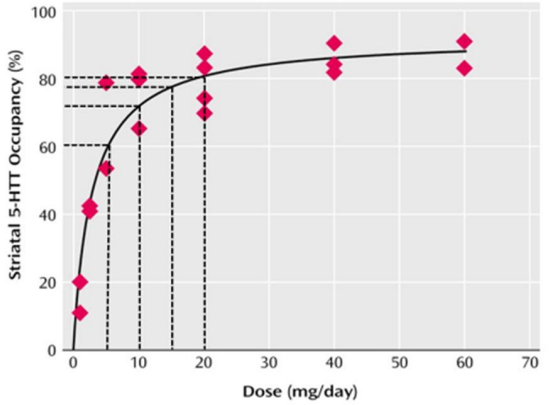

How to safely stop psychiatric drugs

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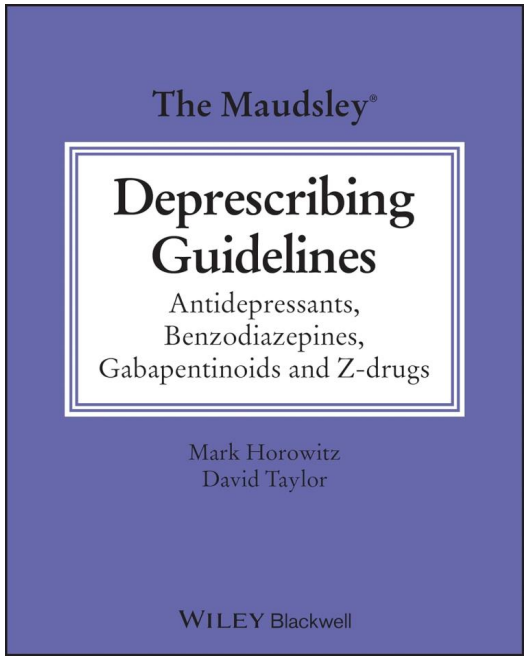


NELFT NHS
NHS Foundation Trust

KING'S College LONDON

UCL

Overview

- I will be talking mostly about antidepressants and antipsychotics but what I am saying about these drugs also applies to:
  - mood stabilisers,
  - benzodiazepines,
  - z-drugs (sleeping tablets),
  - gabapentinoids and
  - stimulants

Overall points

- Many psychiatric drugs can suppress symptoms in the short term but may cause more harm than good in the long term for some patients
- All psychiatric drugs cause withdrawal effects when reduced or stopped
- These withdrawal effects involve mood and behavioural symptoms that can look like a return of a mental health condition or challenging behaviour
- Stopping these drugs more slowly and in a way that follows their pharmacology (slower for the last few milligrams) can prevent withdrawal effects and allow people to stop drugs
- e.g. 5-10% of the most recent dose per month (so that reductions get smaller and smaller as the dose lowers) – process can take months/years to be safe – not days/weeks
- This often requires using formulations of drugs other than widely available tablets – liquids, compounded medication or ‘off-label’ options

Patient montage

These patients are a lot better than those most clinicians will be seeing but they articulate the problems that all patients can have when they reduce or stop medication

https://www.youtube.com/watch?v=bLOj8vvtIjo

Why stop antidepressants/other psychiatric drugs?

- Medication no longer needed
  - Challenging behaviour improved/other non-medication coping skills employed
- Harms of antidepressants
  - Sexual side effects > 50%
  - Emotional numbing >50% (main reason people come to our clinic)
  - Fatigue, impaired memory, concentration
  - Insomnia, worsened anxiety or depression (tardive dysphoria)
  - Weight gain (30%) – worse for mirtazapine
- Avoid potential l-t health consequences. In long-term observational data all are increased in antidepressant users (with debate about the degree attributed to antidepressants or underlying condition):
  - Strokes; Obesity; Falls; Cardiovascular disease; Osteoporosis; Premature mortality

- Harms of antipsychotics:
  - Movement disorders, including tardive dyskinesia
  - Metabolic effects, probably leading to earlier mortality
  - Reduced grey matter over time (initially interpreted as due to schizophrenia itself, increasing studies find antipsychotics themselves cause volume reduction, including RCTs) (Fusar-Poli 2013, Dorph-Peterson 2005, Voineskos 2020)
  - Potential negative effects on long-term recovery and functioning (Wunderink et al. 2013)
  - Subjective adverse effects –e.g. emotional blunting (Moncrieff 2009)

Why stop antidepressants/other psych drugs? 2

- Many patients continue antidepressants because they believe that antidepressants correct a chemical imbalance (e.g. low serotonin)
  - 85% of public believes depression is caused by a ‘chemical imbalance’ (Pilkington, 2013)
  - Belief that antidepressants rectify this chemical imbalance prominent barrier to stopping no longer indicated antidepressants (Eveleigh et al, 2019)
  - Other explanations for mechanisms of action exist (neurogenesis, inflammation, numbing emotions)
- More useful model of drug action: ‘drug centred model’ (Moncrieff)
  - drugs don’t correct underlying abnormality causing behavioural problem (as antibiotics for infection or insulin for diabetes)
  - Rather they suppress symptoms by super-imposing sedation, blunting (more like alcohol for anxiety)
  - Often do so by impairing normal brain function (hence sedation, cognitive impairment, worsening function over time)
  - Can cause more harm than good in long run

Barriers to stopping psychiatric drugs

- 2 main barriers:
  - Return of underlying condition
  - Withdrawal effects
- Return of underlying condition is widely discussed and often exaggerated because withdrawal effects are widely mistaken for a return of the condition
- Discussion of antidepressants but themes relate to all classes of psychiatric medications

Long-standing guidance on antidepressant withdrawal

- Most guidelines say “Discontinuation symptoms are usually mild and last 1 to 2 weeks (but can last a month or longer in some patients).”
- This description was influenced by papers produced by drug companies in the 1990s, which focused on people who had used antidepressants for 8 - 12 weeks
- Analogy to crashing a car at 5km/hr into a wall for a safety test
- At a consensus panel organised by an antidepressant manufacturer the euphemism ‘discontinuation symptoms’ was coined and numerous papers with the description ‘brief and mild’ were distributed to clinicians

Guidance on management of antidepressant withdrawal syndrome

- Current guidance in Australia on how to manage withdrawal symptoms says: "**gradually reduce the dose**, **normally over a 4-week period,** although some people may require longer periods, particularly with drugs with a shorter half-life" (NICE, CG90, 2009)
- This guidance was based on one study that showed that abruptly stopping caused too severe withdrawal effects (Rosenbaum et al., 1998), and that 4 weeks was considered a reasonable time by the committee (i.e. no evidence)
- Most common approach: reduce dose by half for 2-4 weeks, reduce dose to quarter for 2-4 weeks (often by alternating half a tablet every second day)
- Recent RCT found that 40% of patients on ADs >1-2 years who did not meet guidelines for ongoing use, low risk of withdrawal can come off by tapering over 2-4 months (ie slower than guidelines in Oz suggest) (Kendrick et al, 2024)
- Leaves at least 60% of patients trapped on their medications with current approaches
- Even less guidance on stopping other psychiatric drugs

Consequence: people turn to peer support websites online for guidance

750,000 hits a month

150,000 hits a month

- Commonest story: my doctor told me to stop taking my antidepressant over between 0 and 4 weeks
- The effects were so horrendous that I had to go back on them.
- The doctor told me there shouldn't be a problem with coming off them, so that it must be my original condition coming back, diagnosed me with relapse, informed me I should be on this drug life-long
- But it felt different to my original condition eg I had dizziness/brain zaps/panic attacks for the first time
- So I have lost faith in my doctor. The advice on this website was more helpful than my doctor.
- Coming off much more slowly than they suggest – **at 10% of the most recent dose every month (so that reductions become smaller and smaller as the total dose lowers** - has made the process much easier (although still not easy).

Effect of long-term antidepressant use and stopping

A Before Medication

B Medication introduced

C Long term medication

D Medication stopped

Pre-synaptic neuron

Pre-synaptic

Pre-synaptic neuron

Pre-synaptic neuron

Post-synaptic neuron

Changes to serotonin system can persist for 4 years *after* stopping (Bhagwagar, 2004)

Serotonergic receptor

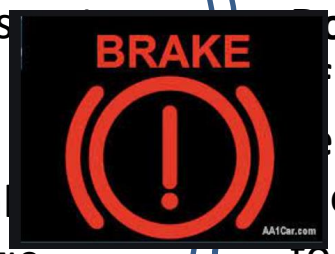
Pre-synaptic serotonin

Synaptic serotonin

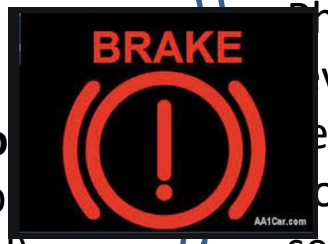
Serotonin transporter

Antidepres
(e.g. SSRI)

Reduced re-uptal
increased synaptic serotonin



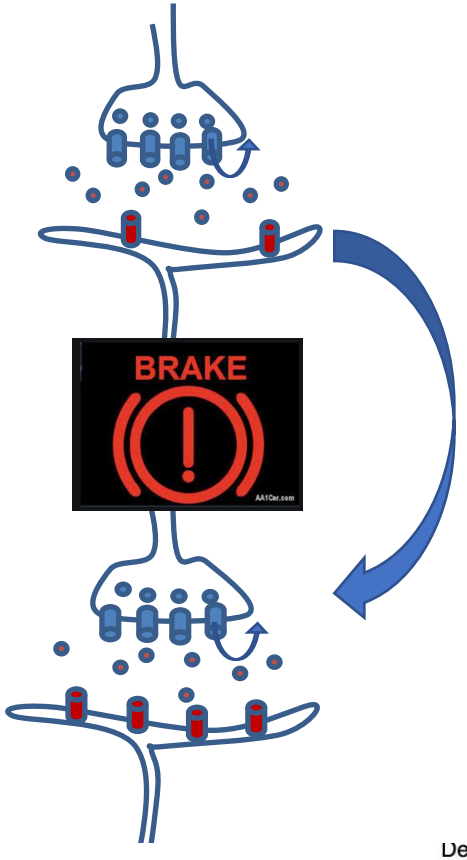
own-regulation
post-synaptic
erotonin recepto
omeostatic resp
to too much signal)
Detected in PET (Meyer et al, 2001; Haahr et al, 2014)



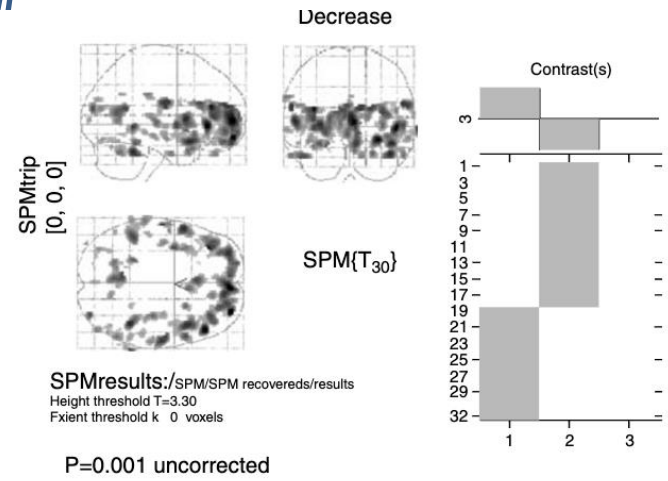
hysiological
vels of
erotonin and
own-regulated
serotonin
receptors =>
withdrawal symptoms

Duration of withdrawal symptoms

- In many studies, withdrawal symptoms went for months or years
- How can symptoms last so long after the drug is out of the body?
- It is the time taken for adaptations (changes) to the drug to resolve that determines the length of the time for withdrawal – not how long it take the drug to be eliminated from the body (sound analogy)
- Long-term use of antidepressants can cause long-term changes to the brain that might account for long-term symptoms:
  - In patients there are changed to the serotonin system (reduced receptors) that has been detected for up to 4 years after stopping (Bhagwagar, 2004)
  - In animal studies (Renoir, 2013) there are changes to the hormonal system and serotonin system that persist for more than a year (in human equivalent time) after stopping

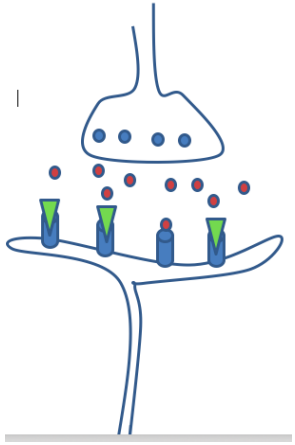


Time taken for down-regulation (and downstream effects) to return to 'pre-drug' conditions



