Antidepressant Withdrawal

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Denial, Dismissal, & Ignorance

Kessing et al (2005) concluded from their survey of inpatient antidepressant users, showing that 57% find it difficult to stop antidepressants when you have taken them for a long period of time and that 56% believe your body can become addicted to antidepressants:

«… a large proportion of the patients had erroneous beliefs regarding the effect of antidepressants … Although all these subjects had been treated in hospital settings they still had major ignorance and negative attitudes, suggesting a need for intensified psychoeducational activities»

Kessing et al, 2005; Psychological Medicine, 35: 1205-1213.

Denial, Dismissal, & Ignorance

Nutt et al (2014), responding to Gotzsche who stressed that many patients experience serious withdrawal difficulties and cannot come off antidepressants:

«In our experience, the vast majority of patients who choose to stay on them do so because they improve their mood and wellbeing rather than because they cannot cope with withdrawal symptoms when they stop. Many of the extreme examples of adverse effects given by the opponents of antidepressants are both rare and sometimes sufficiently bizarre as to warrant the description of an unexplained medical symptom»

Nutt et al, 2014; Lancet Psychiatry, 1: 102-104.

Denial, Dismissal, & Ignorance

Antidepressant users often feel dismissed when they mention withdrawal symptoms.

When patients sought help because of withdrawal symptoms, in 12% of cases the doctor denied that the symptoms were related to withdrawal, in 15% the doctors were helpful but inaccurate, 42% were unhelpful and inaccurate and only 1% were considered helpful (Guy et al, 2020)

Only about 1% of antidepressant users remember being informed about possible difficulties when coming off antidepressants, including discontinuation syndrome or withdrawal reactions (Read et al, 2018)

Guy et al, 2020; Therapeutic Advances in Psychopharmacology, 10: 1-15.

Read et al, 2018; International Journal of Mental Health Nursing, 27: 1805-1815.

Denial, Dismissal, & Ignorance

Leading academic psychiatrists sense an anti-psychiatric conspiracy and ideologically driven campaign, thus using combative and/or defensive rhetoric:

Jauhar and Hayes (2019) titled: «The war on antidepressants»

Nutt et al (2014) titled: «Attacks on antidepressants: sign of deep-seated stigma?»

Perlis (2010) titled: «Anxiety about antidepressants»

Jauhar & Hayes, 2019, Addictive Behaviors, 97: 122-125.

Nutt et al, 2014; Lancet Psychiatry, 1: 102-104.

Perlis, 2018; American Journal of Psychiatry, 175: 500-501.

Withdrawal vs. Discontinuation Syndrome

Antidepressant withdrawal was reported in the scientific literature shortly after the introduction of the first antidepressant drugs, e.g. Kramer et al, 1961; Shatan, 1966.

It was also studied more comprehensively in the 1980s, e.g. Dilsaver et al, 1987.

Most importantly, before the introduction of the SSRI drugs, all these research papers used the term withdrawal symptoms/syndrome!

Dilsaver et al, 1987; International Clinical Psychopharmacology, 2: 1-19.

Kramer et al, 1961; American Journal of Psychiatry, 118: 549-550.

Shatan, 1966; The Canadian Journal of Psychiatry, 11: S150-S158

Withdrawal vs. Discontinuation Syndrome

The SSRIs became blockbuster drugs and among the best-selling drugs of all medicine, because, with the introduction of DSM-III in 1980 conditions formely termed anxiety neurosis became depressive disorders, and the addictive and dependence-forming benzodiazepines were thus replaced by the SSRIs

In the early 1990s, saturation of the depression market led drug companies to further seek approval of antidepressants for anxiety disorders

Horwitz, 2015; Perspectives in Biology and Medicine, 58: 105-119.

Withdrawal vs. Discontinuation Syndrome

Withdrawal symptoms/syndromes are conceptualy closely linked to dependence, thus for marketing reasons the pharmaceutical industry wanted to disconnect that term from antidepressants by inventing a new term: discontinuation syndrome

A clever marketing campaign launched by Eli Lilly (producer of fluoxetine) involving many influential key opinion leaders disseminated the new term discontinuation syndrome as of 1996 very efficiently and replaced the established term withdrawal syndrome almost completely in the scientific literature until very recently

Massabki & Abi-Jaoude, 2021; British Journal of Psychiatry, 218: 168-171.

