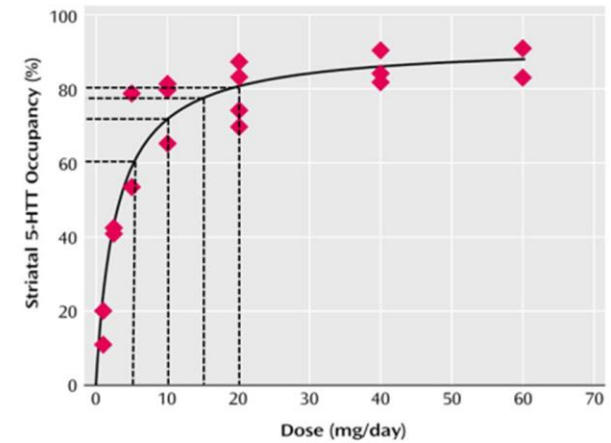




Antidepressant withdrawal syndrome and its management



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Conflicts of interest

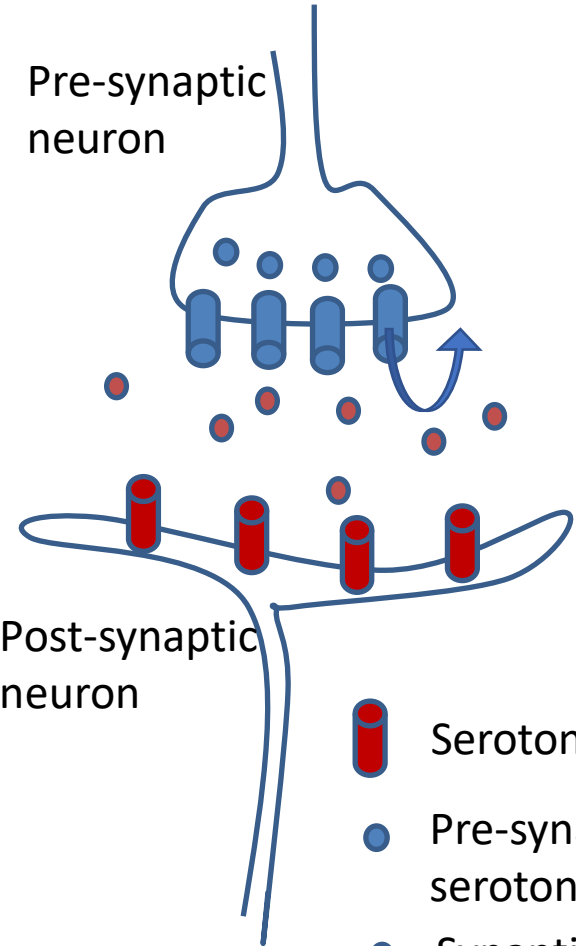
- I have no conflicts of interest

Experience of withdrawal?

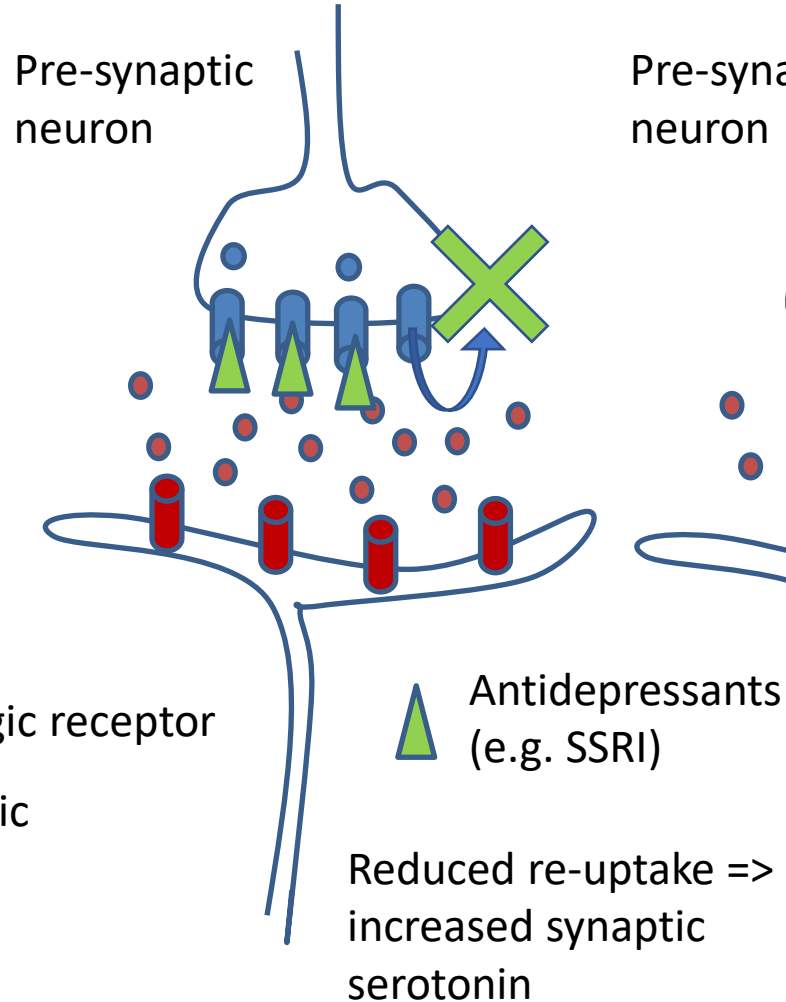
- Who in the audience has seen severe withdrawal symptoms from antidepressants in their patients, friends, family or themselves?
- Who has seen people who have no trouble coming off antidepressants at all?

