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Psychiatry and Addictions Case Conference

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ANTIDEPRESSANT WITHDRAWAL AND HELPING PATIENTS TO STOP SAFELY

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SPEAKER DISCLOSURES

- ✓ I am co-founder of Outro Health, a digital clinic helping patients to stop unnecessary antidepressants via supported gradual hyperbolic tapering in Canada and the US (2023)

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OBJECTIVES

1. To understand what withdrawal symptoms from antidepressants are and why they occur
2. To understand the existing evidence for their incidence, severity and duration
3. Understand why stopping antidepressants should be done gradually and according to a hyperbolic pattern

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SUBJECTIVE ACCOUNTS OF ANTIDEPRESSANT WITHDRAWAL

- “I am currently trying to wean myself off of venlafaxein which honestly is the most awful thing I have ever done. I have horrible dizzy spells and nausea whenever I lower my dose.” (Pestello & Davis-Berman, 2008).
- “It took me almost two years to get off Paroxetine and the side effects were horrendous. I even had to quit my job because I felt sick all the time. Even now that I am off it, I still feel electric shocks in my brain.” (Pestello & Davis-Berman, 2008)
- “The withdrawal effects if I forget to take my pill are severe shakes, suicidal thoughts, a feeling of too much caffeine in my brain, electric shocks…insane mood swings. ….. kinda stuck on them now coz I'm too scared to come off it.” (Gibson, Cartwright, & Read, 2016).

OFFICIAL GUIDANCE ON ANTIDEPRESSANT WITHDRAWAL SYNDROME UNTIL 2019 (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’

OFFICIAL GUIDANCE ON ANTIDEPRESSANT WITHDRAWAL IN THE US

- American Psychiatric Association says in its depression guidance (2010):
  - "Discontinuation-emergent symptoms….typically resolve with specific treatment over 1-2 weeks. However some patients do experience protracted discontinuation syndromes."
  - Suggests these symptoms occur only in the circumstance of "abrupt discontinuation."

OFFICIAL GUIDANCE ON MANAGEMENT OF ANTIDEPRESSANT WITHDRAWAL SYNDROME (UK)

- Until 2022 NICE guidance 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)
- There was no guidance on how to reduce the dose, what 'gradually' means and what a 'longer period' may entail
- 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. expert consensus)

OFFICIAL GUIDANCE ON MANAGEMENT OF ANTIDEPRESSANT WITHDRAWAL SYNDROME (US)

- The APA recommends:
  - "it is best to taper the medication over the course of at least several weeks"
  - For some medications they say patients "may require a slower downward titration" and they also suggest a switch to fluoxetine

CONSEQUENCE: PEOPLE TURN TO PEER SUPPORT WEBSITES ONLINE FOR GUIDANCE

750,000 hits a month

150,000 hits a month

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

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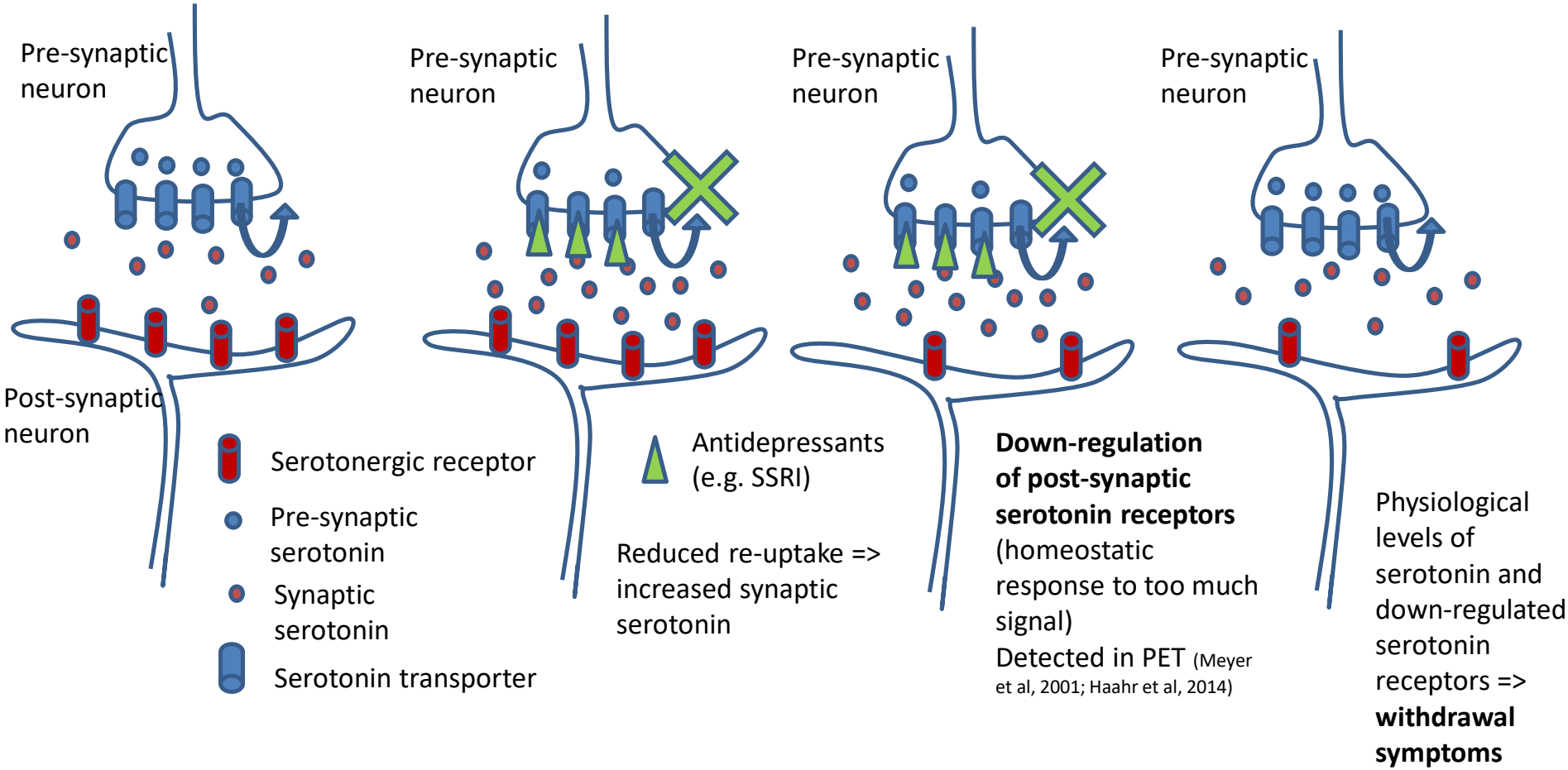
EFFECT OF LONG-TERM ANTIDEPRESSANT USE AND STOPPING

