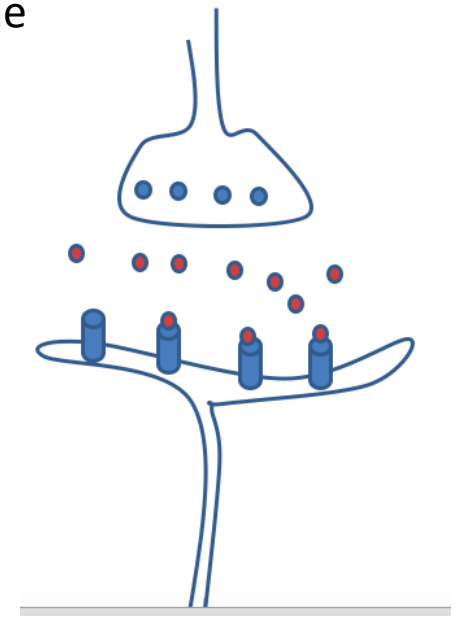
- Antipsychotics, like other medications that act on the brain, cause adaptations to their presence (Reidenberg, 2011)
- Withdrawal effects occur because the drug is eliminated from the body when stopped or reduced "more quickly than the time taken for established adaptations to the drug to resolve"
- 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/adaptations but most well studied 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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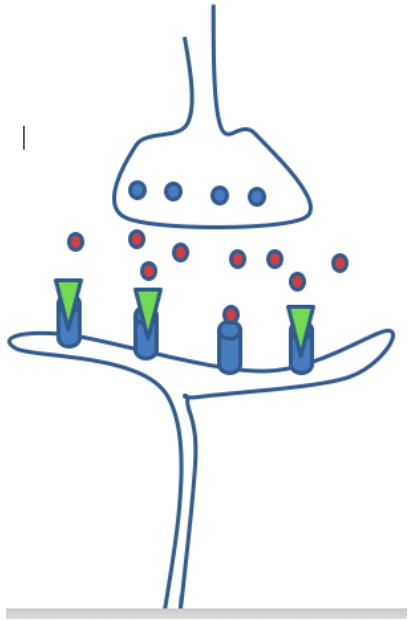
Dopamine activity 30



Antipsychotic blockade

presynaptic dopamine storage

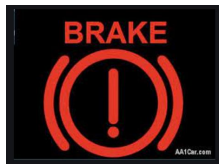
Dopamine in synaptic cleft

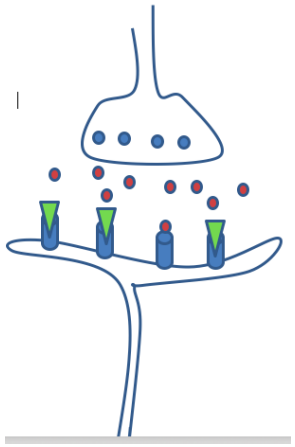
Post-synaptic dopamine receptor

Antipsychotic occupying receptor and blocking dopamine

Upregulation of dopamine receptors

Dopamine activity 30





Antipsychotic blockade

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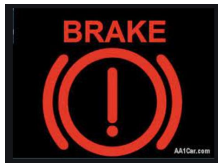
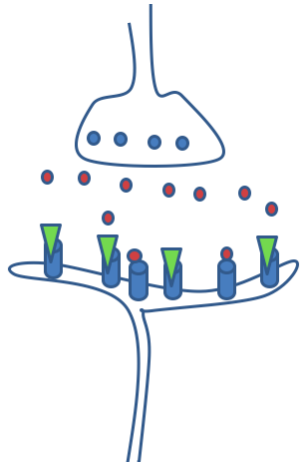
Dopamine activity 30-35