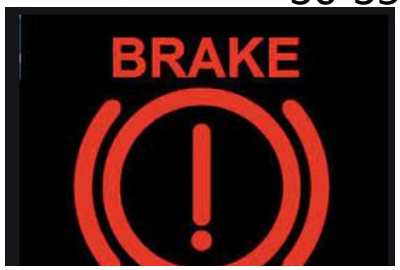
Upregulation of dopamine receptors

Dopamine activity 30

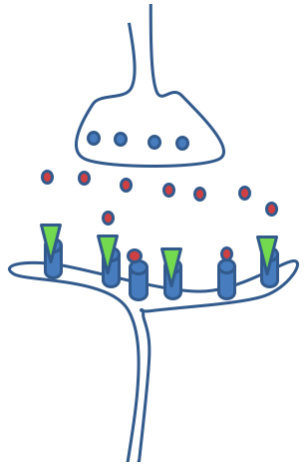


Antipsychotic blockade

→



Dopamine activity 30-35



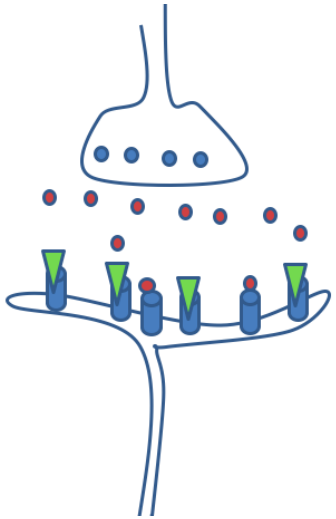
Up-regulation of dopamine receptors

?Breakthrough symptoms over time

- Chronic blockade of post-synaptic dopamine receptors leads to up-regulation to maintain homeostasis

Stopping antipsychotics

Dopamine
activity
30-35



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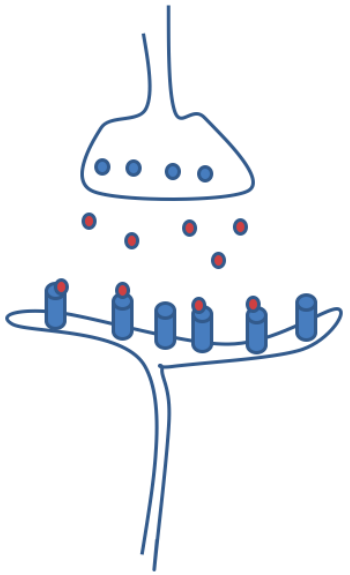
Dopamine
activity
150 or ?more



Up-regulation of
dopamine receptors

antipsychotics leads to rebound of
n up-regulated receptors

Psychiatric drug withdrawal syndrome

- Physiological symptoms that occur on stopping – or reducing the dose – of an antidepressant
- They can manifest in either psychological or physical symptoms (these drugs affect multiple bodily systems)
- Occur because changes (adaptation) to the brain caused by the drug use take time to resolve
- Withdrawal symptoms do not require addiction (compulsion/craving etc) but only adaptation (often called physical dependence – though this term has become conflated with addiction unfortunately) - addiction involves craving, compulsive use etx – not relevant to antidepressants
- Caffeine, etc cause physical dependence which predicts withdrawal on stopping (no need for ‘high’, misuse, abuse, etc) – as for antidepressants and many other psychiatric drugs
- The greater the degree of adaptation (high dose, longer use, etc) the greater the withdrawal effects – the ‘flip-side’ of withdrawal is tolerance which is seen with antidepressants (‘poop out’ in America, lessening of some side effects, drug effect wearing off)

Antidepressant withdrawal syndrome

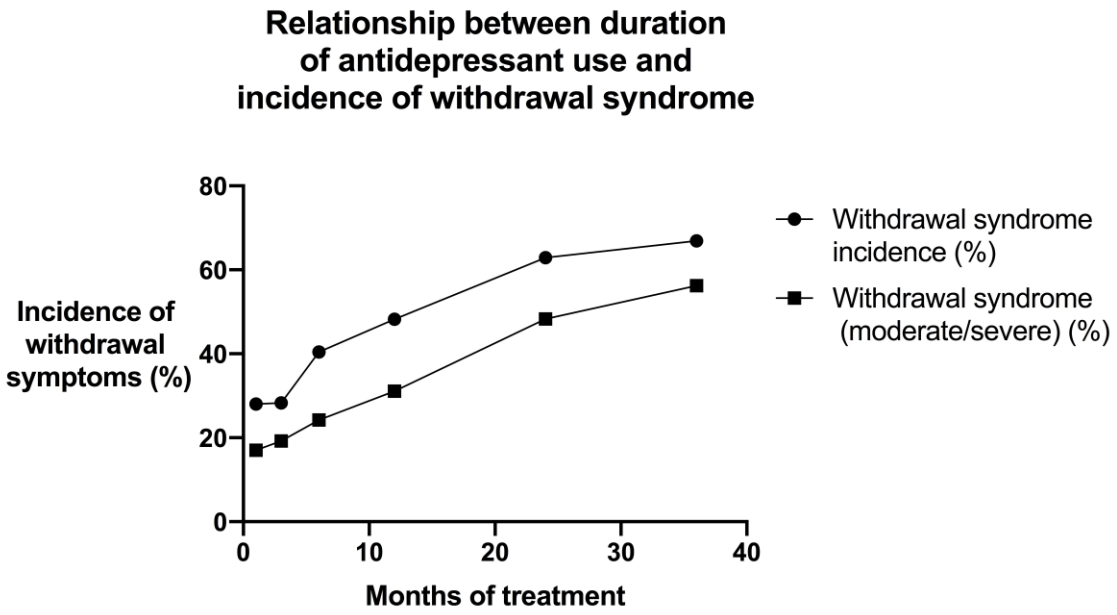
- Most common withdrawal symptoms are (Fava et al. 2015) :
  - **Dizziness**, insomnia, impaired concentration, fatigue
  - Headache, tremor, tachycardia, nightmares
  - Affective symptoms: *depressed mood*, irritability, *anxiety, panic attacks*
  - Sensory symptoms: 'Electric-shock' sensations in the head (often on moving eyes), or in limbs
  - Gastrointestinal symptoms: nausea, vomiting, diarrhoea
  - Increase in suicide attempts in the 2 weeks after stopping an antidepressant (Valuck et al., 2009)
  - **Akathisia** – this is most recognised as a side effect of long-term antipsychotic use but can occur in withdrawal from antidepressants (and other psychiatric drugs) – involving pacing, a sense of terror, often described as the 'feeling like the nervous system is on fire' – high risk of suicide. Often mis-diagnosed as agitated depression, mania when clinicians are not familiar

Antipsychotic withdrawal symptoms

- Meta-analysis finds that 53% of people experience withdrawal symptoms after abrupt cessation of antipsychotics (Brandt et al., 2020)
- Symptoms can include (Chouinard et al. 2017):
  - Insomnia
  - Movement disorders (eg withdrawal dyskinesia)
  - Dizziness
  - Anxiety/ depressed mood
  - Agitation
  - **Psychotic symptoms**
  - Neuroleptic malignant syndrome

How common, severe and long-lasting are withdrawal symptoms

- A review found from an average of 14 trials that measured incidence that **about half of patients (56%) experienced withdrawal symptoms** (Davies and Read, 2018)
- In surveys, about half (46%) of patients reported that their symptoms were ‘severe’
- The longer patients take antidepressants the more likely they are to experience withdrawal symptoms and for those symptoms to be severe



Mis-diagnosing antidepressant/psychiatric withdrawal effects as relapse

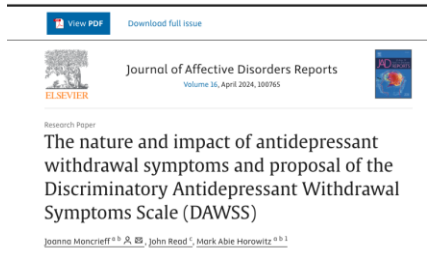
- We surveyed 1000 people out of the 180,000 on peer support websites for tapering off antidepressants (and other similar drugs) – main reason given for being there
- Withdrawal symptoms can include *anxiety, depressed mood, insomnia, appetite changes* (even in people with no underlying mental health condition e.g. those prescribed for migraine)
- Easy to confuse with relapse of depression or anxiety (especially when withdrawal thought to only be ‘mild and brief’)
- As agitaton/akathisia/manic (and even psychotic) symptoms can be withdrawal effects from many psychiatric drugs can easily be mistaken for a return of agitation or behavioural difficulties

Distinguishing withdrawal from relapse

- Clues to distinguish withdrawal from relapse:
  - Quick onset, but can be delayed by weeks or sometimes even months (?perhaps because of time take for downstream effects to accumulate)
  - Specific symptoms - dizziness, electric shock, other symptoms not present in baseline condition, including psychological and behavioural symptoms (or worse in severity)
  - Often quick resolution on re-instatement of drug (hours, day or two) – but can be more unpredictable when delayed
- Can also be mis-diagnosed as chronic fatigue syndrome, medically unexplained symptoms, neurological disorder, onset of a new psychiatric disorder, etc

Protracted psychiatric drug withdrawal syndrome

- Withdrawal syndromes that can last for months or years increasingly recognised for antidepressants (Hengartner, 2020; Guy, 2020; Cosci 2020)
- Can occur for antidepressants, benzodiazepines, antipsychotics and other psychiatric drugs
- These can be debilitating and involve neurological, psychological and other bodily symptoms (similar to symptoms for acute withdrawal)
- People can be bed-bound, lose jobs, relationships, experience financial difficulties
- Very poor recognition by medical community, due to limited education, who generally perceive it as relapse (despite numerous distinguishing features) or other physical conditions (Guy et al, 2020)
- Now, 10,000s of people on peer support sites looking for support for these problems because they can't get suitable help from their medical providers (White et al 2020, Read et al 2023)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Journal of Affective Disorders Reports

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Research Paper

The nature and impact of antidepressant withdrawal symptoms and proposal of the Discriminatory Antidepressant Withdrawal Symptoms Scale (DAWSS)

Joanna Moncrieff, John Read, Mark Abie Horowitz

		Experienced any severity of this symptom BEFORE starting antidepressants	Experienced new onset or worsening of this symptom AFTER stopping
Psychological	Impaired concentration	41.4%	93.0%
	Worsened mood	57.3%	92.5%
	Feeling suicidal	29.6%	60.7%
	Emotional numbing	42.6%	74.1%
Neurological	Electric shocks ('brain zaps')	5.6%	76.8%
	Akathisia/internal sensation of buzzing and tension	11%	63.5%
	Increased sensitivity to light, sound	22.3%	79.2%
	Tinnitus	17.6%	60.7%
	Vivid dreams	27.9%	73.4%
Somatic	Nausea	15.2%	71.1%
	Muscular problems		
	Dizziness/light-headedness	17.9%	88.7%
	Fatigue	61.5%	93.0%
	Diarrhoea	24.4%	73.7%
	Sexual numbing/ unpleasant genital arousal	28.3%	66.1%

0-33%
34-66%
67-100%

How to safely stop psychiatric drugs

Royal College of Psychiatrists guidance on ‘Stopping antidepressants’

