Chapter 1

Introduction to Deprescribing Psychiatric Medications

Deprescribing as an Intervention

Deprescribing is the planned and supervised process of reducing or stopping medication for which existing or potential harms outweigh existing or potential benefits.[1] The term 'deprescribing' originates from geriatric medicine where polypharmacy in frail patients can cause more harm than benefit.[1] Deprescribing is increasingly recognised to be a key component of good prescribing – reducing doses when they are too high, and stopping medications when they are no longer needed.[2] This process cannot occur in a vacuum of theoretical concerns but should take into account the patient's health, current level of functioning and, importantly, their values and preferences.[1] Deprescribing seeks to apply best practice in prescribing to the process of stopping a medication. It requires the same skill and experience as for the process of prescribing from prescribers, as well as support from pharmacists and other healthcare staff to obtain the best results. Importantly, it should place patients at the centre of the process to ensure medicines optimisation.[3]

There has historically been little attention paid to deprescribing in psychiatry. There is a dearth of research into a structured approach to stopping psychiatric medication, with the exception of some early studies examining stopping benzodiazepines[1] and in some specific populations, like people with learning disabilities. The focus of research efforts has been predominantly the prescribing of psychiatric medications – for example, there are estimated to be about 1,000 (published and unpublished) studies on starting antidepressants and only 20 on stopping them.[4] Concern about this imbalance is not specific to psychiatry with other medical specialties, such as cardiology, also engaging in a re-appraisal of long-term medication continuation, with support for developing strategies for repeated risk–benefit analyses over time.[5]

The Maudsley® Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs, First Edition. Mark Horowitz and David Taylor.

The context for deprescribing

Over-prescription in psychiatry

Despite evidence of benefit for psychiatric drug treatment, there have been concerns raised regarding over-prescription. 1 in 6 people in western countries are prescribed an antidepressant in any given year, with rates rising a few per cent each year.[4,6] These increasing prescription numbers are mostly caused by longer periods of prescribing – the median duration of use of antidepressants is now more than 2 years in the UK and more than 5 years in the USA.[6] Some commentators have suggested that the increasing duration of prescriptions in part reflect the difficulty people have in stopping these medications due to withdrawal effects.[7] In practice, 30–50% of patients do not have evidence-based reasons for the continued prescription of antidepressants,[8–10] prompting calls to action to reduce associated risks.[6,11] There have been similar concerns about the high rates of antipsychotic use in conditions other than serious mental illness,[12] as well as a reconsideration of their open-ended use in psychotic conditions for all patients.[13,14] There are long-standing worries about levels of benzodiazepine and z-drug prescribing,[15,16] and more recent concerns about gabapentinoid prescribing.[17]

High rates of medication prescribing has also gained governmental attention in the UK,[17] with a particular focus on psychiatric drugs. A government report has noted that 1 in 4 adults in the UK are prescribed at least one dependence forming medication each year, with some patients having difficulties stopping these medications.[18] One central concern is that short-term symptom control might be prioritised over long-term functional outcomes, especially as most studies guiding treatment protocols measure symptomatic outcomes over short time periods rather than functional outcomes (or other outcomes often valued by patients) over longer time periods.[13,19,20]

Alongside this disquiet regarding over-prescription there has been renewed scrutiny of the effectiveness of some psychiatric medications. There is some consensus in the UK and Europe that benzodiazepines and z-drugs have limited effectiveness in the long term, with guidance recommending against long-term treatment for anxiety and insomnia,[21] matched by guidance in the USA from some health management organisations.[15] Preliminary studies have recently found similar outcomes in the treatment of selected patients with first-episode psychosis with or without antipsychotics in the context of comprehensive psychosocial support,[22,23] and non-drug treatment for serious mental illness has attracted increasing interest, including a large randomised controlled trial (RCT).[24] There have been calls from clinicians and patients for 'minimal medication' options for the treatment of psychotic conditions, such as have been established in Norway and parts of the USA.[25] There has continued to be debate regarding the efficacy of antidepressants[26,27] with arguments being made for their use in selected populations.[28] Concerns have emerged regarding the efficacy and safety of gabapentinoids.[17] In some countries there has been a shift away from a drug-centric approach in some patient groups – for example, in England and Wales the National Institute for Health and Care Excellence (NICE) now recommends that mild depression should not be treated with antidepressants as a first-line treatment, and suggests eight equally effective (and cost-effective) non-pharmacological treatment options for severe depression, alongside medication options.[29]

In addition to the above, there has also been significant critical attention directed towards the relapse prevention properties of psychiatric drugs.[30,31] All psychiatric drug classes are recognised to cause withdrawal effects when stopped that may be misinterpreted as relapse of the initial condition necessitating treatment.[32] These withdrawal symptoms are often ignored in discontinuation studies examining relapse prevention properties.[30,33,34] As a result there have been questions raised as to whether the relapse prevention properties of psychiatric drugs have been over-stated by misclassification of withdrawal effects as relapse,[30,33,34] indicating we should be cautious in our interpretation of these studies.