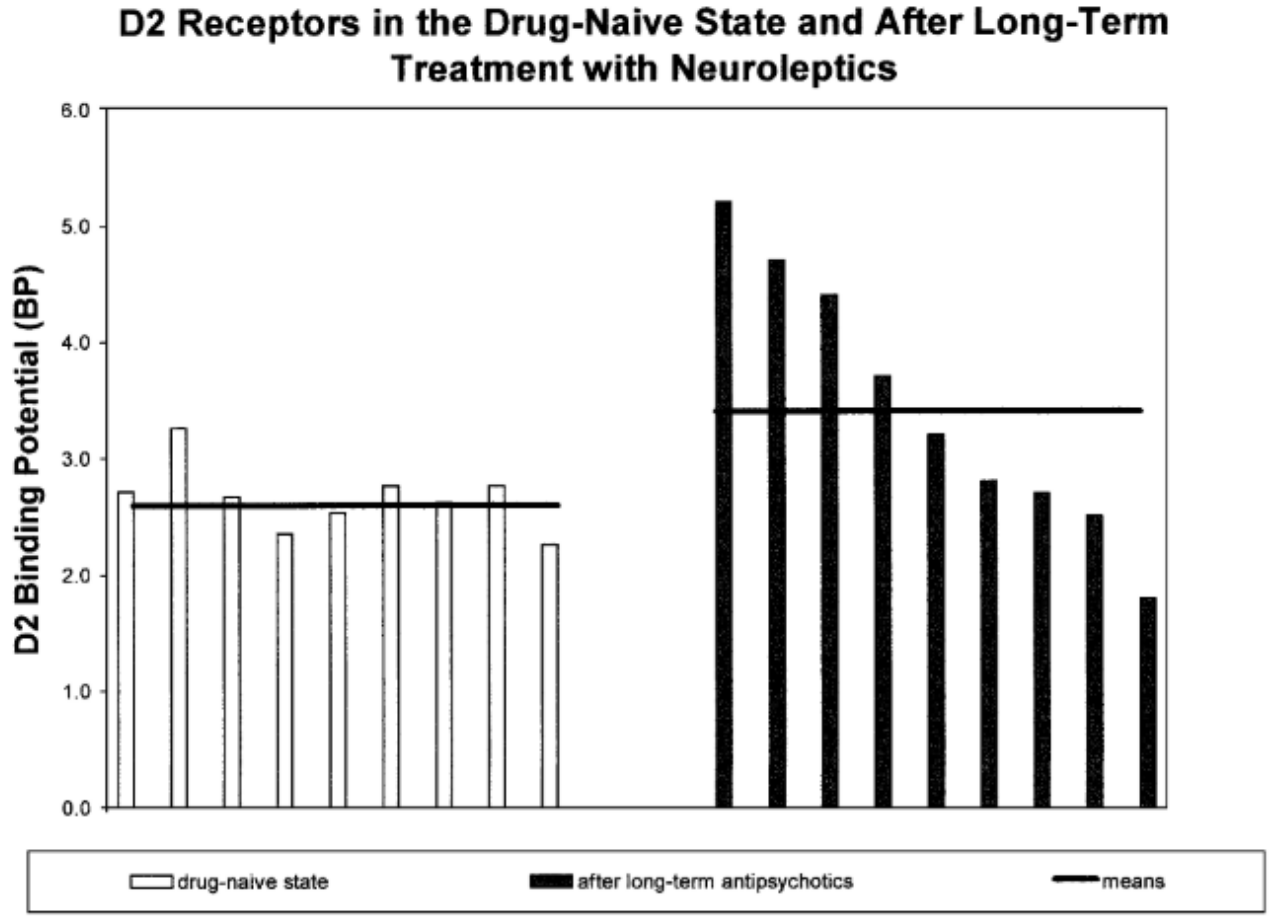


Up-regulation of dopamine receptors

- 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)

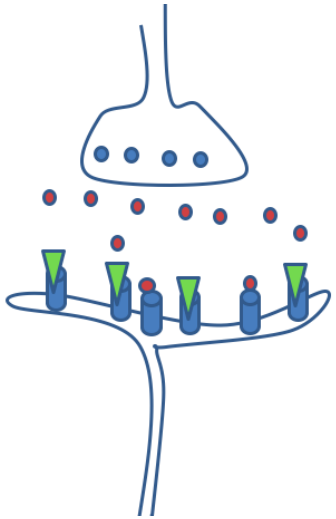
Up-regulation of dopamine receptors in humans

- 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

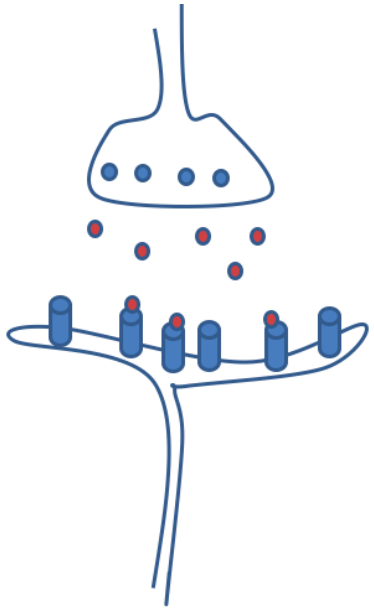
Dopamine activity 30-35



Up-regulation of dopamine receptors

→

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
- Individual patient data meta-analysis in patients on antipsychotics for on average **21 days** found in comparison to patients not on antipsychotics (Brandt et al. 2022, Lancet Psychiatry) :
- Withdrawal symptoms within 4 weeks:
  - Any somatic symptom OR 1.74 (CI 1.27 to 2.39)
  - Any psychiatric symptom OR 2.01 (CI 1.38 to 2.94)
  - Anxiety OR 3.27 (CI 1.50 to 7.11)
  - Diarrhoea OR 3.03 (1.21 to 7.56)
  - Insomnia OR 1.96 (CI 1.21 to 3.19)
- Doubling the duration of treatment increased OR by 1.08
- From other studies - probably most severe for clozapine (including anti-cholinergic effects) and depends on receptor targets of particular drug

Withdrawal effects from antipsychotics may include psychotic symptoms

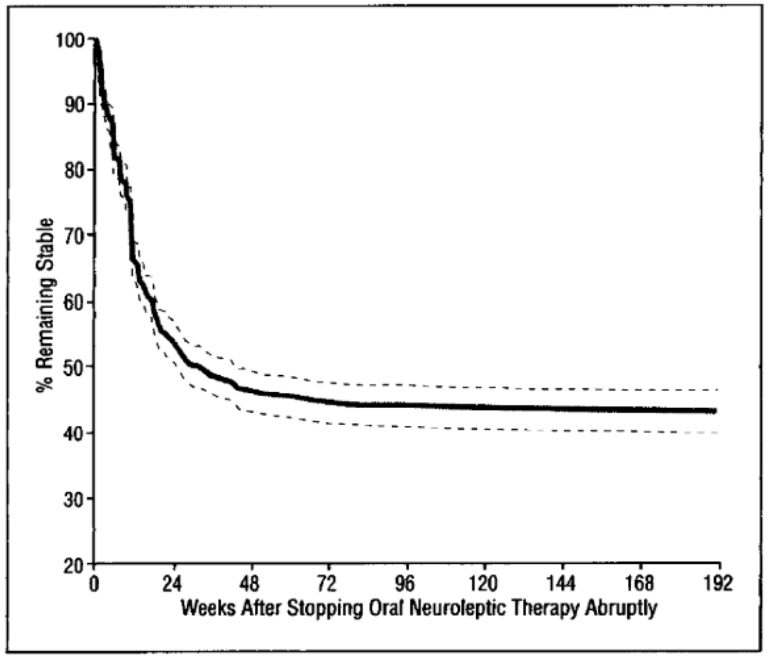
- People who were given antipsychotics or dopamine antagonists (domperidone, ziprasidone, metoclopramide) for reasons other than psychosis (Horowitz et al., 2021)
- E.g. nausea (metoclopramide) or difficulties with lactation (domperidone)
- No psychotic disorder
- On abrupt cessation of the antipsychotic 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