Dependence vs. Addiction

Dependence and addiction are often used interchangeably in common language, but in pharmacology and addiction medicine they have a very specific and distinct meaning:

(Physical) dependence arises when body and brain undergo adaptations to the presence of a drug, countering its effect over time in order to maintain homeostasis (e.g., serotonin receptor downregulation). The only evidence of a state of dependence is the appearance of withdrawal symptoms on reducing or stopping the drug

Thus, dependence is merely a physiological reaction to prolonged drug use

Dependence vs. Addiction

According to a consensus statement from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine:

«Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist»

Dependence vs. Addiction

By contrast, addiction means that someone craves a drug and cannot control its use

Thus, addiction is primarily a psychological reaction (which is why we can become addicted to all sorts of non-pharmacological things, including shopping, games, sex)

People who are dependent on a drug or medicine aren't necessarily addicted! Antidepressants do cause dependence, but are not addictive

Horowitz & Taylor, 2023; Lancet Psychiatry, 10: e23.

Dependence vs. Addiction

Then why do so many psychiatrists and general practitioners erroneously claim that antidepressants are not dependence-forming?

The main culprit is DSM-III-R, published 1987, which conflated addiction with dependence. The committee argued that the word addiction is pejorative and dependence more neutral. The term dependence was thus used to describe uncontrolled drug-seeking behaviour in place of addiction

«There is a normal physiological response called ‘physical dependence’, and there is ‘addiction’, which is drug-seeking behavior called ‘dependence’ in the DSM» (O’Brien, 2011)

O’Brien, 2011; Addiction, 106: 866-867.

Phenomenology of Withdrawal

Antidepressant withdrawal affects 30-60% of users and involves various mental and physical symptoms. The most frequent are:

Dizziness, electric-shock sensations (brain zaps), insomnia, irritability, agitation, anxiety, nervousness, low mood, bouts of crying

Discriminating withdrawal from relapse can be difficult if physicians rely on symptom presentation only.

Considering timing (onset after reaching a low dose), quality (feels different, more extreme, never experienced before), and response to medication (acute symptoms often disappear instantly after reinstating the drug or higher dose)

Horowitz & Taylor, 2022; BJPsych Advances, 28: 297-311.

Phenomenology of Withdrawal

Antidepressant relapse prevention trials are prone to serious withdrawal confounding, because drug treatment is stopped abruptly/rapidly. Moreover, depression relapse is assessed with depression symptom rating scales, which include many symptoms that are also part of withdrawal reactions (e.g., low mood, nervousness, anxiety, agitation, insomnia)

A placebo-controlled discontinuation trial has shown that 5-8 days of abrupt placebo interruption causes withdrawal symptoms that are classified as depression relapse based on the Hamilton Depression Rating Scale in up to 27% of people with remitted depression

Rosenbaum et al, 1998; Biological Psychiatry, 44: 77-87.

Phenomenology of Withdrawal

In antidepressant relapse prevention trials, putative depression relapses occur disproportionally often in the first few weeks after treatment discontinuation (excess effect)

Censoring events that occur within 6 weeks of treatment discontinuation would reduce the relapse-preventive effect by 50%