Research and guideline establishment in deprescribing

In recent years interest in psychiatric deprescribing has increased exponentially. Numerous studies have been conducted or are ongoing exploring reducing and stopping antipsychotics in first and multi-episode psychotic conditions, in Taiwan, France, Denmark, the Netherlands, England, Australia and Germany, including the establishment of an international research consortium.[14] Some of these studies are examining gradual reductions, or hyperbolic dose reductions specifically.[14,35] Alongside this there are studies looking at how to help patients stop antidepressants – in the UK,[36] the Netherlands[37] and in Australia[38] – as well as several published studies looking at substitutions for antidepressant treatment like preventative cognitive therapy or mindfulness-based cognitive therapy.[39–41]

There has been increasing interest in the process of stopping medication based on the pharmacological properties of the drugs,[42–45] as well as in the practical means for making gradual dose reduction (for example, using compounded tablets in very small doses).[46–48] There has also been increased focus on the non-pharmacological aspects of reducing and stopping medication – the positive and negative impact on people's lives, as well as the barriers and the facilitators.[1,49–52]

In parallel, there has been increasing institutional interest in deprescribing in some countries. In the UK, in recent years, there has been guidance issued by the Royal College of Psychiatrists on how to safely stop antidepressants,[53] as well as guidance from NICE on how to stop antidepressants, benzodiazepines, z-drugs, opioids and gabapentinoids.[54] Similar guidance on how to stop antipsychotics has been called for.[55] In England, the National Health Service (NHS) has introduced structured medication reviews to reduce the use of unnecessary medication, including some psychiatric drugs,[56] and the Department of Health and Social Care has been tasked with upscaling deprescribing capacity in the NHS.[18]

Many clinicians report an interest in deprescribing and in receiving training for its practice. In total, 75% of UK clinicians working in first-episode psychosis services thought that early discontinuation of antipsychotic medication was beneficial for most patients.[57] In patients with multiple psychotic episodes English psychiatrists reported that they would feel comfortable supporting about 20% of their patients to discontinue their antipsychotics, with a minority of psychiatrists comfortable to support greater proportions.[58] In a survey 68% of GPs expressed a desire for more training on the withdrawal effects of antidepressants.[59] As mentioned, in Norway, government directives have led to the establishment of 'drug-free' wards, in which deprescribing is a central activity.[25] There are several dedicated psychiatric drug deprescribing services established around the world situated either in public or private healthcare settings or run by

NGOs partnered with health systems.[60] Indeed, several academics and psychiatrists have written about their own experience stopping psychiatric medication, often with the theme that this process was far more difficult than the published literature or their training had intimated.[61–63]

Patient knowledge and advocacy

This rise in academic, professional and institutional interest in psychiatric drug deprescribing has lagged behind decades of interest in the topic by patient groups who have sought ways to rationalise (and generally reduce) their medication in the relative absence of professional help. This movement seems driven by the subjectively unpleasant effects and physical health consequences from being on such medications.[64–67] It is noteworthy that much of the academic work now being conducted in deprescribing borrows from the expertise developed by patient groups.[44,48,62,66] Groups of patients (often supported by clinicians) have created guidance and advice on the topic of deprescribing in various guides and websites.[64,66,68] Manuals like *The Ashton Manual* (written by the clinical pharmacologist Professor Heather Ashton) are widely used in peer-led withdrawal communities,[69] and this manual has influenced NICE guidance on withdrawing from benzodiazepines.[70] Alongside this there has been substantial patient advocacy for more clinical services for deprescribing, which has been part of the driving force in the shift of interest to this topic,[64,71–73] as well as increasing media attention to the issue of how to safely stop psychiatric medications and the adverse consequences of stopping too rapidly.[74–78]

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Why deprescribe?

A variety of clinical scenarios may warrant deprescribing. These include:

- high-dose prescribing,
- polypharmacy (drug-drug interactions, effects on adherence, and medical risk in vulnerable populations).
- inappropriate prescribing (wrong drug, dose or duration),
- patient preference,
- harms outweighing benefits,
- condition improved, resolution of stressors or alternative coping strategies developed.

High-dose prescribing, polypharmacy, inappropriate prescribing

It is widely agreed that high-dose prescribing and polypharmacy can, in many instances, produce more harm than benefit.[1] For many psychiatric conditions, including major depressive disorder, there is no clear advantage to high-dose pharmacotherapy, although the risks of adverse effects can increase as a function of dose.[2] The lower range of licensed doses is thought to achieve an optimal balance between efficacy, tolerability and acceptability in acute treatment.[2] The potential harms of high-dose antipsychotic prescribing and psychiatric drug polypharmacy are also well recognised.[1] Additionally, potentially inappropriate prescribing of psychiatric medication occurs commonly – including chronic polypharmacy for patients with personality disorders, in which guidance generally recommends avoiding pharmacological treatment or employing it for short-term use.[3] Deprescribing may be warranted for long-term benzodiazepine and z-drug use, which is generally officially frowned upon,[4] and in the substantial proportion of patients on antidepressants with no evidence-based reason for ongoing treatment (for example, the antidepressant may have had no beneficial effect or it might have been effective but has been continued for too long).[5]

Patient preference

In an era in which medical treatment in general is moving towards patient-centred treatment and away from paternalism, patient preference should be a central consideration, unless a patient is legally required to comply with treatment via a community treatment order.[6,7] Many patients report that their clinicians decline to help them reduce or stop their medication.[8] In some cases this can lead to patients following more risky options like stopping abruptly, the technique most likely to lead to aversive outcomes. Many people feel compelled to seek advice from online peer-support communities instead of their clinicians because of their clinicians' reluctance to support deprescribing, or lack of knowledge of how to do so.[8,9] Clinicians and patients may have different priorities with clinicians concerned with risk of relapse, symptom control and potential legal consequence for aversive outcomes, while patients may prioritise fulfilling social roles or quality of life, over being symptom free (although there is wide variation on this matter).[10] Negotiating a balance between differing priorities amongst patients and clinicians may be beneficial for outcomes, including treatment alliance and adherence to treatment recommendations in general.[7]

Harms outweigh benefits

For a portion of patients the benefits of medication will be outweighed by adverse effects.