OF LONG-TERM ANTIDEPRESSANT USE AND STOPPING



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ANTIDEPRESSANT WITHDRAWAL SYNDROME

- A collection of psychological and physical symptoms that occur on stopping – or reducing the dose – of an antidepressant
- Occur because changes to the brain caused by antidepressant use take time to resolve
- Most common symptoms are (Fava et al. 2015) :
  - **Dizziness**, insomnia, impaired concentration, fatigue
  - Headache, tremor, tachycardia, nightmares
  - Neurological: muscle tremor, akathisia
  - 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)

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MINIMAL ROLE FOR PSYCHOSOMATIC EFFECTS

- Some have suggested these may be nocebo effects (expectations of negative outcomes from stopping medication, opposite of the placebo effect)
- However animals have been demonstrated to have withdrawal effects (Renoir et al. 2013)
- Neonates from mothers on antidepressants show withdrawal effects (Gastaldon et al. 2022)
- Withdrawal effects demonstrated in double-blind staggered randomized controlled trials (where neither the researcher or patient know whether the drug has been stopped or continued) (Rosenbaum et al 1998)
- In studies of nocebo effects – i.e. when antidepressant is not stopped – causes withdrawal effects in about 10% of participants compared to 40-50% when antidepressants are stopped(Rosenbaum et al, 1998)
- Like any experience, there are likely to be psychological factors, but a minor effect for antidepressant withdrawal

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). Some patients have delayed effects even after short half-life antidepressants (physiology not yet understood)
  - 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-inciding 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

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

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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

ELSEVIER

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?

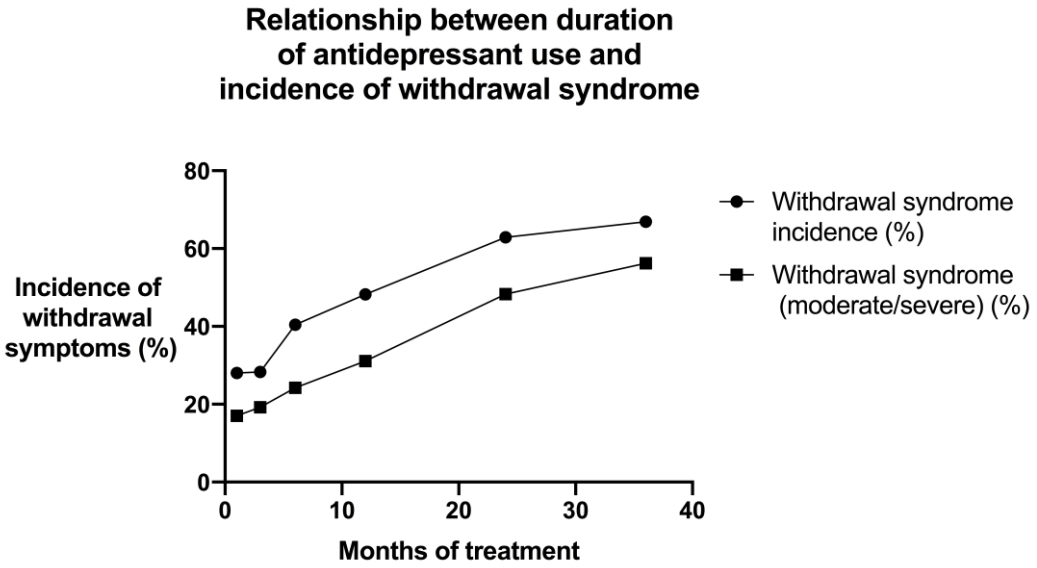
James Davies [a, b], John Read [c, d]

SYSTEMATIC REVIEW (DAVIES AND READ, 2019) - INCIDENCE

- This review found from a weighted average of 14 trials (of varying methodology) that measured incidence that **about half of patients (56%) experienced withdrawal symptoms** (range 27% to 85%) (Davies and Read, 2018)
- Restricting studies just to double-blind RCTs, gives a value of 53.9% for incidence of withdrawal effects