Effect of long-term antidepressant use and stopping

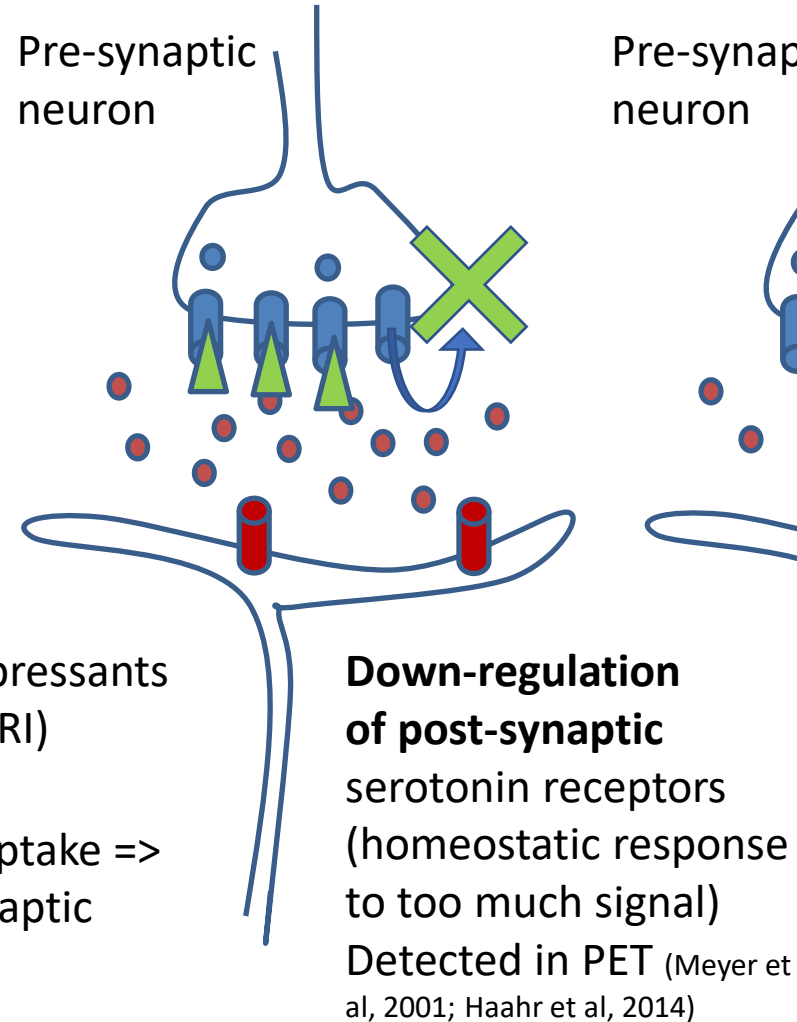
A Before Medication



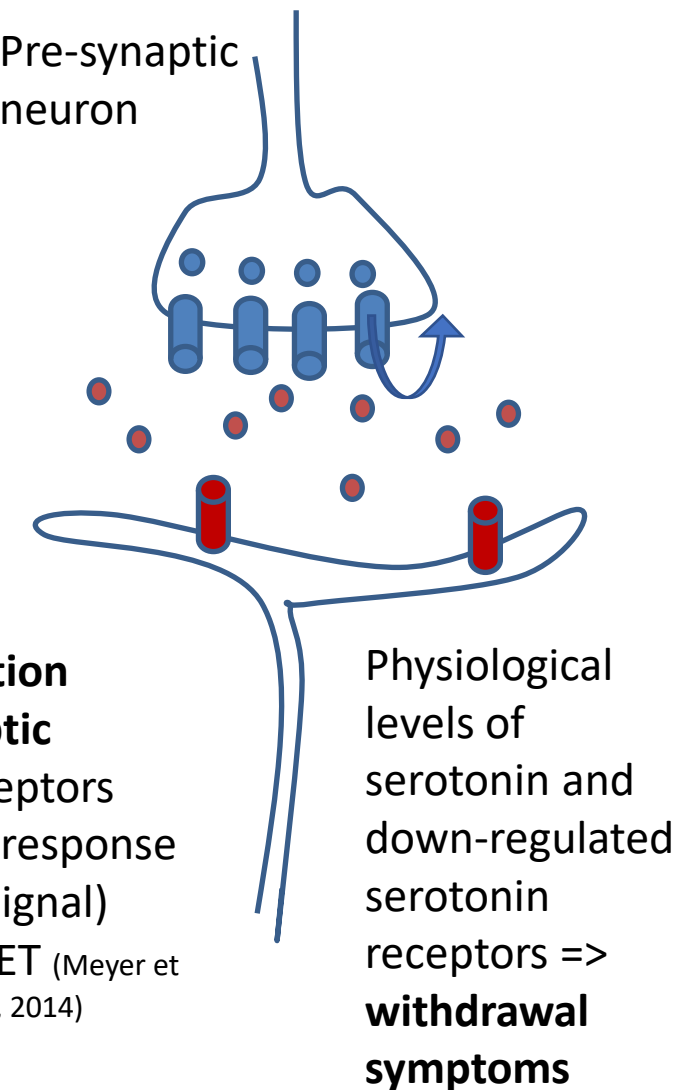
B Medication introduced








C Long term medication



D Medication stopped



-  Serotonergic receptor
-  Pre-synaptic serotonin
-  Synaptic serotonin
-  Serotonin transporter

 Antidepressants (e.g. SSRI)

Reduced re-uptake => increased synaptic serotonin

Down-regulation of post-synaptic serotonin receptors (homeostatic response to too much signal)
Detected in PET (Meyer et al, 2001; Haahr et al, 2014)

Physiological levels of serotonin and down-regulated serotonin receptors => **withdrawal symptoms**

Currently: people turn to peer support websites online for guidance



301,768
posts



mdwstrx: Lexapro taper or ...
By mdwstrx
4 minutes ago

750,000 hits a month



150,000 hits a month

- Commonest story: my GP/psychiatrist 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 GP 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 and brain zaps.
- So I don't trust my doctor any more. The advice on this website was more helpful than my doctor.
- Coming off much more slowly than they suggest has made the process much easier (although still not easy).

How did this happen?

Official guidance on antidepressant withdrawal syndrome until 2019 (in UK)

- NICE guidelines stated: '*discontinuation* symptoms are **usually mild and self-limiting over about one week**, but can be severe, particularly if the drug is stopped abruptly' (NICE, CG90, 2009)
- This description was based on the output of a 'consensus panel' put together by a drug company in 1998
- They coined the euphemism 'discontinuation symptoms' and distributed numerous papers with the description 'brief and mild'

Antidepressant withdrawal syndrome



- Physiological symptoms that occur on stopping – or reducing the dose – of an antidepressant
- They can manifest in either psychological or physical symptoms
- Occur because changes (adaptation) to the brain caused by antidepressant use take time to resolve
- Withdrawal symptoms do not require addiction (compulsion/craving etc) but only adaptation (often called physical dependence)
- 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)

Mis-diagnosing antidepressant withdrawal effects as relapse

- Reported to occur by patients often but not studied in detail
- 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’)
- Clues to distinguish withdrawal from relapse:
 - Quick onset– days, compared with weeks or months for relapse (except fluoxetine with long half-life);
 - Specific symptoms (dizziness, electric shock, other symptoms not present in baseline condition). More likely to develop withdrawal symptoms than to develop a new psychiatric condition co-occurring exactly with stopping/reducing medication;
 - Often quick resolution on re-instatement of antidepressant (hours, day or two).