Limited benefits

In some people the medication may never have been particularly effective but has continued because of inertia, a lack of attention to deprescribing or a desire not to 'rock the boat'.[11,12] Even in short-term trials the number needed to treat (NNT) for many forms of psychiatric medication is 6–10 or more meaning many patients are not helped by a specific effect of the medication to an appreciable degree. For some patients the medication may have been initially helpful, but through the development of tolerance to the drug this benefit has diminished.[13,14] This is well recognised for benzodiazepines and z-drugs, is also an issue for gabapentinoids,[15] and has also been somewhat controversially implicated in the long-term use of antidepressants,[16,17] and antipsychotics.[18,19]

Many medications are continued after initial symptoms have resolved with the intention of preventing future relapse. However, as above, there are significant concerns about the certainty of the evidence for the prophylactic properties for psychiatric drugs.[20–23] These discontinuation studies often stop psychiatric drugs abruptly or rapidly, do not take into account withdrawal effects, which are likely to be mis-classified as relapse in the discontinuation arms of these trials.[20–23] This phenomenon would provide an exaggerated estimation of the relapse prevention properties of psychiatric drugs,[20–23] and should lead us to be more cautious in interpreting the extent of the relapse prevention properties of some long-term psychiatric medications.

Adverse effects

The myriad adverse effects from psychiatric drugs range from weight gain and other metabolic consequences, particularly noted for atypical antipsychotics, to more subtle effects such as impaired capacity for feeling, memory or concentration caused by many psychiatric drug classes. Sexual side effects are very common, especially with selective serotonin reuptake inhibitors (SSRIs), where they occur in half or more of patients[24,25] and other adverse effects often thought to be short term have been found to persist.[26] There are also risks of long-term use such as possible cortical loss with antipsychotic treatment,[19,27] increased risk of dementia for some medications,[28,29] as well as falls and increased mortality, especially as people age.[30,31] Extra-pyramidal side effects from first-generation antipsychotics and tremor from lithium can be aversive.[1] When substantial benefits to a patient are provided by psychiatric drugs, these risks may be acceptable, but in other cases the balance of harms and benefits may not be favourable. As patients age the risks may increase owing to impaired metabolism of drugs and greater frailty, while the benefits may decrease, due to tolerance and perhaps the improvement of their condition over time.[7] Lastly, withdrawal effects are particularly associated with increased duration of medication use; one reason to stop medication earlier rather than later.[32,33]

Mental health condition improved or alternative coping

For some patients the original condition for which they were prescribed medication will have resolved or improved over time. The most obvious example is the circumstance in which a stressor that precipitated depression or anxiety has resolved, with a

corresponding improvement in the patient's condition. Even conditions often considered life-long such as psychotic conditions or affective disorders can improve with time – as reported in several cohorts of patients,[19,34,35] with up to 40% of people with psychotic conditions being well and on no or little medication years after first diagnosis.[19,36] The behaviours diagnosed as personality disorders generally improve over time;[37] patients may have found more stable personal or professional circumstances and maturity may limit emotional instability. For some patients, especially those who are stable, medication may have less benefit than during more active periods of their condition. Or patients may have developed or be interested in pursuing alternative approaches to managing their mental health conditions. As one example, NICE has identified a dozen treatments that are as effective (and cost-effective) as antidepressants in the treatment of depression.[38]

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Barriers and facilitators to deprescribing

There are numerous factors that can facilitate or hinder deprescribing. A narrative review outlined these factors with regard to stopping antidepressants, many of which are applicable to a variety of drug classes (Table 1.1).[1] Some of these factors can be addressed through education and support, as discussed in subsequent chapters. Additionally, there are many institutional factors that act as barriers to deprescribing: while deprescribing can produce benefits for patient health and well-being, as well as health services (e.g. reduced adverse effect burden) in the long term, in the short term it often involves greater resources (e.g. increased contact, monitoring and support), which can act as a deterrent.[2]

Importantly, previous experience of stopping medication – either planned or, more usually, spontaneously by the patient, often abruptly or rapidly – with negative consequences can deter patients and clinicians from wishing to trial this process again.[2] The sometimes alarming presentations with severe symptoms after drug cessation that have generally been interpreted as relapse can strongly re-enforce the impression of a need for medication. However, there is some evidence now that these presentations – even when they are delayed for some time after drug cessation – may in fact represent withdrawal effects or the consequence of withdrawal effects, sometimes called withdrawal-associated relapse (e.g. genuine relapse as a consequence of withdrawal effects such as insomnia).[3,4] There is further evidence, presented in subsequent chapters, that in at least some of these cases a more gradual, structured and pharmacologically informed approach to reduction may minimise or avoid some of the more negative aspects of this process.[2]

Table 1.1 Barriers and facilitators for patients to stop psychiatric medications. Adapted from [1] (2019).

Domain	Barriers	Facilitators
Psychological and physiological factors	■ Stressful life circumstances ■ Aversive experience of discontinuation in past leading to deterioration (withdrawal effects or relapse) ■ Lack of effective coping strategies ■ Physical dependence on psychiatric medications (leading to withdrawal effects)	■ Confidence in ability to discontinue ■ Life circumstances stable ■ Well-informed about approach to tapering
Perceived cause of mental health condition	■ Long-term (perhaps life-long) condition requiring long-term treatment ■ Primarily biochemical (or other biological) cause	■ Primarily life circumstances
Fears	■ Fear of relapse ■ Fear of withdrawal effects	■ Fear of 'addiction', physical dependence ■ Fear of adverse effects and long-term health complications
Personal goals/ motivations	■ Self-identity as 'disabled' ■ Stopping as threat to stability ■ Benefit of continuing to others around them ■ Cure is not possible, only management	■ Self-identity as 'healthy' ■ Desire to function without psychiatric medication ■ Feeling better ■ Dislike having to take a psychiatric medication

(*Continued*)

Table 1.1 (*Continued*)