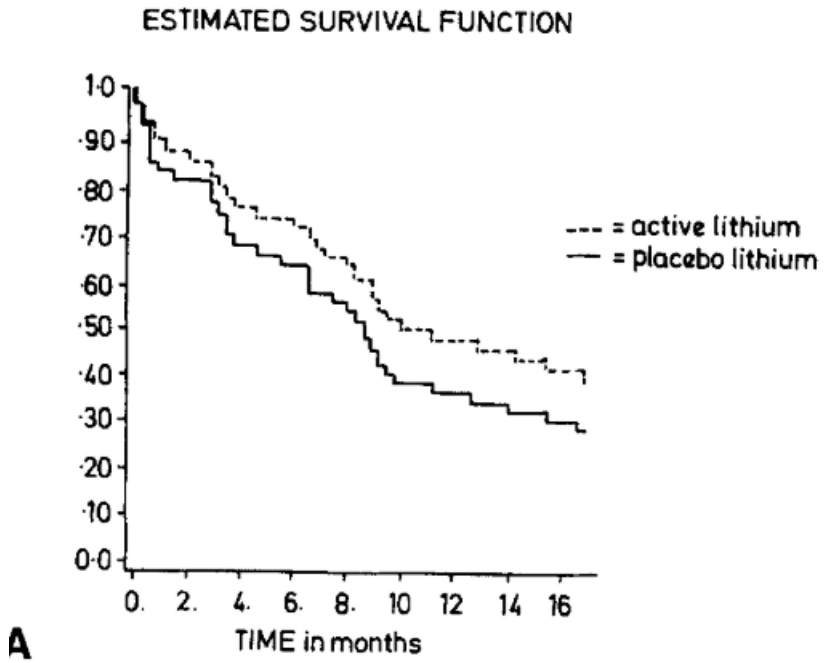
Kent and Wilber [50]	Woman with no psychiatric history	Resperine (dopamine depleting agent) for hypertension for 20 years	Euphoric, visual hallucinations, hyperactivity, and pressured speech Only extinguished by recommencement of reserpine
Witschy et al[51]	26 M BPAD with brief DIP and no other psychotic 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 treated with placebo have relapses evenly spread over time