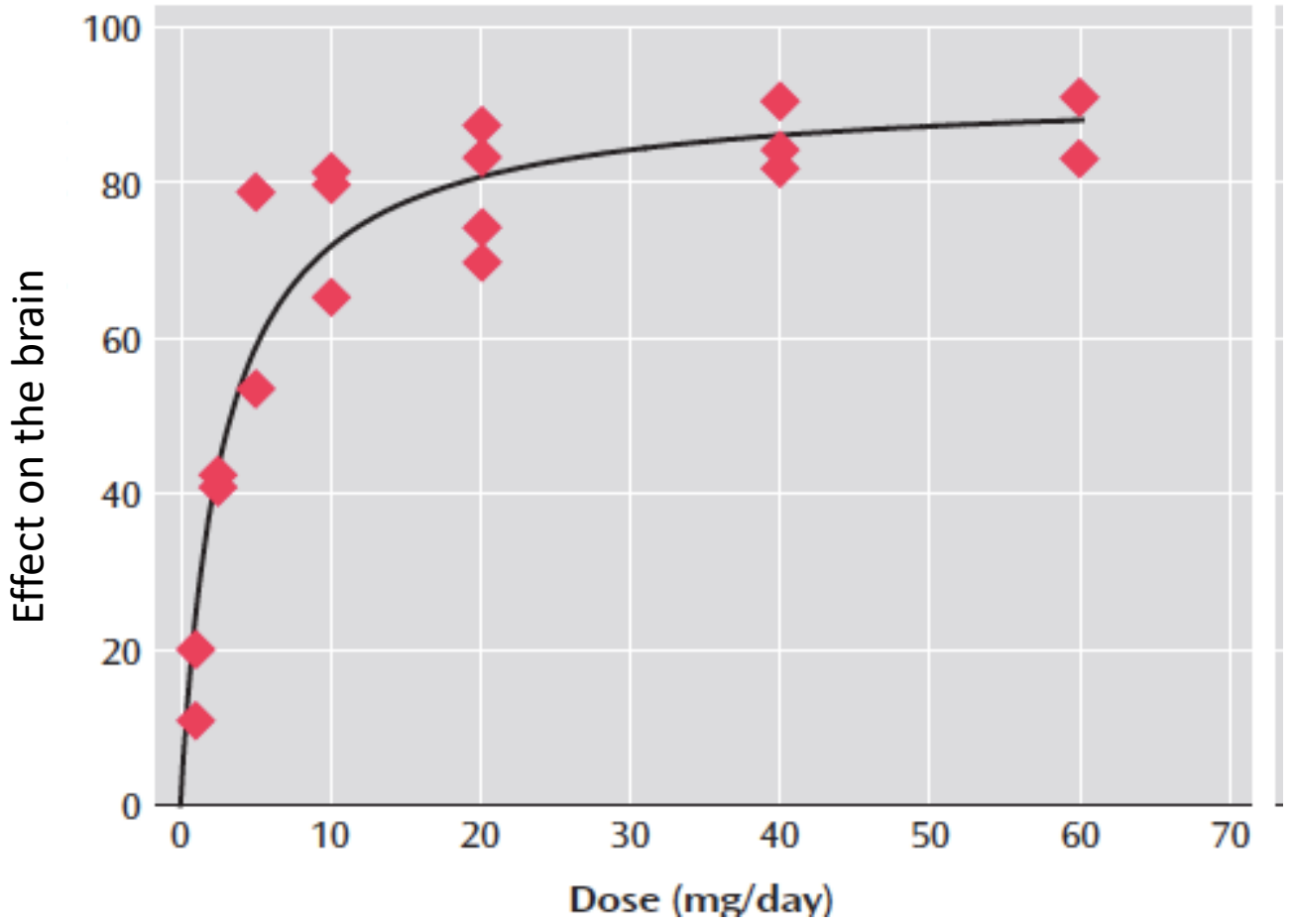
- Published in October 2020
- Recommends patients who have been on antidepressants for more than a few weeks weeks taper off over **“months or longer”**
- Suggest going down to **very small doses (<1mg) before stopping**
- Recommends going down in **smaller and smaller sized reductions**
- Rate **titrated to the individual**’s ability to tolerate the process

RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

Stopping antidepressants

Management of the antidepressant withdrawal syndrome

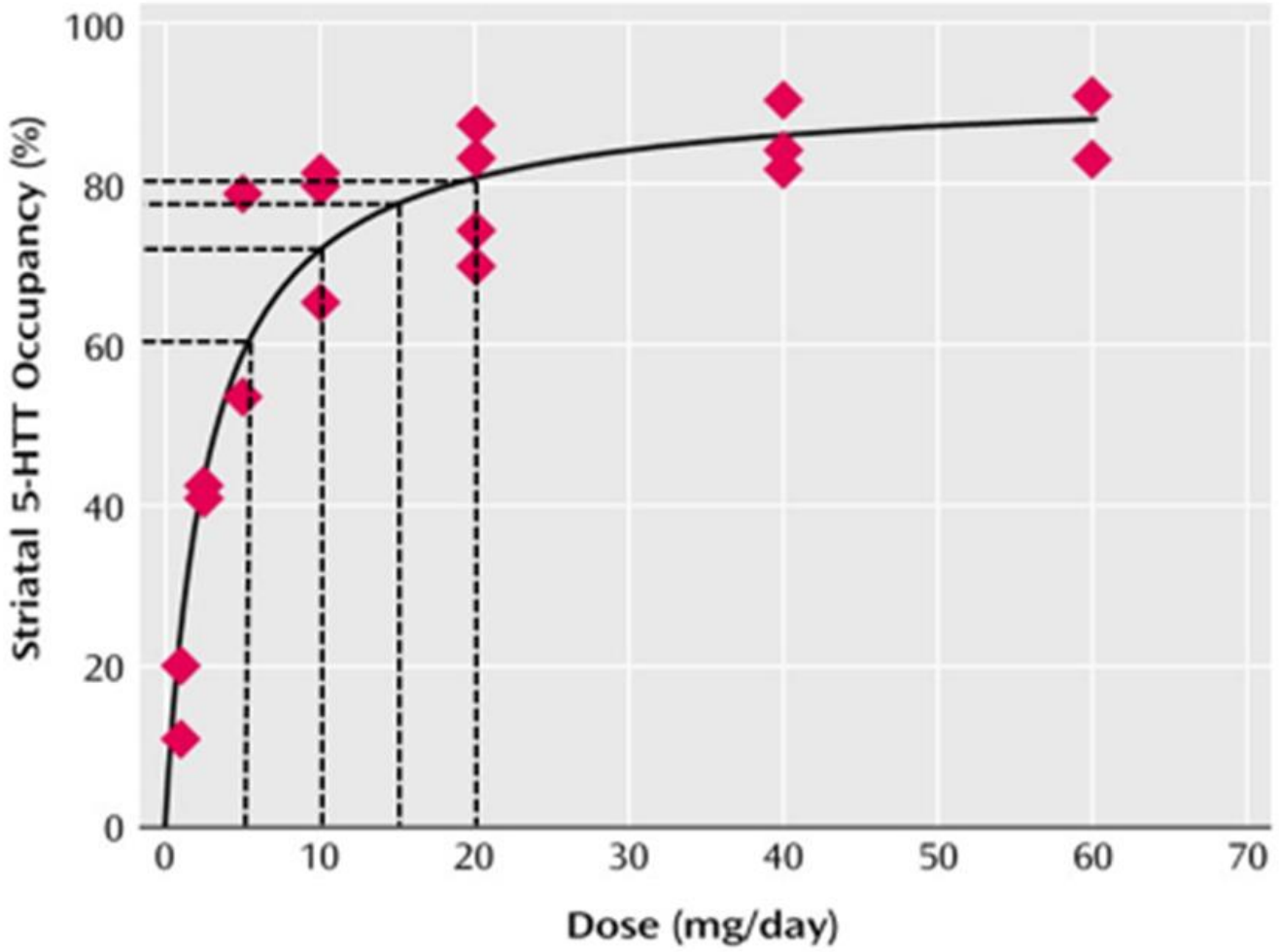
- We used brain imaging (PET) data of antidepressant action to develop rational tapering guidance for antidepressants
- E.g. Citalopram's effect on the serotonin transporter, its major target
- This also applies to all other psychiatric medications



Citalopram

What happens when you taper linearly?

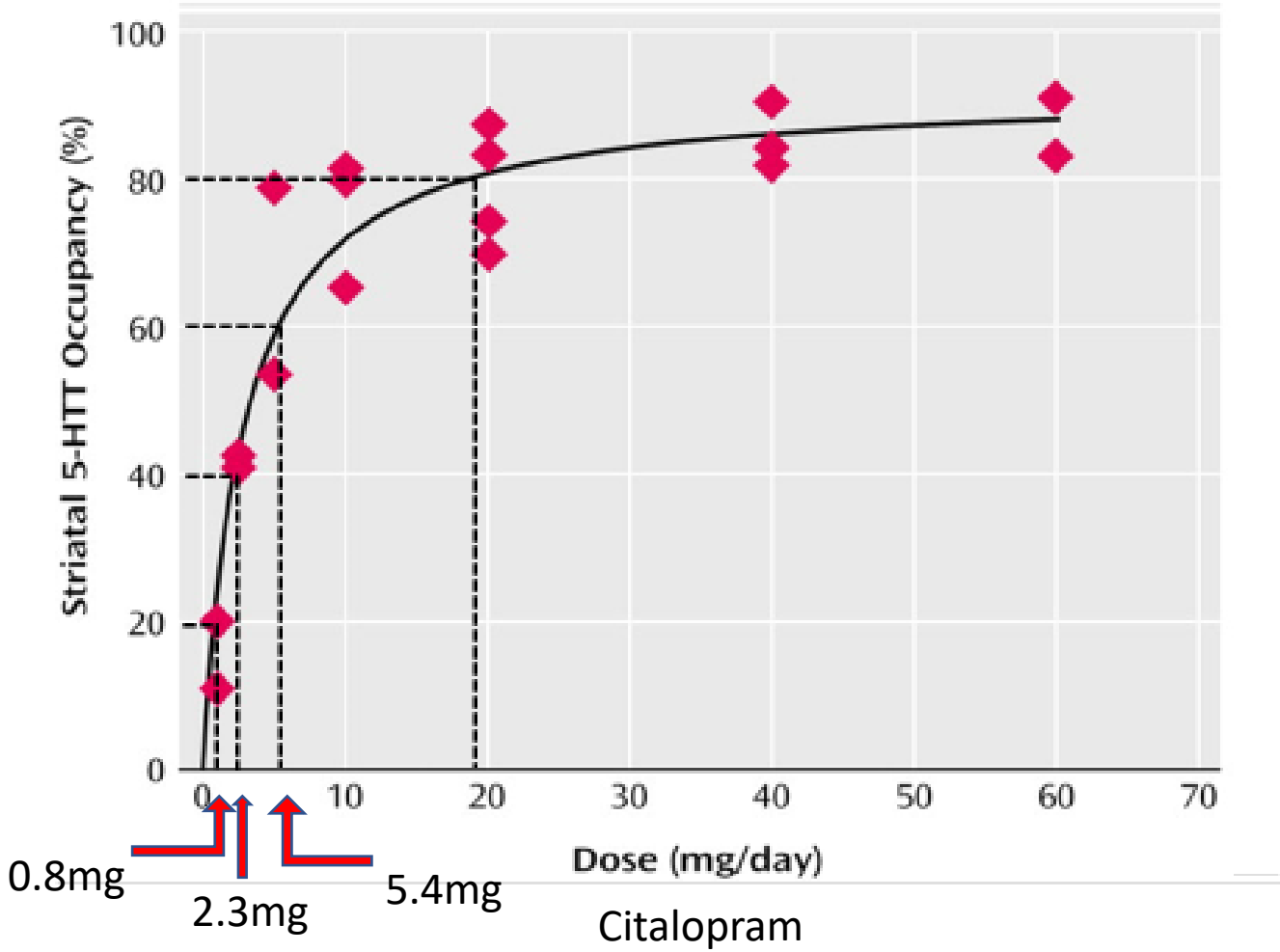
- Citalopram linear taper
- 20mg to 15mg -> 3% change
- 15mg to 10mg -> 6% change
- 10mg to 5mg -> 13% change
- 5mg to 0mg -> 58% change
- This correspond to the increasingly severe withdrawal symptoms reported by patients as dose gets lower
- 10mg is smallest tablet available. Sometimes split in half to make 5mg
- **Most common tapering by clinicians is: 20mg, 10mg, 5mg, stop.**



Citalopram

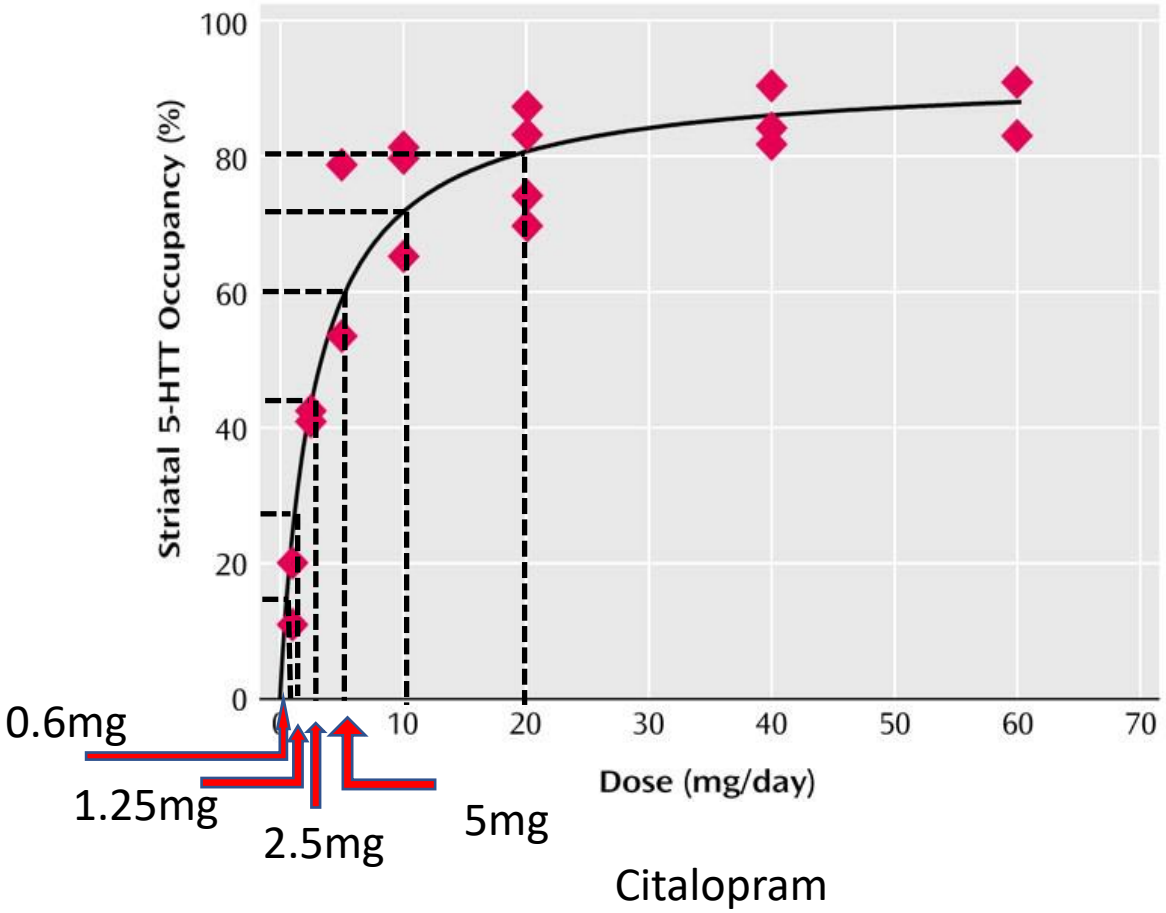
What happens when you taper by fix amounts of effect on the brain? Hyperbolic dose decrease