Domain	Barriers	Facilitators
Perception of psychiatric medications	■ Positive effect ■ Natural or benign ■ Lack of concern over adverse/side effects	■ Ineffectual ■ Unacceptable adverse/side effects ■ Unnatural ■ Unhappy about long-term use
Information about the discontinuation process	■ Inadequate information about the discontinuation process, and risks and benefits of this	■ Information on how to safely discontinue and what to expect
Support network (friends, family, professionals)	■ Pressure to stay on medication	■ Support to come off medication

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Withdrawal Effects from Psychiatric Medications

The two major negative consequences of reducing and stopping psychiatric medication are relapse and withdrawal. The risks of relapse are well known and explored extensively elsewhere so we will focus on the less-commonly addressed issue of withdrawal effects. All classes of psychiatric drugs can cause withdrawal effects.[1,2] These include benzodiazepines, z-drugs, gabapentinoids, mood stabilisers, stimulants, antipsychotics and antidepressants.[1,2] There is a great degree of overlap in the withdrawal symptoms from different drug classes, including symptoms such as dizziness, nausea, anxiety, impaired concentration, irritability, agitation, headache, tremor, sleep disturbances, depressed mood and fatigue.[1] There are also withdrawal symptoms more typical of specific classes of drug that may reflect effects on particular receptor targets and downstream processes – for example, brain zaps, myoclonus, depersonalisation and derealisation in SSRI and serotonin and norepinephrine reuptake inhibitor (SNRI) withdrawal, and derealisation/depersonalisation and delirium in benzodiazepine withdrawal.[2]

Withdrawal effects have not been systematically evaluated for all classes of psychiatric medication but they are common – about 50% of patients who stop antidepressants[3] will experience withdrawal effects, and 32%–42% of people taking benzodiazepines will be unable to stop their drug because of withdrawal effects.[4] The other commonality across drug classes are that withdrawal effects can manifest in psychological symptoms,[1,2] likely due to effects on the central nervous system.[1] Psychological withdrawal symptoms can include low mood, anxiety, insomnia, panic attacks, obsessive thinking, suicidality and there are reported cases of psychotic symptoms due to withdrawal from antidepressants,[1] benzodiazepines[2] and antipsychotics.[5]

Mis-diagnosis of withdrawal effects as relapse

The presence of withdrawal symptoms that manifest psychologically makes it easy to mistake these symptoms for relapse of an underlying condition by both patients and clinicians.[6–8] Patients commonly report that their withdrawal symptoms are mis-diagnosed as relapse of the condition for which their drug was originally prescribed, or as a new-onset mental health disorder.[6–8] Such mis-diagnosis is understandable, given the limited awareness of withdrawal symptoms from psychiatric drugs, including their severity and duration and because they have often been downplayed as 'discontinuation' symptoms, or characterised as 'mild and brief' based on short-term industry trials.[9] The waters have also been muddied by commentators claiming that some psychiatric drugs can not cause withdrawal effects because they are not addictive[10,11] – whereas adaptation to a drug over time (often called 'physical dependence') is all that is required for withdrawal symptoms to emerge when reducing or stopping the drug, without the need for addiction (which involves psychological dependence as well, characterised by craving, compulsion, etc).[12,13]

On the other hand, physicians are well practised at detecting relapse: when patients present with mood or anxiety symptoms, other psychiatric symptoms or disordered behaviour, especially when such symptoms are severe and long lasting, relapse is often higher on a list of differentials than withdrawal.[6,8] However, over the past few years

there has been increasing recognition that withdrawal effects from psychiatric drugs can cause severe symptoms, which can themselves be long-lasting and in some instances appear similar to the presentation of other mental health conditions.

Physical dependence vs addiction

The term 'dependence' has come to be used interchangeably with 'addiction' (to mean uncontrolled drug-seeking behaviour).[12] Inevitably this has led to some unfortunate confusion.[12] This choice of language was made in DSM-III-R because the term 'addiction' was thought to be pejorative whilst the word 'dependence' was thought more neutral.[12] However, the original usage of the word 'dependence' referred to 'physiological adaptation that occurs when medications acting on the central nervous system are ingested with rebound when the medication is abruptly discontinued'.[12] The National Institute on Drug Abuse (NIDA) in the USA states 'Dependence means that when a person stops using a drug, their body goes through "withdrawal": a group of physical and mental symptoms that can range from mild (if the drug is caffeine) to life-threatening … Many people who take a prescription medicine every day over a long period of time can become dependent; when they go off the drug, they need to do it gradually, to avoid withdrawal discomfort. But people who are dependent on a drug or medicine aren't necessarily addicted.'[13] In addition, Goodman and Gilman's textbook of pharmacology points out 'The appearance of a withdrawal syndrome when administration of the drug is terminated is the only actual evidence of physical dependence.'[14]

All major classes of psychiatric drugs can be associated with withdrawal symptoms on cessation or dose reduction. These symptoms occur in a substantial proportion of patients, as a result of physical dependence (a normal neurobiological response to drugs that act on the central nervous system).[2,12,15–18] Physical dependence to psychiatric drugs arises because the body and brain undergo adaptations to the presence of a drug, countering its effect in order to maintain homeostasis.[12,19,20] It is also clear that many psychiatric drugs – with the exception of benzodiazepines, stimulants and some antidepressants such as tranylcypromine and amineptine – do not cause addiction, as they do not induce compulsion, craving and other symptoms of addiction.[11,21] Sometimes misunderstanding that withdrawal symptoms arise merely from adaptation to psychiatric drugs after chronic use leads to misplaced accusations of addiction, misuse or abuse when patients report withdrawal symptoms on trying to stop.

Some patients may be less interested in academic distinctions between dependence and addiction and more interested in the reality that they cannot stop their psychiatric drugs because of unpleasant withdrawal effects. They may therefore describe them colloquially as 'addictive',[22,23] though most psychiatric drugs do not fit the strict definition of this property. Some patients may also not be happy being described as 'dependent' on psychiatric drugs (which they may still associate with the concept of addiction), and in this case, it may be better to talk in terms of 'neuroadaptation' or 'adaptation'.