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



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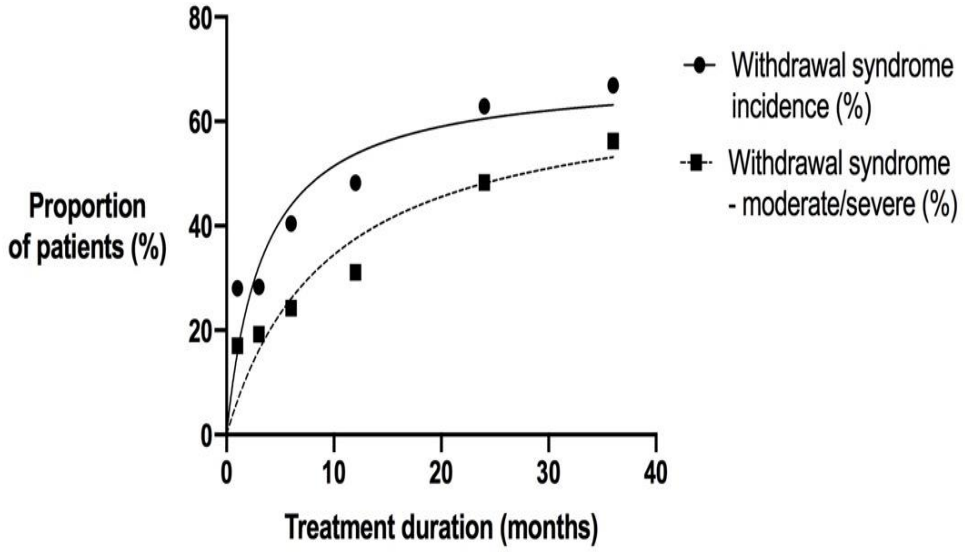
SEVERITY ALSO DEPENDS ON DURATION OF AD USE(DAVIES AND READ REVIEW)



Duration of antidepressant use	Withdrawal effects – any severity (%)	Withdrawal effects – **moderate or severe** (%)
<3 months	28.0	17.0
3-6 months	28.3	19.2
6-12 months	40.4	24.2
1-2 years	48.2	31.1
2-3 years	62.9	48.3
>3 years	66.9	56.2

- Data derived from survey of patients (Read et al., 2018)
- May not be representative of wider population but dose-response evident for longer term use

Unpublished data, article submitted

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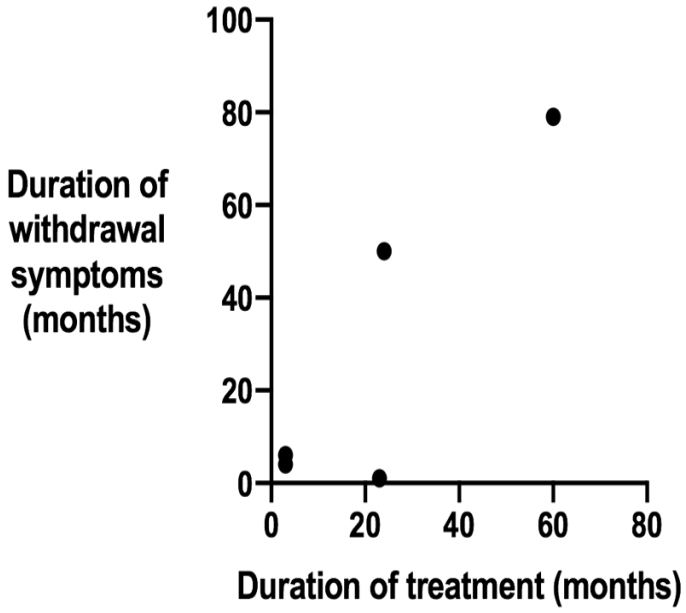
SYSTEMATIC REVIEW – DURATION (DAVIES AND READ, 2018)



Duration of antidepressant use (months)	Duration of withdrawal symptoms (weeks)	Study
3	4	Zajecka et al., 1998
3	6	Narayan & Haddad, 2010
23	1	Bogetto et al., 2002
24	50	Davies et al., 2018
60	79	Stockmann et al., 2018

WITHDRAWAL SYMPTOMS LAST FOR SEVERAL MONTHS (RCT)

- In a large double blind RCT, patients who were on antidepressants for more than 2 years and felt well enough to stop were randomized to continue or stop their antidepressants
- withdrawal symptoms in patients who were discontinued were increased above maintenance patients for 39 weeks

The NEW ENGLAND JOURNAL of MEDICINE

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Maintenance or Discontinuation of Antidepressants in Primary Care

Gemma Lewis, Ph.D., Louise Marston, Ph.D., Larisa Duffy, B.Sc., Nick Freemantle, Ph.D., Simon Gilbody, Ph.D., Rachael Hunter, M.Sc., Tony Kendrick, M.D., David Kessler, M.D., Dee Mangin, F.R.N.Z.C.G.P., Michael King, Ph.D., Paul Lanham, B.A., Michael Moore, F.R.C.G.P., Irwin Nazareth, Ph.D., Nicola Wiles, Ph.D., Faye Bacon, B.Sc., Molly Bird, M.Sc., Sally Brabyn, M.Sc., Alison Burns, B.Sc., Caroline S. Clarke, Ph.D., Anna Hunt, M.Sc., Jodi Pervin, B.Sc., and Glyn Lewis, Ph.D.