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

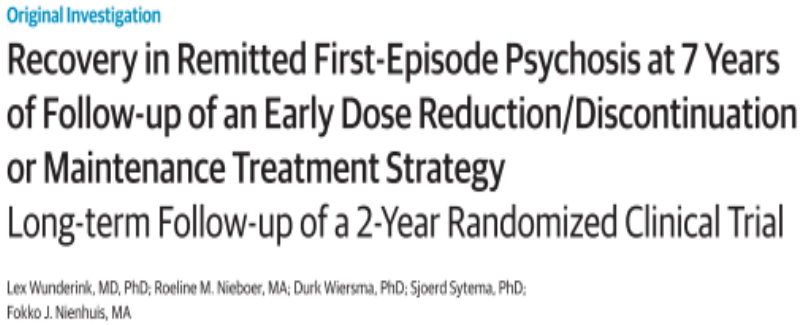
Randomised trial

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

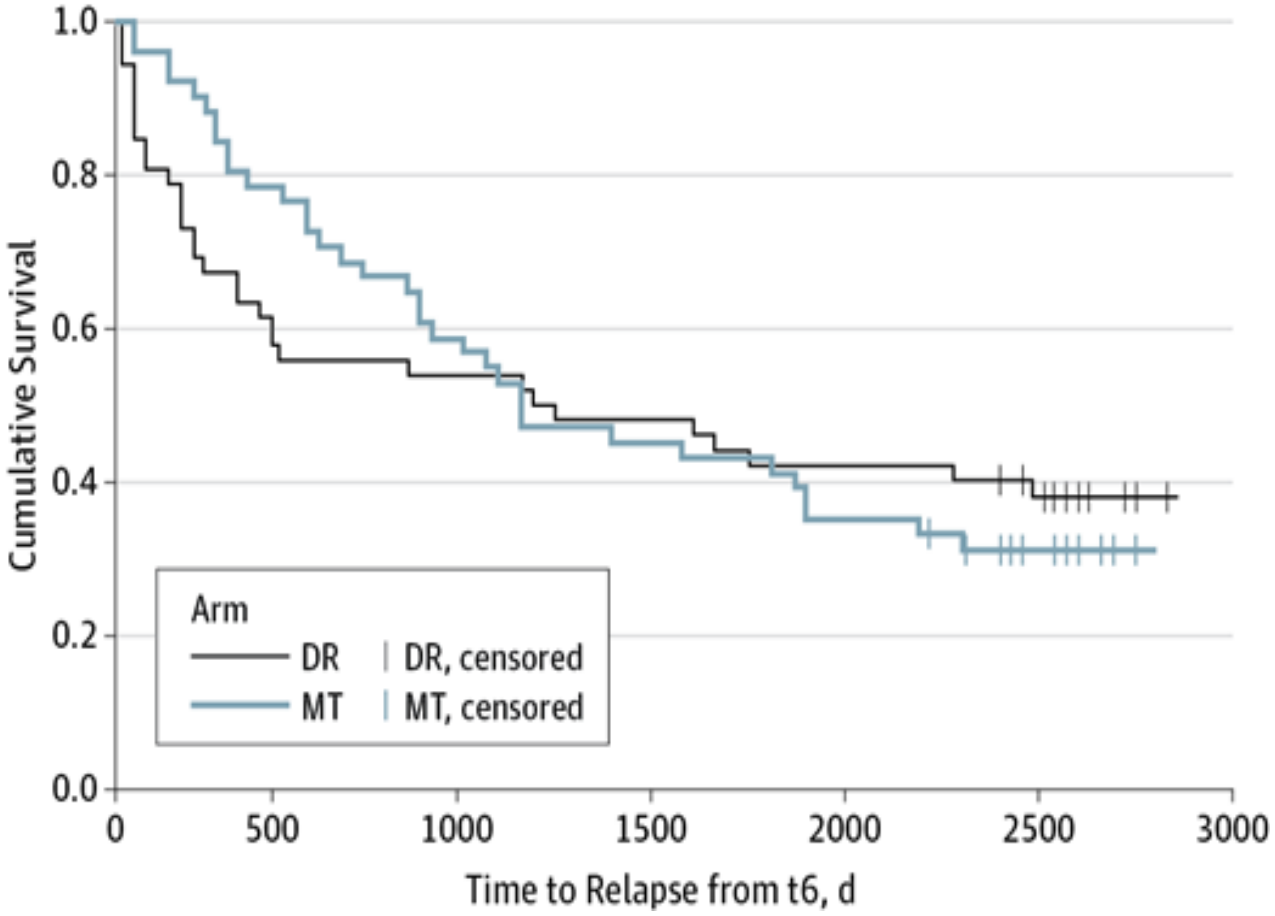


Figure 1. Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18-months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT)

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

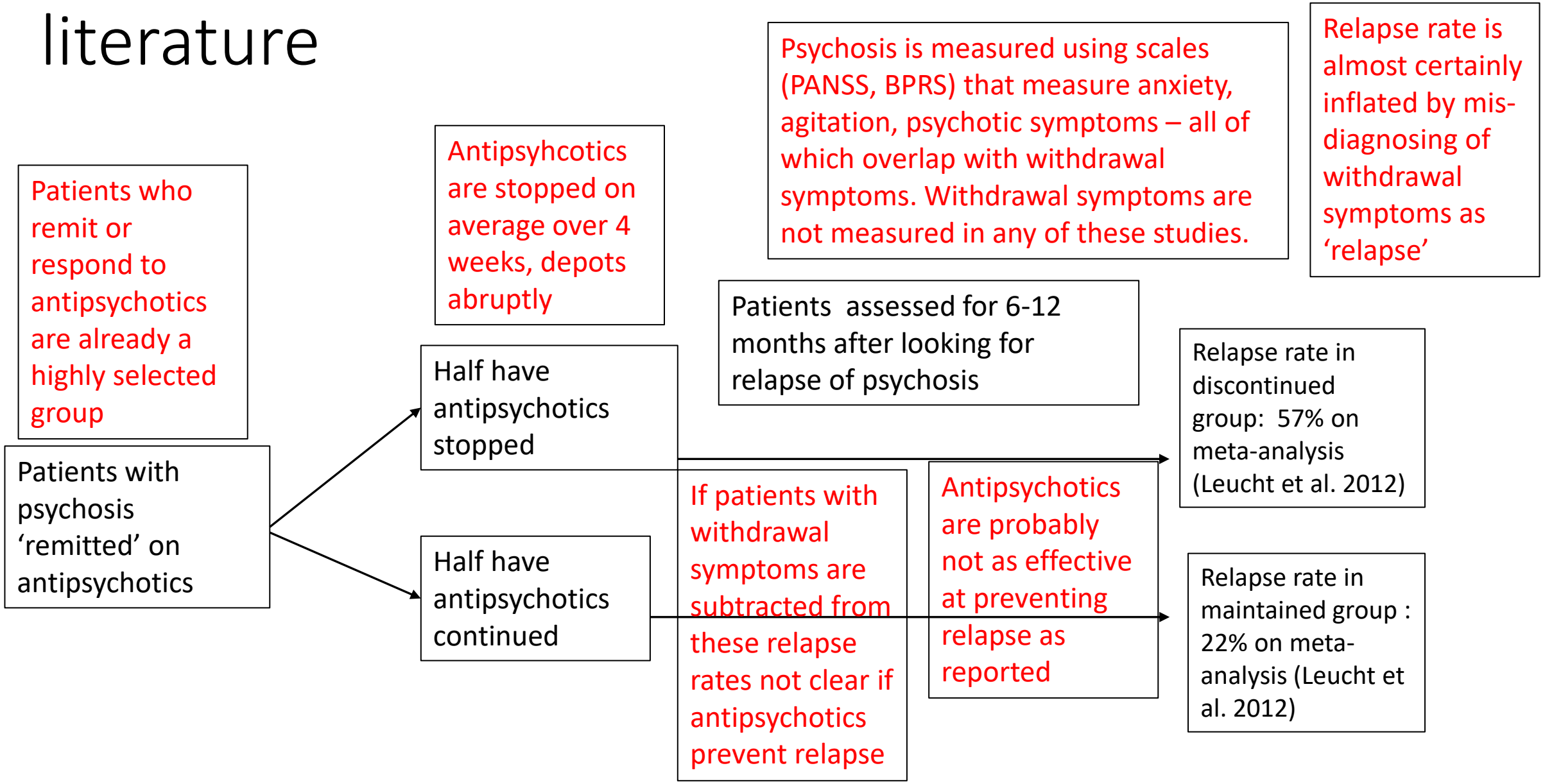
Leucht et al, 2012.