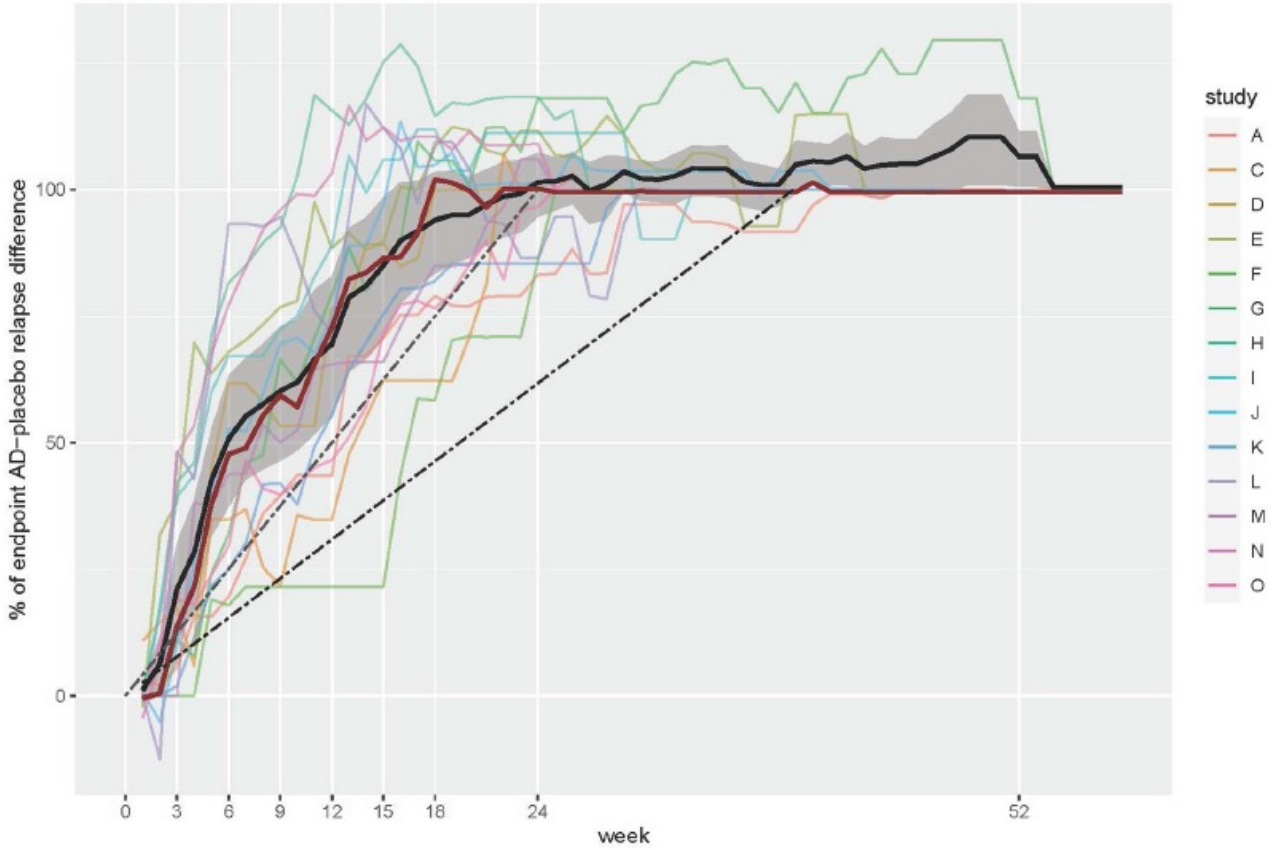
After 18 weeks of treatment discontinuation, placebo prevents “relapses” as good as continued drug treatment

These findings strongly indicate that continued drug treatment often prevents withdrawal reactions rather than genuine depression relapses

Hengartner, 2020; Therapeutic Advances in Psychopharmacology, 10: 1-10.

Hengartner & Plöderl, 2021; Therapeutic Advances in Psychopharmacology, 11: 1-12.

Phenomenology of Withdrawal



Hengartner & Plöderl, 2021; Therapeutic Advances in Psychopharmacology, 11: 1-12.

Neurobiology of Withdrawal

Taking antidepressants leads to neurophysiological adaptations within a few weeks. These adaptations are assumed to play a role in withdrawal (Horowitz et al., 2023)

Specifically, various neuroimaging studies have shown that, during SSRI treatment, the body downregulates serotonin receptors in the brain (Gray et al, 2013; Haahr et al, 2014)

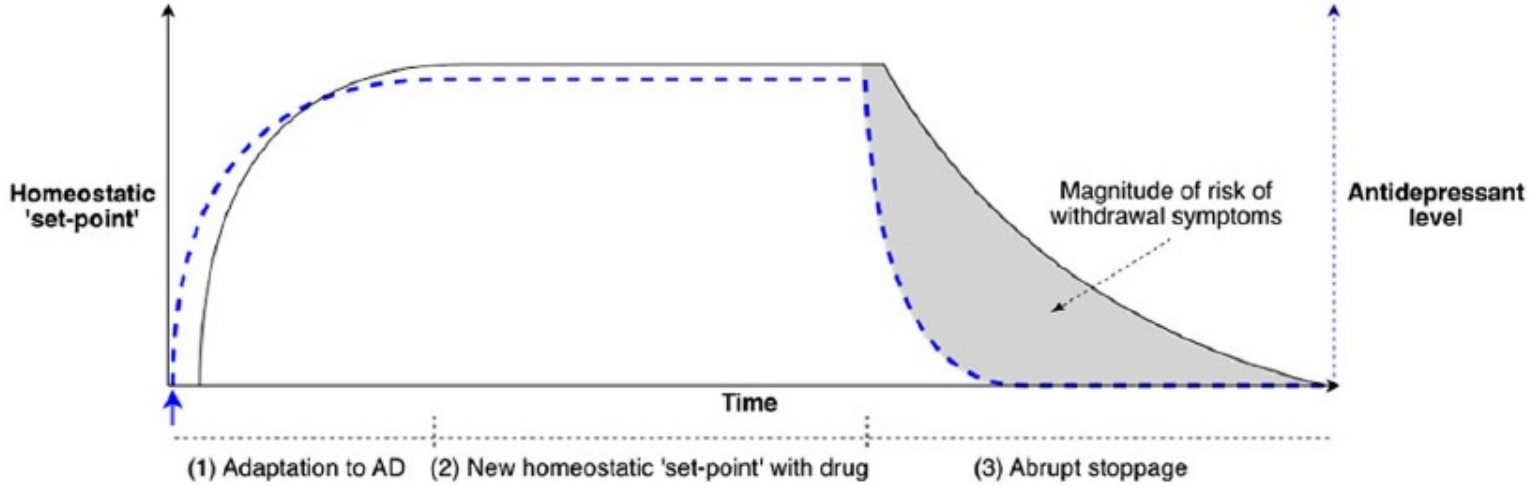
Gray et al, 2013; Biological Psychiatry, 74: 26-31.