- Tapering according to equal change in effects at the serotonin transporter
- Yields hyperbolically reducing regimen
- Final dose before stopping will need to be very small



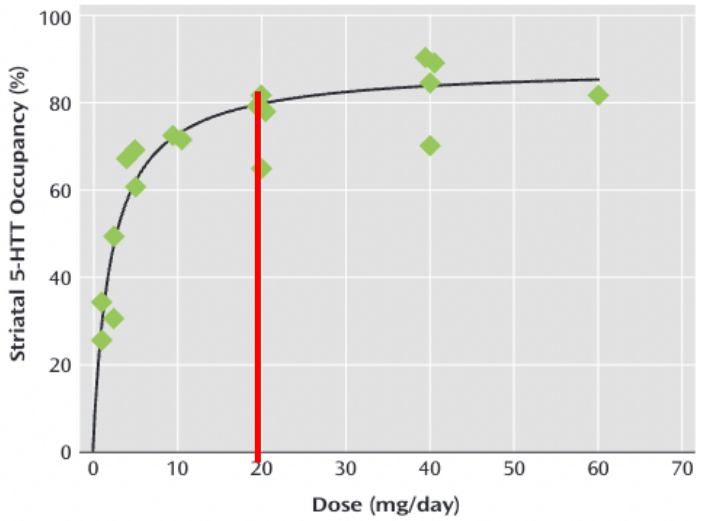
What happens when you taper by fixed amounts of effect on the brain? Proportionate dose decrease

- Hyperbolic reductions roughly approximated by *proportional* reductions
  - e.g., 5 halvings (50% reductions): 20mg, 10mg, 5mg, 2.5mg, 1.25mg, 0.6mg, 0mg
- Slower reductions required for many: such as 10% of the last dose/month

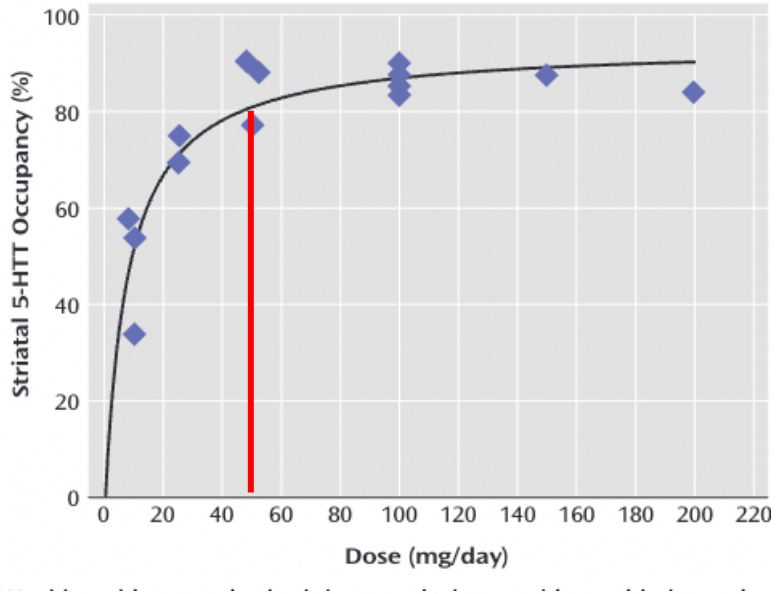


True for all antidepressants

Fluoxetine

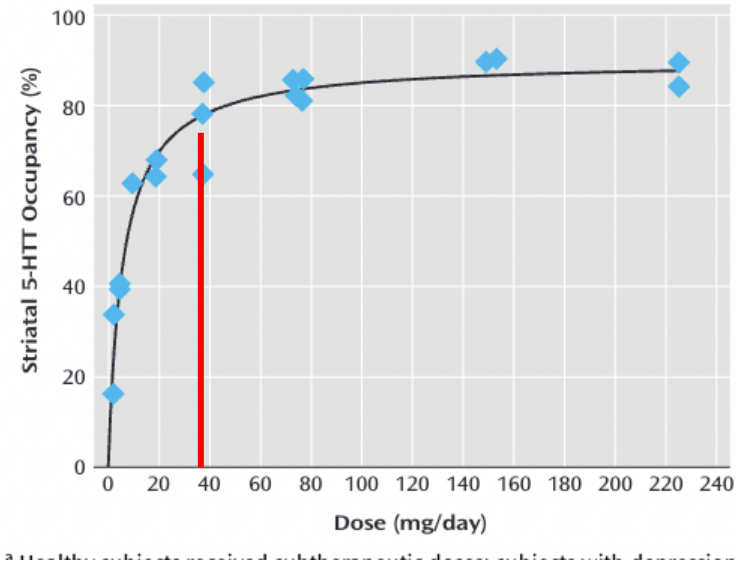


Sertraline

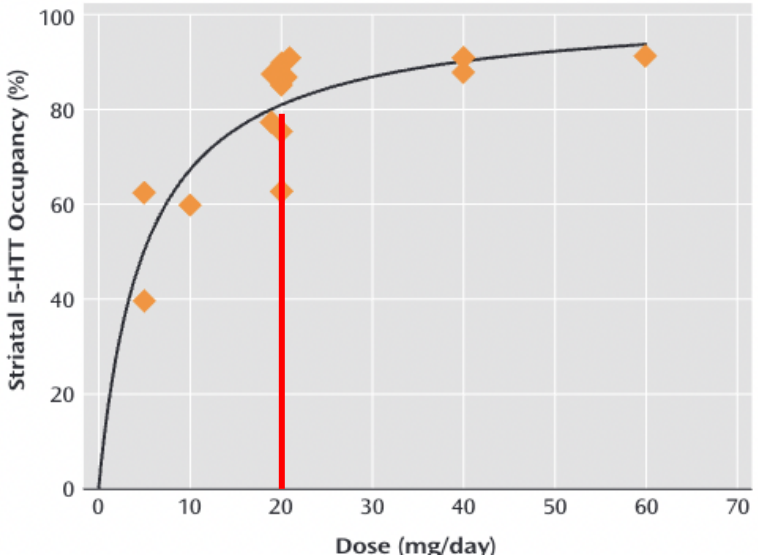


Red line= The smallest available tablet or capsule in Australia

Venlafaxine

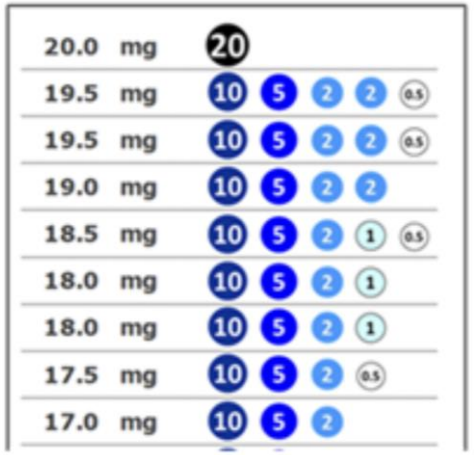


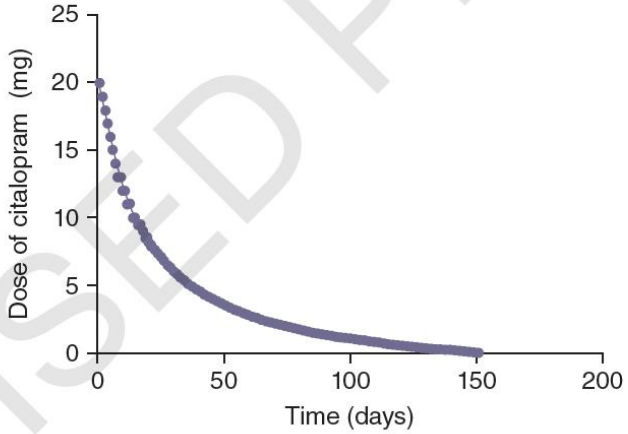
Paroxetine



Evidence for gradual, hyperbolic tapering

- In one study of 895 patients where two-thirds had been unable to stop antidepressants in usual quick linear taper 71% were able to stop with a hyperbolic taper over months (Groot and van Os, 2018)





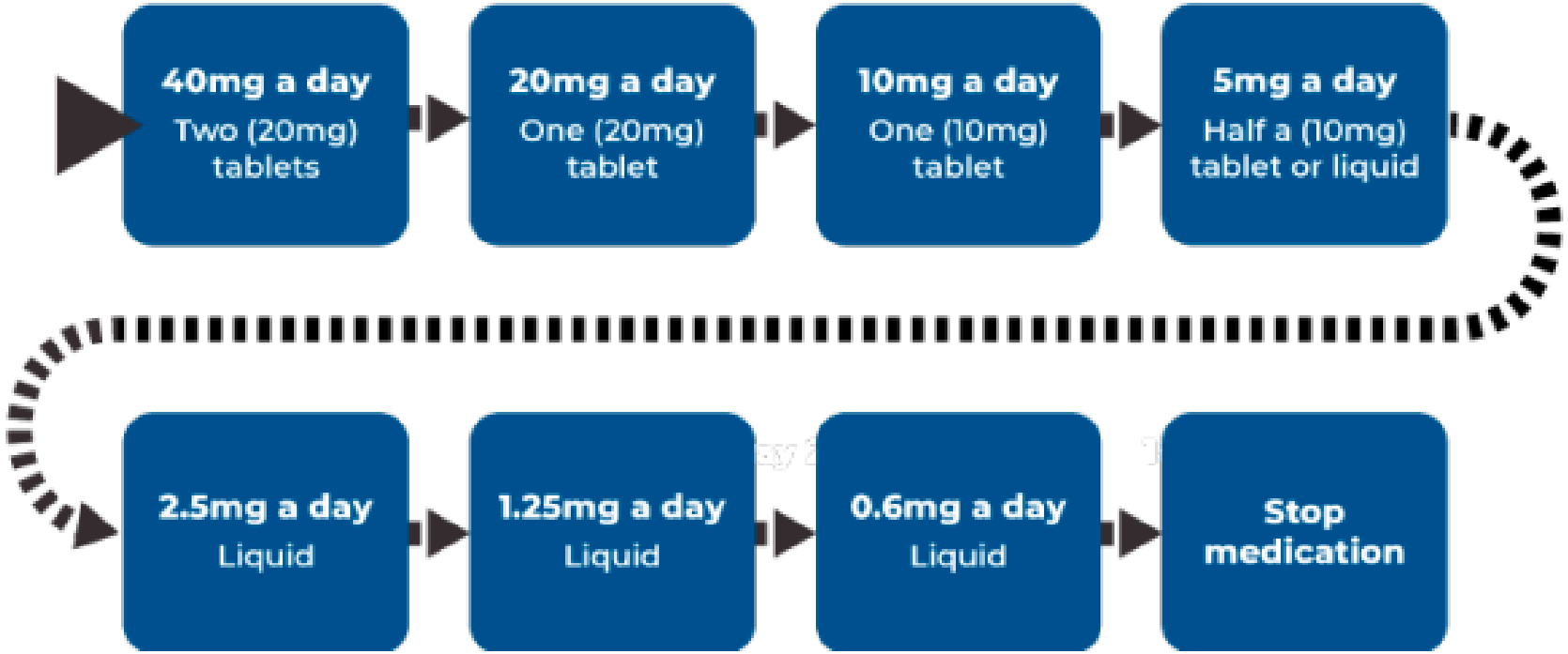
Royal College of Psychiatrists guidance on ‘Stopping antidepressants’