Withdrawal symptoms vs discontinuation symptoms

The term 'discontinuation symptom' was promoted by drug manufacturers to minimise patient concerns regarding their product and to prevent an association with the idea of addiction.[9,24] There is now widespread recognition that this euphemism is misleading and that its use minimises the potentially adverse consequences of stopping psychiatric drugs; withdrawal symptoms do not imply addiction.[9,25,26] The more pharmacologically

accurate term is 'withdrawal symptoms', now adopted by Royal College of Psychiatrists,[9,27] the British Medical Association[9] and NICE in the UK for antidepressants[28,29] and by academics for antipsychotics,[1,2,30] mood stabilisers,[2] and long used with regards benzodiazepines, stimulants and gabapentinoids.[2]

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Pathophysiology of psychiatric drug withdrawal symptoms

Drug withdrawal effects are effectively part of the pharmacology of any drug which the body eliminates faster than adaptations to the presence of the drug take to subside.[1] Based on this definition, any evidence of adaptation to a drug strongly suggests that withdrawal symptoms will occur when the drug is stopped.[1]

Homeostatic adaptation to psychiatric drugs

During ongoing administration of psychiatric drugs, as with other drugs acting on the central nervous system, neuroadaptation establishes a new homeostatic equilibrium, in which the system accommodates to alterations produced by the drug. When the medication is reduced or stopped, the new homeostatic set-point is perturbed, resulting in withdrawal symptoms.[1–3] Adaptations to the presence of the drug predict withdrawal effects because these adaptations do not resolve instantaneously upon stopping the drugs but will persist for some further period.

There are a variety of specific adaptations to each class of drug, explored in the relevant chapters. In general, because of a homeostatic drive towards equilibrium, the brain responds to antagonists by up-regulating the number or sensitivity of receptors to increase signal (e.g. dopaminergic hypersensitivity in response to long-term treatment with dopamine antagonists).[4] The brain responds to agonists or drugs that increase synaptic availability of transmitters by down-regulating the number or sensitivity of receptors to reduce the signal (e.g. reduced serotonergic receptor sensitivity in response to blockade of the serotonin transporter).[5] It is also likely that withdrawal symptoms are not mediated simply by changes to the receptors that are directly affected by medications, but also by the myriad transmitters and processes downstream or otherwise connected to these effects.[1,6]

Animal studies and some human studies show that these changes can persist after the drugs are removed from the body and can be long-lasting for months and years in some cases. This has been demonstrated in clinical studies of antidepressants[7] and suggested by long-lasting changes to some people who have taken antipsychotics manifesting in tardive dyskinesia,[8] and supported by animal studies.[9]

Homeostatic disruption on psychiatric medication discontinuation

When a psychiatric drug taken long-term is reduced in dose or stopped, the homeostatic equilibrium that had been established is perturbed. The difference between the 'expected' level of activity by the system and the actual 'input' by the drug is responsible for withdrawal symptoms (Figure 1.1).[1–3] Withdrawal symptoms will persist for the time taken for the brain to re-adapt to lower levels (or the absence) of the drug – that is, the time taken for a new homeostatic equilibrium to be established.

It is sometimes erroneously believed that withdrawal symptoms last for the time taken for the drug to be eliminated from the system.[6] This misunderstanding sometimes leads clinicians to tell patients that they could not be experiencing long-lasting withdrawal symptoms because 'the drug is out of their system' – however, as in Figure 1.1, it can be seen that while the onset of withdrawal symptoms is strongly determined by the elimination half-life of a drug (shorter half-life, quicker onset), the duration of

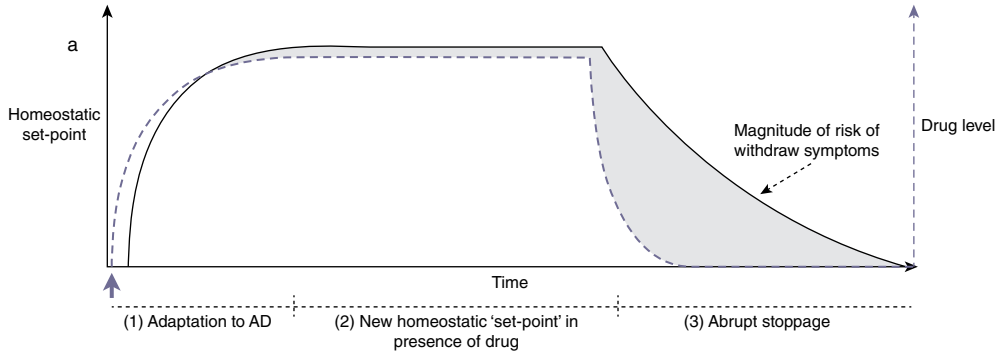

Figure 1.1 The neurobiology of psychiatric drug withdrawal. In this diagram, the homeostatic 'set-point' is shown in black and psychiatric drug levels are shown in purple dashed lines. Adapted from Horowitz and Taylor (2021).[10] (1) The system is at baseline. At the Solid purple arrow, a psychiatric mediation is administered; drug plasma levels increase. Physiological adaptations of the system to the presence of the drug begin. (2) At the plateau, drug plasma levels (and target receptor activation) have reached a steady state with a new homeostatic set-point of the system established. (3) The drug is abruptly ceased, and plasma drug levels drop to zero (exponentially, according to the elimination half-life of the drug). This difference between the homeostatic set-point (the 'expectations' of the system) and the level of drug in the system (dashed purple line) causes withdrawal symptoms. Hence, withdrawal symptoms may worsen or peak even long after the drug has been eliminated from the system. The shaded area under the curve, representing the difference between the homeostatic set-point and the level of the drug, indicates the degree of risk of withdrawal symptoms: the larger the area the greater the risk. With permission of Elsevier.

