Antidepressant withdrawal effects and safe deprescribing

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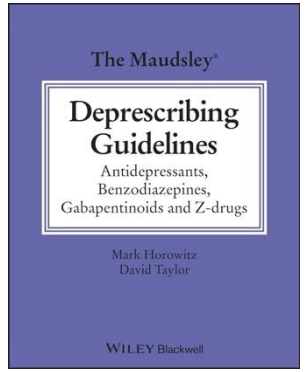
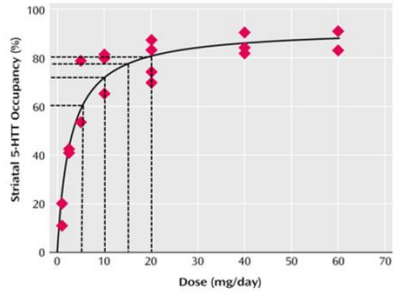




Australian antidepressant use

- 1 in 7 people (1 in 6 adults) in Australia on an antidepressant, about 3 million people
- Average duration of use is 4 years
- Most guidelines recommend 6-12 months of use for an episode of anxiety or depression
- Australia is amongst highest users of antidepressants in OECD
- Sertraline and escitalopram now in top 10 most prescribed drugs in Austrailia
- 1.5 fold more women than men
- 2-fold increase for older people
- More likely to be prescribed to poorer, inner regional regions

Patient montage

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

Long-standing Australian guidance on antidepressant withdrawal

- TG, RANZCP, etc: “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
- 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

Australian guidance on management of antidepressant withdrawal syndrome

- TG: “Reduce the antidepressant dose by 25 to 50% every 1 to 4 weeks until the daily dose is half the lowest unit strength available. Continue at the lowest dose for 2 weeks then stop.”

- Identical guidance in the UK 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 in practice: reduce dose by half for 2 weeks, reduce dose to quarter for 2 weeks (often by alternating half a tablet every second day)

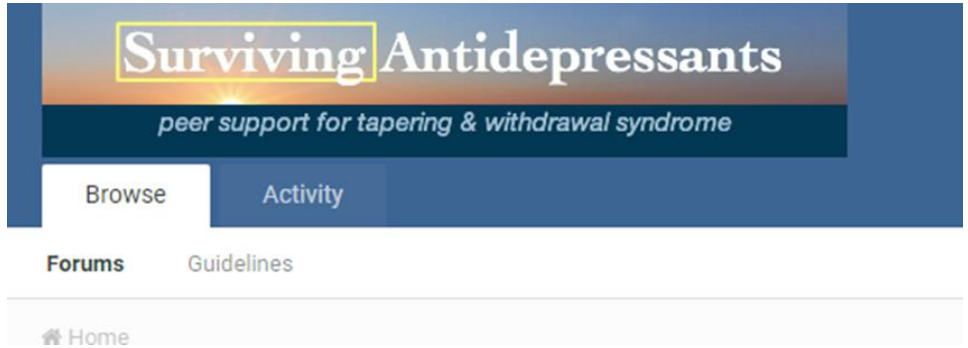
- Recent RCT found that 40% of patients on ADs >1-2 years who did not meet guidelines for ongoing use, low risk of withdrawal can come off by tapering over 2-4 months (ie slower than guidelines in Oz suggest).

- Leaves at least 60% of patients trapped on their medications with current approaches

Consequence: people turn to peer support websites for guidance

- 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).

150,000 hits a month

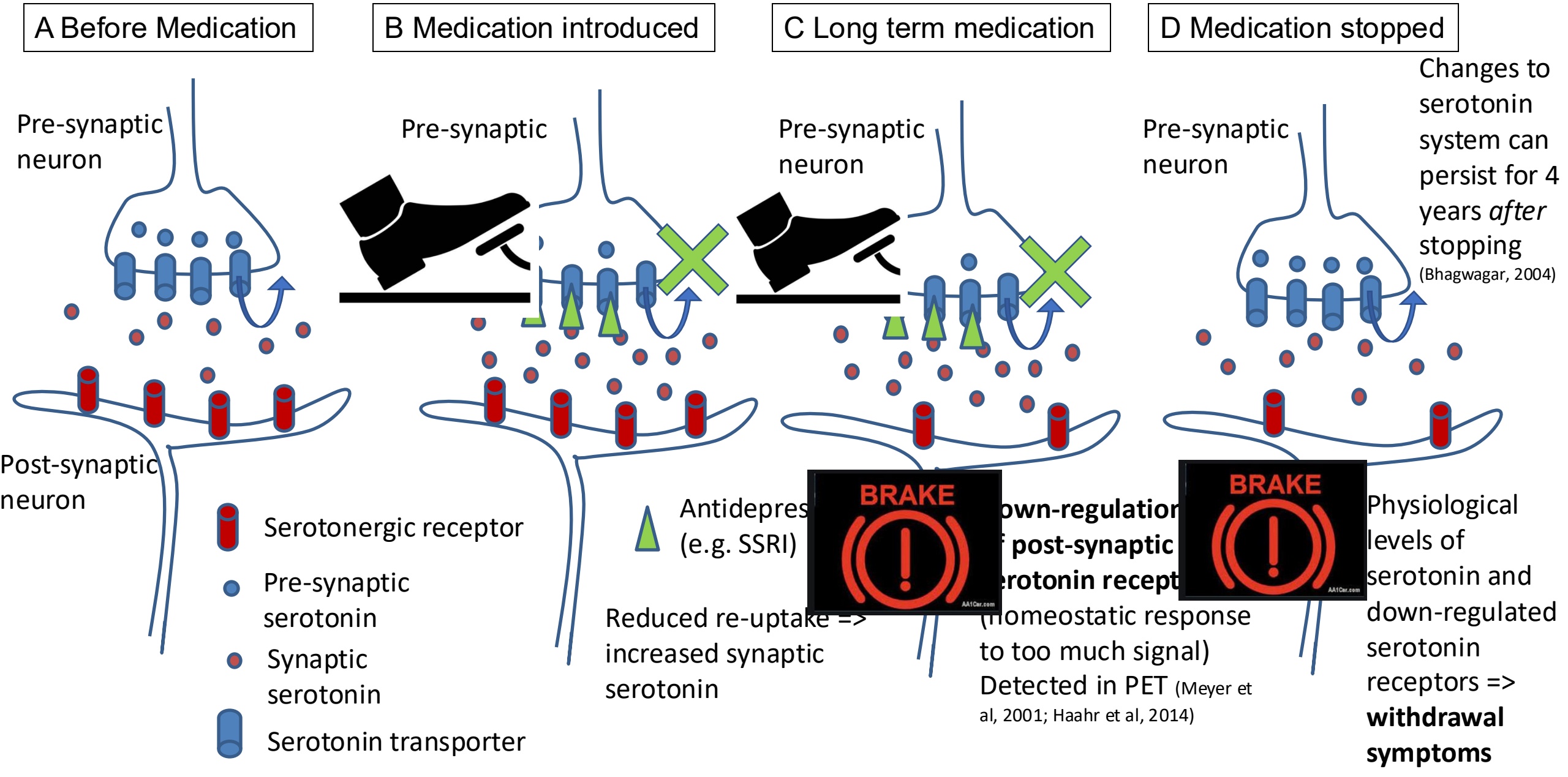


750,000 hits a month

Patients' experience and what they want

- 71% of respondents found their doctors' advice unhelpful. Main reasons:
  - 'Recommended a reduction rate that was too quick for me',
  - 'Not familiar enough with withdrawal symptoms to advise me' and
  - 'Suggested stopping antidepressants would not cause withdrawal symptoms'
- The most common tapering period suggested by doctors was 2 weeks and 4 weeks
- What patients wanted:
  - 'Access to smaller doses (e.g. tapering strips, liquid, smaller dose tablets) to ensure gradual reduction' (88%) and
  - 'A health professional providing a personalised, flexible reduction plan' (79%).

Effect of long-term antidepressant use and stopping



Duration of withdrawal symptoms

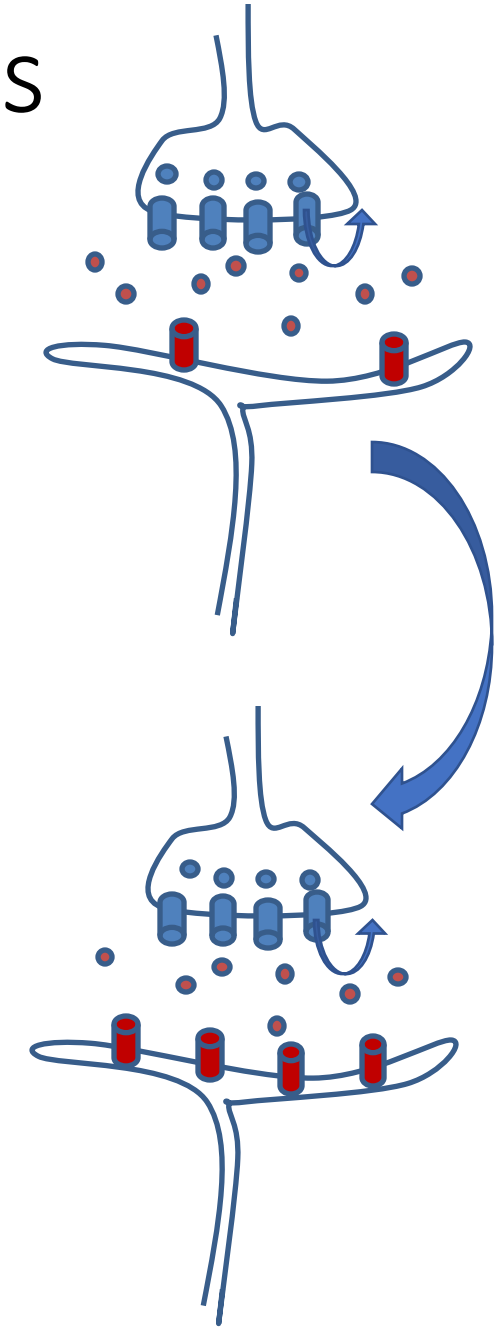
In 7 out of 10 studies identified, withdrawal symptoms went for longer than weeks

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) – also seen in animal studies (Renoir, 2013)



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

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 the drug use take time to resolve

Withdrawal symptoms do not require addiction (compulsion/craving etc) but only adaptation (often called physical dependence)

addiction involves craving, compulsive use etc – not relevant to antidepressants

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

Mis-diagnosing antidepressant withdrawal effects as relapse

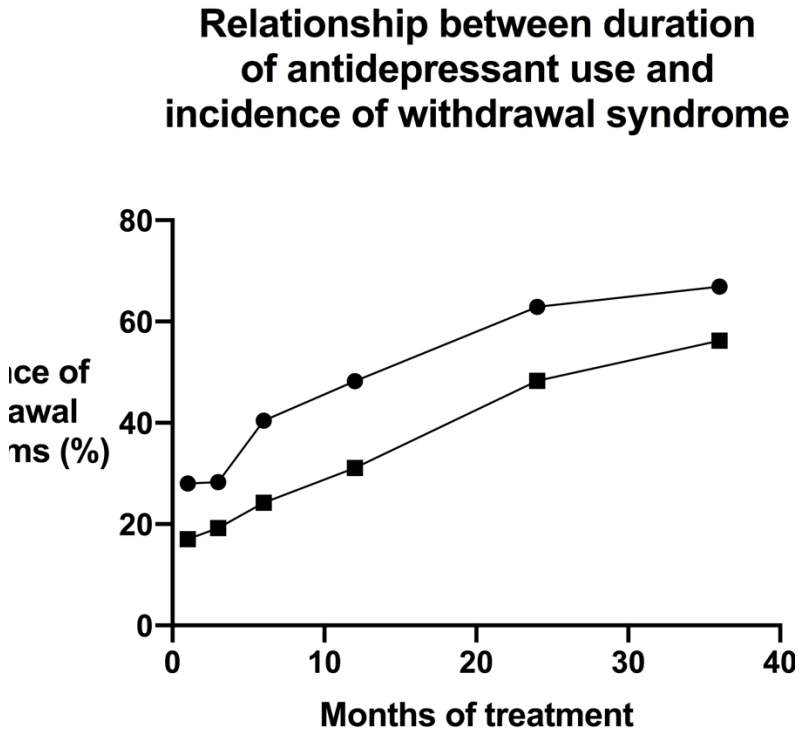
- Reported to occur by patients often but not studied in detail
- We surveyed 1400 people out of the 180,000 on peer support websites for tapering off antidepressants (and other similar drugs) – main reason given for being there
- Withdrawal symptoms can include *anxiety, depressed mood, insomnia, appetite 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')

- Clues to distinguish withdrawal from relapse:
  - Quick onset, but can be delayed (?perhaps because of slower dissociation from central compartment)
  - Specific symptoms (dizziness, electric shock, other symptoms not present in baseline condition)
  - Often quick resolution on re-instatement of antidepressant (hours, day or two)

- Can also be mis-diagnosed as chronic fatigue syndrome, medically unexplained syndrome, neurological disorder, onset of a new psychiatric disorder, etc

How common, severe and long-lasting are withdrawal symptoms?