- Importantly, recommends individualizing rate of reduction to the rate that can be *tolerated by the patient*
- If withdrawal symptoms become too severe, then reduction should be *halted or dose increased until symptoms resolve*. Then reduction should proceed at a *slower pace*
- Many patients can only reduce their dose at *10% of the most recent dose per month* (which means reductions get smaller and smaller)

A rapid reduction schedule (RCPsych, 2020)

Citalopram

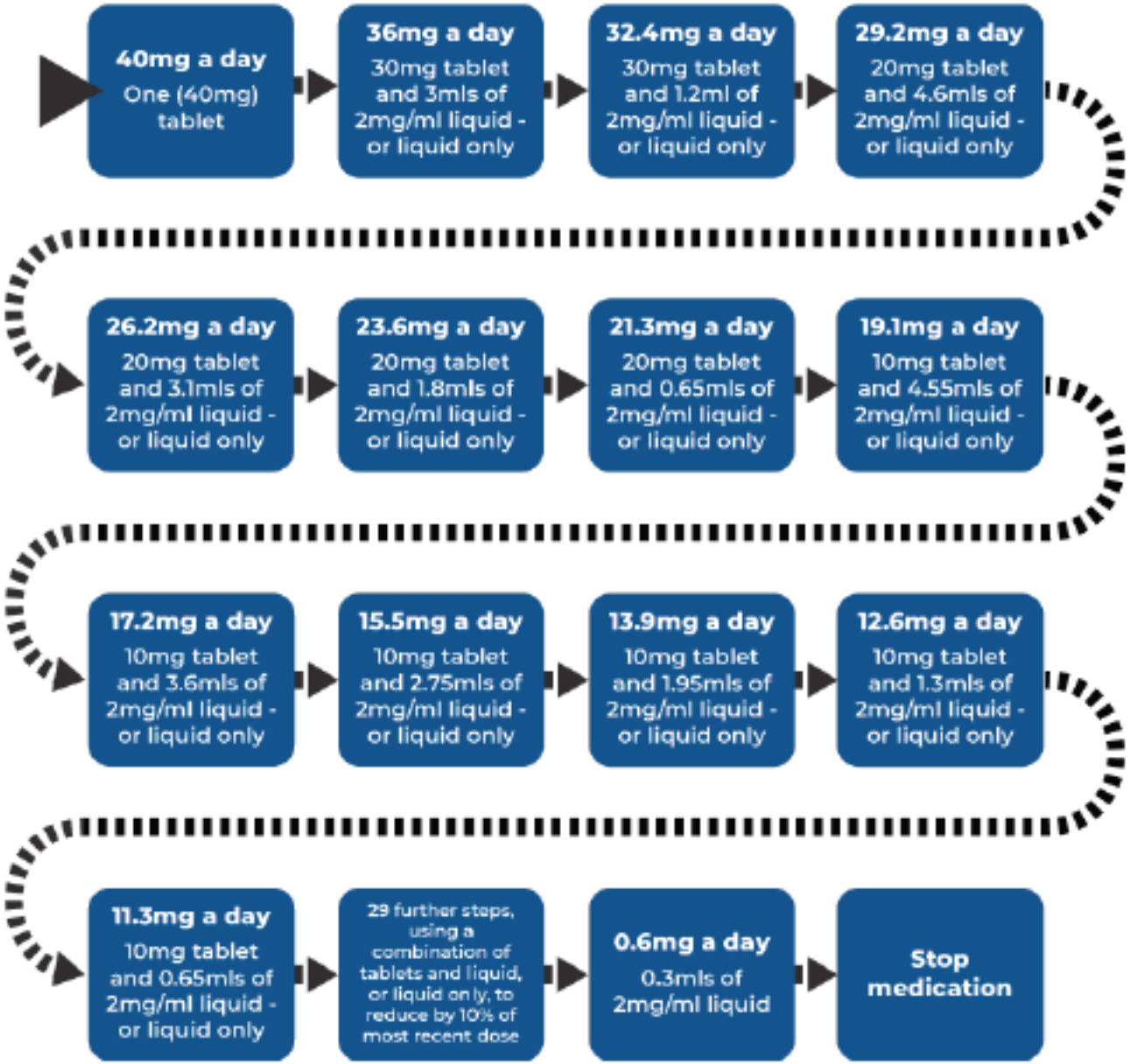
Reduction of dose by 50%, every 2-4 weeks. Some people may need to reduce more slowly.



- Total time required: 3-6 months

Paroxetine

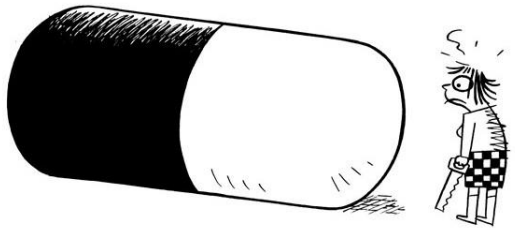
Reduction by 10% of the last dose, every 2-4 weeks using tablets and liquid. Some people may need to reduce more slowly. (Updated October 2020)



- Reduce dose by 10% of the dose every 2-4 weeks
- Calculated on the last dose, so that the reductions get smaller and smaller as the total dose decreases
- Reduce down to 0.6mg before stopping
- Approximate duration: 2-3 years (often what people take)

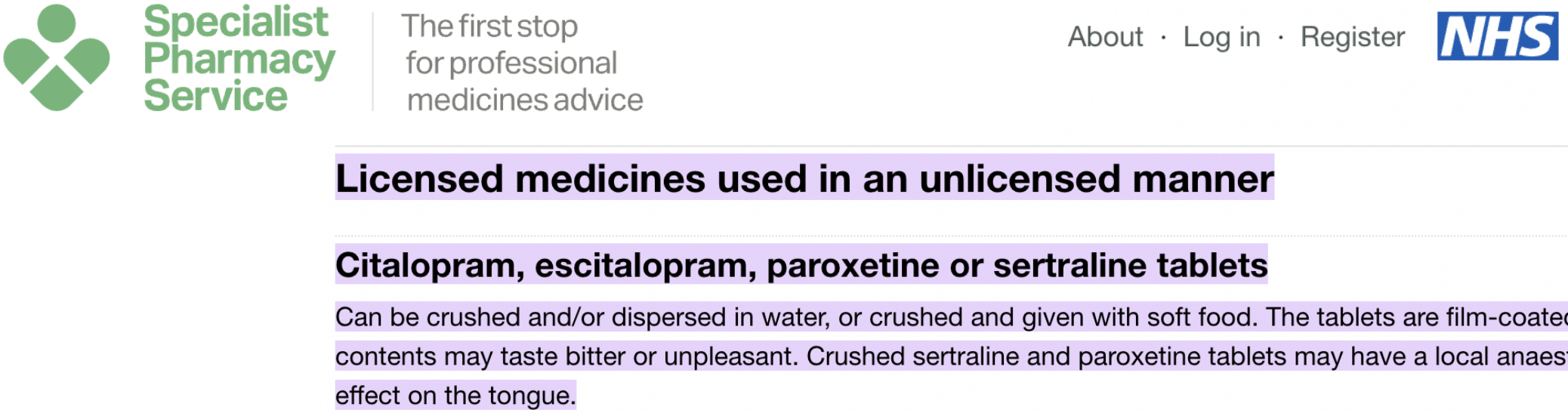
How to make these small doses?

- Tablet cutters will be needed to divide tablets – into halves and quarters
- Liquid preparations can be used – but only currently available for escitalopram in Oz
- Compounded medications (e.g. tapering strips)
- Don’t skip doses (except for fluoxetine) – can precipitate withdrawal effects because of large changes in plasma levels – most antidepressants have half-lives of 24 hours and so every second day dosing will mean that levels fall to ¼ of peak levels
- Switching to fluoxetine based on a manufacturer’s study. Fluoxetine has substantial withdrawal effects (incidence: 50%), cannot be stopped abruptly, switching process more difficult than textbooks suggest. May be considered in some circumstances



Off-label options for tapering

- There are also ’off-label’ options such as compounding pharmacies, opening up capsules to count beads
- Or crushing tablets (or opening capsules) and dispersing them in water. This is recommended by pharmaceutical authorities in the UK for example for giving small doses of medication to children
- Manufacturers could make liquids as they have in the UK



Other examples

- Mirtazapine dispersible tablets can be dispersed in water to make a mixture. E.g. 15mg in 150mL. Mixed well – then can reduce by 10% by discarding 15mL down the sink and drinking the rest
- Escitalopram comes as liquid drops which can be used to reduce mg by mg (also diluted with water and measured with a syringe)
- Compounding pharmacies can make up smaller doses

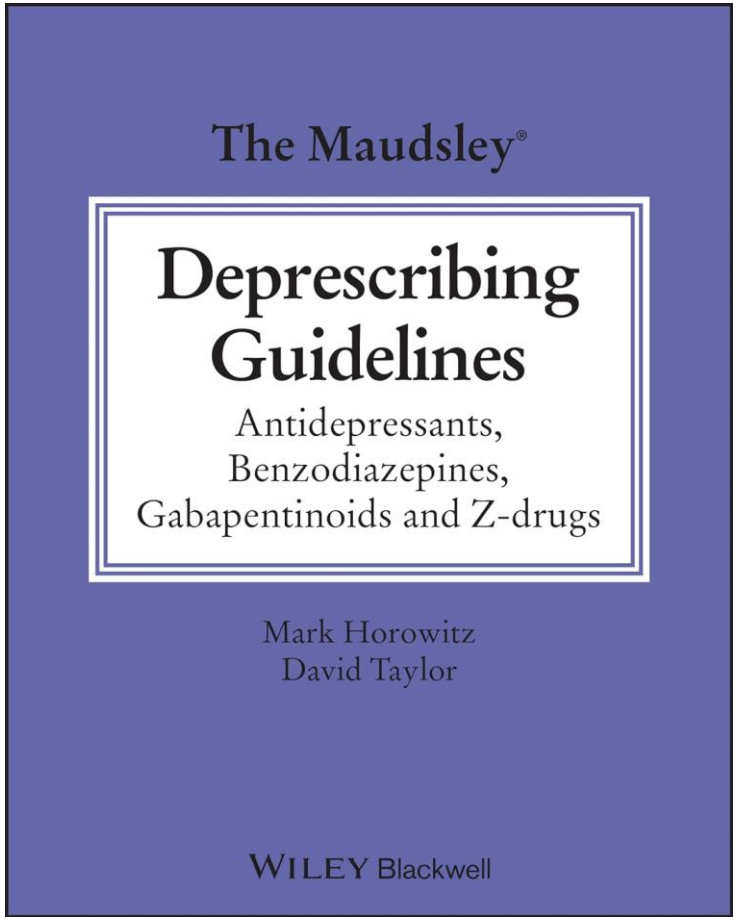
Details of tapering venlafaxine or duloxetine (capsules containing beads)

- Tapering venlafaxine: if there are 300 beads in a 75mg capsule of venlafaxine, you can reduce dose by 10% each month by taking out 30 beads the first month (down to 270 beads) and 27 beads the second month and so on

Maudsley Deprescribing Guidelines:

Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs

- Companion to the Maudsley Prescribing Guidelines, written with the primary author Professor David Taylor from Maudsley Psychiatry
- We set out with this clinical handbook to cover all the information a GP, psychiatrist, pharmacist, nurse, etc would need:
  - To recognize withdrawal effects from these drugs classes
  - To distinguish withdrawal effects from relapse
  - To be able to safely taper each specific antidepressant, etc with fast, moderate and slow schedules as well as advice on how tailor it for an individual
  - Covers all the formulations of medications available in Australia to safely taper with licensed and off-label uses



Guidance for stratifying risk

Table 2.11 Preliminary tool for evaluation of risk of withdrawal for an individual patient, adapted from Horowitz et al. 2022.[1]

Determinant of withdrawal risk	Weighting
Duration of use[a]	
■ Short term (1–6 months)	0 points
■ Intermediate term (6–12 months)	1 point
■ Long term (1–3 years)	2 points
■ Very long-term use (>3 years)	3 points
Antidepressant type	
■ Lowest risk (e.g. agomelatine)	0 points
■ Low risk (e.g. vortioxetine, trimipramine, dosulepin)	1 point
■ Moderate risk (e.g. SSRIs: citalopram, escitalopram, sertraline, fluvoxamine, fluoxetine; TCAs: amitriptyline, nortriptyline, clomipramine, imipramine; other: bupropion)	2 points
■ High risk (e.g. SNRIs: desvenlafaxine, duloxetine, venlafaxine; MAOIs: phenelzine, moclobemide; Other: paroxetine, mirtazapine)	4 points
Dosage	
■ Minimum therapeutic dosage or lower	0 points
■ Greater than the minimum therapeutic dosage	1 point
Past experience of withdrawal symptoms	
■ Stopped antidepressant in past with no withdrawal symptoms/unknown	0 points
■ Mild to moderate withdrawal symptoms	1 point
■ Severe withdrawal symptoms	2 points
■ Very severe withdrawal symptoms	3 points

[a] Note that very short-term use (<4 weeks) is not normally associated with significant risk of withdrawal.
MAOI monoamine oxidase inhibitor, SSRI selective serotonin reuptake inhibitor, SNRI serotonin and norepinephrine reuptake inhibitor, TCA tricyclic antidepressant

Table 2.12 Estimation of risk category for withdrawal for an individual patient, adapted from Horowitz et al. 2023.[1]

Risk category	Low	Medium	HIgh	Very high
Point score	0	1–4	5–8	≥ 9

Table 2.22 Estimation of tapering rate based on risk of withdrawal symptoms (see Tables 2.11 and 2.12).