Mis-diagnosing withdrawal as other conditions

- All the following are mis-diagnoses reported by patients that they receive after stopping antidepressants –a long with the withdrawal symptoms that may cause mis-diagnosis

Antidepressant withdrawal symptom mis-diagnosed as	Antidepressant withdrawal symptoms that may mimic condition
Chronic Fatigue Syndrome	Fatigue, insomnia, muscle aches
Medically Unexplained Symptoms/ Functional Neurological Disorder	Tremor, muscle weakness, muscle spasm, pain, fatigue
Gastrointestinal condition	Diarrhoea, constipation, nausea
Stroke/neurological disorder	Muscle weakness, 'electric zaps', tremor, headache, visual changes, sensory changes
Onset of new psychiatric disorder	New onset of anxiety, depression, panic attacks, insomnia, worry, suicidality

Antidepressant withdrawal systematic review (2019)

- A recent systematic review with an aim to determine incidence, duration and severity from the published literature (Davies and Read, 2019)
- First systematic review to attempt to do this



Addictive Behaviors
Volume 97, October 2019, Pages 111-121

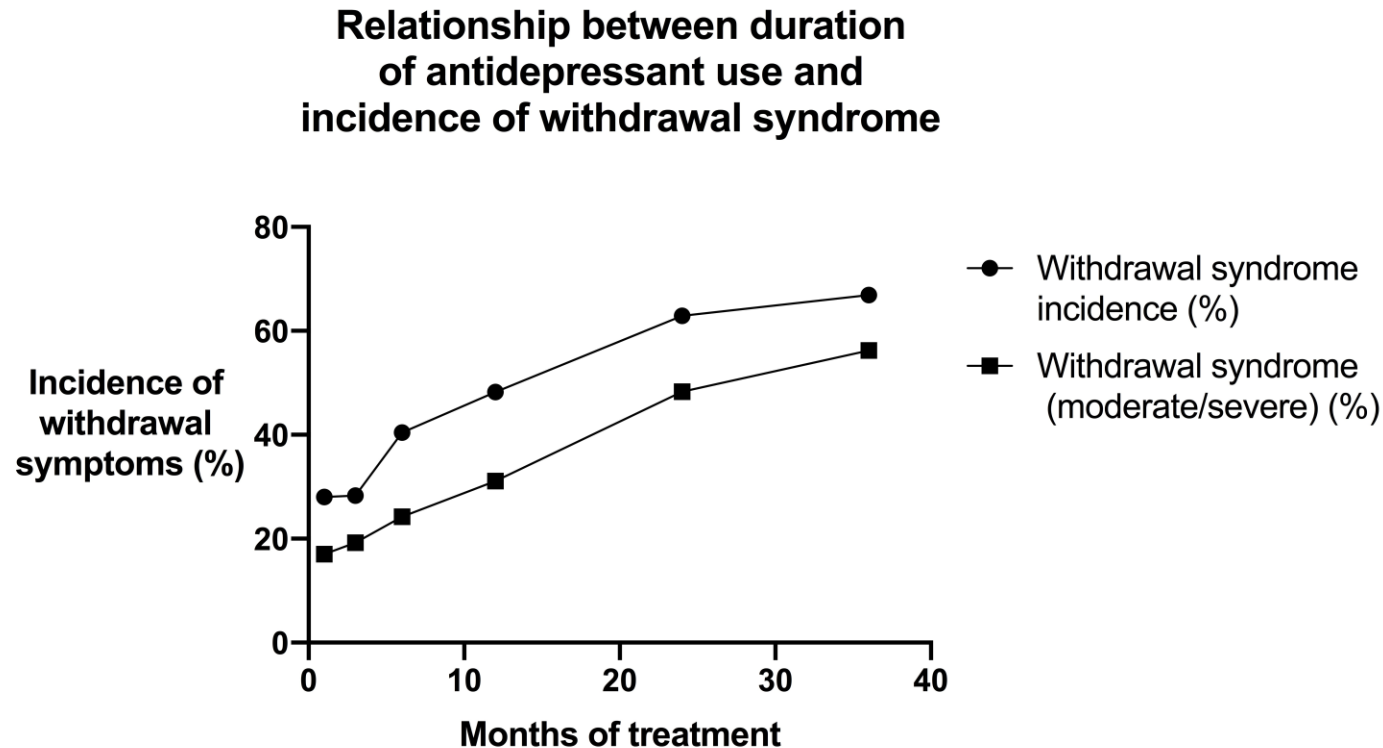


A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based?