- Average duration of exposure to antidepressants in captured studies: 25 weeks
  - US: half of patients on ADs for > 5 years (25 million)
  - Australia: average duration of use is 4 years
- Known that longer exposure to antidepressants is associated with more common and severe withdrawal symptoms (as for all drugs)
- In one survey,
  - After 3-6 months of AD use: 30% reported withdrawal effects, 1 in 5 as moderate or severe (similar to Henssler study) (Horowitz et al 2023)
  - After 3 years 65% reported withdrawal effects, 1 in 2 moderate or severe (similar to average Australian user)
- Longer term users of ADs have more common and more severe withdrawal effects



Protracted antidepressant withdrawal syndrome

- Withdrawal syndromes that can last for months or years increasingly recognised for antidepressants (Hengartner, 2020; Guy, 2020; Cosci 2020)
- 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, 100,000s 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)

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

		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%

Moncrieff et al, JAD Reports, 2024

Updates in official guidance on withdrawal

- For the last two decades the NICE guidelines has described withdrawal effects from antidepressants as “brief and mild” “lasting a week or two”
- In 2019 the Royal College of Psychiatrists reported that patients should be informed of “the potential in some people for **severe and long-lasting withdrawal symptoms** on and after stopping antidepressants”
- NICE in 2021: “[Withdrawal symptoms] can last longer (in some cases, several weeks, occasionally **several months**) and can sometimes be severe, particularly if the antidepressant medication is stopped suddenly.”
- Minimal update to TG/other guidelines

How to minimise withdrawal symptoms by safely tapering

Why deprescribe antidepressants?

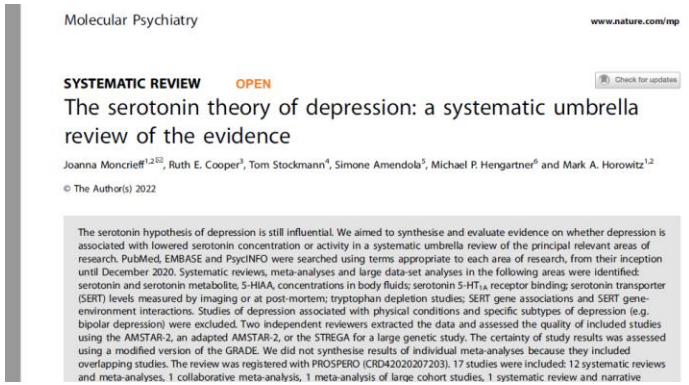
- Medication no longer needed
  - Stressor resolved (many patients prescribed these drugs in the context of divorce, job loss, physical health problem, death in family, etc – with relapse unlikely)
  - Alternative coping skills developed
  - Use for longer than guidelines recommend (mostly recommend 6-12 months for uncomplicated depression or anxiety): 30-50% of patients do not meet criteria for ongoing use (Kendrick, 2021)
- Improve quality of life by removing unwanted effects (harms outweigh benefits)
  - 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%)

Why deprescribe antidepressants?

- **Many patients continue antidepressants because they believe that antidepressants correct a chemical imbalance (e.g. low serotonin)**
  - 85% of Australian 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)
- **Avoid 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
- **Patient wishes to stop**
  - Desire to pursue alternative strategies
  - Woman wishes to become pregnant (antidepressants increase risk of foetal abnormality 2.5 to 3-fold (from low base rate))
- **Reduce pill burden, interactions with other medication**

What causes depression?

- For many years the public (and doctors) have been told that antidepressants work by ‘rectifying an underlying chemical imbalance’, normally said to be low serotonin
- Often translated to patients as ‘antidepressants for depression is like insulin for diabetes’
- Initially a scientific hypothesis, amplified by the manufacturers of antidepressants
- 6 decades of research has found no evidence of a difference between depressed people and healthy volunteers



Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2✉], Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

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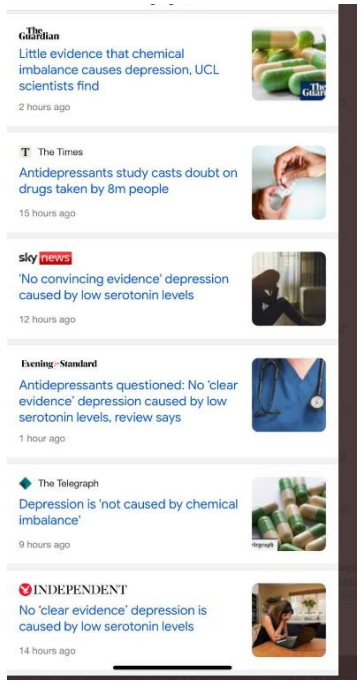
The serotonin hypothesis of depression is still influential. We aimed to synthesise and evaluate evidence on whether depression is associated with lowered serotonin concentration or activity in a systematic umbrella review of the principal relevant areas of research. PubMed, EMBASE and PsycINFO were searched using terms appropriate to each area of research, from their inception until December 2020. Systematic reviews, meta-analyses and large data-set analyses in the following areas were identified: serotonin and serotonin metabolite, 5-HIAA, concentrations in body fluids; serotonin 5-HT_{1A} receptor binding; serotonin transporter (SERT) levels measured by imaging or at post-mortem; tryptophan depletion studies; SERT gene associations and SERT gene-environment interactions. Studies of depression associated with physical conditions and specific subtypes of depression (e.g. bipolar depression) were excluded. Two independent reviewers extracted the data and assessed the quality of included studies using the AMSTAR-2, an adapted AMSTAR-2, or the STREGA for a large genetic study. The certainty of study results was assessed using a modified version of the GRADE. We did not synthesise results of individual meta-analyses because they included overlapping studies. The review was registered with PROSPERO (CRD42020207203). 17 studies were included: 12 systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of large cohort studies, 1 systematic review and narrative



The Guardian
Little evidence that chemical imbalance causes depression, UCL scientists find
2 hours ago

The Times
Antidepressants study casts doubt on drugs taken by 8m people
15 hours ago

sky news
'No convincing evidence' depression caused by low serotonin levels
12 hours ago

Evening Standard
Antidepressants questioned: No 'clear evidence' depression caused by low serotonin levels, review says
1 hour ago

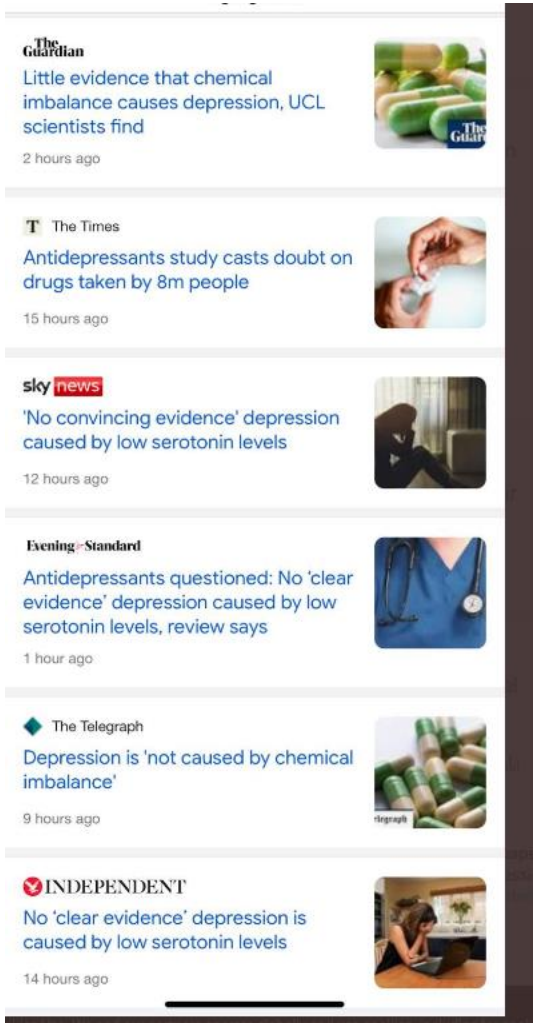
The Telegraph
Depression is 'not caused by chemical imbalance'
9 hours ago

INDEPENDENT
No 'clear evidence' depression is caused by low serotonin levels
14 hours ago

The serotonin hypothesis of depression

- It is now broadly held by academic psychiatrists that the serotonin/monoamine hypothesis is not supported
- The Royal College of Psychiatrists said: “the old idea that ADs [antidepressants] correct a chemical imbalance in the brain is an over-simplification and we do not support this view”. Their leaflet on depression no longer mentions low serotonin as a potential cause of depression
- Prominent psychiatric thought leaders have rejected it
  - Prominent US psychiatric leader referred to the "chemical imbalance" notion as a "kind of urban legend - never a theory seriously propounded by well-informed psychiatrists” (Pies, 2011)
  - The American Psychiatric Association has said “Additional experience has not confirmed the monoamine depletion hypothesis”
  - Prominent UK academic psychiatrists have said “the serotonin theory of depression has not been clearly substantiated” (Cowen and Browning, 2015)

However, the public has not been informed



- The paper is in the top 300 papers most shared or reported on out of 22 million papers tracked

Why deprescribe antidepressants? Barriers

- Many patients continue antidepressants because they believe that antidepressants correct a chemical imbalance (e.g. low serotonin)
  - 85% of Australian 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 unproven biological explanations for mechanisms of action exist (neurogenesis, inflammation, etc)

Molecular Psychiatry (2020) 25:321–338
https://doi.org/10.1038/s41380-019-0585-z

REVIEW ARTICLE

Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis

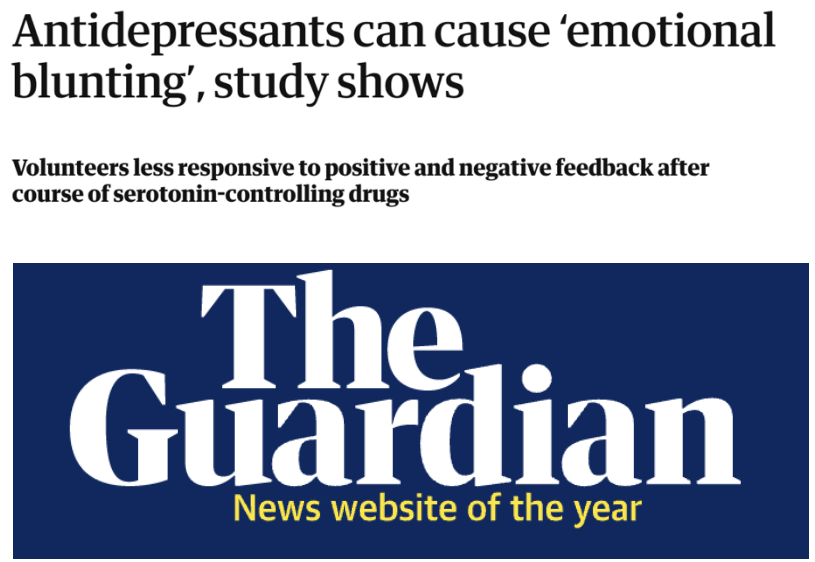
Mitzy Kennis[1] · Lotte Gerritsen[1] · Marije van Dalen[1] · Alishia Williams[1,2] · Pim Cuijpers[3] · Claudi Bockting[4,5]

Received: 18 January 2019 / Revised: 9 July 2019 / Accepted: 19 August 2019 / Published online: 19 November 2019

  - Obvious, plausible explanation for effect exists… emotional numbing

Emotional numbing/blunting

- Reported by 50-70% of people on antidepressants in surveys (Read and Williams, 2018; Goodwin et al 2017)
- Reduced intensity of negative and positive emotions
- May be related to genital numbing reported by many people on antidepressants
- If you chew up many antidepressants they will numb the mouth
- Some suggest it is the depression causing the numbing but recent high-profile study finding emotional numbing in healthy volunteers (no MH issues) given antidepressants (Langley et al 2023) – and this impaired emotional learning processes
- This effect may provide relief from strong emotions in the short term but may have consequences to relationships, quality of life
- It is the number one reason patients give for wanting to stop their antidepressants



What does cause depression?

- A study followed a random sample of about 1000 people in Dunedin for 45 years and gave them diagnostic interviews every few years.
- By the age of 45 guess what proportion had met the criteria for a mental illness (mostly depression and anxiety)?