withdrawal is determined by the plasticity of the system in returning to a 'pre-drug' homeostatic equilibrium.[1,6]

An analogy might be made to the experience of walking out of a loud concert (more signal as with the increased synaptic neurotransmitter during agonist treatment) into a quiet street (physiological levels of transmitter after drug removal), where sounds appear muted. This experience of muted sounds arises because of reduced tympanic sensitivity (as for reduced receptor sensitivity) for a few minutes while your tympanic membrane re-accommodates to a lower average amount of sound (analogous to the delay for the system to re-adapt to less transmitter signal – although it takes much longer than a few minutes). The time for the sound to dissipate (or for synaptic transmitter levels to normalise on removal of the drug) is trivial; it is the time taken for tympanic re-accommodation that determines the duration of the withdrawal effects (as for re-accommodation of the processes affected by long-term psychiatric drug use – which can take months or years).

Factors influencing development of withdrawal effects

Although there has been limited research on the topic, there are several factors that are thought to have an effect on incidence, severity and duration of withdrawal symptoms. In general, a greater degree of adaptation to a drug is likely to lead to greater withdrawal effects, brought about, for example, by higher dose or longer use, as well as some variation among drugs and individual sensitivity to withdrawal effects.[6]

Physical dependence to psychiatric drugs resulting in a clinically significant withdrawal syndrome can occur within weeks of daily administration of some psychiatric medications.[6] Indeed, the FDA has warned that for some drugs, like benzodiazepines,

physical dependence can occur within days of regular use.[11] Aspects of the pharmacology of a particular medication also plays a role – with short half-life medications more implicated in withdrawal than longer acting drugs, and specific receptor targets, such as noradrenergic effects (for example, with SNRIs) also particularly implicated.[6,12] There are a number of individual characteristics hypothesised to play a role, including variations in liver enzymes involved in the metabolism of psychiatric medications, sensitivity to adaption to the presence of a drug, but this has received little research attention.[6,13]

In general women have been observed to experience greater severity of withdrawal symptoms for a variety of psychotropic medications.[6] Age plays some role in withdrawal effects, with children more likely to demonstrate visual hallucinations, agitation, facial grimacing, myoclonus and other movement disorders in benzodiazepine withdrawal than adults.[6] Older adults are more likely to demonstrate confusion, disorientation and, sometimes, hallucinations than younger people.[6]

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Clinical aspects of psychiatric drug withdrawal

Distinguishing withdrawal symptoms from relapse

As mentioned, withdrawal symptoms, which include poor mood, anxiety, insomnia, agitation and a range of other psychological symptoms may be often mistaken for relapse of the underlying disorder for which the patient was prescribed psychiatric medication.[1,2] A thorough history can allow identification of several characteristics that help to distinguish withdrawal effects from relapse:

- time of onset
- presence of distinctive – often physical, though sometimes psychological - symptoms
- response to re-instatement

The presence of severe symptoms that are long-lasting is not as helpful for distinction as once thought as it is now recognised that these symptoms can be characteristic of withdrawal and not just of relapse.[3]

Time of onset

Withdrawal symptoms usually occur hours or days after skipping, reducing or stopping a psychiatric drug.[4] There is some variability in this depending on the half-life of elimination such that longer half-life medications can have delays in onset of symptoms by weeks.[5] It has also been reported that some symptoms of psychiatric drug withdrawal may not manifest for weeks or longer after discontinuation, even for drugs with short half-lives, although the mechanism for this is not well understood.[6] A delayed decrease in central receptor occupancy, lagging behind plasma concentration decline, is one suggested explanation.[7]

Since withdrawal syndromes are recognised to last for months, or even years in some patients symptom duration past a few weeks is not an indication of relapse rather than withdrawal.[6,8,9] Relapse would be expected to have onset weeks, or months after drug cessation, depending on the usual frequency of episodes in the individual's original condition and be similar in nature to the original mental health episode.[10]

Characteristic symptomology of withdrawal

Symptoms that differentiate withdrawal from relapse may be revealed by taking a careful history inquiring after the more common symptoms of withdrawal. If physical symptoms co-occur with psychological symptoms, this indicates a high likelihood of a withdrawal syndrome.[3] For example, if a patient were to experience a surge of anxiety and lowered mood on stopping a psychiatric medication, and this was also accompanied by nausea, dizziness or electric-shock sensations or 'zaps', it is more likely that this represents a withdrawal syndrome rather than relapse of a depressive condition.[3] Some commentators have suggested that withdrawal symptoms and relapse may co-occur and while this is a possibility, Occam's razor suggests that it is more likely that a single condition will cause several symptoms, rather than several conditions co-occurring.[11] Some symptoms are so distinctive – such as the electric 'zaps' (head sensations some experience, especially on lateral eye movements)[12] that they could be considered pathognomonic of psychiatric drug withdrawal.[3]

Even when symptoms on stopping psychiatric drugs are solely psychological in nature, these can be quite distinct from the symptoms of the original condition, or more severe in nature.[13] For example, if a patient experiences agitation and panic on stopping a psychiatric medication when the patient's original condition involved depressed mood and poor appetite after a loss, the diagnosis of a withdrawal syndrome should be strongly considered,[3,14] rather than onset of a new mental health condition co-incidentally occurring at just the moment that the mediction was stopped. Withdrawal symptoms can be new and qualitatively different from the patient's original condition, while relapse is reminiscent of it.[13] Sometimes, the patient will provide the clue themselves when they say 'This is nothing like my original condition.'[4]

However, sometimes the symptoms experienced in withdrawal are very difficult to differentiate from the patient's underlying condition. This may be because some people are prone to characteristic symptoms – for example obsessive thinking or low mood – in periods of stress, whether that stress is psychological, or physiological, such as in medication withdrawal. This presentation of worsening of underlying symptoms in withdrawal is often referred to as 'rebound symptoms' (see below).[15]

Response to re-instatement

Another means of distinction is the time taken for symptoms to resolve on re-instatement of a psychiatric medication: for withdrawal symptoms this will be more rapid than for relapse, as demonstrated by resolution within a few days of re-instatement of an antidepressant (after several days of placebo treatment) in a large study[16] – withdrawal symptoms may even improve within a few hours of re-instatement. However, re-instatement might be less successful when it is delayed for months after the onset of withdrawal symptoms.[6]

The major distinguishing features between withdrawal and relapse are summarised in Table 1.2. Of course, a clinician should continue to be vigilant for genuine

Table 1.2 Distinguishing features between psychiatric drug withdrawal symptoms and relapse of an underlying condition.