James Davies ^{a, b}  , John Read ^{c, d}

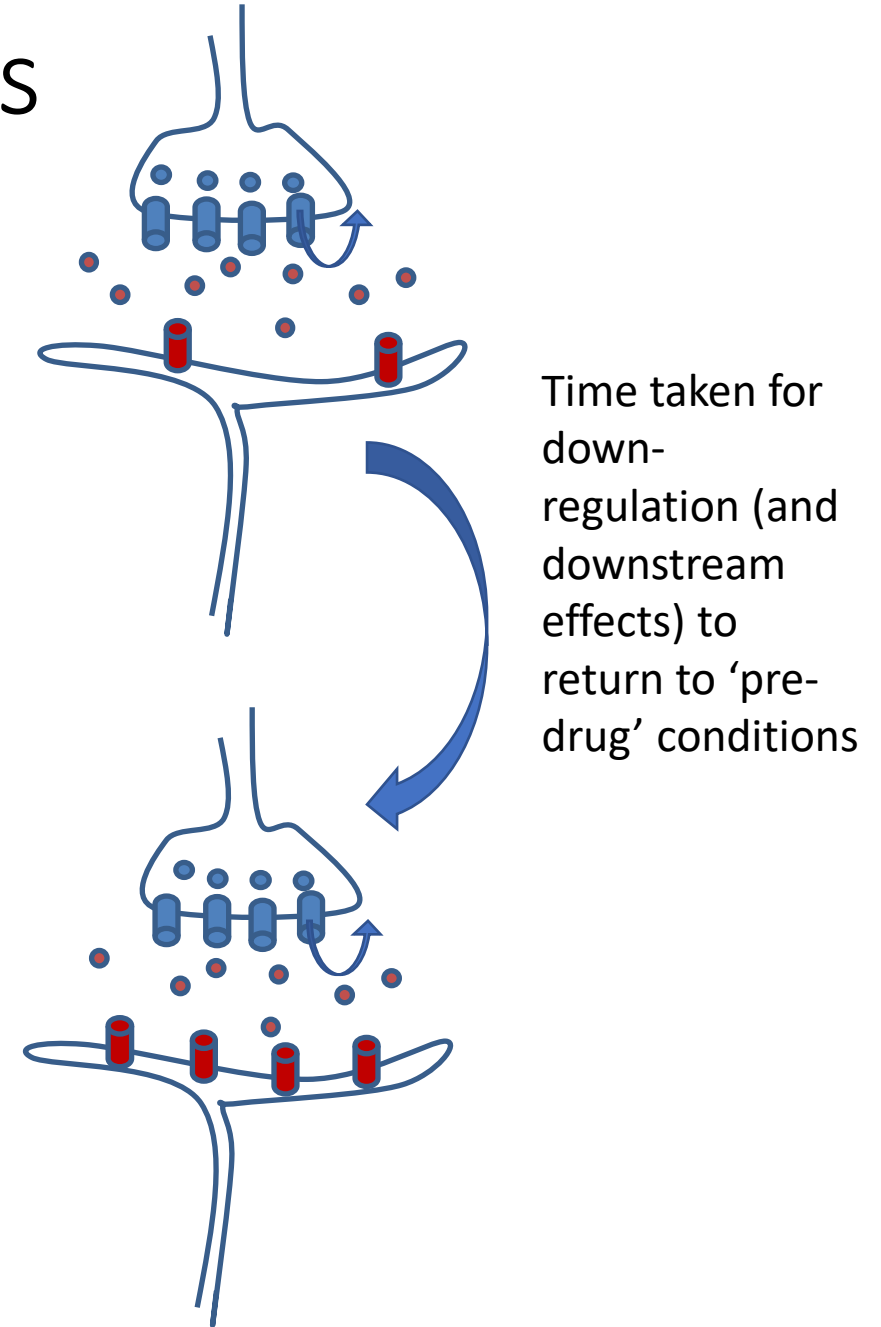
Systematic review (Davies and Read, 2018) – Incidence and severity

- This review found from a weighted average of 14 trials that measured incidence that **about half of patients (56%) experienced withdrawal symptoms** (range 27% to 85%) (Davies and Read, 2018)
- In surveys, 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



Duration of withdrawal symptoms

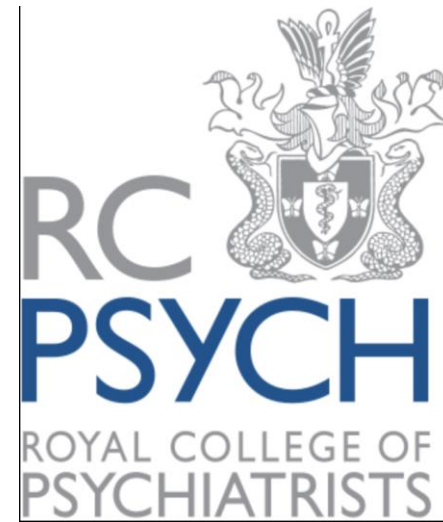
- In 7 out of 10 studies identified, withdrawal symptoms went for longer than weeks
- Some surveys found patients had withdrawal symptoms for months or years
- How can symptoms last so long after the drug is out of the body?
- It is the time taken for adaptations to the drug to resolve that determines the length of the time for withdrawal – not how long it takes the drug to be eliminated from the body
- Long-term use of antidepressants can cause long-term changes to the brain (identified on PET scanning even after short-term use)



Why so much variation between people?

- Why do some people have great difficulty in stopping and others no trouble?
- Likely due to differing degree of adaptation to the drug – e.g. fast metabolisers will be exposed to less drug, adapt less and have less trouble when they stop
- Psychological factors likely to be minimally contributory
 - in studies of placebo effects – i.e. when antidepressant is not stopped – causes withdrawal effects in about 10% of participants compared to 40-50% when antidepressants are stopped

Royal College of Psychiatrists updates guidance (2019)



- Report says patients should be informed of “the potential in some people for **severe and long-lasting withdrawal symptoms** on and after stopping antidepressants”
- When an antidepressant is being considered this is part of informed consent for a patient



PS04/I9

**Position statement
on antidepressants
and depression**

NICE updates its Depression guidance CG90 (2019)

- “Explain that whilst the withdrawal symptoms which arise when stopping or reducing antidepressants can be mild and self-limiting, there is substantial variation in people's experience, **with symptoms lasting much longer (sometimes months or more) and being more severe for some patients**”

NICE

National Institute for
Health and Care Excellence

How to minimise withdrawal symptoms by
safely tapering

Royal College of Psychiatrists guidance on 'Stopping antidepressants'



Stopping antidepressants

- Published in October 2020
- Recommends patients who have been on antidepressants for more than a few 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