JAMA Network | Open

Original Investigation | Psychiatry

Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study

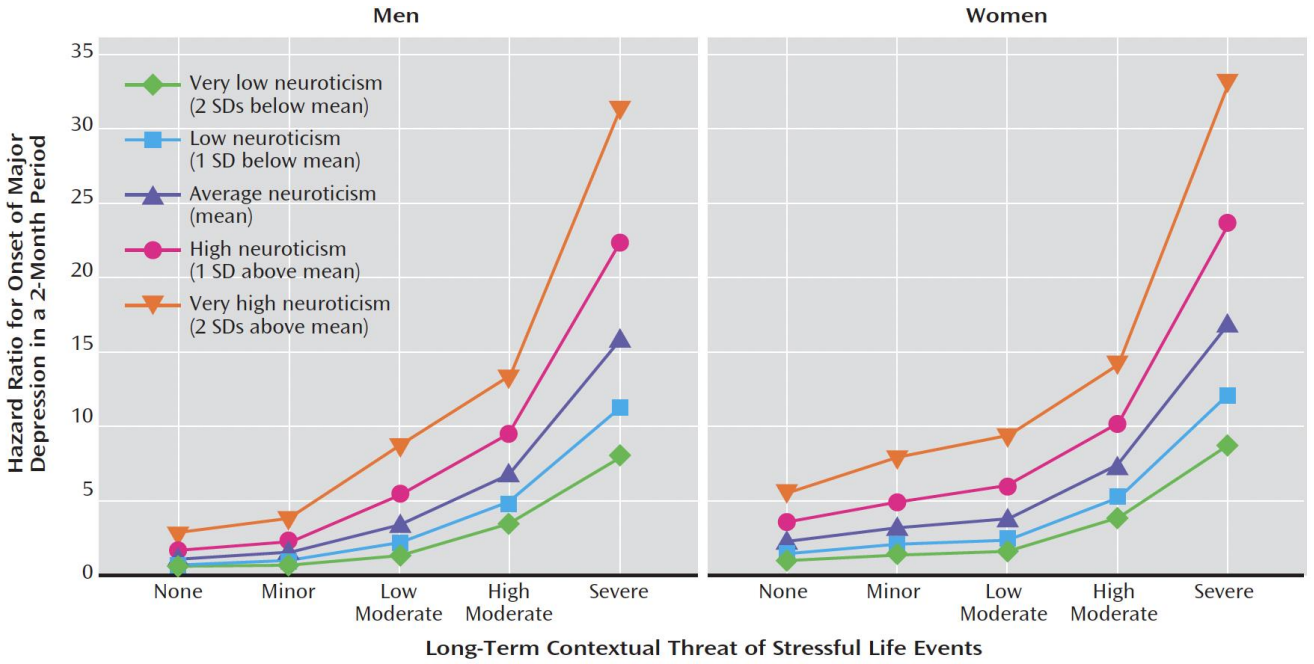
Avshalom Caspi, PhD; Renate M. Houts, PhD; Antony Ambler, MS; Andrea Danese, MD, PhD; Maxwell L. Elliott, MS; Ahmad Hariri, PhD; HonaLee Harrington, BS; Sean Hogan, MSW; Richie Poulton, PhD; Sandhya Ramrakha, PhD; Line J. Hartmann Rasmussen, PhD; Aaron Reuben, MEM; Leah Richmond-Rakerd, PhD; Karen Sugden, PhD; Jasmin Wertz, PhD; Benjamin S. Williams, BS; Terrie E. Moffitt, PhD

What does cause depression?

- A study followed a random sample of about 1000 people in Dunedin for 45 years and gave them diagnostic interviews every few years.
- By the age of 45 guess what proportion had met the criteria for a mental illness (mostly depression and anxiety)?
- 86% (70% in total depression/anxiety)

What causes depression

- Stressful life events include: death of loved one, onset of physical illness, job loss, etc
- Number of stressful life events strongly predicts depression in the next 12 months
- Neuroticism (=sensitivity to stress) a moderator, and this can certainly involve biology, upbringing, genetics
- But general agreement from geneticists that genetics plays a minor role in depression (maximum 37% variance explained, compared with 90% for height)



Article

The Interrelationship of Neuroticism, Sex, and Stressful Life Events in the Prediction of Episodes of Major Depression

Kenneth S. Kendler, M.D.

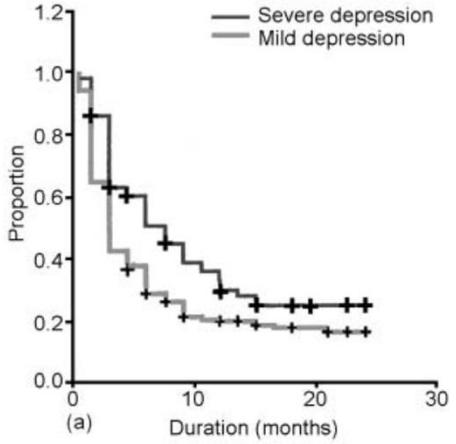
Jonathan Kuhn, Ph.D.

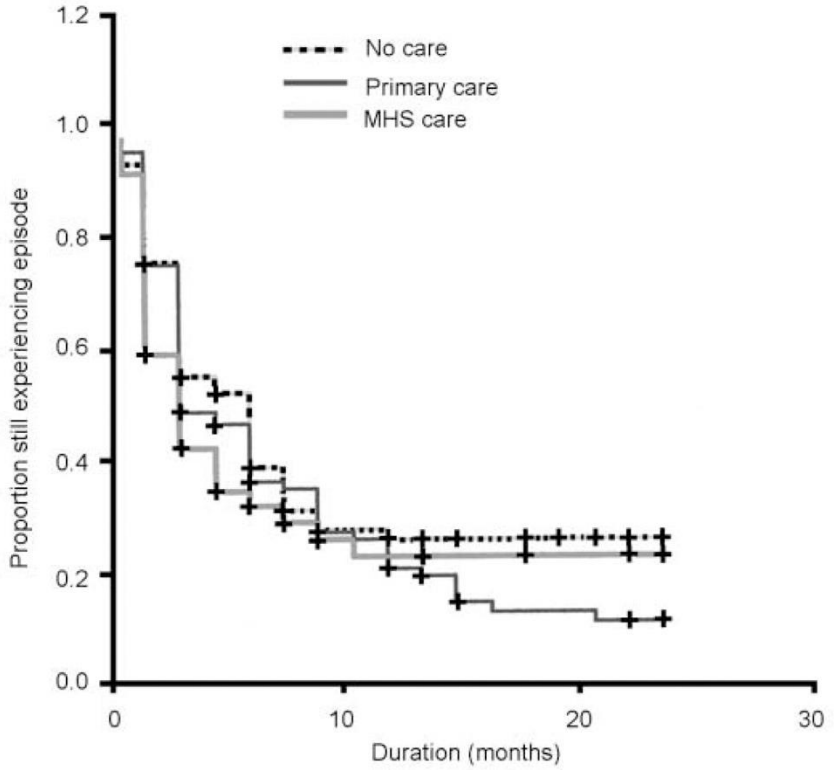
Carol A. Prescott, Ph.D.

Objective: Three potent risk factors for major depression are female sex, the personality trait of neuroticism, and adversity resulting from exposure to stressful life events. Little is known about how they interrelate in the etiology of depressive sion. An interaction was seen between neuroticism and adversity such that individuals with high neuroticism were at greater overall risk for major depression and were more sensitive to the depressogenic effects of adversity. An interaction

Natural recovery for depression

- Recovery rates for depression WITHOUT treatment are very high (van Spijker, 2002)
- Various studies estimate 75%+ recovery by 12 months without treatment
- No care, primary or secondary care show very little difference
- Severe or mild depression showed similar trajectories





Proportion experiencing depression after initial symptoms

Watchful waiting

Journal of Affective Disorders Reports
Volume 16, April 2024, 100753

Research Paper

Watchful waiting for depression using depathologization, advice and shared decision making

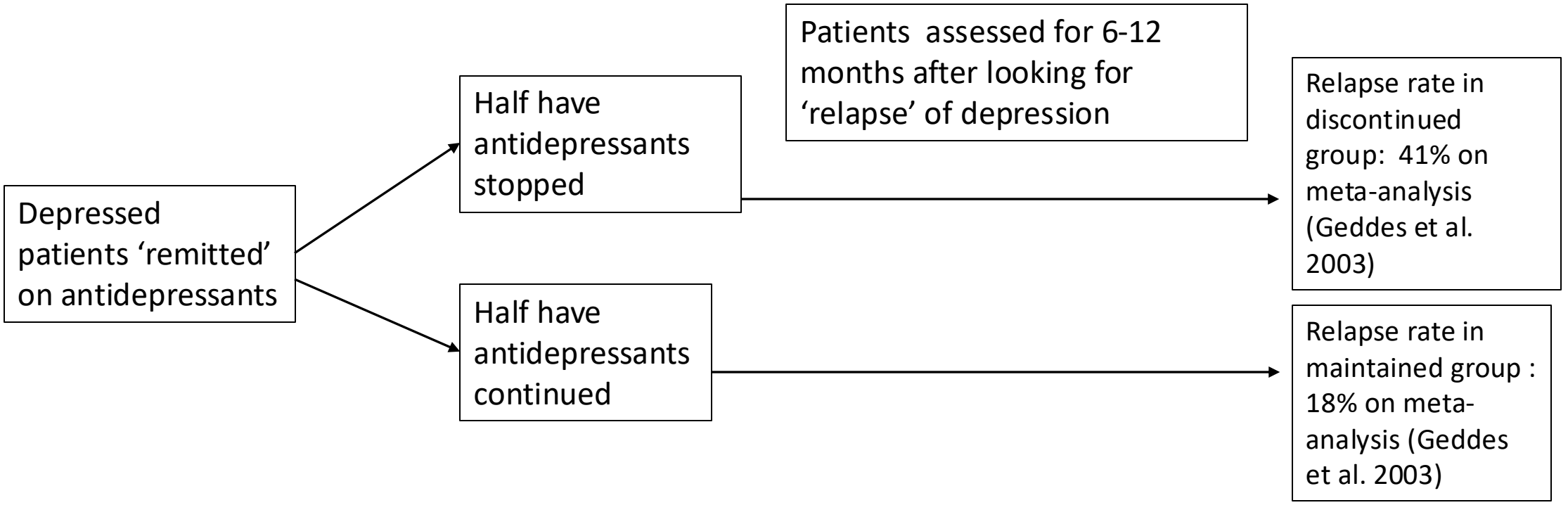
Milutin Kostic [a b], Teodora Milojevic [a], Jelena Buzejic [a], Marija Spasić Stojakovic [a], Jovana Maslak [a], Mihailo Ilic [a], Ana Jakovljevic [a], Ana Munjiza Jovanovic [a b], Ana Podgorac [a c], Marija Dabetic [a], Milica Vezmar [a c], Miloš Lazarevic [a]

- In a study in secondary care, 75 consecutive patients presenting with depressive symptoms (without suicidality) were provided:
  - Psychosocial advice
  - Depathologisation (normalization of low mood as not a brain condition)
  - Shared decision making
- This intervention (no medication, no therapy) was effective in 65% of patients at 3 month follow up
- Expectation from the patient that they should receive medication was the main factor influencing whether they ended up with medication
- Authors suggest that expectation of medication/belief that depression was an illness requiring treatment needed to be actively addressed

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?

Patients who remit or respond to antidepressants are already a highly selected group

Antidepressants are stopped mostly in 1 day, average 5 days

Depression is measured using scales (HAM-D, MADRS) that measure mood, anxiety, sleep, appetite changes – all of which overlap with withdrawal symptoms. Withdrawal symptoms are not measured in any of these studies.

This 'relapse' rate is almost certainly inflated by mis-diagnosing of withdrawal symptoms as 'relapse'

Patients assessed for 6-12 months after looking for 'relapse' of depression

Depressed patients 'remitted' on antidepressants

Half have antidepressants stopped

Half have antidepressants continued

Relapse rate in discontinued group: 41% on meta-analysis (Geddes et al. 2003)

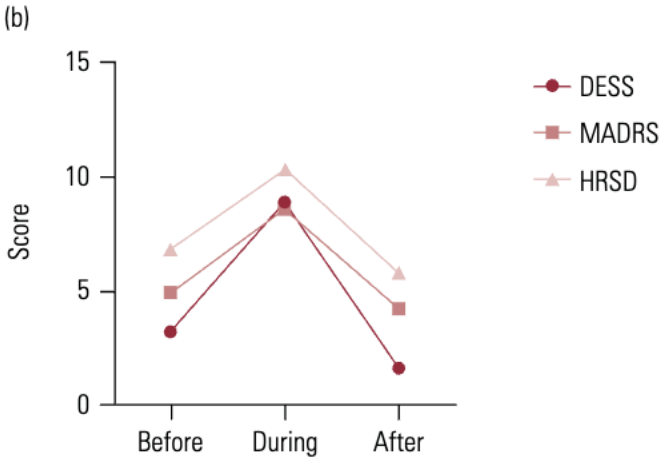
Relapse rate in maintained group : 18% on meta-analysis (Geddes et al. 2003)

If patients with withdrawal symptoms are subtracted from these relapse rates not clear if ADs prevent relapse

Antidepressants are probably not as effective at preventing relapse as reported

Overlap of withdrawal effects on depression scales

sertraline



paroxetine

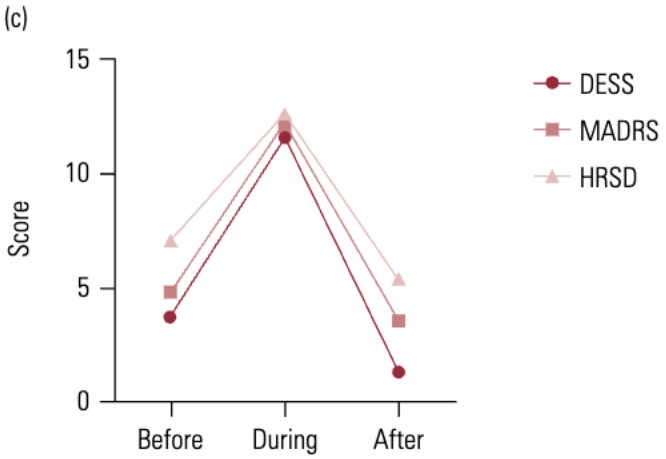


TABLE 4 **Patients who met criteria for 'discontinuation syndrome'[a] and experienced an increase in score on the Hamilton Rating Scale for Depression for different antidepressants**

	Fluoxetine ($n = 63$), n (%)	Sertraline ($n = 63$), n (%)	Paroxetine ($n = 59$), n (%)
DESS (≥4 symptoms)	9 (14%)	38 (60%)	39 (66%)
HRSD-28 (≥8-point increase)	4 (6%)	19 (30%)	21 (36%)
HRSD-8 (≥10-point increase)	2 (3%)	12 (19%)	16 (27%)

HRSD-28 and HRSD-8, 28-item and 8-item Hamilton Rating Scale for Depression.
a. Discontinuation syndrome: ≥4 symptoms on the Discontinuation-Emergent Signs and Symptoms checklist (DESS).
Source: Rosenbaum et al (1998).