Outcome	Maintenance Group (N=238)	Discontinuation Group (N=240)	Effect Size or Difference (95% CI)†
No. of new or worsening symptoms on modified DESS			
12 wk	1.3±2.4	3.1±3.5	1.9 (1.5 to 2.3)
26 wk	1.4±2.3	1.9±2.9	0.5 (0.1 to 0.9)
39 wk	0.8±1.6	1.7±2.7	0.9 (0.6 to 1.3)
52 wk	0.8±1.8	1.1±2.5	0.3 (–0.0 to 0.6)

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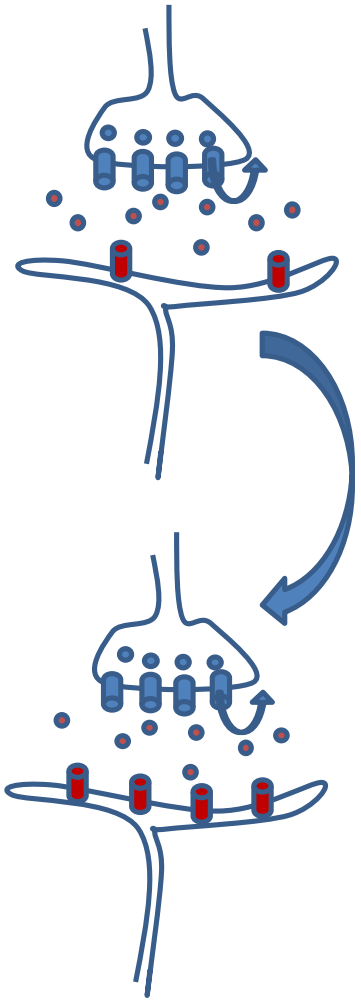
DURATION OF WITHDRAWAL SYMPTOMS

- 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 take 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)



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

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WHY SO MUCH VARIATION BETWEEN PEOPLE?

- Why do some people experience severe withdrawal symptoms and others do not?
  - Which drug they are taking
  - Duration of use
  - Dose
  - Previous history of medication switching/stopping
- 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
- Little research into variation in sensitivity to antidepressant withdrawal
- Psychological factors likely to be minimally contributory
  - In studies of nocebo effects – i.e. when antidepressant is not stopped – causes withdrawal effects in about 10% of participants compared to 40-50% when antidepressants are stopped; severity not measured (Rosenbaum et al, 1998)

ROYAL COLLEGE OF PSYCHIATRISTS UPDATES GUIDANCE (2019)

RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

PS04/19

Position statement on antidepressants and depression

- 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

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NICE UPDATES ITS DEPRESSION GUIDANCE CG90 (2022)

1.4.15 Explain to people taking antidepressant medication that:

- withdrawal symptoms can be mild, may appear within a few days of reducing or stopping antidepressant medication, and usually go away within 1 to 2 weeks
- withdrawal can sometimes be more difficult, with symptoms lasting longer (in some cases several weeks, and occasionally several months)
- withdrawal symptoms can sometimes be severe, particularly if the antidepressant medication is stopped suddenly. **[2022]**

- We know that in some patients withdrawal symptoms can last for years, and for some they can be disabling (Guy et al. 2020, Hengartmer et al. 2020)

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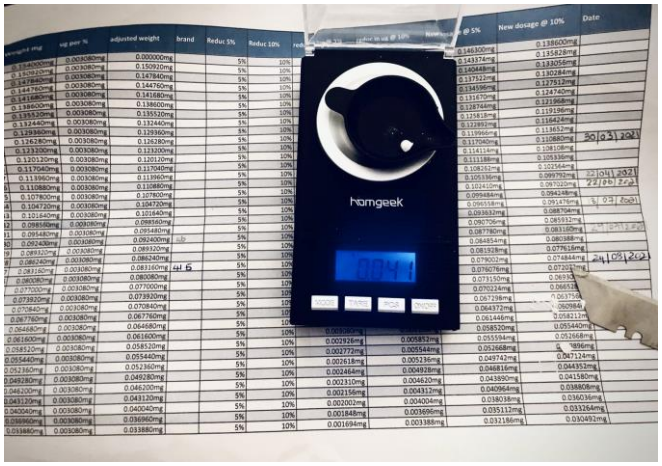

SAFE TAPERING OF ANTIDEPR

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NICE UPDATE TO TAPERING ANTIDEPRESSANTS

- In June 2022 NICE updated its guidance on how to safely stop antidepressants
- Based in part on the Royal College of Psychiatrists' guidance on this topic, which is linked to in the NICE depression guidance

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** for some patients
- Recommends going down in **smaller and smaller sized reductions**
- Rate **titrated to the individual**'s ability to tolerate the process