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

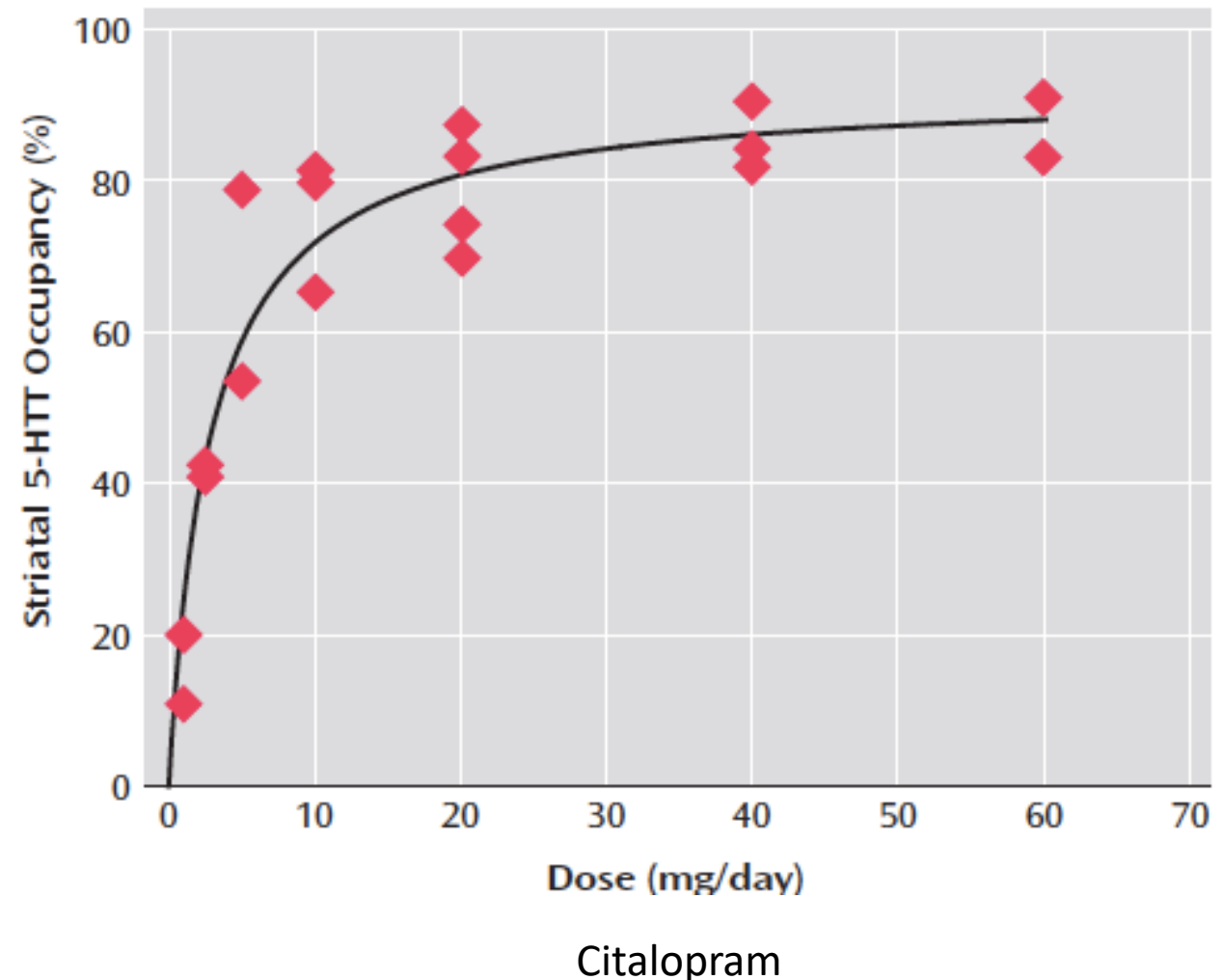
THE LANCET
Psychiatry

PERSONAL VIEW | VOLUME 6, ISSUE 6, P538-546, JUNE 01, 2019

Tapering of SSRI treatment to mitigate withdrawal symptoms

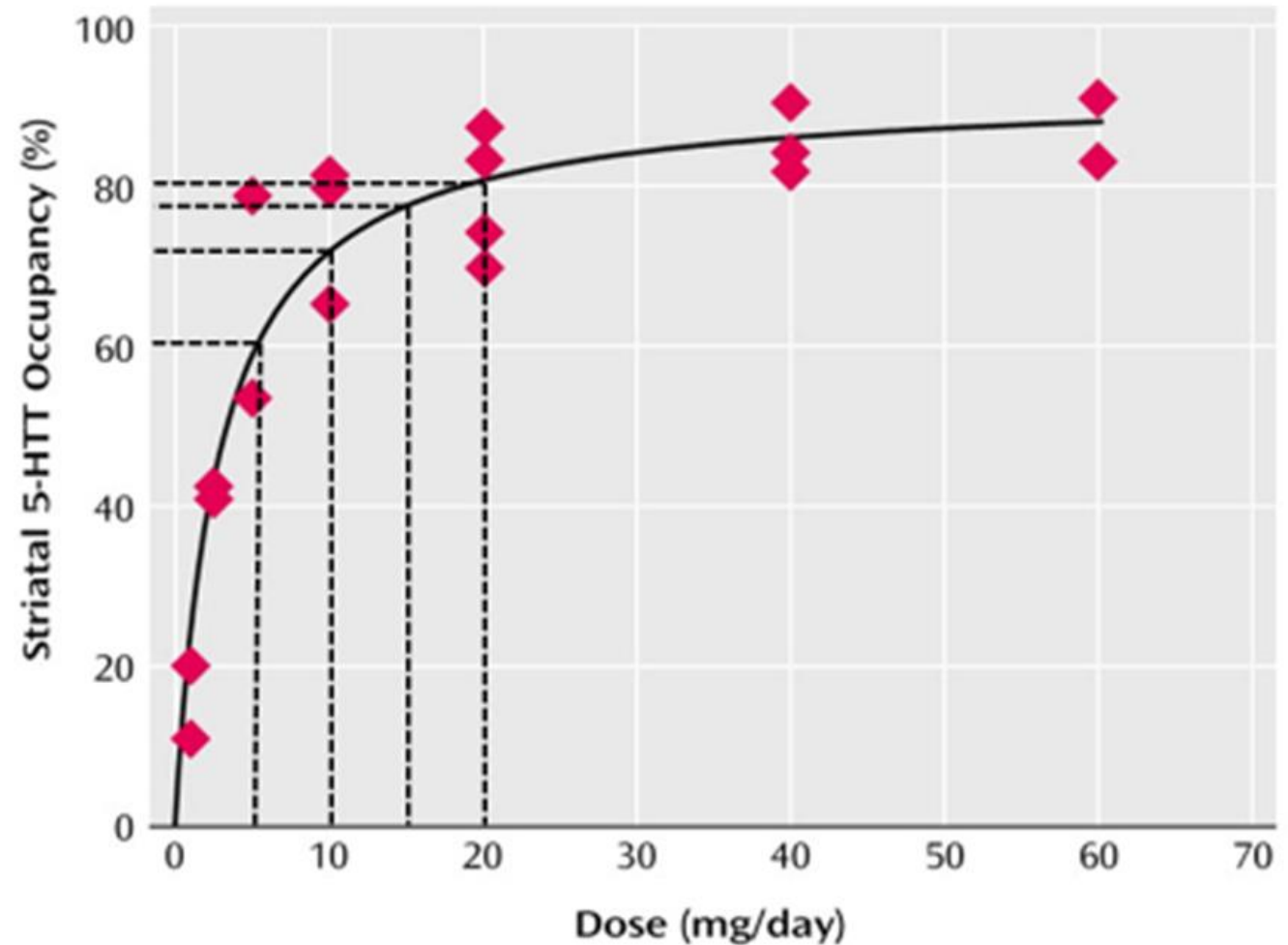
Mark Abie Horowitz, PhD • Prof David Taylor, PhD