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"**

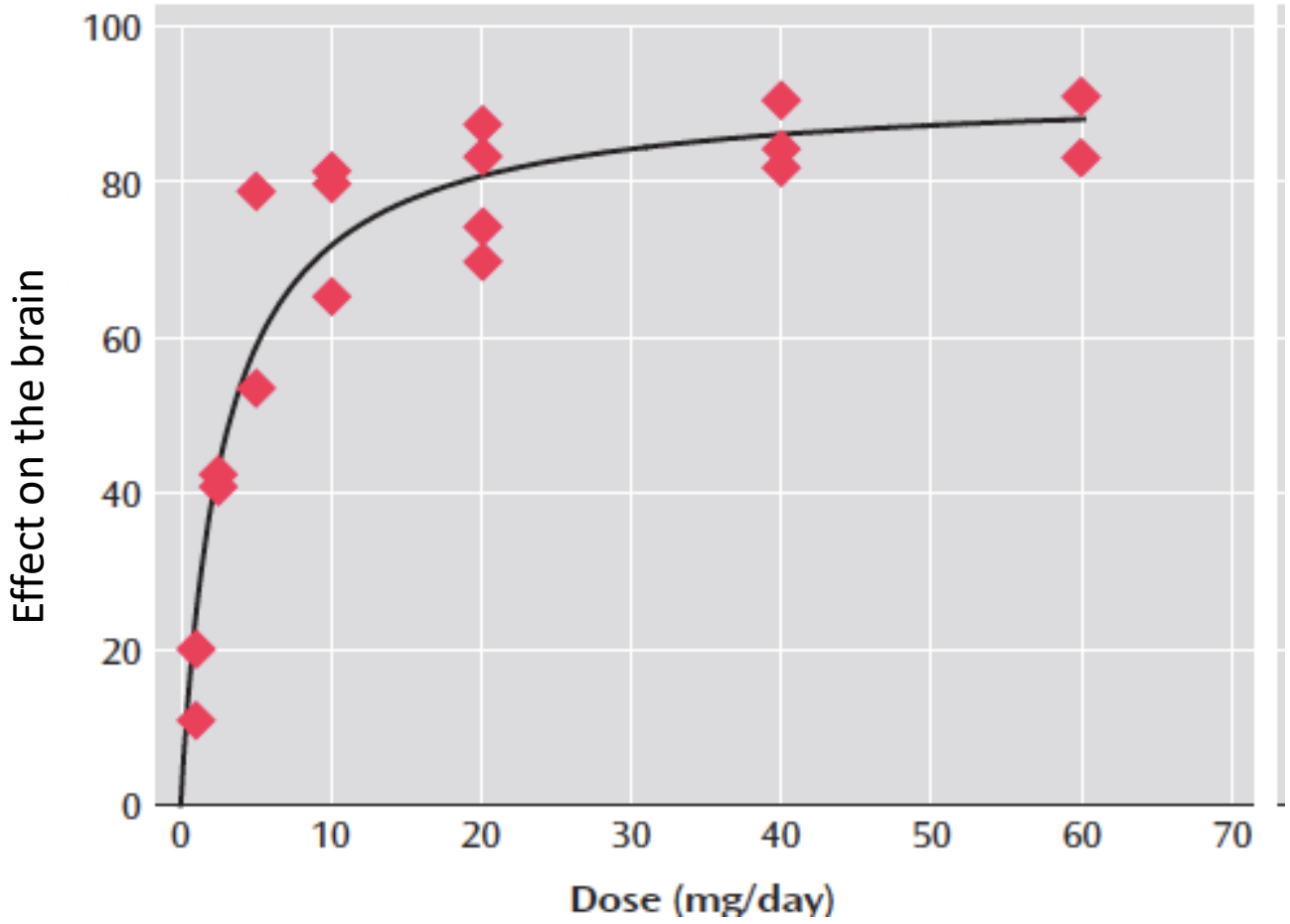
Suggest going down to **very small doses (<1mg) before stopping**

Recommends going down in **smaller and smaller sized reductions**

Rate **titrated to the individual**'s ability to tolerate the process

Management of the antidepressant withdrawal syndrome

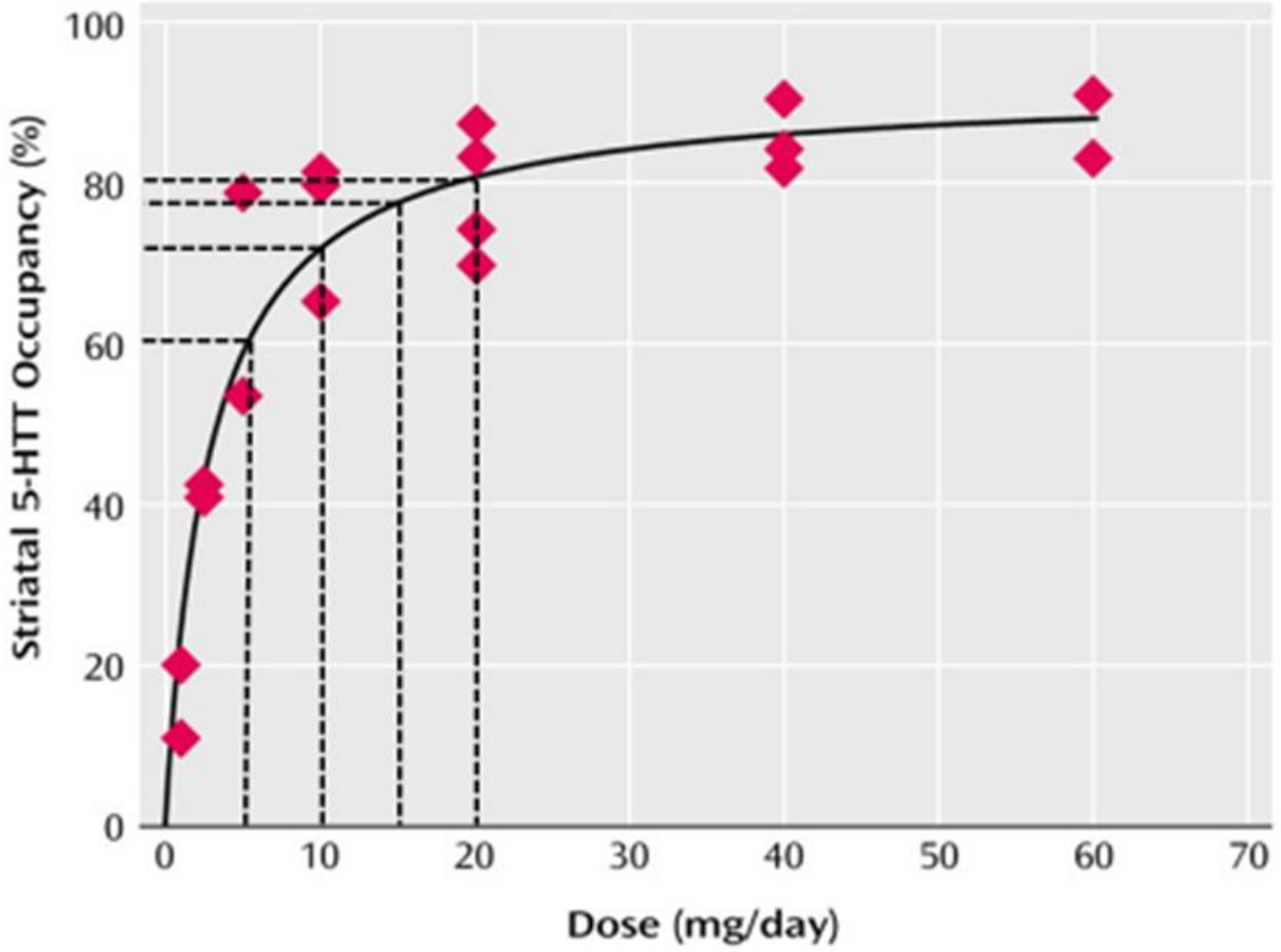
- We used brain imaging (PET) data of antidepressant action to develop rational tapering guidance for antidepressants
- E.g. Citalopram's effect on the serotonin transporter, its major target
- This also applies to all other psychiatric medications



Citalopram

What happens when you taper linearly?

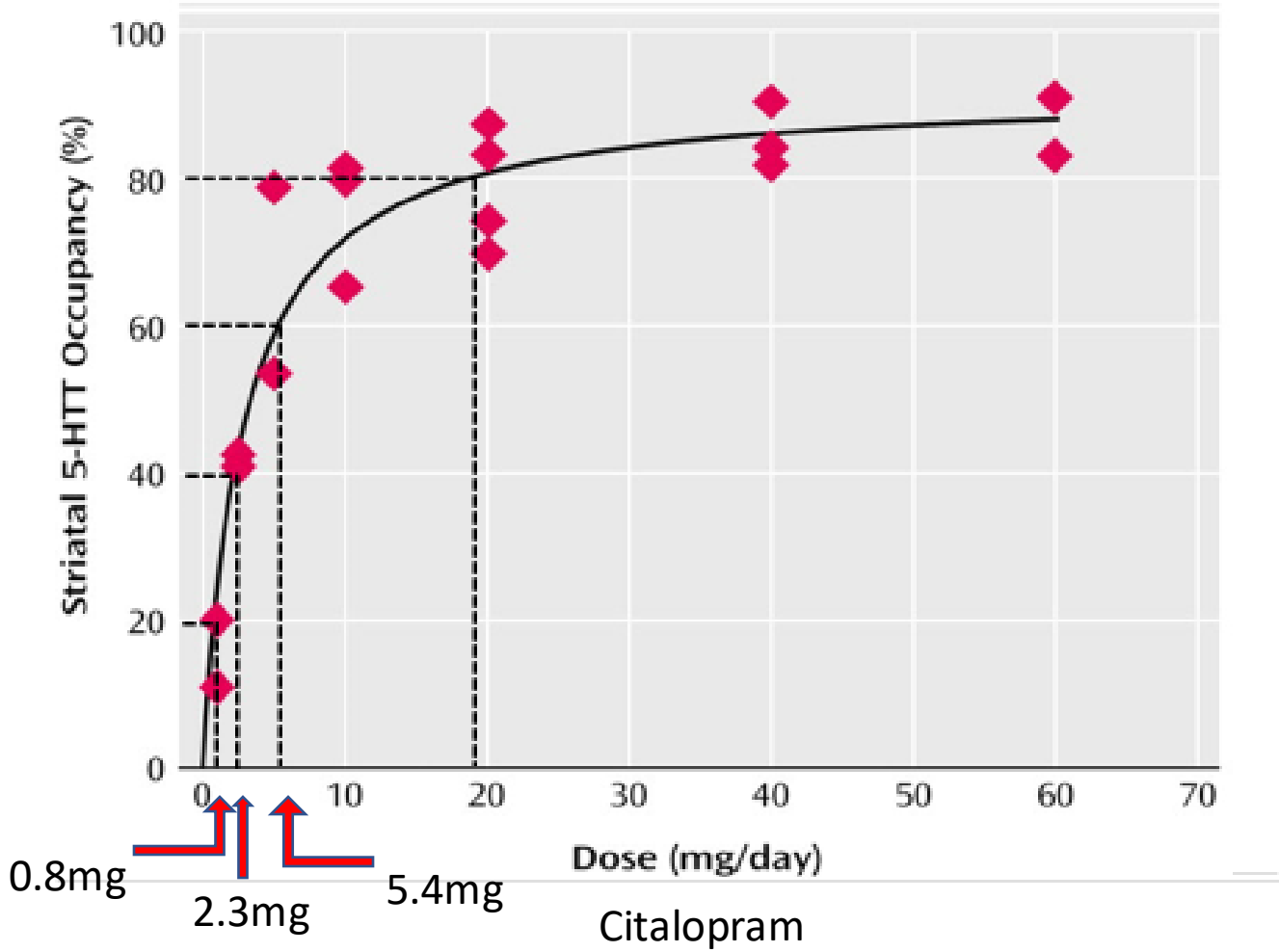
- Citalopram linear taper
- 20mg to 15mg -> 3% change
- 15mg to 10mg -> 6% change
- 10mg to 5mg -> 13% change
- 5mg to 0mg -> 58% change
- This correspond to the increasingly severe withdrawal symptoms reported by patients as dose gets lower
- 10mg is smallest tablet available. Sometimes split in half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