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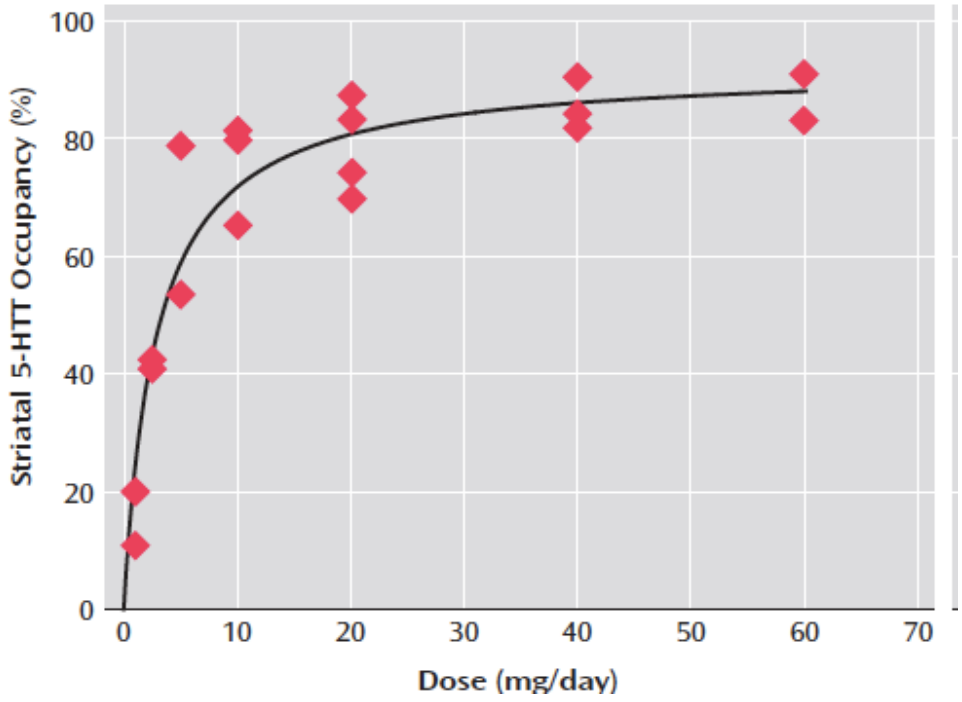
MANAGEMENT OF THE ANTIDEPRESSANT WITHDRAWAL SYNDROME

- 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



Citalopram

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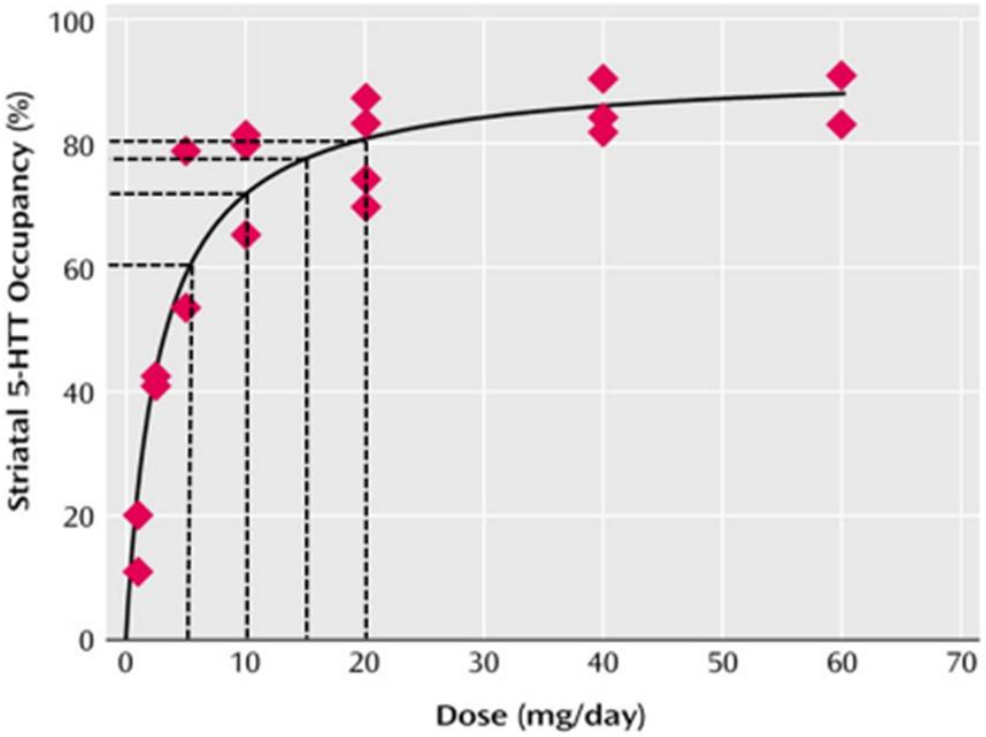
WHAT HAPPENS WHEN YOU TAPER LINEARLY?

- 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

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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.’

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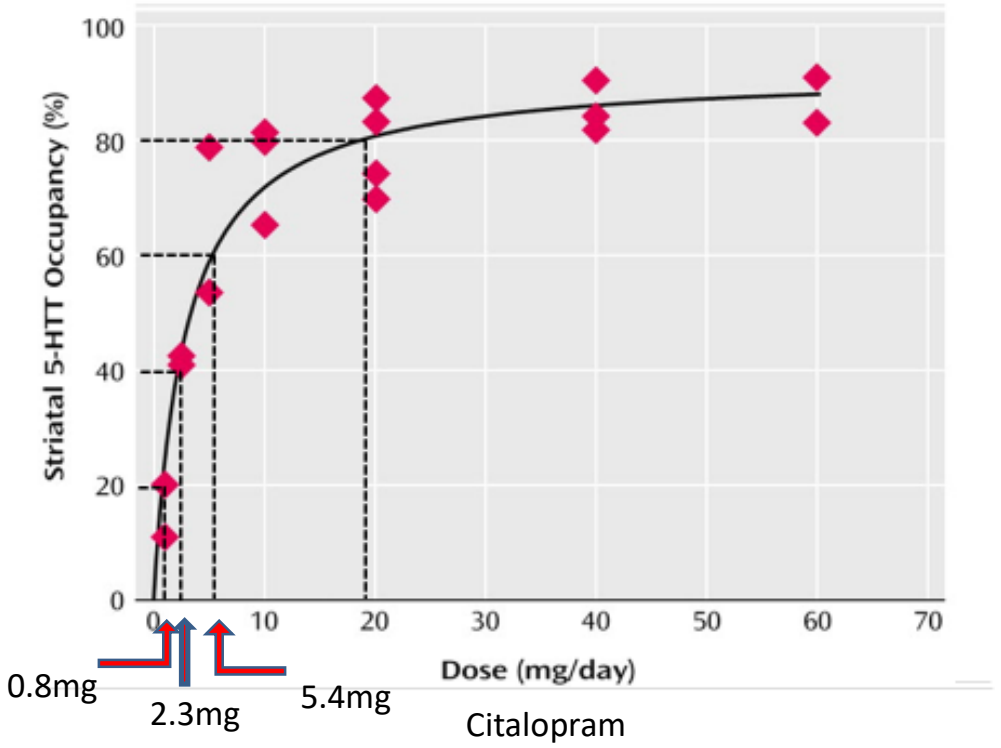
WHAT HAPPENS WHEN YOU TAPER BY FIX AMOUNTS OF EFFECT ON THE BRAIN? HYPERBOLIC DOSE DECREASE