Published: March 05, 2019 • DOI: [https://doi.org/10.1016/S2215-0366\(19\)30032-X](https://doi.org/10.1016/S2215-0366(19)30032-X) • [Check for updates](#)



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



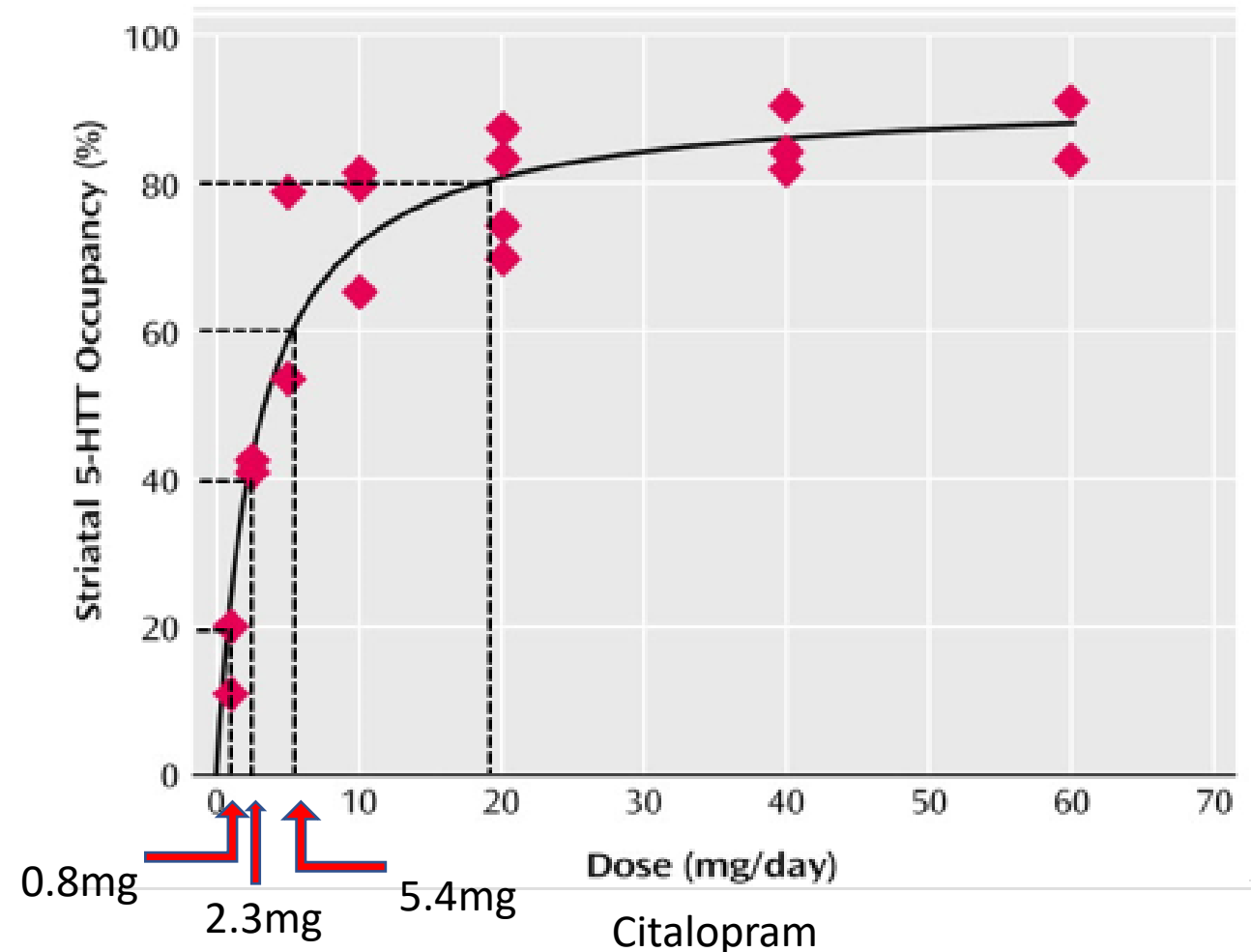
Citalopram

Patient perspective – the lower the dose the harder it is to reduce

- ‘It was the last few beads [of the drug] that were the hardest to come off’
- ‘I started on 75mg of venlafaxine. I had no problem tapering down till I got down to 15mg. Every time I would go down another 5mg I was so dizzy and had so many zaps I couldn’t handle it. I had to go down by 1 mg at a time. I still can’t get below 5mg.’