Citalopram

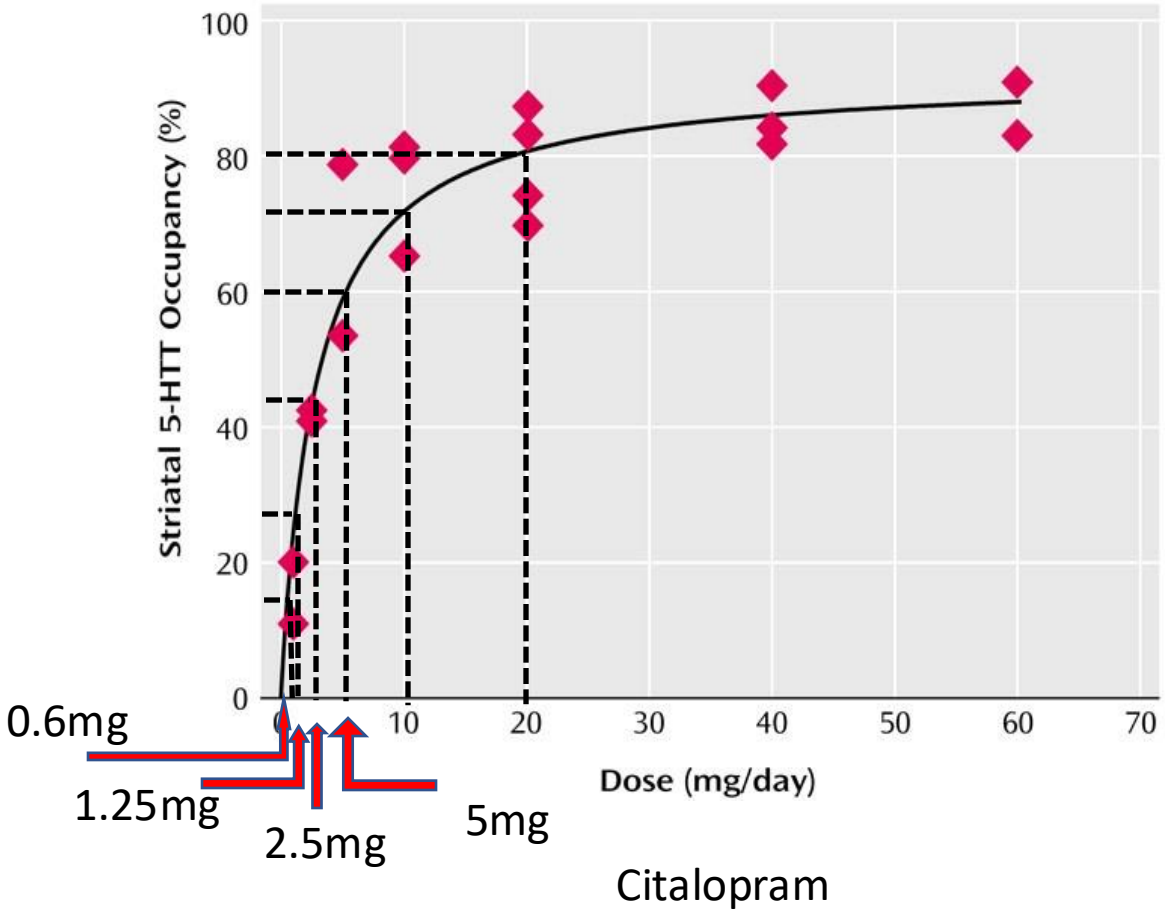
What happens when you taper by fix amounts of effect on the brain? Hyperbolic dose decrease

- 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



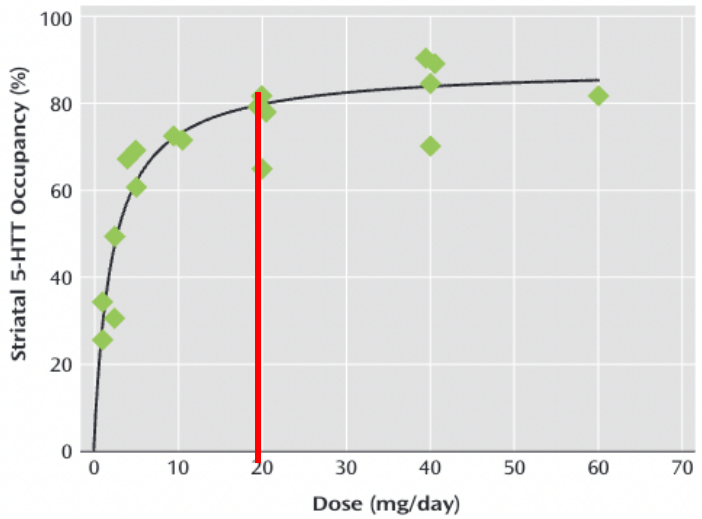
What happens when you taper by fixed amounts of effect on the brain? Proportionate dose decrease

- 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

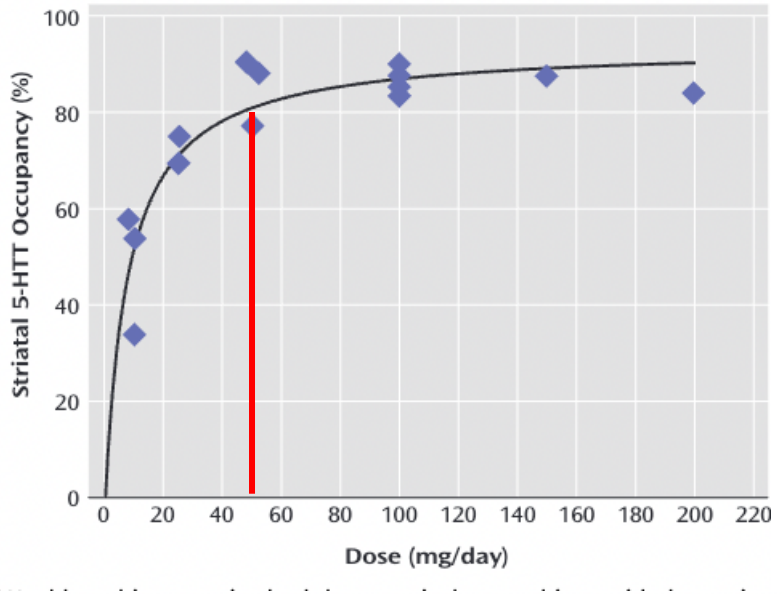


True for all antidepressants

Fluoxetine

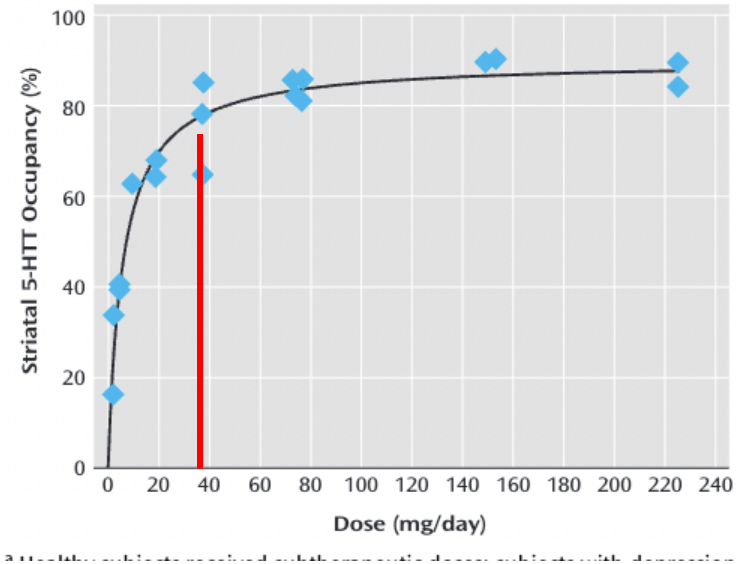


Sertraline

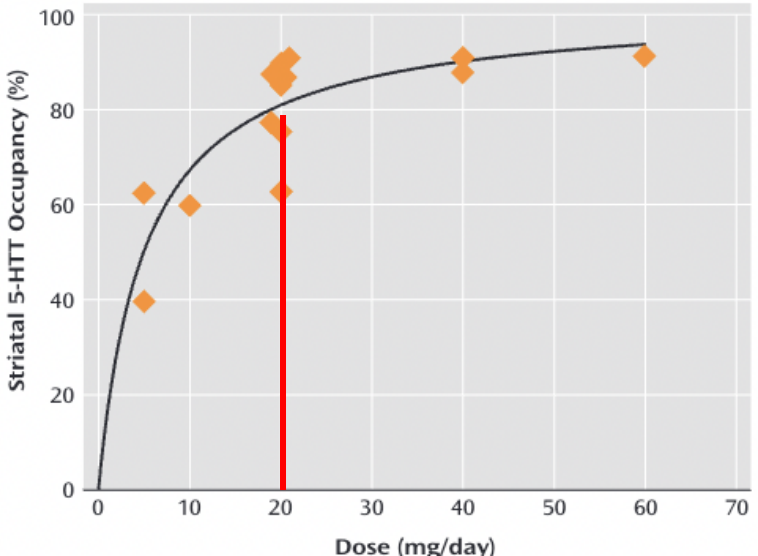


Red line= The smallest available tablet or capsule in Australia

Venlafaxine



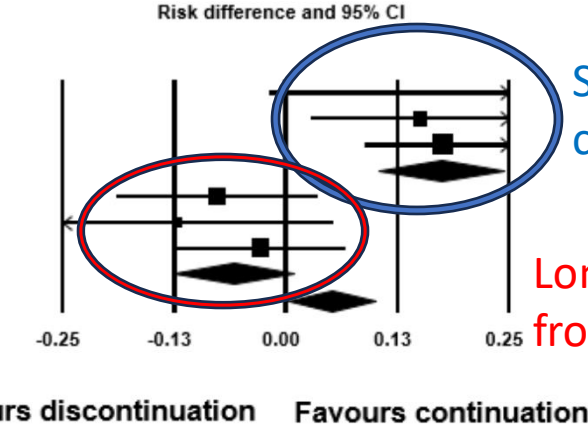
Paroxetine



Evidence for gradual tapering

- A meta-regression of 13 antidepressant discontinuation studies found that the length of taper correlated highly with risk of relapse (p=0.00001) (Gotzsche and Demasi, 2023)
- In the three trials that tapered over about 6 months no difference in relapse rates from maintenance (MT) (17% difference for rapid tapering vs MT) (Gotzsche and Demasi, 2023)

Length of taper	Study name	Statistics for each study: Risk difference	Standard error	Variance	Lower limit	Upper limit	Z	P
Short	Cook 1986	0.333	0.180	0.032	-0.019	0.685	1.857	0.063
Short	Huijbers 2016	0.151	0.062	0.004	0.028	0.273	2.411	0.016
Short	Lewis 2021	0.176	0.045	0.002	0.088	0.264	3.913	0.000
Overall		0.174	0.036	0.001	0.104	0.244	4.862	0.000
Long	Bockting 2018	-0.077	0.057	0.003	-0.190	0.035	-1.342	0.179
Long	Kuyken 2008	-0.121	0.089	0.008	-0.296	0.054	-1.359	0.174
Long	Kuyken 2015	-0.028	0.048	0.002	-0.123	0.067	-0.585	0.558
Overall		-0.059	0.034	0.001	-0.126	0.008	-1.733	0.083
Overall		0.052	0.025	0.001	0.004	0.100	2.106	0.035