	Withdrawal symptoms	**Relapse**
Time of onset	Often within hours or days of reducing or stopping a psychiatric medication (but can be delayed for long-acting drugs – and sometimes even for short-acting medications as well)	Usually weeks or months after stopping a psychiatric drug (depending on the characteristic periodicity of the condition)
Duration	Can range from days to months (or, sometimes, years)	Variable
Response to re-instatement	Improvement can be within hours or days (especially if re-instatement occurs soon after symptoms onset)	Usually delayed
Distinctive symptoms	Characteristic accompanying symptoms e.g. dizziness, headache, sweating, muscle ache; brain 'zaps' may be pathognomonic. Any symptoms not present in the underlying condition (including psychological symptoms)	Episodes of individual patients have typical characteristics

relapse of the patient's underlying condition, which may come on weeks or months after treatment is stopped and may have characteristics that are quite typical for the patient.

Distinguishing withdrawal symptoms from new onset of a psychiatric or medical condition

In addition to withdrawal effects being diagnosed as a relapse of an underlying mental health condition, many patients report that they have had withdrawal symptoms mis-diagnosed as the onset of a new psychiatric condition.[4,17,18] As symptoms of psychiatric drug withdrawal can include agitation, anxiety, depressed mood, panic, obsessive thoughts and in some cases manic and psychotic symptoms (in people who have not experienced these symptoms previously) as well as a range of behavioural disturbances, these can be mis-diagnosed as a variety of mental health conditions including agitated depression, bipolar disorder, psychotic disorders, psychosomatic disorders, panic and other anxiety disorders.[4,15,17] It should be considered that the onset of a de novo psychiatric disorder that happens to coincide with the process of stopping medication is less likely than experiencing quite typical withdrawal symptoms on stopping.[17]

Withdrawal symptoms can also be mis-diagnosed as a new-onset medical condition, or placed in the category of 'medically unexplained symptoms' or functional neurological disorder, or even attributed to malingering (Table 1.3).[17] This interpretation likely arises because of the wide array of symptoms that psychiatric drug withdrawal can produce and a lack of familiarity with withdrawal symptoms.[17] There are numerous overlapping symptoms of psychiatric drug withdrawal with these conditions: tremor, weakness (functional neurological disorder); fatigue, tiredness (chronic fatigue syndrome) and numerous symptoms that could be grouped under the category of 'medically unexplained symptoms' when the symptoms are not attributed to psychiatric drug withdrawal.[17] These misdiagnoses can lead to a failure to recommend appropriate treatment, extensive medical investigation and a feeling on behalf of patients that they were not listened to.[17]

Table 1.3 Potential mis-diagnoses of drug withdrawal syndromes.

Mis-diagnosis of psychiatric drug withdrawal	Psychiatric drug withdrawal symptoms which overlap with diagnostic criteria
Onset of new psychiatric diagnosis (e.g. agitated depression, mania, anxiety disorder, depression, psychotic episode)	New onset of anxiety, depression, panic attacks, agitation, obsessive thinking, insomnia, worry, suicidality, and more rarely, de novo manic or psychotic symptoms
Chronic fatigue syndrome	Fatigue, insomnia, muscle aches
Medically unexplained symptoms/ Functional neurological disorder	Tremor, muscle weakness, muscle spasm, pain, fatigue
Stroke, neurological disorder	Muscle weakness, 'electric zaps', tremor, headache, visual changes, vertigo, unsteadiness on feet, sensory changes

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Specific issues in psychiatric drug withdrawal

Rebound symptoms

A specific sub-set of withdrawal symptoms identified by many commentators are rebound withdrawal symptoms, which are defined as a rapid return of the patient's original symptoms at greater intensity than before treatment.[1,2] This phenomenon may occur because people have characteristic patterns of thoughts or feelings that are triggered by the process of withdrawal. For example, on exposure to an anxiogenic substance (such as high doses of caffeine), many people are likely to experience anxiety, but the nature of that anxiety is likely to be expressed idiosyncratically for each individual and influenced by their usual expression of anxiety (e.g. health-related, obsessive), despite being clearly chemically induced. This seems to apply in the process of withdrawal as well where typical patterns of thoughts and feelings are stimulated by the withdrawal process.[3,4] This may present a particularly confusing presentation for both the clinician and patient to distinguish from relapse. Quick resolution on dose increase, resolution over time with no change to medication dose and the accompaniment of these familiar symptoms with other symptoms (physical or psychological) of withdrawal can help to characterise these symptoms as rebound withdrawal symptoms rather than relapse[4,5] – but sometimes this distinction may be challenging.