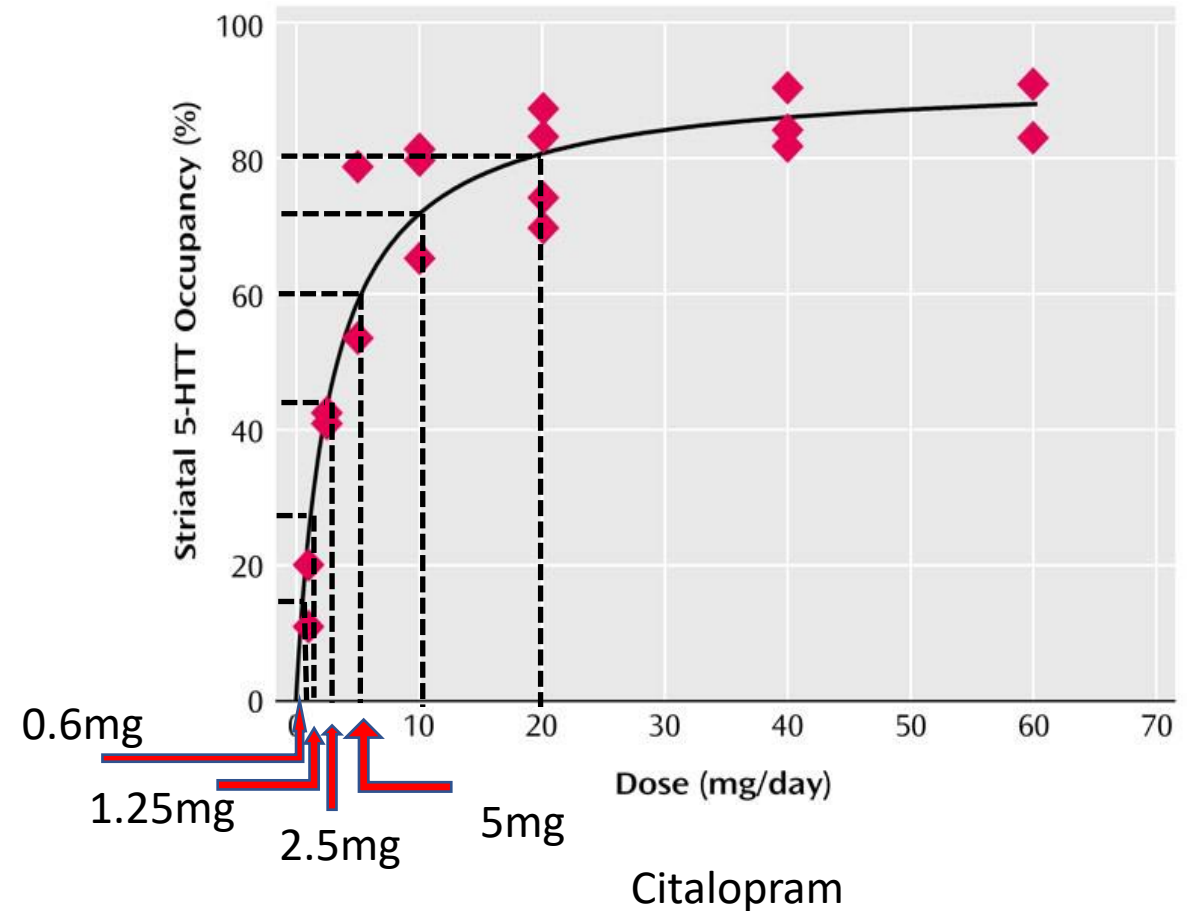
What happens when you taper by fix amounts of effect on the brain? Hyperbolic dose decrease

- 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 fix 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 (which preserves a roughly hyperbolic regime)



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)

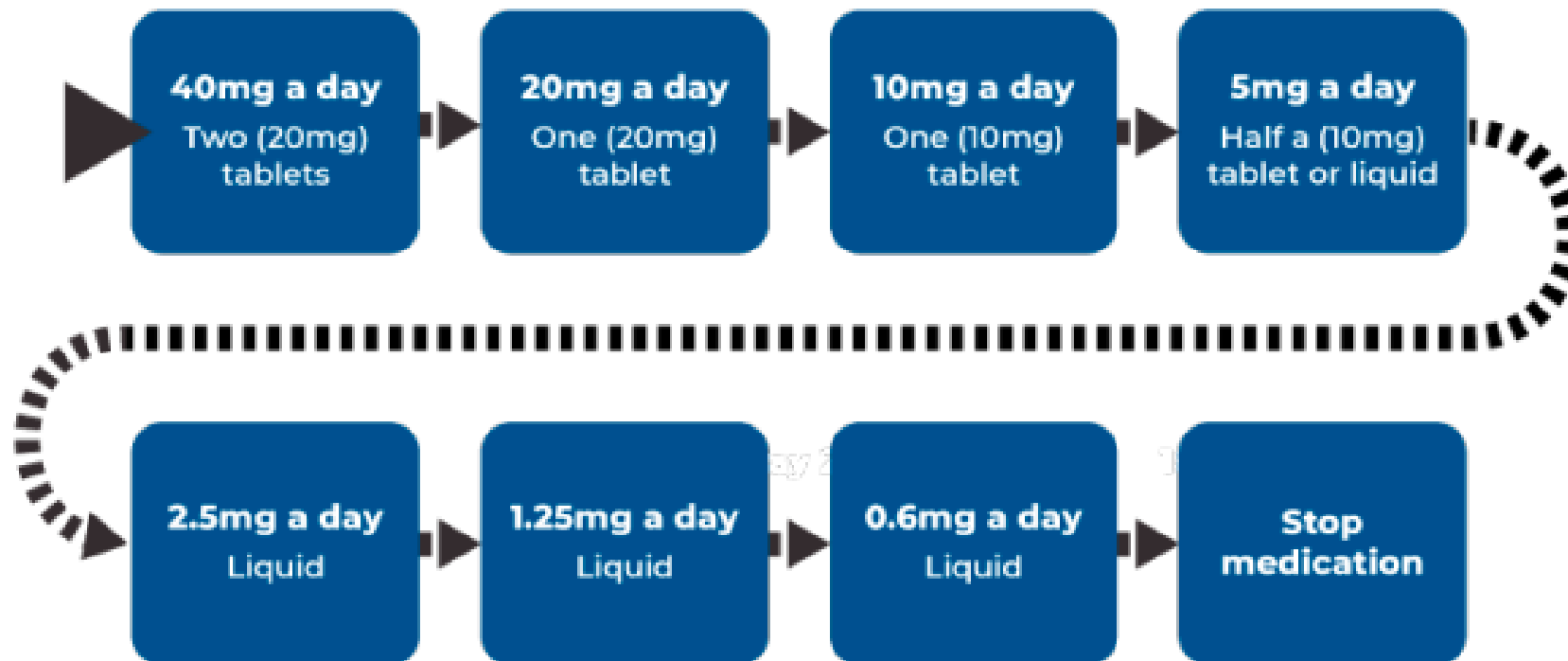


Stopping antidepressants

A rapid reduction schedule (RCPsych, 2020)