Haahr et al, 2014; Molecular Psychiatry, 19: 427-432.

Horowitz et al, 2023; CNS Drugs, 37: 143-157.

Neurobiology of Withdrawal

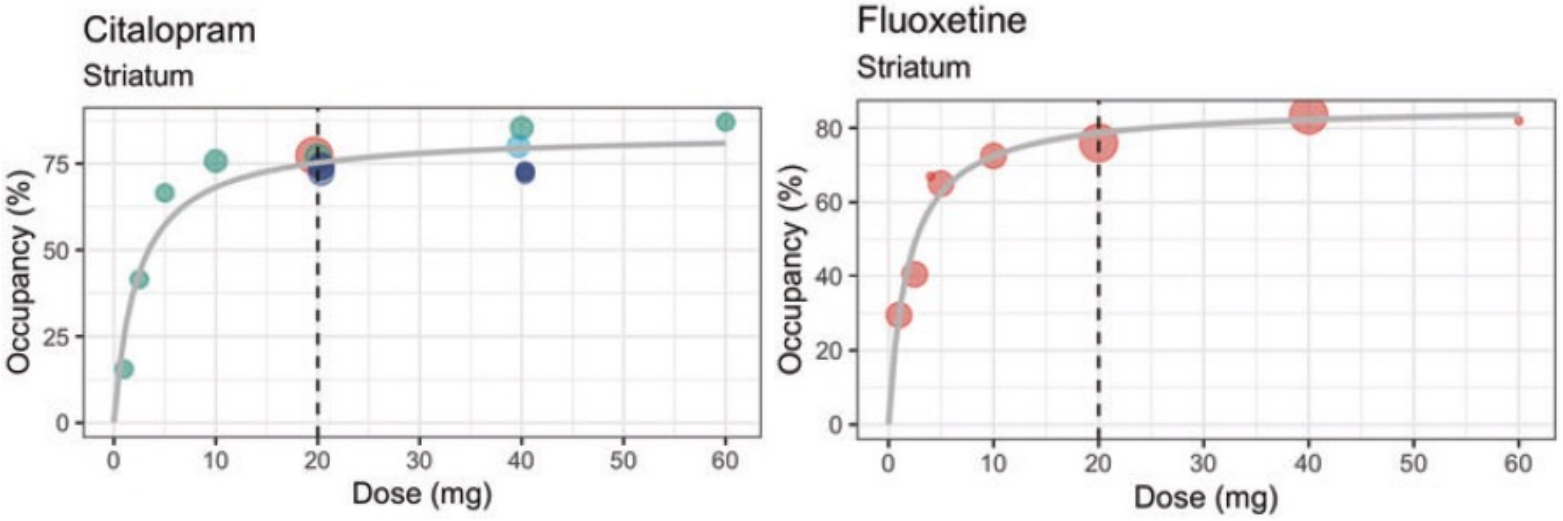
When antidepressants are abruptly/rapidly stopped, serotonin falls below the level to which the body has adapted, thus leading to a disequilibrium until adaptions resolve (Horowitz et al, 2023):



Horowitz et al, 2023; CNS Drugs, 37: 143-157.

Neurobiology of Withdrawal

Association between SSRI dose and serotonin transporter occupancy is not linear. Occupancy declines greatly at very low doses, whereas above minimum recommended dose occupancy barely increases



Sorensen et al, 2022; Molecular Psychiatry, 27: 192-201.