- 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 to the relapse prevention literature



Modern trials of antipsychotics show no difference from placebo in context of psychosocial care

- FEP (n=90), both groups given cognitive-behavioural case management (CBCM), one half randomized to antipsychotics, the other just to CBCM (Francey et al., 2020, Schiz Bull Open)
- Excluded if high levels of suicidality or aggression
- No difference in outcome in terms of symptoms, social functioning
- 2nd trial RCT in FEP, assigned to antipsychotic(AP) OR CBT or AP+CBT. (Morrison et al 2020)
- On PANSS AP produced 6.2 lower scores, CBT 13.1 lower scores, combination 13.9 scores

Psychosocial Intervention With or Without Antipsychotic Medication for First-Episode Psychosis: A Randomized Noninferiority Clinical Trial

Shona M Francey, Brian O'Donoghue, Barnaby Nelson, Jessica Graham, Lara Baldwin, Hok Pan Yuen, Melissa J Kerr, Aswin Ratheesh, Kelly Allott, Mario Alvarez-Jimenez ... Show more

Schizophrenia Bulletin Open, Volume 1, Issue 1, January 2020, sgaa015, https://doi.org/10.1093/schizbullopen/sgaa015

Published: 20 March 2020 **Article history**

THE LANCET Psychiatry

ARTICLES | VOLUME 7, ISSUE 9, P788-800, SEPTEMBER 01, 2020

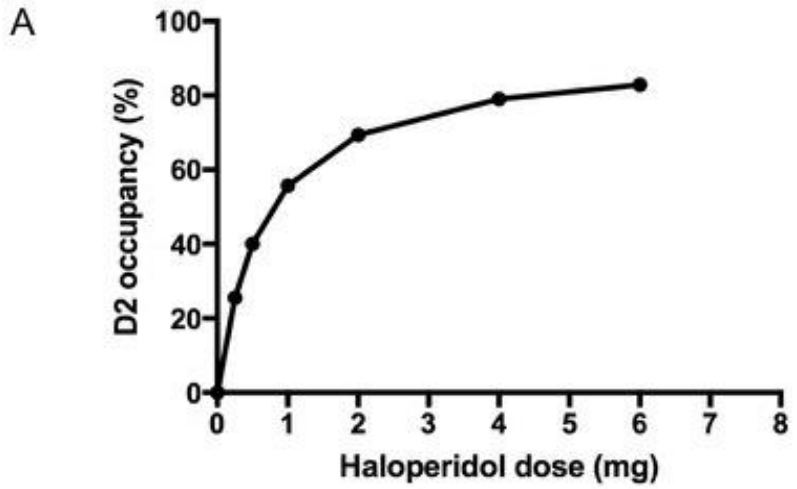
Antipsychotic medication versus psychological intervention versus a combination of both in adolescents with first-episode psychosis (MAPS): a multicentre, three-arm, randomised controlled pilot and feasibility study

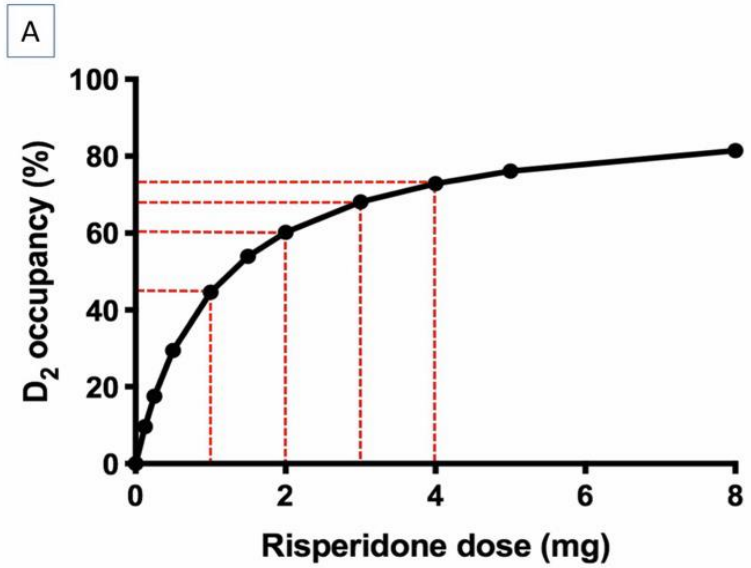
Prof Anthony P Morrison, ClinPsyD • Melissa Pyle, PhD • Daniel Maughan, MBChB • Louise Johns, DClinPsy • Prof Daniel Freeman, DClinPsy • Prof Matthew R Broome, MBChB • et al. Show all authors • Show footnotes

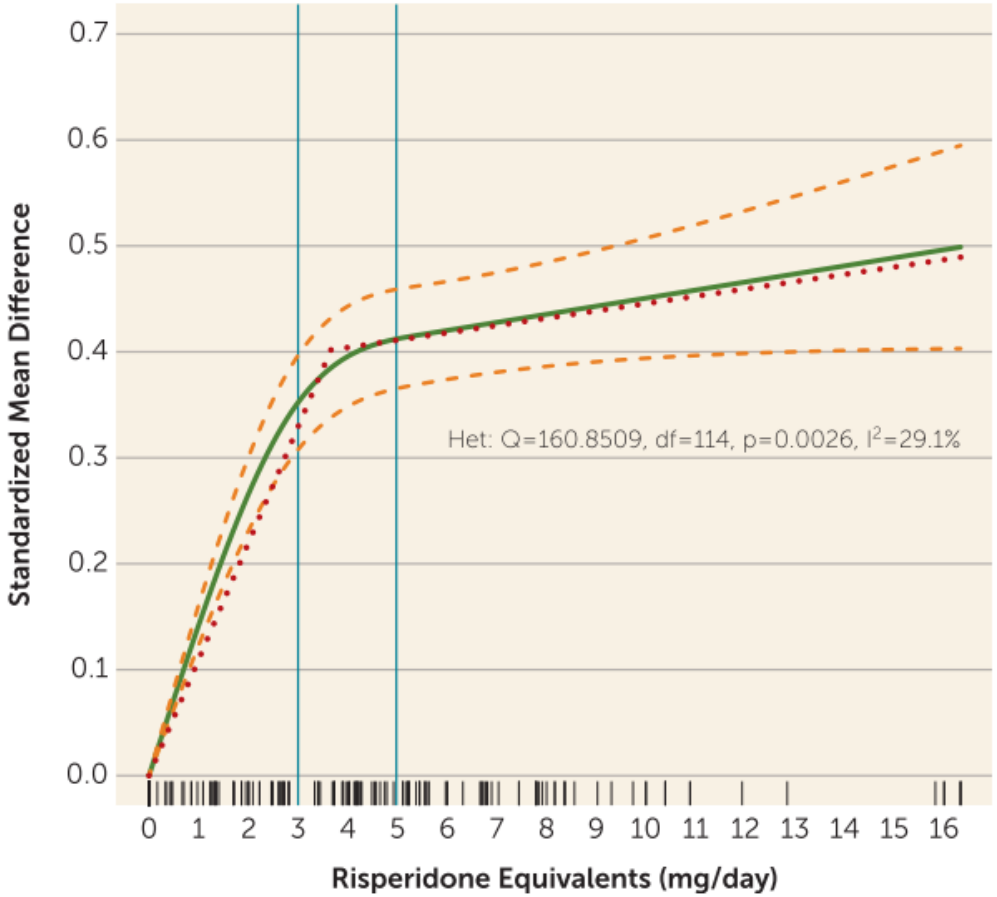
Open Access • Published: July 07, 2020 • DOI: https://doi.org/10.1016/S2215-0366(20)30248-0 •