Evaluation of risk	Initial tapering trajectory (see individual drug sections)	Initial dose reduction equivalent (approximately)*
Low risk = 0 points	Faster[a]	50% reduction
Medium risk = 1–4 points	Moderate[b]	25% reduction
High risk = 5–8 points	Slower[c]	10% reduction
Very high risk ≥ 9 points	Slowest[d]	5% reduction (or less)

For example, a person using 20mg citalopram for 4 years who has had moderate trouble when missing doses in the past would score 3 + 2 +1 + 1 = 7 points and start with a slower taper

Example of citalopram tapering regimen (faster)

A. **Faster taper** with up to 10 percentage points of SERT between each step – with reductions made every 2–4 weeks.*

Step	RO (%)	Dose (mg)	Volume**	Step	RO (%)	Dose (mg)	Volume**
1	79	40	Use tablets	6	37	2	0.4mL
2	75	20	Use tablets	7	27	1.2	0.24mL
3	68	10	Use tablets	Switch to citalopram **0.4mg/mL dilution**			
4	57	5	Use ½ tablets	8	17	0.7	1.4mL
Switch to citalopram **4mg/mL dilution**				9	7	0.3	0.6mL
5	47	3	0.6mL	10	0	0	0

RO = receptor occupancy

*The time between each decrease may be shortened to ~~one~~ week if the patient is able to make the first couple of reductions with no withdrawal symptoms. The interval between reductions should never be less than ~~one~~ week because this might increase the risk of relapse, even in the absence of withdrawal effects.[14,15]

**Note: citalopram drops come as citalopram hydrochloride which are 25% more bioavailable than citalopram hydrobromide (the tablet form) i.e. 8mg in liquid version is equivalent to 10mg in tablet form because they come as different salts.[1] Therefore the volume required is multiplied by 0.8 to get the required value.

A slower taper for citalopram for people with greater difficulties

B. **Moderate taper** with up to 5 percentage points of SERT between each step – with reductions made every 2–4 weeks.

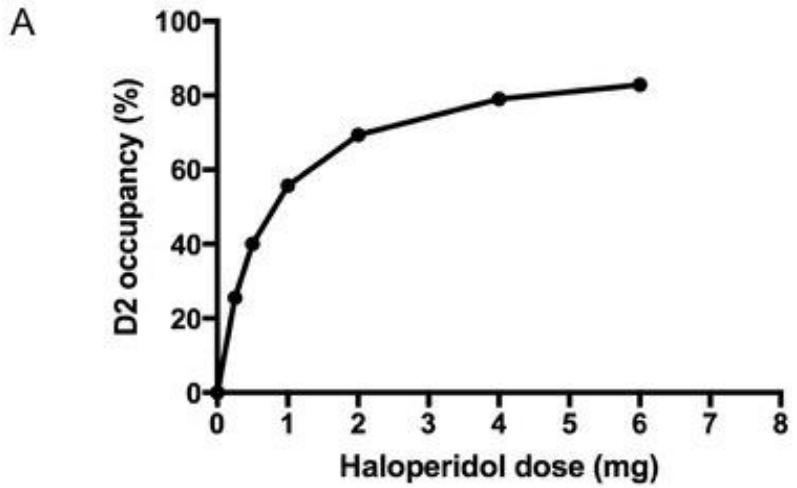
Step	RO (%)	Dose (mg)	Volume*	Step	RO (%)	Dose (mg)	Volume*
1	79	40	Use tablets	11	38	2	0.4mL*
2	75	20	Use tablets	12	34	1.6	0.32mL*
3	70	15	Use ½ tablets**	13	30	1.3	0.26mL*
4	68	10	Use tablets	14	26	1	0.2mL*
5	64	7.5	Use ¾ tablets**	Switch to citalopram **0.4mg/mL dilution***			
Switch to citalopram **4mg/mL dilution***				15	21	0.8	1.6mL*
6	60	5.5	1.1mL*	16	17	0.6	1.2mL*
7	55	4.5	0.9mL*	17	13	0.4	0.8mL*
8	51	3.6	0.72mL*	18	8.5	0.25	0.5mL*
9	47	2.9	0.58mL*	19	4.3	0.1	0.2mL*
10	43	2.4	0.48mL*	20	0	0	0
See further steps in the right-hand column							

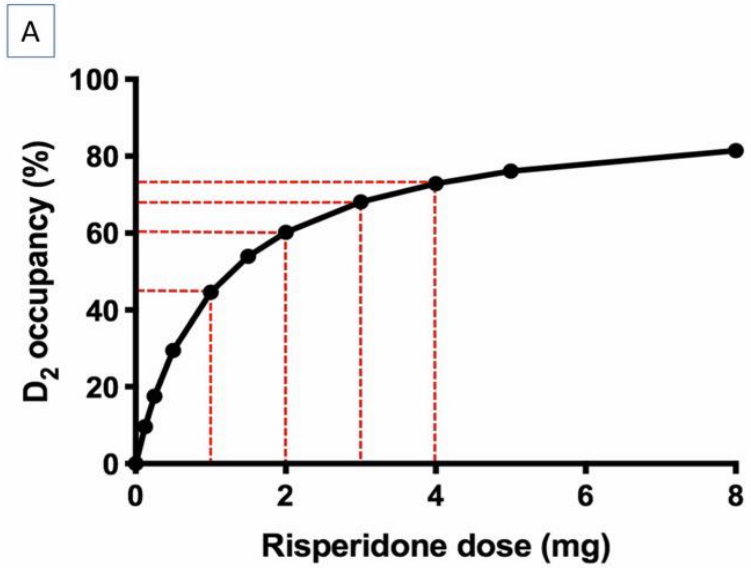
RO = receptor occupancy

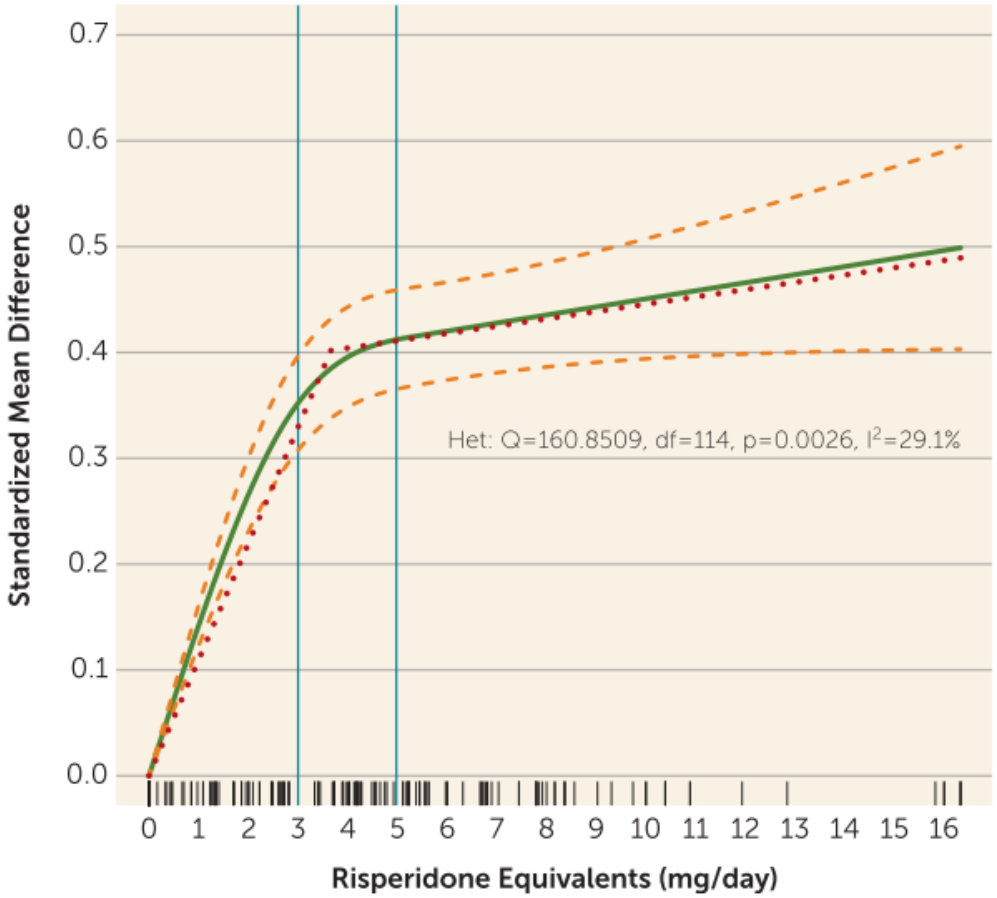
*Note: citalopram drops come as citalopram hydrochloride which are 25% more bioavailable than citalopram hydrobromide (the tablet form) i.e. 8mg in liquid version is equivalent to 10mg in tablet form because they come as different salts.[1] Therefore the volume required is multiplied by 0.8 to get the required value.

**Alternatively, this dose could be made up with a liquid preparation.

Pharmacology of antipsychotics

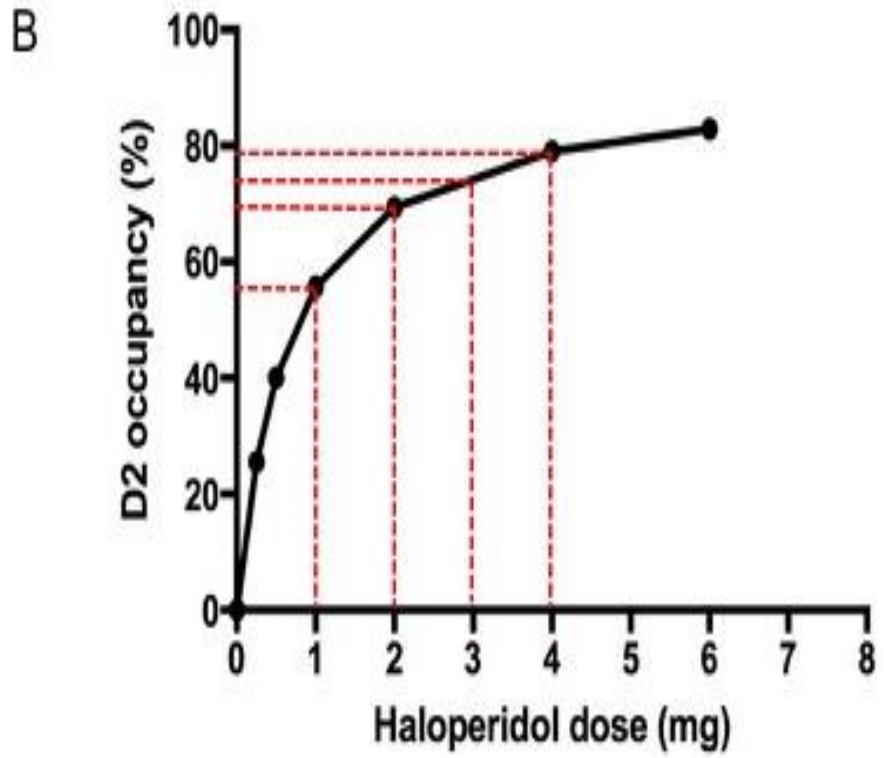






Relationship between dose and effect on symptoms (Leucht et al., 2020)