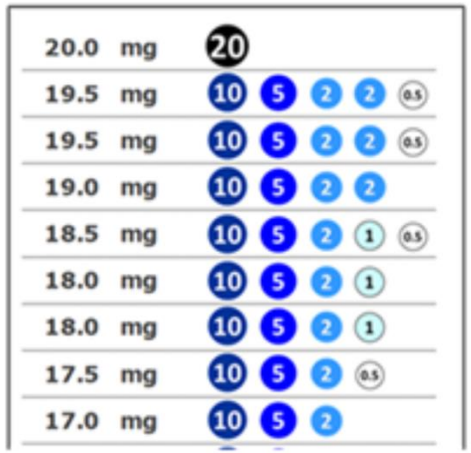


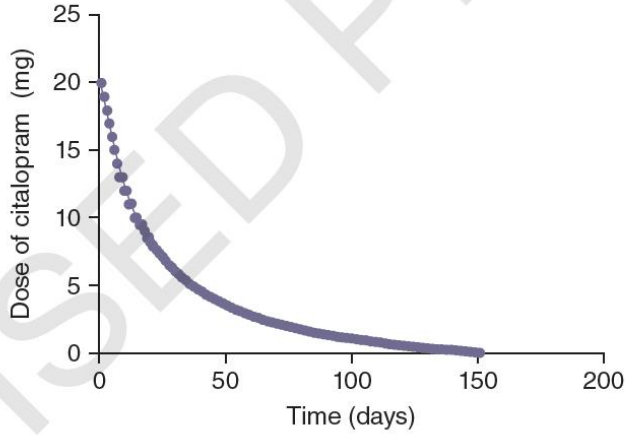
Short tapering – favours continuation

Long tapering (6 months) – no diff from continuation

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*

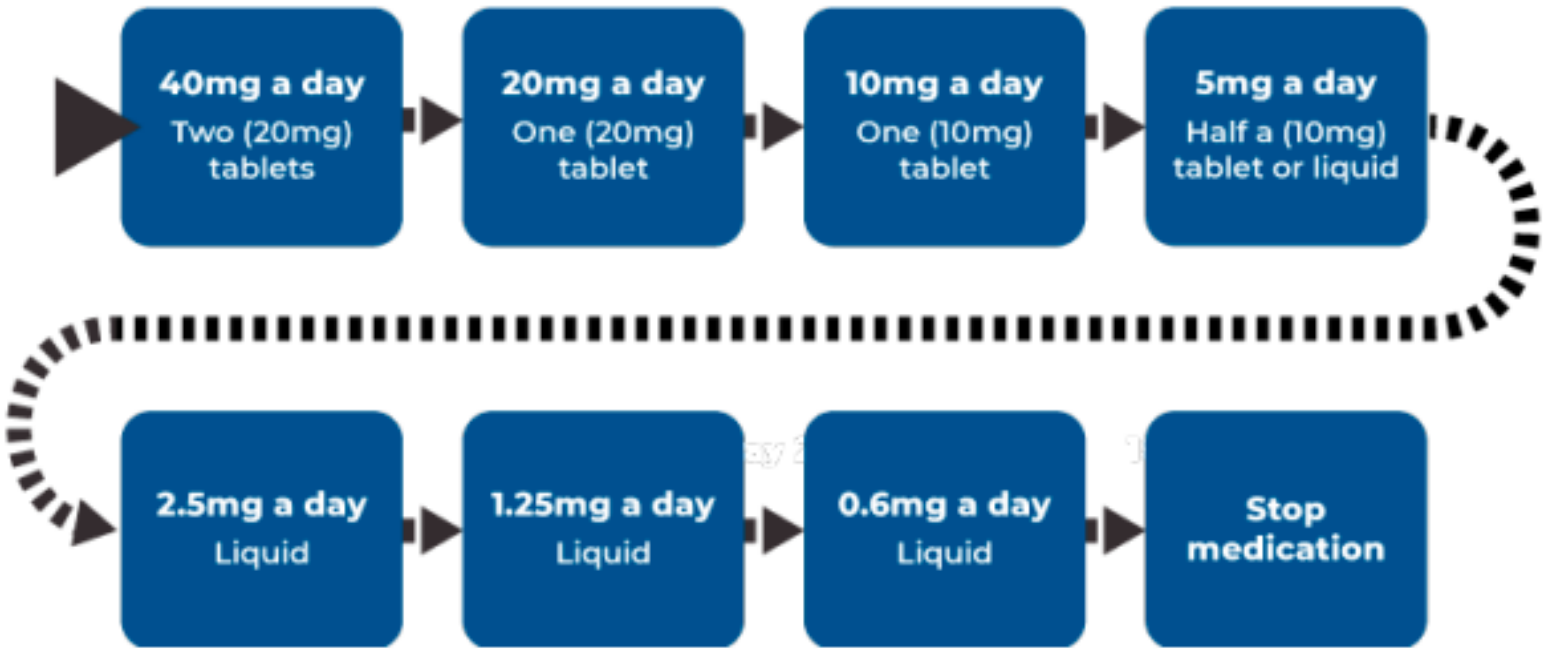
Many patients can only reduce their dose at *10% of the most recent dose per month* (which means reductions get smaller and smaller)

A rapid reduction schedule (RCPsych, 2020)

Total time required: 3-6 months

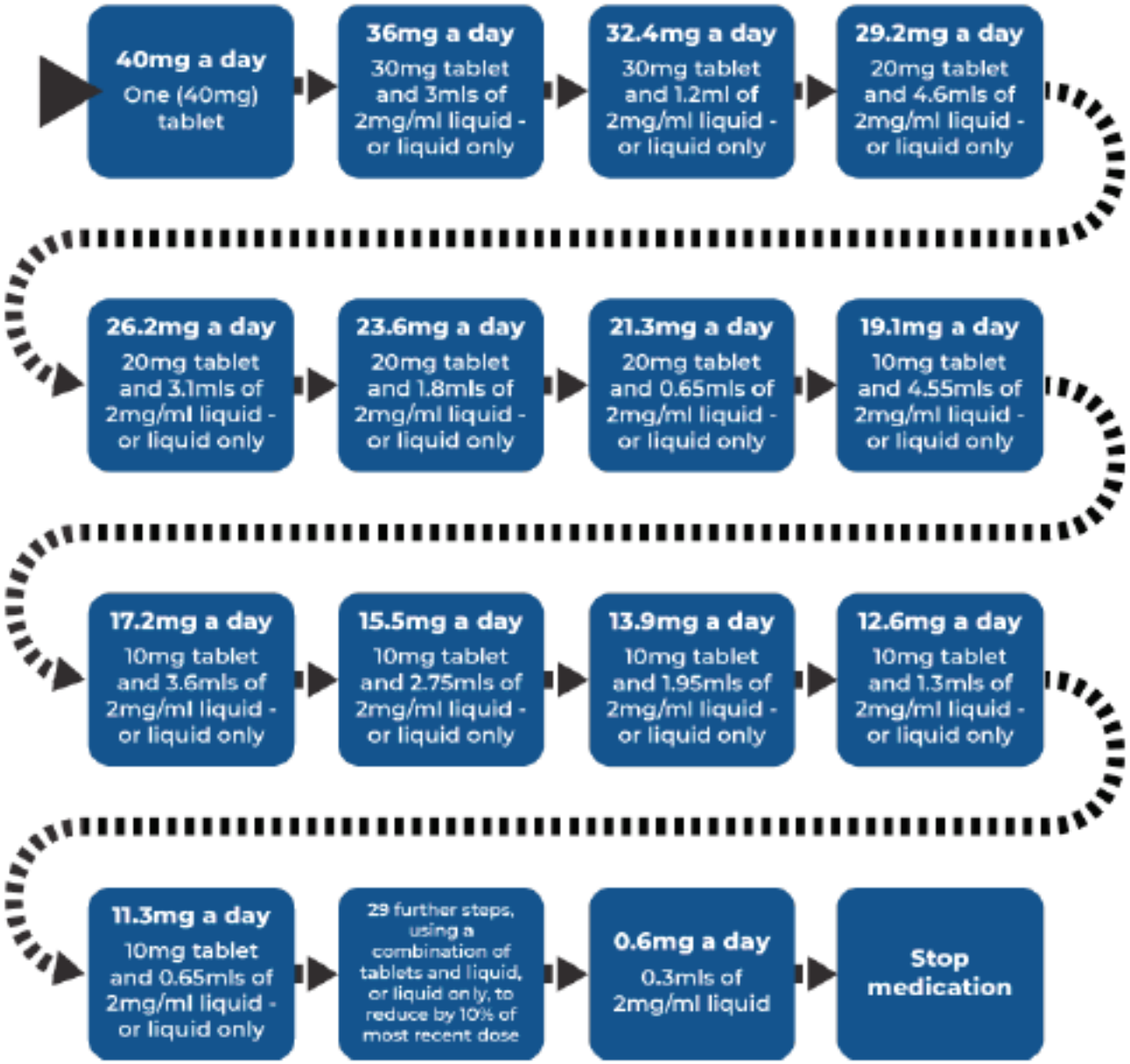
Citalopram

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



Paroxetine

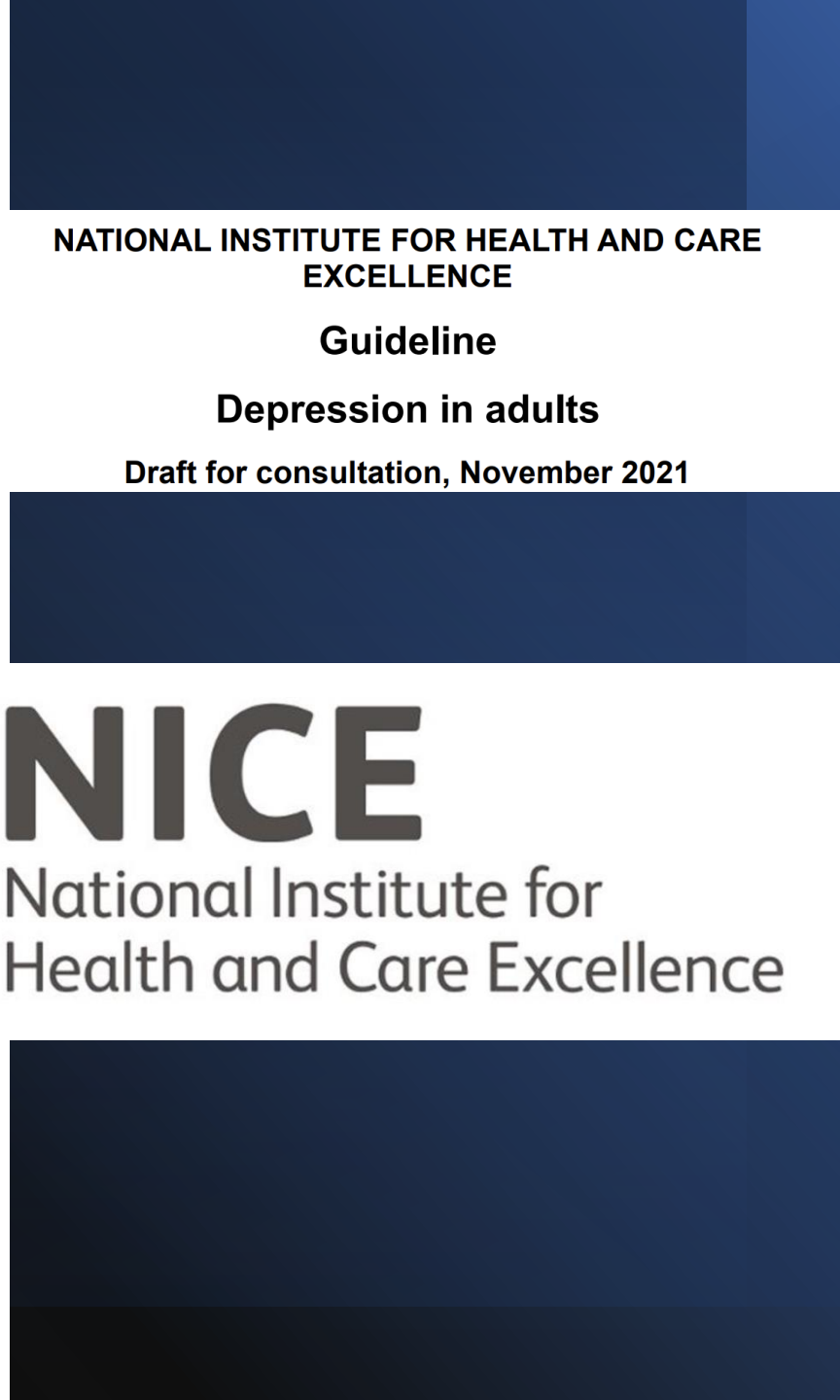
Reduction by 10% of the last dose, every 2-4 weeks using tablets and liquid. Some people may need to reduce more slowly. (Updated October 2020)



- 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)

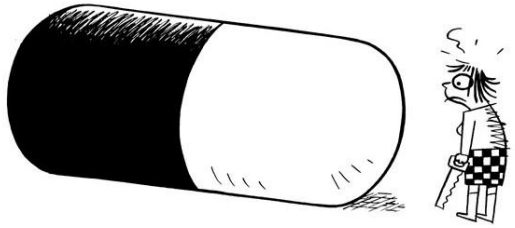
NICE guidelines

- Update to Depression guidelines published in June 2022, 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].



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. Might be considered in some circumstances



Off-label options for tapering

Licensed medicines used in an unlicensed manner

Citalopram, escitalopram, paroxetine or sertraline tablets

Can be crushed and/or dispersed in water, or crushed and given with soft food. The tablets are film-coated and contents may taste bitter or unpleasant. Crushed sertraline and paroxetine tablets may have a local anaesthetic effect on the tongue.