Neurobiology of Withdrawal

By consequence, risk of withdrawal symptoms becomes disproportionally larger at very low doses (way below available minimum dose)

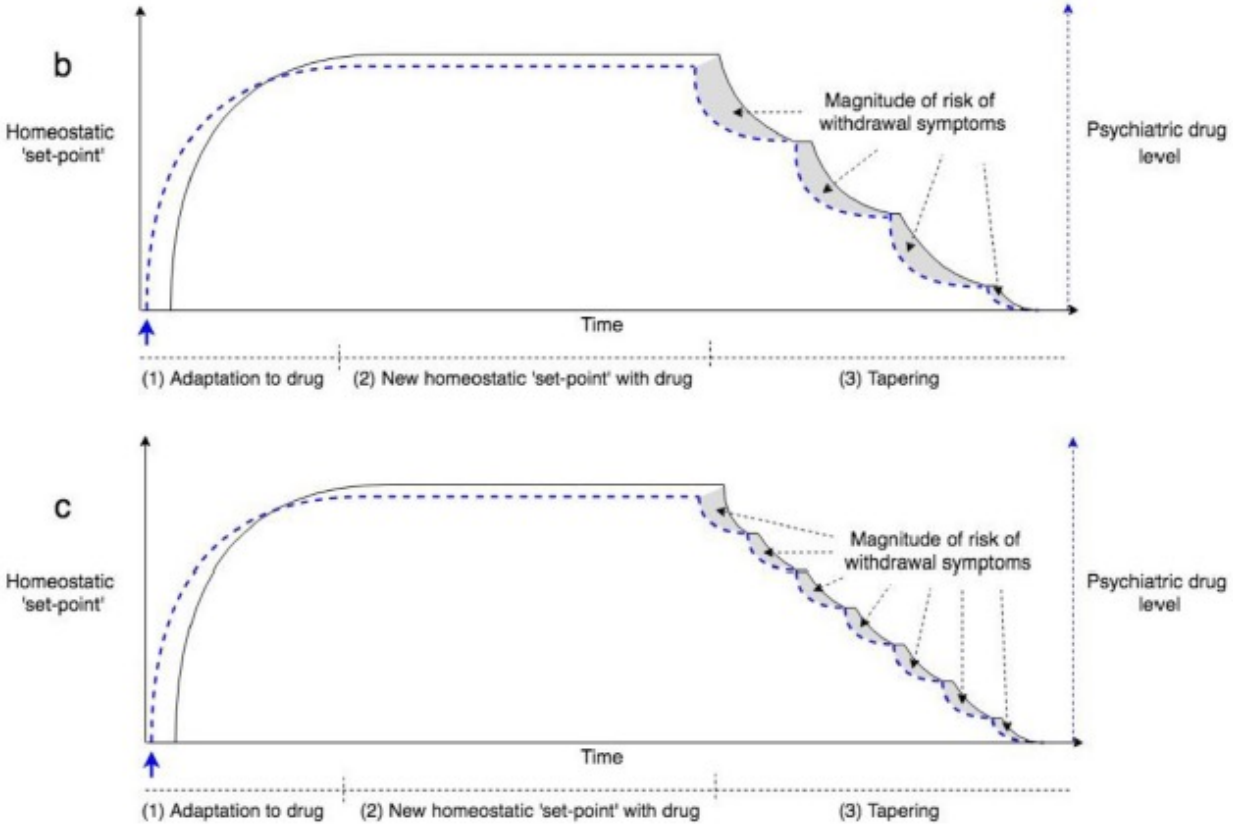
To avoid or diminish withdrawal symptoms, very small hyperbolic tapering is necessary in some users, e.g. 10% dose reduction every 2-3 weeks. Dose reductions thus become increasingly smaller (e.g. 10mg -> 9mg -> 8.1mg -> 7.3mg -> 6.6mg -> 5.9mg -> 5.3mg)

Tapering the drug may thus require many months or even years in some cases

Horowitz & Taylor, 2019; Lancet Psychiatry, 6: 538-546.

Sorensen et al, 2022; Molecular Psychiatry, 27: 192-201.

Neurobiology of Withdrawal



Horowitz & Taylor, 2022; European Neuropsychopharmacology, 55: 4-7.

Acknowledgment

Thank you for your attention!

A special thank you to Paulius Skruibis for the invitation.

For further reading and a comprehensive evaluation, see:

Hengartner MP (2022). Evidence-biased Antidepressant Prescription: Overmedicalisation, Flawed Research, and Conflicts of Interest. Palgrave Macmillan (Springer Nature Publishing): London, UK.