Check for updates

Pharmacology of antipsychotics





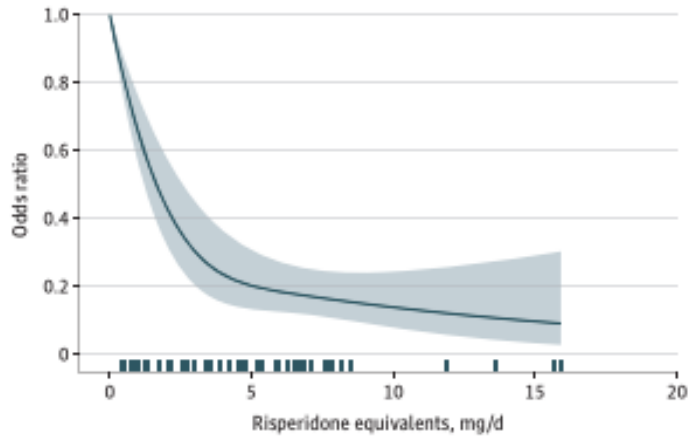


Relationship between dose and effect on symptoms (Leucht et al., 2020)

Pattern of relapse matches receptor occupancy

- As dose is reduced from high dose to lower dose in dose reduction studies the relationship between final dose and chance of relapse is hyperbolic, matching the pattern of receptor occupancy, as predicted

Figure 1. Relapse



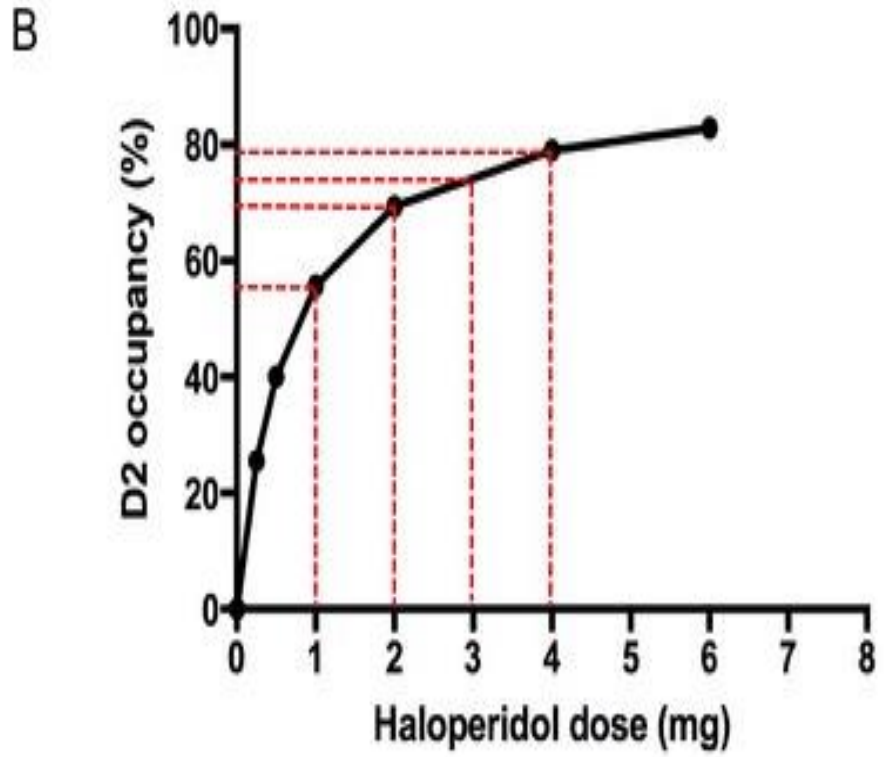
The dose-response curve for the primary outcome relapse after pooling all drugs using the primary scientific dose-equivalence method (the maximum effective dose method). The marks on the x-axis indicate for which doses data from study arms were available. A total of 26 studies with 71 individual dose arms including 4749 patients were included (1 publication reported on 2 studies).[27,32-55] The shaded areas indicate 95% CIs for the primary outcome.

JAMA Psychiatry | Original Investigation

Examination of Dosing of Antipsychotic Drugs for Relapse Prevention in Patients With Stable Schizophrenia
A Meta-analysis

Stefan Leucht, MD; Sofia Bauer, Cand Med; Spyridon Siafis, MD; Tasnim Hamza, MSc; Hui Wu, MD; Johannes Schneider-Thoma, MD; Georgia Salanti, PhD; John M. Davis, MD