- 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

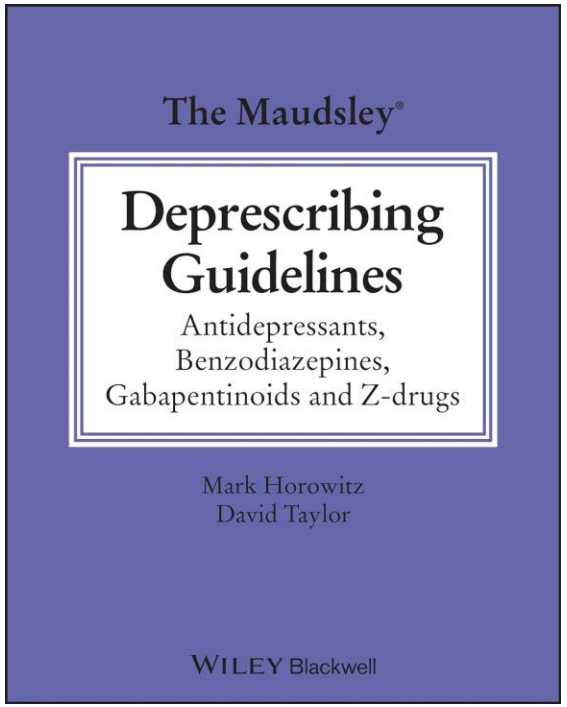
Off-label suspension from tablets

- https://www.youtube.com/watch?v=dOTZo5hcS54 (from 2min 40 seconds)

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
- Endorsed by the RACGP
- 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



bitly

RACGP

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~~ 1 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~~ 1 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.

Tapering other psychiatric drugs

- “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”

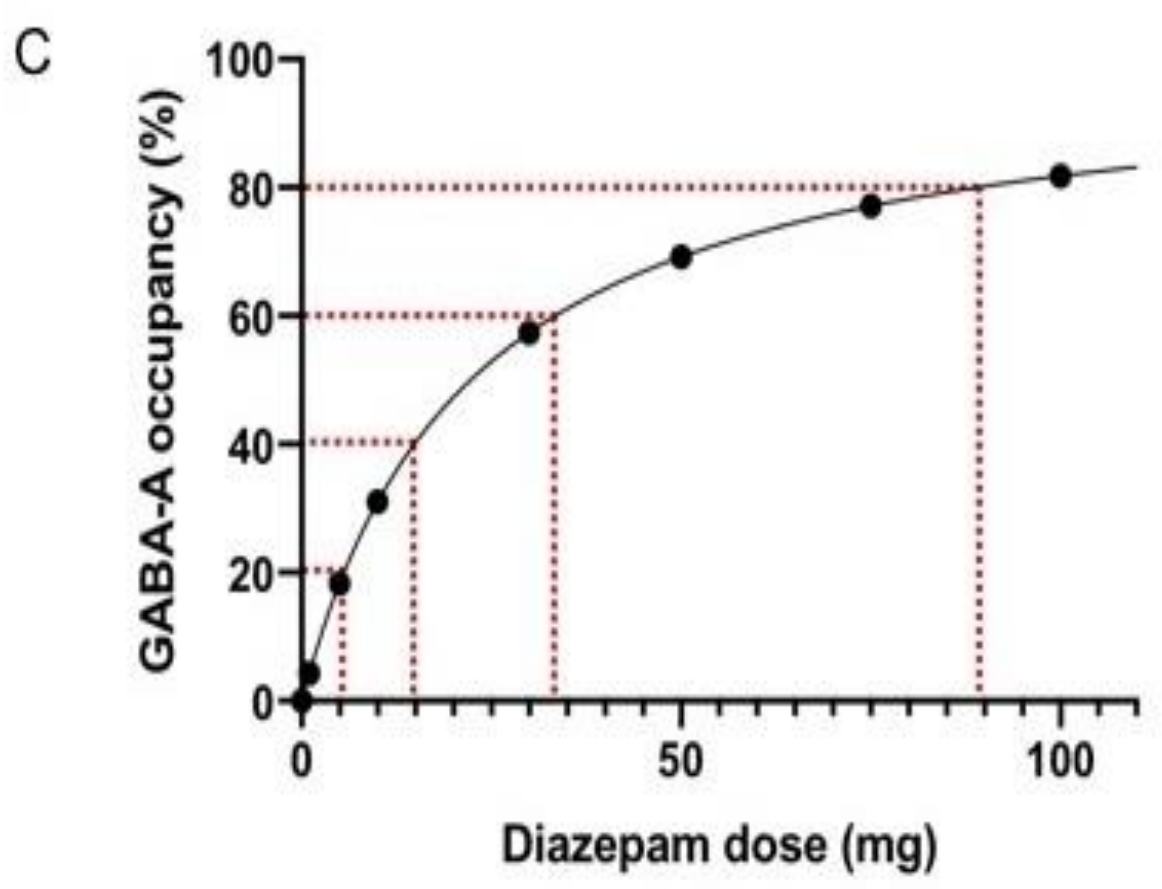
NICE
National Institute for Health and Care Excellence

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

Including guidance on when to switch shorting acting benzodiazepines to diazepam

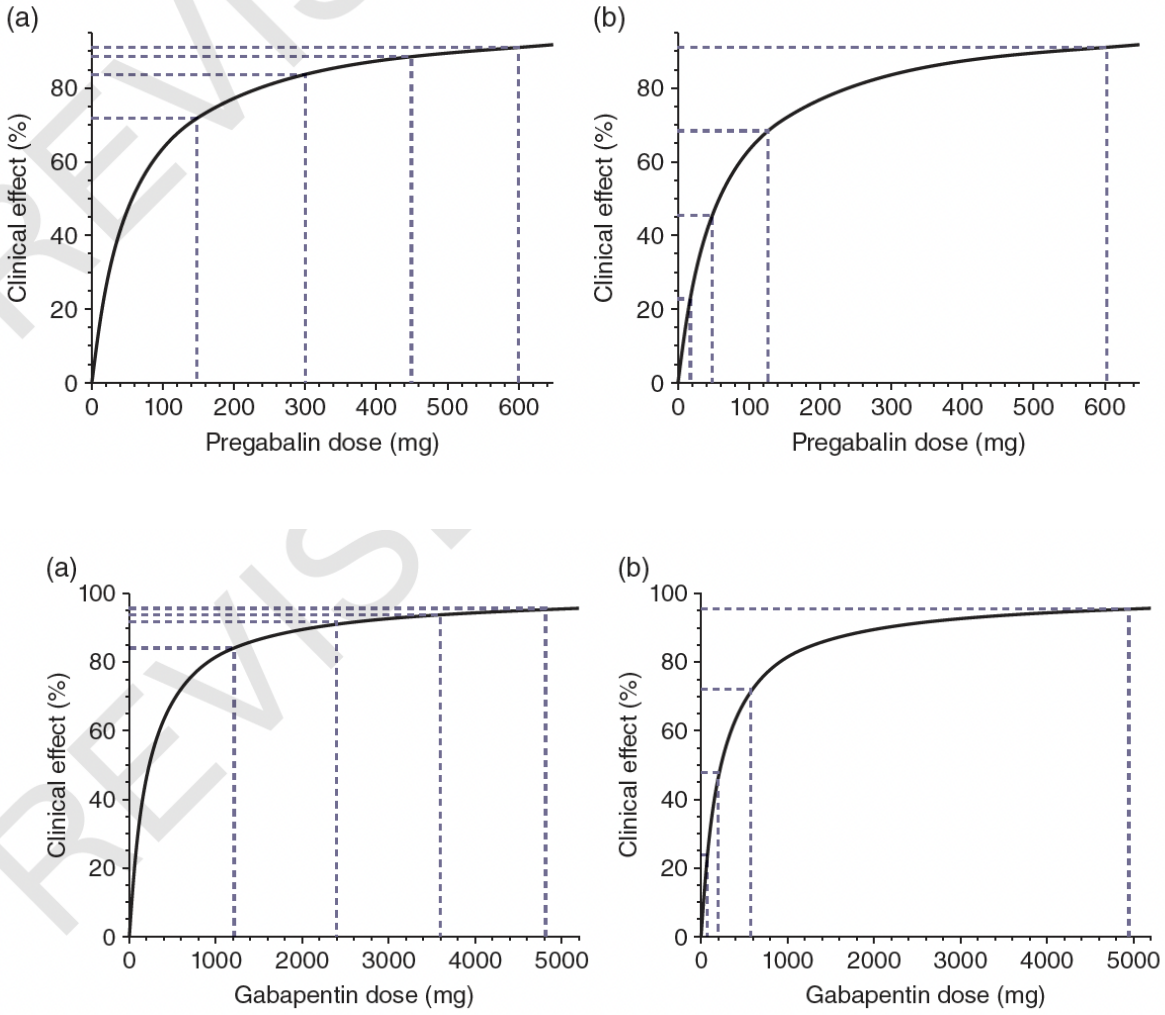
A. **A faster taper** with up to 5 percentage points of $GABA_A$ occupancy between each step – with reductions made every 1–4 weeks*.

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											

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,
  - antipsychotics,
  - stimulants (although generally easier to stop),
  - opioids
  - Also physical health meds: beta blockers, PPIs, etc

Practical aspects of tapering

Details of tapering escitalopram

- Escitalopram hydrobromide available as 20mg per mL
- Each drop is 1mg
- E.g. to give 1.5mg – two drops in 20mL of water, stir well, measure 15mL with syringe
- Alternative options: Compounding pharmacy can make up any strength solution, capsules or tablets.

Details of tapering Venlafaxine

- Tapering venlafaxine: if there are 300 beads in a 75mg capsule of Effexor, 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
- Beads can be different sizes and so some people weigh rather than count the beads (using a jeweller's scale from e.g. Amazon ($25))
- Microtapering: rather than reduce by 30 beads per month, could reduce by 1 bead per day (lessens the destabilization caused by each reduction)
- Alternatively: venlafaxine can be compounded into a liquid from by a compounding pharmacy (needs to be taken twice a day) – or they can re-encapsulate beads (by weight) or beads can be pulverized and turned into a suspension with water

Other examples

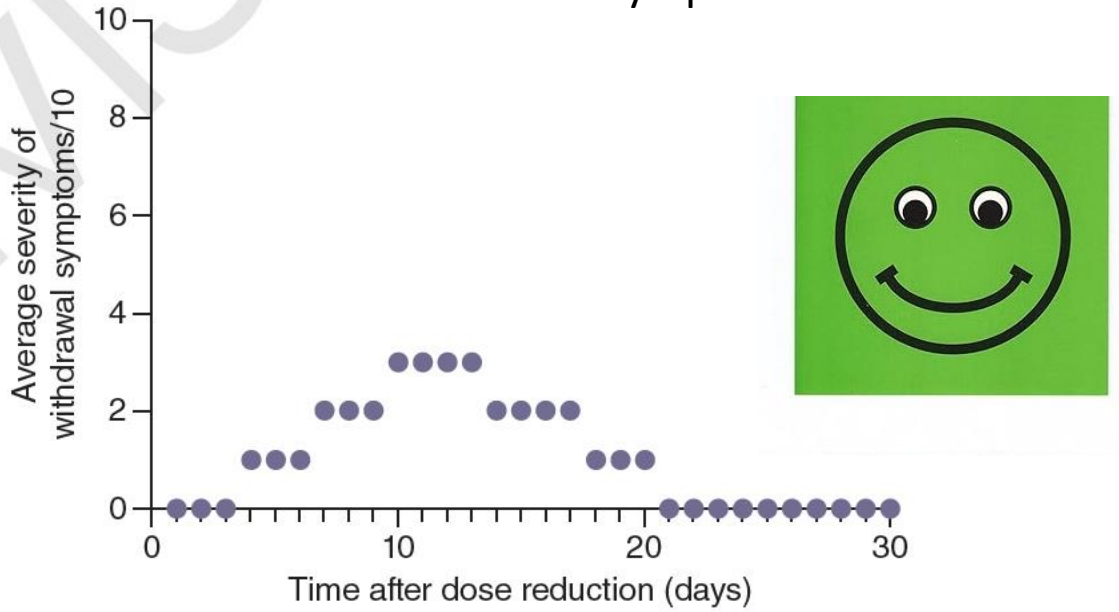
- Mirtazapine oral distintegrating tablet can be dispersed in water to make a mixture. E.g. 15mg in 150mL. Mix well – then can reduce by 10% by discarding 15mL down the sink and drinking the rest
- Can also reduce 1mL a day, and slow down when symptoms become unpleasant
- Crushing and suspending easier with instant release than extended release tables (dose dumping a possibility)