- 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



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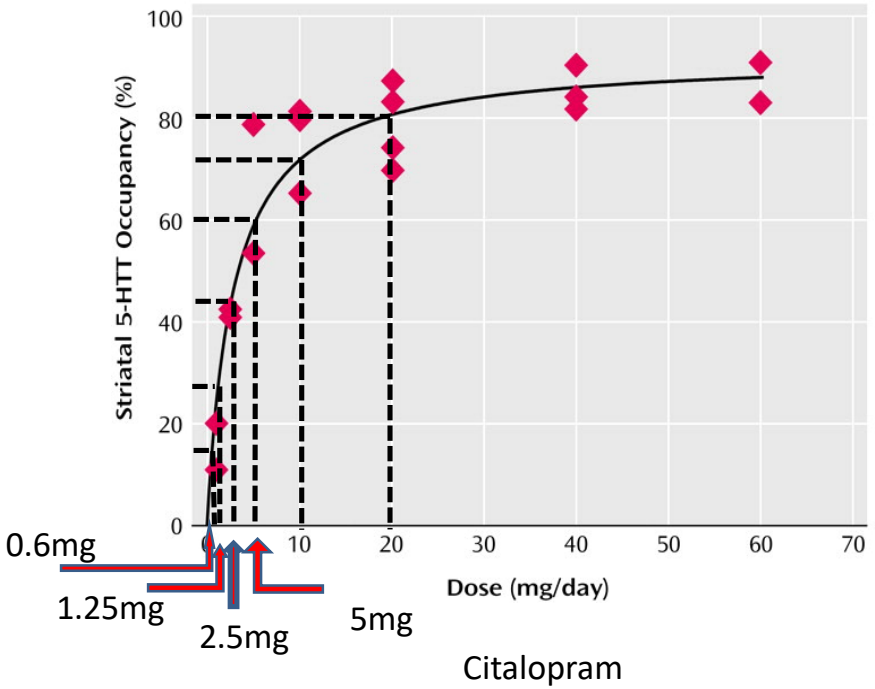
WHAT HAPPENS WHEN YOU TAPER BY FIX AMOUNTS OF EFFECT ON THE BRAIN? PROPORTIONATE DOSE DECREASE

- 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)



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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

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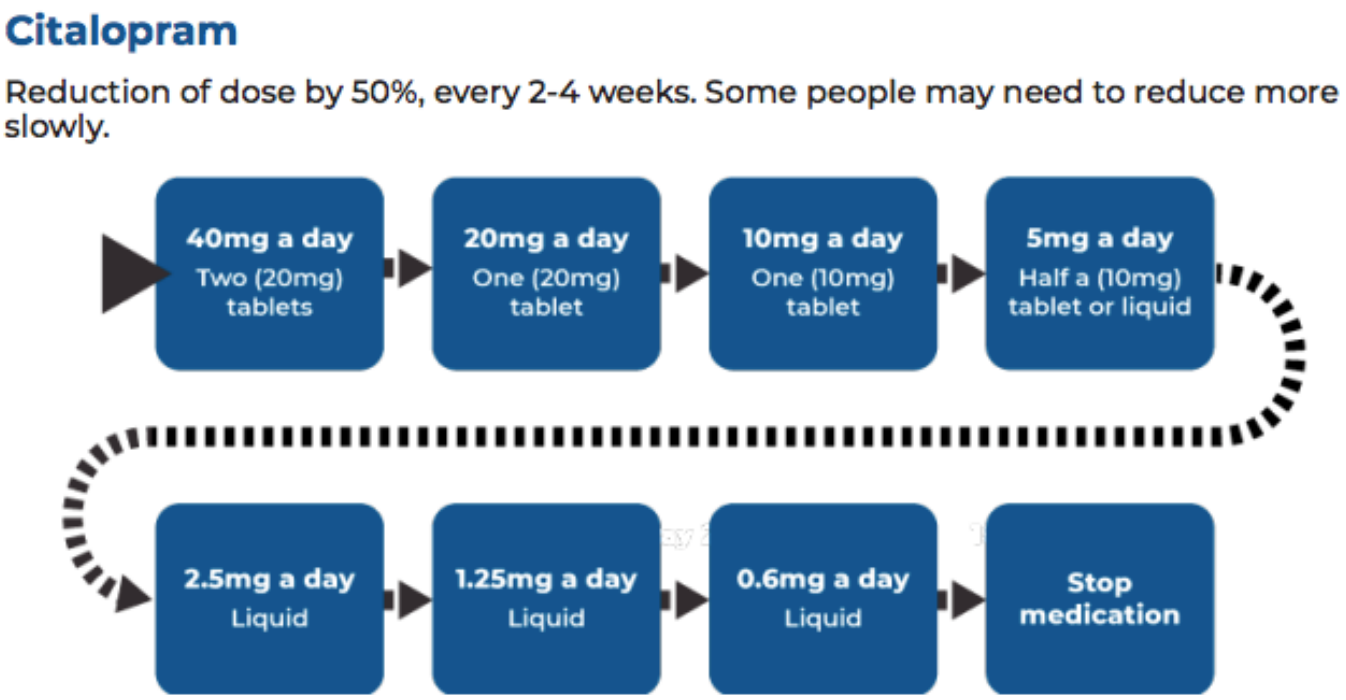
A RAPID REDUCTION SCHEDULE (RCPSYCH, 2020)