Tapering antipsychotics

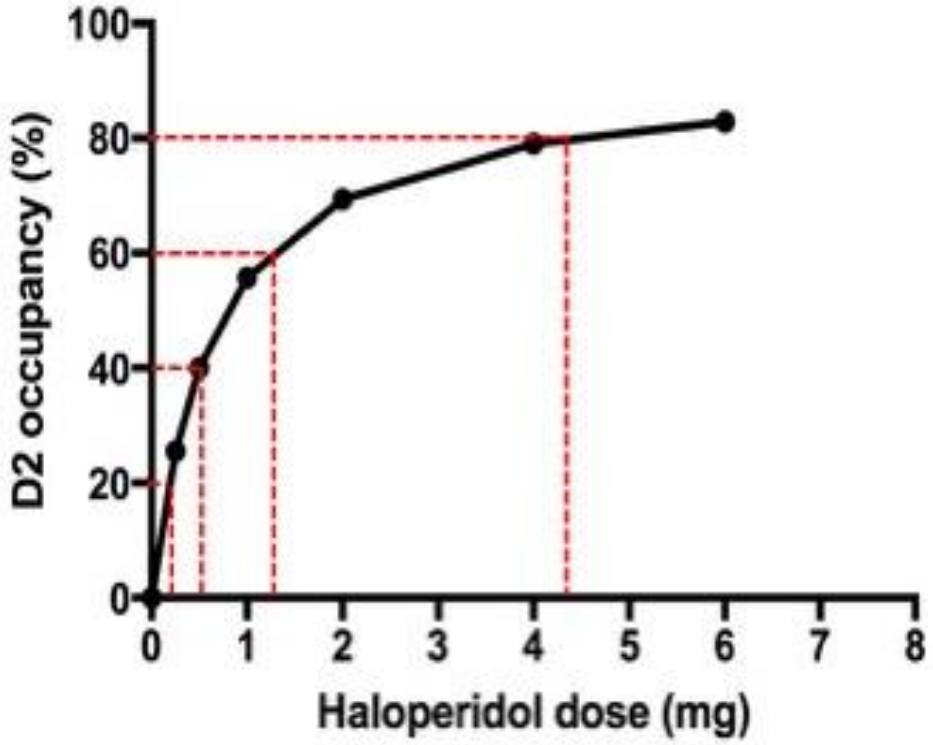


Haloperidol dose (mg)	D2 occupancy (%)
10	86.3
8	85.0
6	82.9
4	79.0
3	75.5
2	69.4
1	55.7
0.5	40.0
0.25	25.5
0	0

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

Hyperbolic tapering of antipsychotics

C



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.

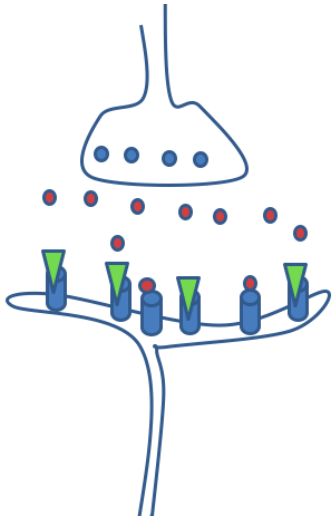
Pharmacologically rational reduction regimens