Tapering antipsychotics

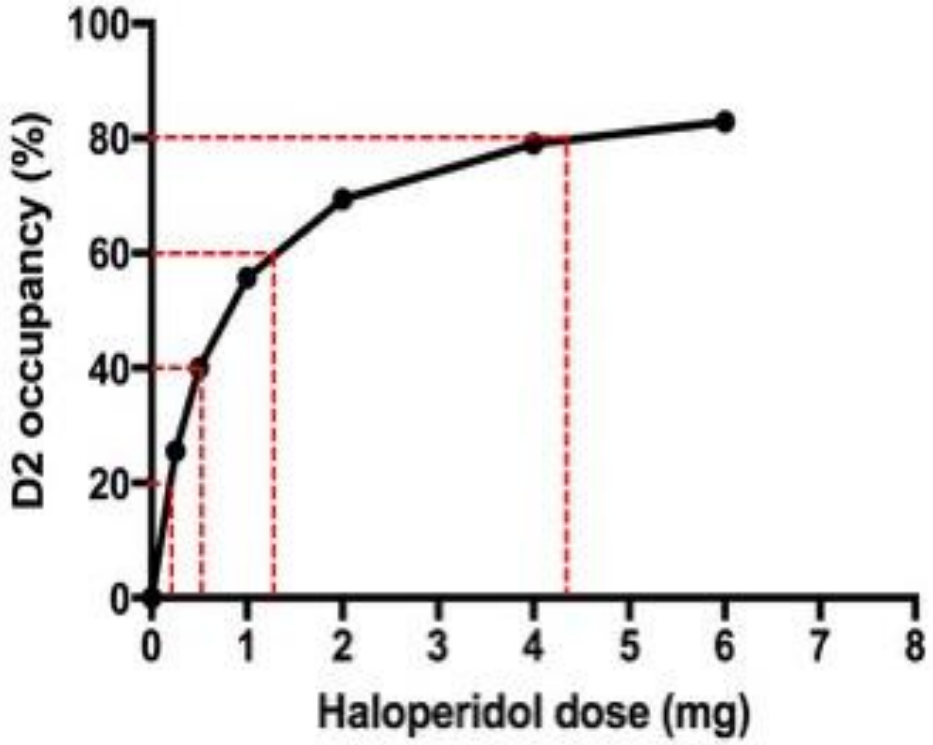


Haloperidol dose (mg)	D2 occupancy (%)
10	86.3
8	85.0
6	82.9
4	79.0
3	75.5
2	69.4
1	55.7
0.5	40.0
0.25	25.5
0	0

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

Hyperbolic tapering of antipsychotics

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.

Tapering rate

- This is equivalent to about a reduction of 5-10% of dose every month (so that reductions become smaller and smaller as total dose gets smallers)
- The most important thing is to titrate it to the tolerability of the patient – if they experience insomnia, slight worsening of behavioural symptoms, the rate should be slowed down or a slight updose before reducing at a more cautious rate

Tapering other psychiatric drugs

NICE
National Institute for Health and Care Excellence

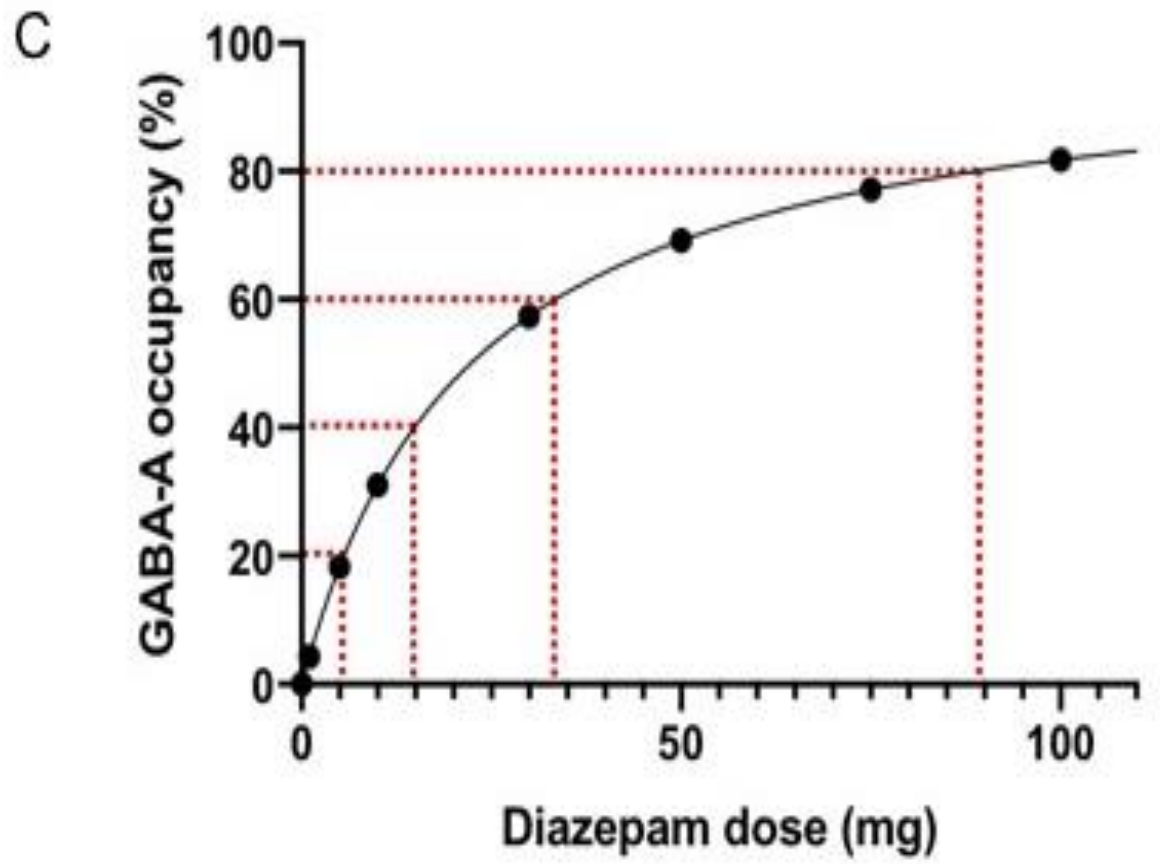
- “for opioids, benzodiazepines, Z-drugs and antidepressants, suggest a slow, stepwise rate of *reduction* ***proportionate*** *to the existing dose,* ***so that decrements become smaller as the dose is lowered***, unless rapid withdrawal is needed”

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults

Draft for consultation, October 2021



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

Diazepam Dosage (mg)	GABA-A occupancy (%)
200	90.0
100	81.8
75	77.1
50	69.2
37.5	62.7
25	52.9
12.5	35.9
10	31.0
5	18.3
2	8.2
1	4.3
0.5	2.2
0	0

A. **A faster taper** with up to 5 percentage points of $GABA_A$ occupancy between each step – with reductions made every 1–4 weeks*.

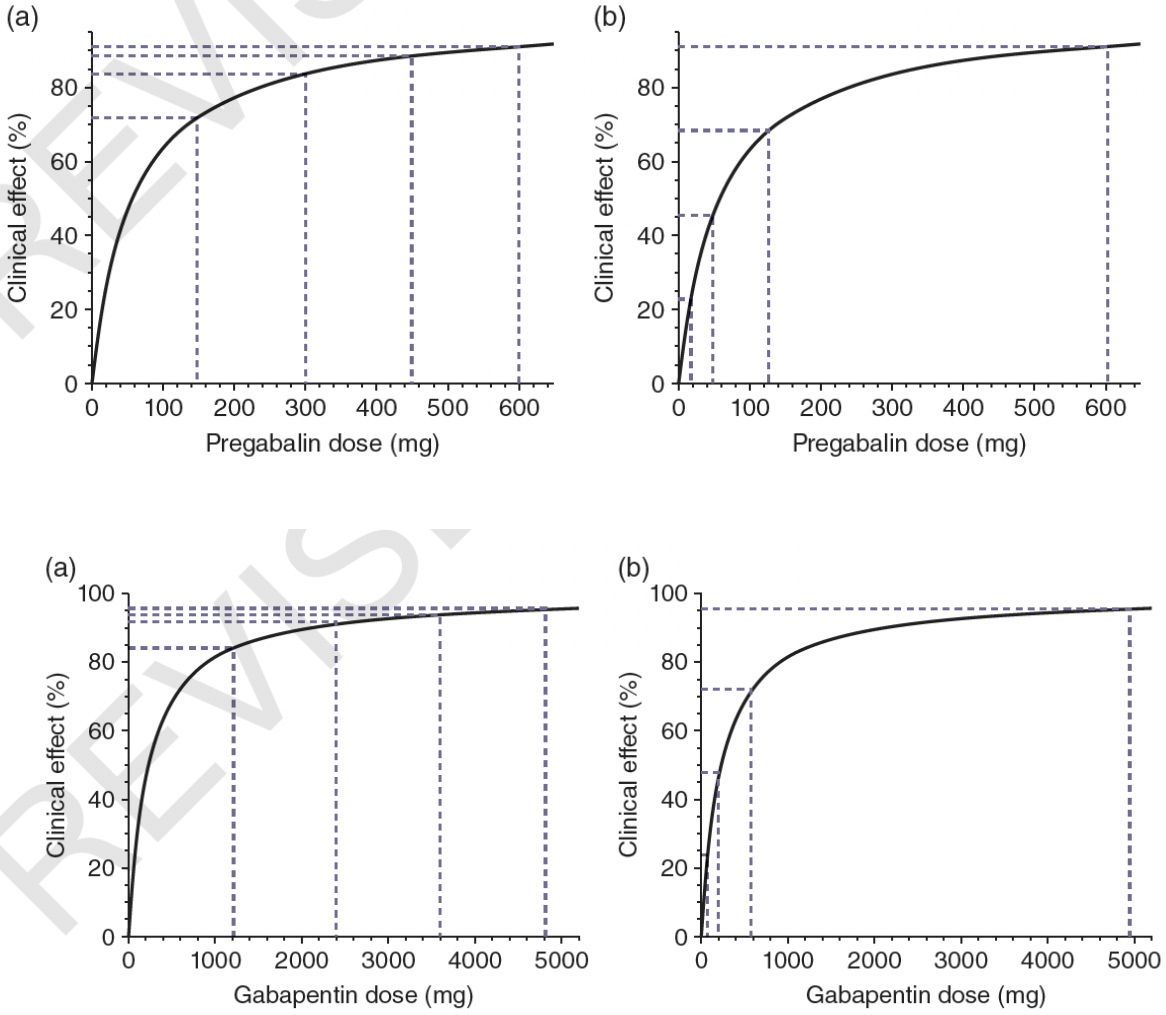
Step	RO (%)	AM (mg)	PM (mg)	Total daily dose (mg)	Form	Step	RO (%)	AM (mg)	PM (mg)	Total daily dose (mg)	Form
1	70.8	30	30	60	Use tablets	13	36.2	7	7	14	Use tablets
2	69	25	30	55	Use tablets	14	32.7	6	6	12	Use tablets
3	66.9	25	25	50	Use tablets	15	28.8	5	5	10	Use tablets
4	64.6	20	25	45	Use tablets	16	24.5	4	4	8	Use tablets
5	61.8	20	20	40	Use tablets	17	22.1	3	4	7	Use ½ tablets**
6	59.3	18	18	36	Use tablets	18	19.5	3	3	6	Use ½ tablets**
7	56.4	16	16	32	Use tablets	19	16.8	2	3	5	Use ½ tablets**
8	53.1	14	14	28	Use tablets	20	13.9	2	2	4	Use tablets
9	49.3	12	12	24	Use tablets	21	10.8	1	2	3	Use ½ tablets**
10	44.7	10	10	20	Use tablets	22	7.5	1	1	2	Use ½ tablets**
11	42.2	9	9	18	Use tablets	23	3.9	0.5	0.5	1	Use ¼ tablets**
12	39.3	8	8	16	Use tablets	24	0	0	0	0	
See further steps in the right-hand column											

Including guidance on when to switch shorting acting benzodiazepines to diazepam

B. **A moderate taper** with up to 2.5 percentage points of $GABA_A$ occupancy between each step – with reductions made every 1–4 weeks.