- Total time required: 3-6 months

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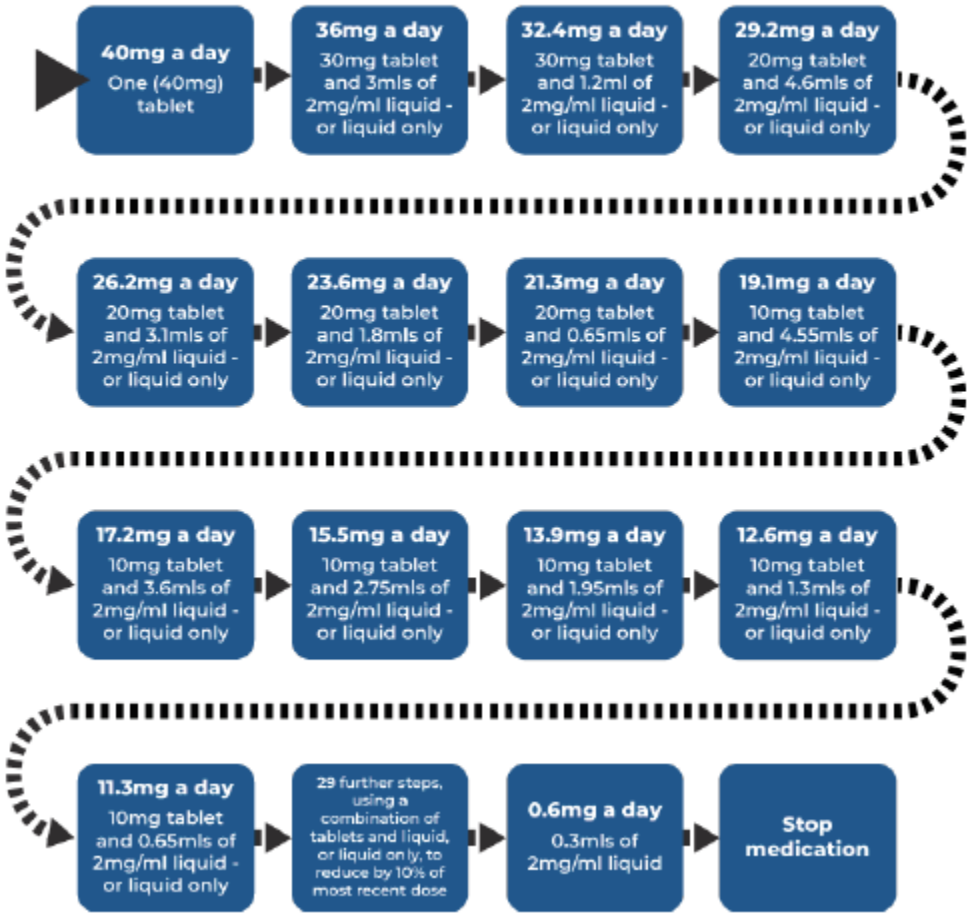
Paroxetine

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)

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NICE GUIDELINES

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Depression in adults

Draft for consultation, November 2021

- Update to Depression g 2, including guidance on stopping antidepressants, including (my italics and bolding):
  - "slowly reduce the dose to zero in a step-wise fashion, at each step prescribing a *proportion* of the previous dose (for example, 50% of the previous dose)"
  - "Consider using smaller reductions (for example, 25%) as the dose becomes lower"
  - "if, once very small doses have been reached, slow tapering cannot be achieved using tablets or capsules, consider using ***liquid preparations*** if available"
  - "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 or are tolerable before making the next dose reduction"
  - "recognise that withdrawal [the process of discontinuation] may take weeks or months to complete successfully" [It can take years in some patients].

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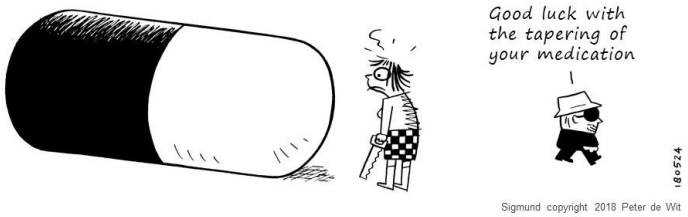
HOW TO MAKE THESE SMALL DOSES?