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

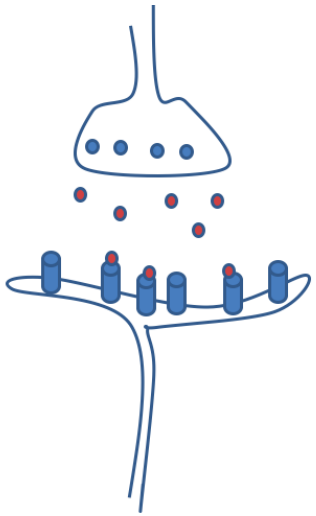
Dopamine activity 30-35



Up-regulation of dopamine receptors

→

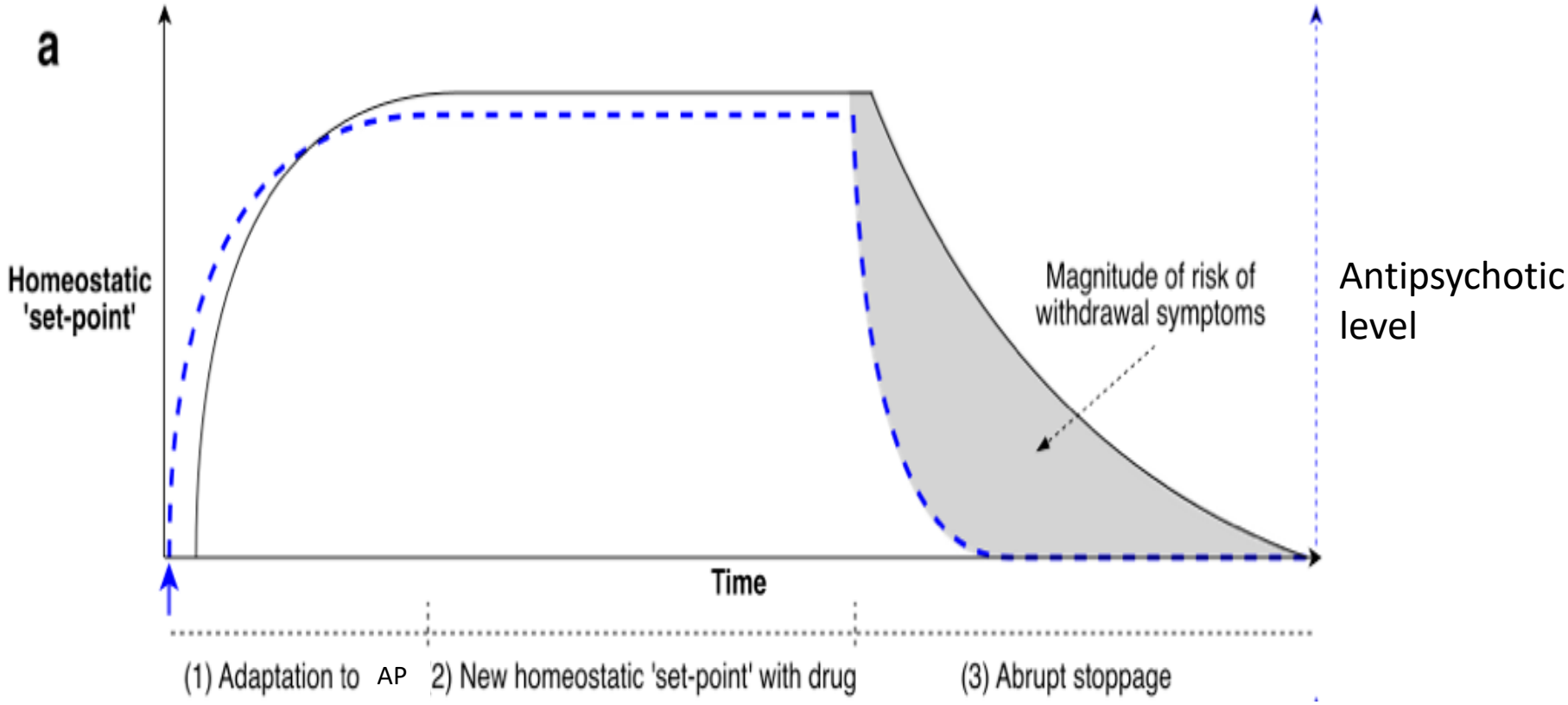
Dopamine activity 150 or ?more



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

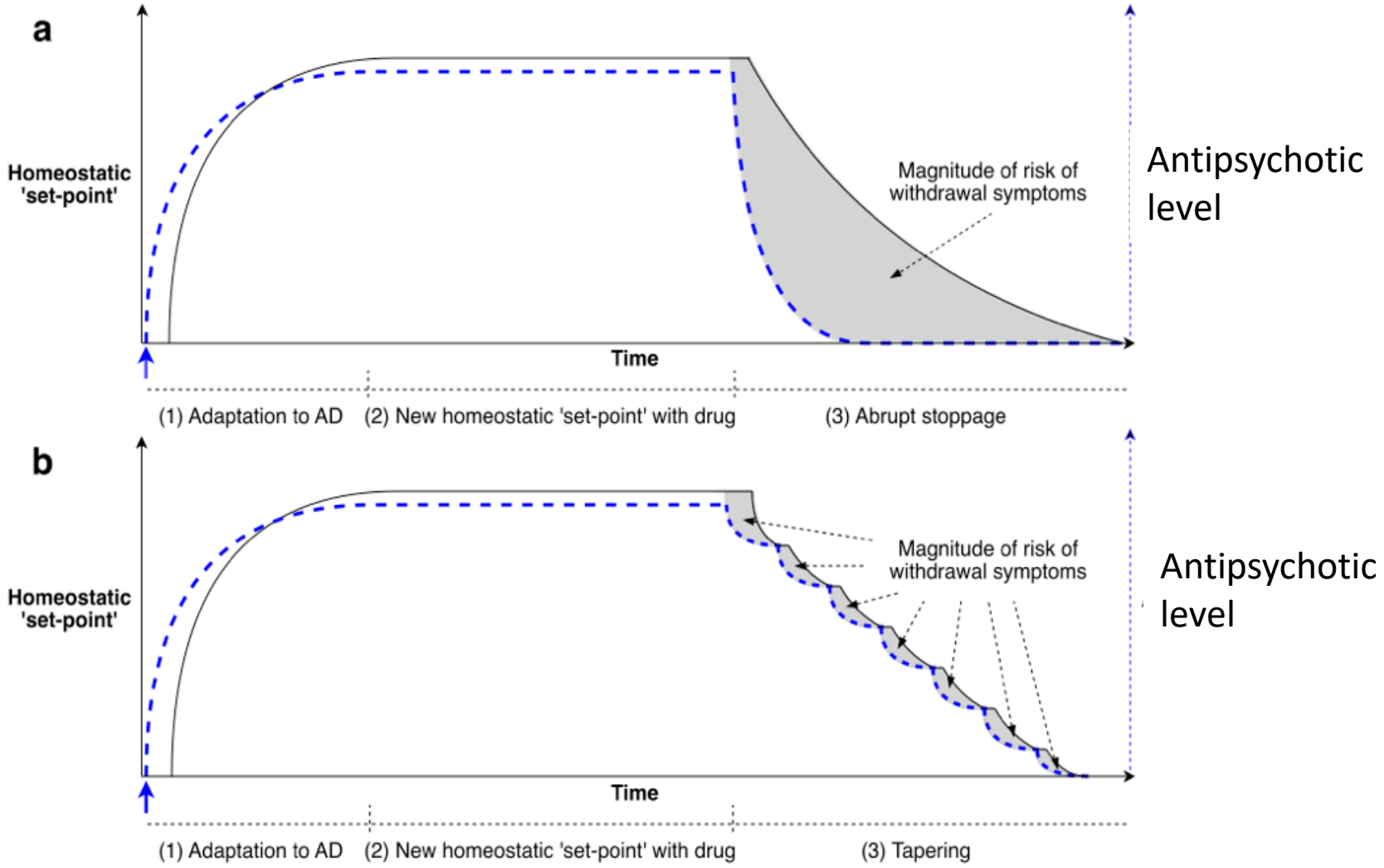
- Most likely method to cause withdrawal effects or relapse

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

Liquid preparations available for antipsychotic tapering

Antipsychotic	Smallest tablet	Liquid version available	Orodispersible tablets	Other comments
Chlorpromazine	25mg	X		
Haloperidol	500microg	X		
Sulpiride	200mg	X		
Zuclopenthixol	2mg	X		
Flupentixol	500microg			
Amisulpride	50mg	X		
Aripiprazole	5mg	X		
Olanzapine	2.5mg		X	
Quetiapine	25mg	X		
Risperidone	250 microg	X	X	
Lurasidone	18.5mg			
Paliperidone	3mg			Can be switched to risperidone
Clozapine	25mg	X	X	

References - Antipsychotics

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Thank you for listening

- Questions?

- My email for any further questions:

m.horowitz@ucl.ac.uk