Step	RO (%)	AM (mg)	PM (mg)	Total daily dose (mg)	Form*	Step	RO (%)	AM (mg)	PM (mg)	Total daily dose (mg)	Form
1	70.8	30	30	60	Use tablets	23	34.5	6.5	6.5	13	Use ¼ tablets*
2	69.4	28	28	56	Use tablets	24	32.7	6	6	12	Use tablets
3	67.8	26	26	52	Use tablets	25	30.8	5.5	5.5	11	Use ¼ tablets*
4	66	24	24	48	Use tablets	26	28.8	5	5	10	Use tablets
5	64	22	22	44	Use tablets	27	26.7	4.5	4.5	9	Use ¼ tablets*
6	61.8	20	20	40	Use tablets	28	24.5	4	4	8	Use tablets
7	60.6	19	19	38	Use tablets	29	23.3	3.5	4	7.5	Use ¼ tablets*
8	59.3	18	18	36	Use tablets	30	22.1	3.5	3.5	7	Use ¼ tablets*
9	57.9	17	17	34	Use tablets	31	20.8	3	3.5	6.5	Use ¼ tablets*
10	56.4	16	16	32	Use tablets	32	19.5	3	3	6	Use ½ tablets*
11	54.8	15	15	30	Use tablets	33	18.2	2.5	3	5.5	Use ¼ tablets*
12	53.1	14	14	28	Use tablets	34	16.8	2.5	2.5	5	Use ¼ tablets*
13	51.3	13	13	26	Use tablets	35	15.4	2	2.5	4.5	Use ¼ tablets*
14	49.3	12	12	24	Use tablets	36	13.9	2	2	4	Use tablets
15	47.1	11	11	22	Use tablets	37	12.4	1.5	2	3.5	Use ¼ tablets*
16	44.7	10	10	20	Use tablets	38	10.8	1.5	1.5	3	Use ¼ tablets*
17	43.5	9.5	9.5	19	Use ¼ tablets*	39	9.2	1	1.5	2.5	Use ¼ tablets*
18	42.2	9	9	18	Use tablets	40	7.5	1	1	2	Use ½ tablets*
19	40.8	8.5	8.5	17	Use ¼ tablets*	41	5.7	0.5	1	1.5	Use ¼ tablets*
20	39.3	8	8	16	Use tablets	42	3.9	0.5	0.5	1	Use ¼ tablets*
21	37.8	7.5	7.5	15	Use ¼ tablets*	43	2	0	0.5	0.5	Use ¼ tablets*
22	36.2	7	7	14	Use tablets	44	0	0	0	0	
See further steps in the right-hand column											

Gabapentinoid tapering



A. **A faster taper** with up to 10 percentage points of 'clinical effect' between each step – with reductions made every 2–4 weeks*.

Step	CE (%)	AM (mg)	PM (mg)	Total daily dose (mg)	Form
1	91	300	300	600	Tablets or capsules
2	83	150	150	300	Tablets or capsules
3	79	100	125	225	Tablets or capsules
4	72	75	75	150	Tablets or capsules
5	63	50	50	100	Tablets or capsules
6	56	37.5	37.5	75	Use ½ tablets**
7	46	25	25	50	Tablets or capsules
8	39	18.75	18.75	37.5	Use ¾ tablets**
9	30	12.5	12.5	25	Use ½ tablets**
Switch to pregabalin **20mg/mL solution**					
10	24	9	9	18	0.45mL AM and PM
11	17	6	6	12	0.3mL AM and PM
12	9	3	3	6	0.15mL AM and PM
13	0	0	0	0	

Other drug classes

- The relationship between dose of drug and effect on target receptors is hyperbolic for all psychiatric drug classes and so the same principles of hyperbolic tapering will apply to all these classes as well:
  - mood stabilisers,
  - stimulants (although generally easier to stop),
  - Z-drugs
  - opioids

Thank you for listening

- Questions?

- My email for any further questions:

  mark.horowitz@nelft.nhs.uk

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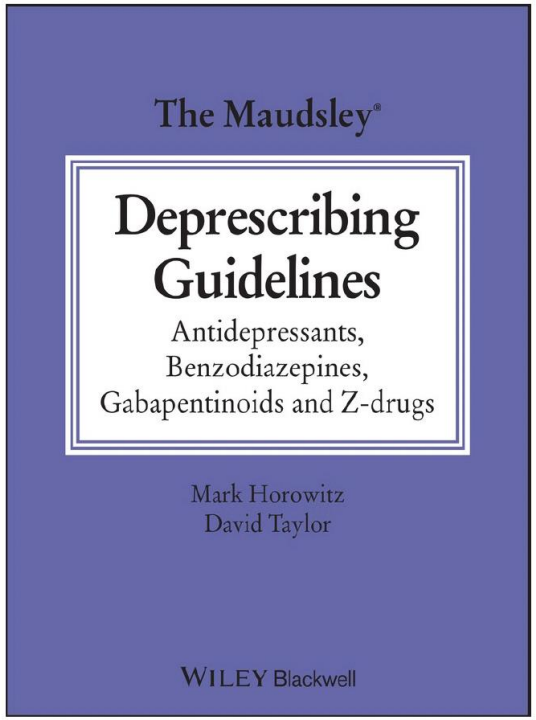

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Dealing with polypharmacy

- Where to start?
- Start somewhere!
- Easiest drugs to stop to give confidence in the process
- Or drugs that are likely to have the worst risk/benefit ration
- Start off one drug at a time; if becomes routine can introduce a second drug (e.g. if first drug reducing at 10% per month with predictable consequences could trial a second)

How to deprescribe in vulnerable populations

- Deprescribing in older adults or people with cognitive impairment/language issiues
- More difficult because tapering relies on feedback about the process from the patient to determine the rate: much more difficult with communication issues
- There can be non-verbal cues as to increased distress (a signal to slow down the rate of taper)
- When thinking about the difficulties of deprescribing in older adults – presents a reason to deprescribe unnecessary medications BEFORE people are too old or unwell to tolerate the process

Disease-centred model

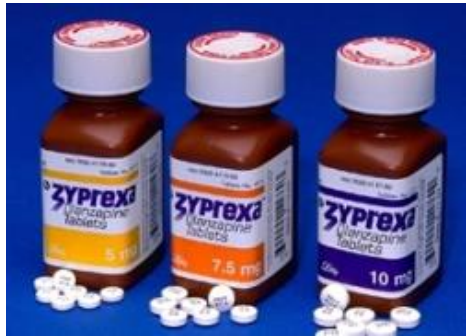
- Imported from general medicine, where most modern drugs are correctly understood this way
- Drugs act on underlying abnormalities
  - Blood pressure medication relax blood vessels to reverse high blood pressure
  - Insulin replaces a lack of it in diabetes
- In mental health disease centred model relates closely to chemical imbalance theories
  - Ie antidepressants correct a deficiency of serotonin that is the underlying cause of depression

Disease-centred model -2

- As above the serotonin theory of depression is not supported by research and most researchers and psychiatrists now do not accept this hypothesis
- Indeed, despite decades of intensive research brain abnormalities that are responsible for psychiatric illness have not been definitively established
- There is also a lack of evidence that drugs that are meant to have specific effects in certain conditions are better than other sorts of drugs
- For example, stimulants, anti-anxiety drugs and antipsychotics all have similar effects in people with depression as do antidepressant drugs
- There is little evidence of any specificity

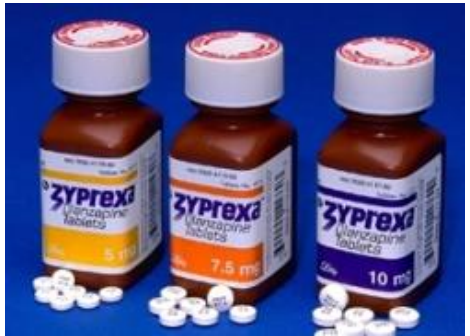
Drug-centred model

- In this model, psychiatric drugs are seen to be psychoactive drugs
- That is, they cross the blood-brain barrier and affect brain functioning
- This produces an altered brain state that affected how people think, feel and act
- There is no distinction in this view between drugs that are used for psychiatric treatment and those used recreationally like alcohol and cocaine
- Often the effects of recreational drugs are experienced as pleasant and desirable, but the effects of many psychiatric drugs such as lithium and antipsychotics are experienced as unpleasant when given to volunteers who do not have mental disorders



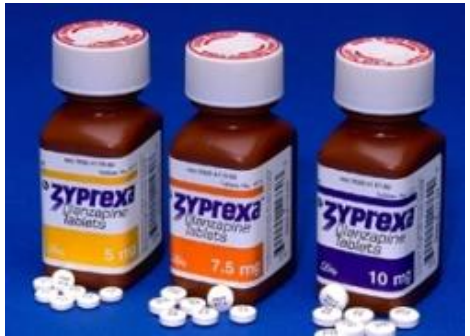
Drug-centred model -2

- The effect of the drug (eg sedation and relaxation in short term benzodiazepine use) may be experienced as relief for someone who is agitated or anxious
- However, this drug is not returning a person to their 'normal' state or 'pre-symptom' state
- The drug-induced state is superimposed on the symptoms and may or may not be preferable either to the sufferer themselves or by others
- In psychiatry it is generally accepted that alcohol acts on social anxiety in a 'drug-centred' way – mild intoxication can lessen social inhibitions
- It is not thought that alcohol reverses a biochemical imbalance (or alcohol deficiency) but rather that an abnormal state is super-imposed on the anxious state



Drug-centred model - 3

- As for recreational drugs, psychiatric drugs tend to cause tolerance to their effects which means that the drugs have less and less effect over time (or need higher doses to have the same effect)
- When the drug is stopped the biological adaptations that arose during treatment are no longer opposed by the presence of the drug and these give rise to unpleasant withdrawal symptoms
- Whereas the disease centred model assumes that psychiatric drugs help to restore normal brain function, the drug-centred model stresses that taking a drug creates an abnormal biological state.
- The effects associated with these altered effects may be perceived as worthwhile in certain situations – however, often by distorting normal bodily functions drugs have an adverse impact
- Therefore they may do more harm than good, especially in the long-term

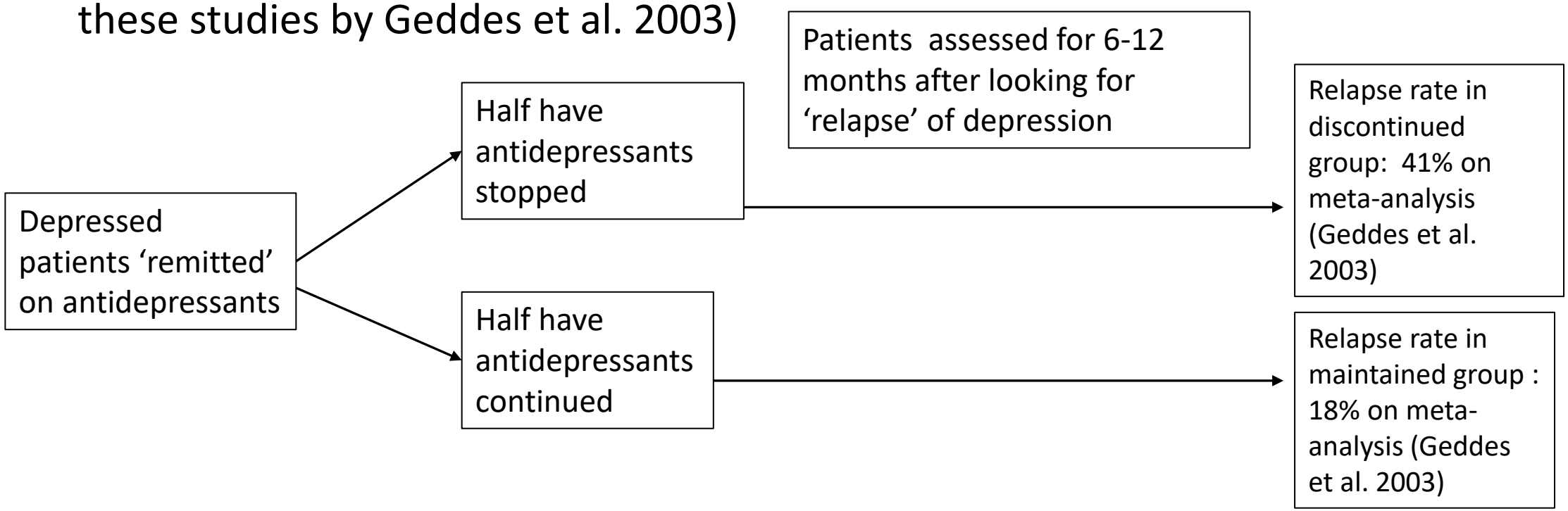


Models of drug action

Disease centred model	Drug centred model
Drugs correct an abnormal brain state	Drugs *create* an abnormal/altered brain state
Therapeutic effects arise from drugs effects on the biological mechanisms that produce symptoms	Useful effects are a consequence of drug-induced changes to normal brain functioning being superimposed on symptoms (unwanted thoughts, feelings and behaviour)
Example (general medicine): asthma treatments, aspirin, paracetamol	Examples: alcohol for social anxiety or depression, opiate anaesthetics

Evidence for long-term use of antidepressants

- There is a recommendation to “continue antidepressants for at least 2 years if they are at risk for relapse” in the NICE depression guidelines
- This advice is based on discontinuation studies (in particular, a meta-analysis of these studies by Geddes et al. 2003)



Limitations to the relapse prevention literature

- Limitations?