Adjusting the taper to an individual

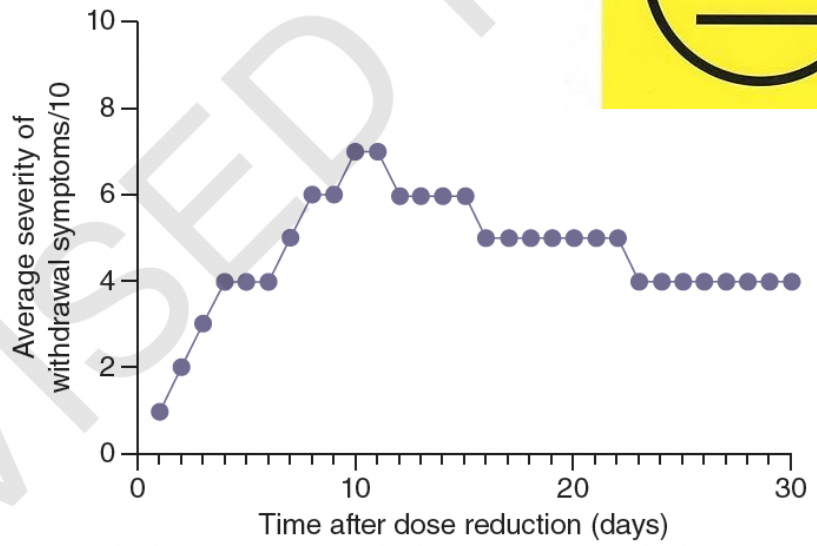
Miss Y, Citalopram, April 2021.					
Day	Dose (mg)	Anxiety /10	Dizziness /10	Insomnia /10	Overall symptom /10
1	20	1	0	0	1
2	20	1	0	0	1
3	20	1	0	0	1
4	20	1	0	0	1
5	15	1	0	0	1
6	15	1	0	0	1
7	15	2	1	1	2
8	15	2	1	2	2
9	15	2	1	2	2
10	15	3	2	2	3
11	15	3	2	3	3
12	15	4	3	3	4
13	15	4	3	4	4
14	15	4	3	4	4
15	15	4	4	3	4
16	15	4	4	3	4
17	15	3	3	2	3
18	15	3	3	2	3
19	15	3	3	2	3
20	15	2	2	2	2
21	15	2	2	2	2
22	15	2	2	1	1
23	15	1	1	1	1
24	15	1	1	1	1
25	15	1	1	1	1

Record of withdrawal symptoms

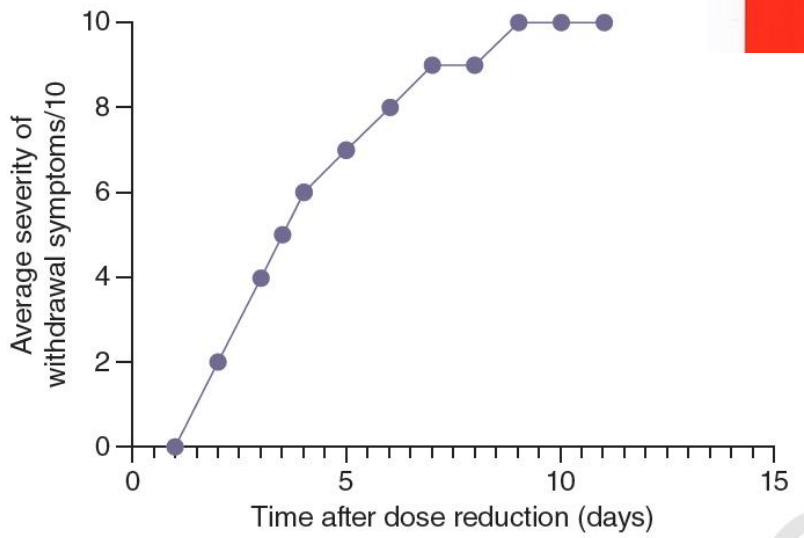
Withdrawal symptoms in graph form (to view) - ‘tolerable symptoms’



Adjusting the taper to an individual - 2



Moderately severe withdrawal symptoms -> wait longer before next reduction + taper more gradually



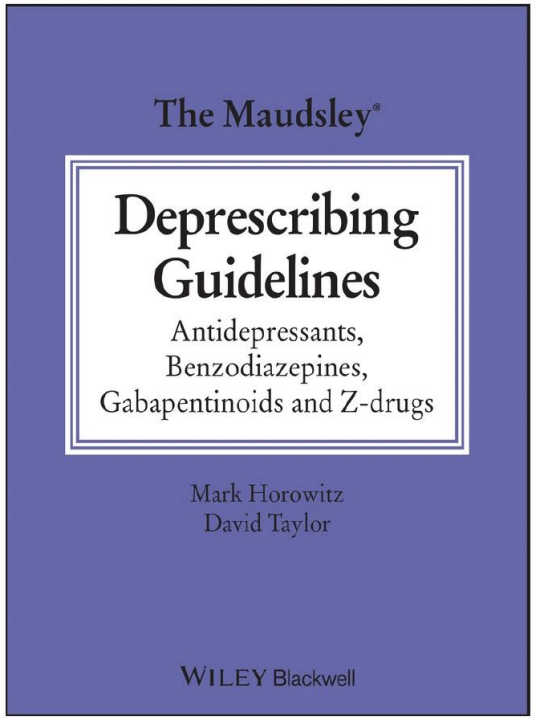
Severe withdrawal symptoms -> return to previous dose, wait to stabilize + taper much more gradually

Thank you for listening

- Questions?

- My email for any further questions:

  mark.horowitz@nelft.nhs.uk



You can redeem a free electronic copy of The Maudsley Deprescribing Guidelines (endorsed by RACGP) by scanning this QR code:

RACGP

Disease-centred model

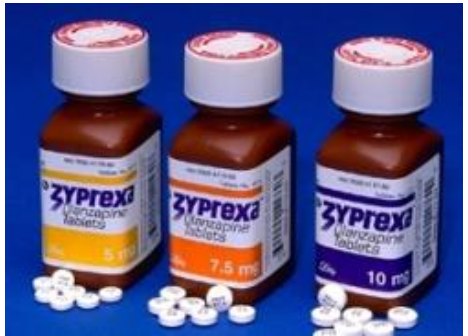
- Imported from general medicine, where most modern drugs are correctly understood this way
- Drugs act on underlying abnormalities
  - Blood pressure medication relax blood vessels to reverse high blood pressure
  - Insulin replaces a lack of it in diabetes
- In mental health disease centred model relates 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/anxiety as do antidepressant drugs
- There is little evidence of any specificity

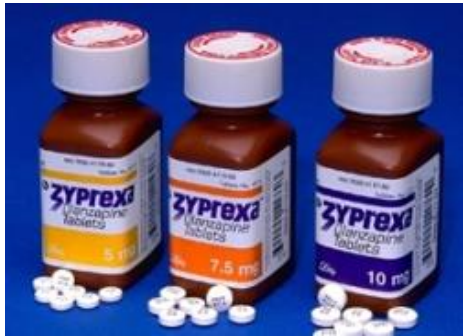
Drug-centred model

- 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



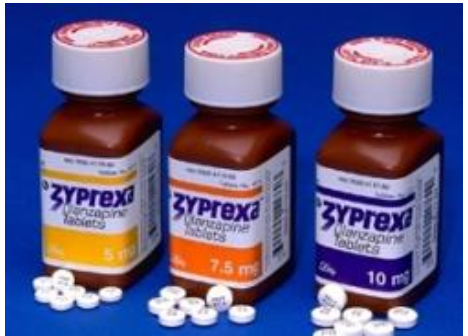
Drug-centred model -2

- 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

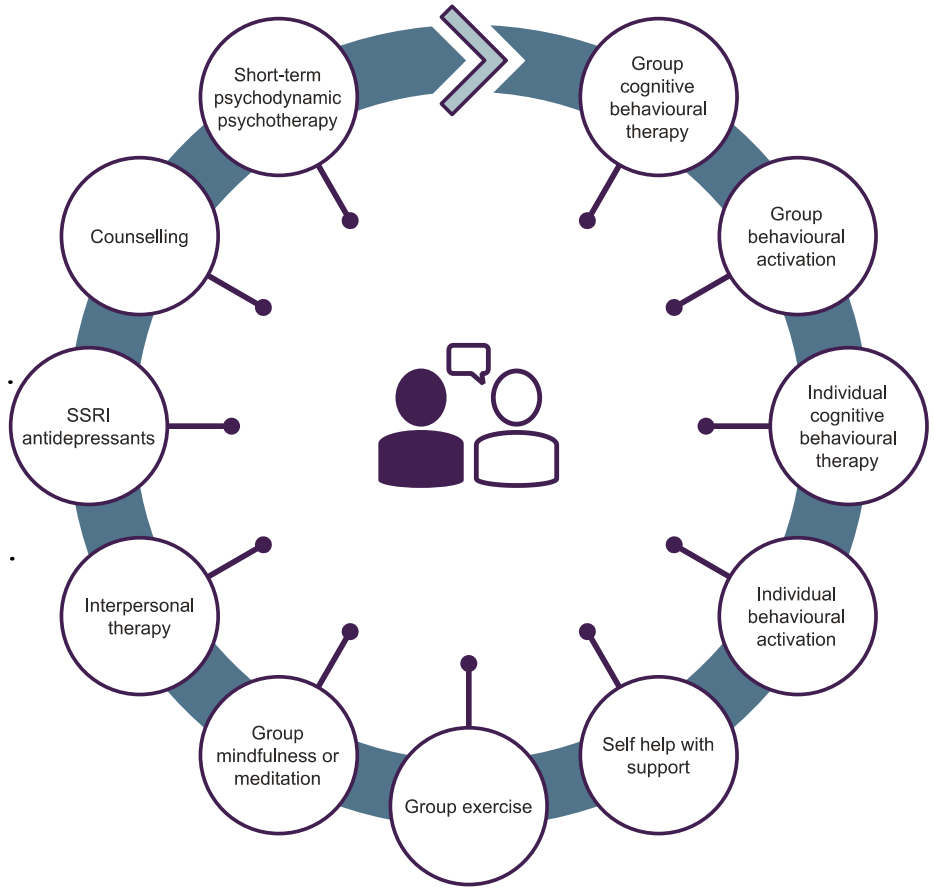
Treatments for ‘less severe depression’

Depression in adults: choosing a first-line treatment for less severe depression

If the person has **no preference**: move clockwise from the start (**>**) around the cycle of options, and reach a shared decision on which treatment to try first

If the person has a **clear preference**, or **experience from previous treatment** to use as a guide: support the person’s choice, unless there are concerns about suitability for this episode of depression

Do not routinely offer antidepressants as a first-line treatment, unless that is the person’s preference



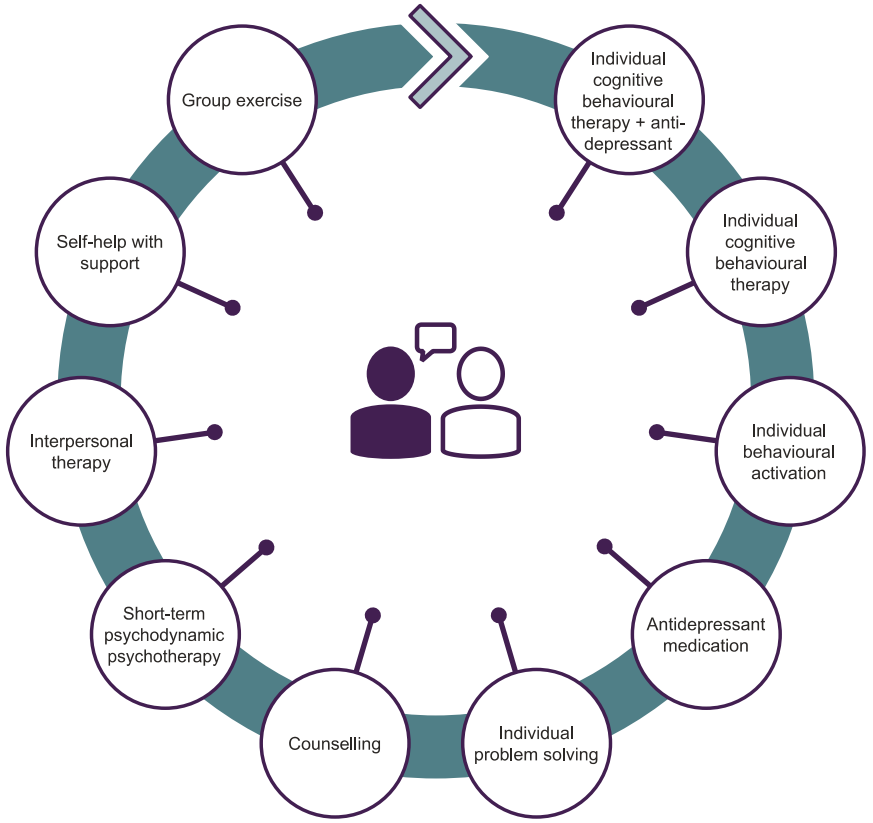
NICE National Institute for Health and Care Excellence

Treatment for ‘more severe depression’

Depression in adults: choosing a first-line treatment for more severe depression

If the person has **no preference**: move clockwise from the start (**>**) around the cycle of options, and reach a shared decision on which treatment to try first

If the person has a **clear preference**, or **experience from previous treatment** to use as a guide: support the person’s choice, unless there are concerns about suitability for this episode of depression



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