Citalopram

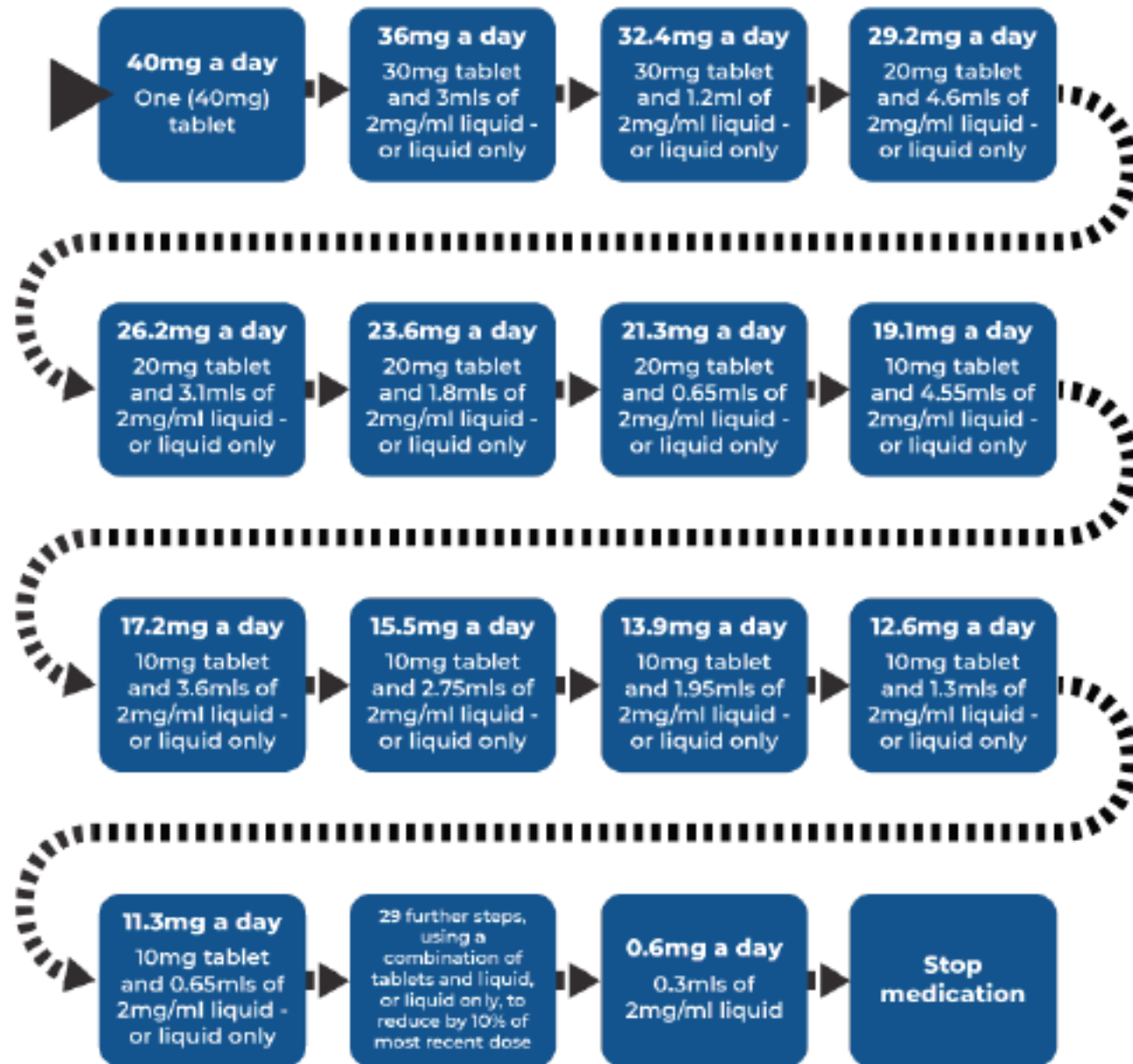
Reduction of dose by 50%, every 2-4 weeks. Some people may need to reduce more slowly.



- 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)

NICE guidelines



NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE

Guideline

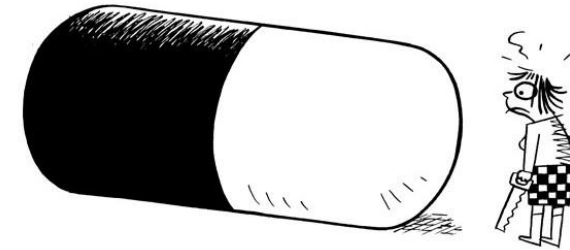
Depression in adults

Draft for consultation, November 2021

- Update to Depression guidelines will be published in June 2020, including guidance on stopping antidepressants, including:
 - “slowly reduce the dose to a *proportion* of the previous dose (for example, prescribe 75% or 50% of the previous dose), rather than by a fixed dose reduction [linear]”
 - “use liquid preparations if necessary to allow slow tapering, once small doses have been reached”
 - “ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have resolved before making the next dose reduction”
 - “recognise that withdrawal [the process of discontinuation] may take weeks or months to complete successfully [and can take years in some].”

How to make these small doses?

- Tablet cutters will be needed to divide tablets – into halves and quarters
- At smaller doses liquid preparations will be required – available for many antidepressants (e.g. in UK and Europe) – using small syringes



Good luck with
the tapering of
your medication



Sigmund copyright 2018 Peter de Wit

180524

Liquid	Oral drops	Dispersible tablets
Fluoxetine	Citalopram	Mirtazapine
Imipramine	Escitalopram	Fluoxetine
Mirtazapine		
Paroxetine		
Amitriptyline		
Trazadone		

How to make these small doses?

- Another alternative is compounding pharmacies that make up small dose tablets
- One example is a Dutch pharmacy that manufacturers ‘tapering strips’ which make drugs up in small dose tablets:
 - e.g. for citalopram - 0.1mg, 0.2mg, 0.5mg, 1mg, 2mg, 5mg – allowing many doses to be made up
 - Shown to be helpful in several observational trials (Groot and van Os, 2019, 2020, 2021)



20.0 mg	20
19.5 mg	10 5 2 2 0.5
19.5 mg	10 5 2 2 0.5
19.0 mg	10 5 2 2
18.5 mg	10 5 2 1 0.5
18.0 mg	10 5 2 1
18.0 mg	10 5 2 1
17.5 mg	10 5 2 0.5
17.0 mg	10 5 2

Thank you for listening

- Questions?
- My email for any further questions:
m.horowitz@ucl.ac.uk

References

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