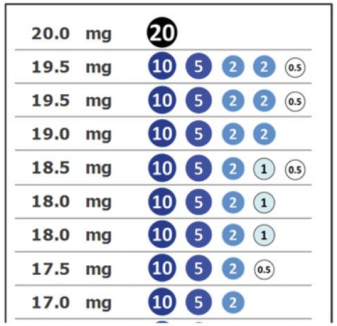
- Tablet cutters will be needed to divide tablets – into halves and quarters
- At smaller doses liquid preparations will be required – available for many antidepressants (e.g. in UK, Europe and the US) –using small syringes



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)



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TAKE HOME MESSAGES 1

- 1 -Feeling anxious or depressed when reducing/stopping antidepressants is not necessarily a sign of relapse – these symptoms are common in withdrawal (and can be very familiar) but high index of suspicion for withdrawal
- 2 – Tapering antidepressants over much longer periods (months or sometimes years) than usual practice (weeks) is more likely to be successful
- 3 - Make reductions by smaller and smaller amounts as total dose gets lower (called proportionate or hyperbolic tapering)
- 4 – Some patients will need to go down to very small doses before stopping eg a fraction of a mg for many antidepressants

TAKE HOME MESSAGES - 2

- 5 – In order to make these small reductions patient will need access to ***liquid versions of drugs*** (or other small doses e.g. tapering strips)
- 6 – The rate of tapering should be modified based on the ability of the patient to tolerate reductions (i.e. withdrawal symptoms)
- 7 - With the exception of fluoxetine the short half-life of antidepressants means that every other day dosing risks withdrawal symptoms – it is better to the same does every day
- 8 – Guidance from the Royal College of Psychiatry, NICE, and the Maudsley Prescribing Guidelines are useful sources of information

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THANK YOU FOR LISTENING

- Questions?

- My email for any further questions:

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EXTRA SLIDES

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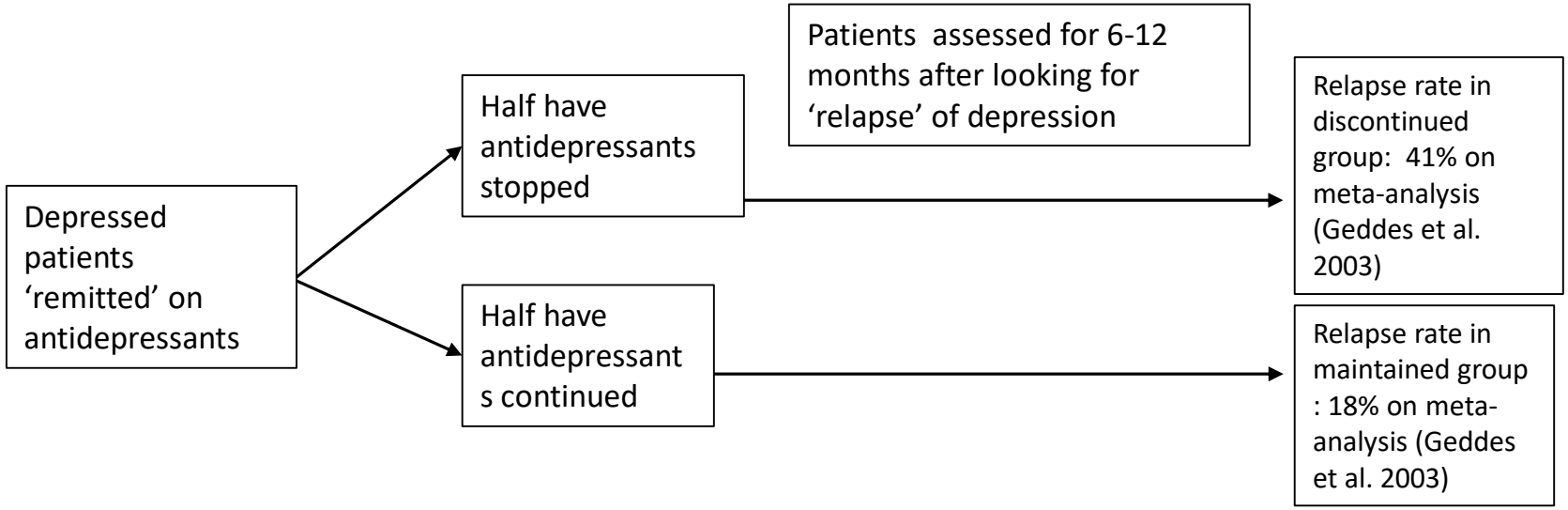
WITHDRAWAL SYMPTOMS VS DISCONTINUATION SYMPTOMS; ADDICTION VS DEPENDENCE

- In the UK the correct term ‘withdrawal symptoms’ are used for antidepressants not ‘discontinuation symptoms’ (an industry euphemism intended to distinguish their medication from benzodiazepines)
- Withdrawal symptoms do not imply addiction (which required craving, compulsion, etc) but only physical dependence
- Physical dependence is defined pharmacologically as the state of adaptation to a drug that forms over long-term use and manifests in a withdrawal syndrome on stopping –e.g. nicotine
- Dependence and addiction have become unfortunately conflated by their use in DSM (dependence chosen because it was thought less pejorative than addiction) – leading to confusion (O’Brien et al. 2011)
- Most antidepressants are not addictive – but they do cause physical dependence and withdrawal effects

EVIDENCE FOR LONG-TERM USE OF ANTIDEPRESSANTS IN RELAPSE PREVENTION

- There is a current 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

- Confounding issue?