Delayed onset withdrawal effects

Delayed onset withdrawal effects are widely recognised for drugs with long half-lives such as fluoxetine,[6] because the onset of symptoms is delayed by the long elimination half-life of its active metabolite norfluoxetine (7–15 days). However, it has also been observed that withdrawal effects from other psychiatric drugs, even those with short half-lives can also emerge for the first time after weeks and sometimes months.[6,7] For example, in one analysis, the mean time to onset of withdrawal symptoms following discontinuation or reduction of dose of SSRIs was 4.5 weeks, with a standard deviation of 13 weeks, indicating that some patients experienced onset of withdrawal symptoms up to 4 months after stopping their antidepressant.[7] Vigilance for withdrawal effects should be maintained even weeks after psychiatric drugs are ceased, especially when typical physical symptoms are reported. A lack of recognition of delayed onset withdrawal effects is likely responsible for mis-diagnosis in some patients.[4]

Withdrawal akathisia

Although there are myriad psychological and physical withdrawal symptoms from psychiatric drugs, perhaps the most distressing potential consequence is akathisia, a neuropsychiatric condition, characterised by severe agitation, restlessness and a sense of terror.[8–11] This condition is most often recognised as a side effect of antipsychotic use, but it has also been observed to occur in withdrawal from various psychiatric medications, including antidepressants and benzodiazepines.[8–12] Patients report a very distressing subjective feeling of restlessness and dysphoria, and they often fidget, pace, rock and are unable to sit or stand still. However, akathisia can also manifest more subtly without obvious motor symptoms, typified by terror and a subjective feeling of restlessness.[13]

The pathophysiology is poorly understood, with leading theories implicating a reduction in dopaminergic activity in the mesocortical pathway projecting from the ventral tegmental area to the limbic system and prefrontal cortex, leading to suppression of the usual inhibitory effects on motor function, producing unwanted involuntary movements.[12] Other theories implicate changes to serotonin and noradrenaline levels that can have indirect effects on dopaminergic activity.[14]

This pronounced state of agitation can be mis-diagnosed as a manic state,[10] an anxiety disorder, a panic disorder, a personality disorder, ADHD, health anxiety, restless leg disorder and functional neurological disorder, or a factitious disorder by clinicians unfamiliar with the syndrome in psychiatric drug withdrawal.[12,15,16] It has been associated with increased suicidality because of the distress and agitation it engenders.[12,15,17]

Protracted withdrawal syndrome

Severe and persistent withdrawal syndromes (months or years) are recognised for a range of psychotropic medications, including benzodiazepines, antipsychotics and antidepressants.[2,3,9,17] Protracted withdrawal syndrome, sometimes called post-acute withdrawal syndrome (PAWS) or persistent post-withdrawal syndrome (PPWS) or prolonged withdrawal syndrome, occurs in an unknown proportion of patients after stopping psychiatric medications.[9,17,18] This syndrome has long been neglected or minimised,[17] with poor education about its existence leading to mis-attribution of these symptoms to relapse or the emergence of new mental health conditions.[4,5,17,19] Protracted withdrawal symptoms are thought to be caused by changes to the brain secondary to exposure (generally long-term) to psychiatric drugs, which persist for months and years after stopping;[2,17,20] with speculation that for some patients these effects may be permanent, or very slowly reversible.[2] The long-lasting brain changes that persist after long-term psychiatric drug use has ceased is consistent with these clinical observations.[21,22] These long-lasting symptoms may cause considerable disruption and disability in people's lives and the lack of recognition by clinicians often compounds the difficulties experienced by such patients.[9,17]

Withdrawal symptoms during maintenance treatment

Missed doses causing withdrawal symptoms

Although psychiatric drug withdrawal symptoms are most often discussed when the dose is being deliberately reduced or medication stopped, it is a common occurrence even during maintenance treatment. After a patient has been taking a psychiatric medication daily for only a few weeks, doses that are accidentally missed, skipped, taken in the wrong dosage or even taken a few hours late (depending on the half-life of the medication) may result in withdrawal symptoms.[23–26] These odd withdrawal symptoms might be reported to the clinician as sudden onset psychological or physical symptoms (e.g. dizziness, headache or mood changes).

Insomnia or other psychological withdrawal effects might be mis-identified as emerging treatment resistance or worsening of the original condition.[27,28] If not recognised, intermittent dosing may bring about the additional risk and expense of inappropriate

medical care and prescriptions.[29] Departures from a regular dosing schedule are common among patients, with estimates for irregular dosing being 50% or more.[30,31]

Withdrawal symptoms after switching psychiatric medications

Withdrawal symptoms may also emerge after a switch from one psychiatric drug to another, although there has been almost no research on the incidence of withdrawal symptoms in the process of switching.[4] Various techniques for switching have been suggested,[32] though evidence is lacking for the best way to switch psychiatric medications to minimise the risk of withdrawal and other adverse effects.[6] The more dis-similar the pharmacodynamic actions (receptor targets) of two psychiatric drugs the more likely they are to give rise to withdrawal symptoms on switching. Care should be taken not to mistake withdrawal symptoms from the psychiatric drug being stopped for adverse reactions to the new drug or manifestation of new psychiatric symptoms.[33] Slower cross-titration of psychiatric drugs may minimise the risk of withdrawal effects.

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How to Deprescribe Psychiatric Medications Safely

Although there is somewhat limited research evidence on how to stop psychiatric drugs, some advice can be offered by using data from existing studies, an understanding of the pharmacology of psychiatric drugs as well as lessons from practical clinical experience (including patient-reported experience).[1–5] In light of a lack of definitive empirical evidence, shared decision making between the patient and clinician may be the best approach to managing the uncertainty.[6,7]

Stopping psychiatric medications can be a difficult process for a significant proportion of patients.[1,8–11] However, by applying pharmacological principles and taking care to modify the rate of reduction to manage withdrawal effects for a given patient, the tapering process can often be made more tolerable. The broad principles for tapering off psychiatric drugs are:

- taper gradually (over months more often than weeks, and sometimes longer) unless there are urgent risks to manage;
- taper at a rate that the individual finds tolerable;
- taper in a hyperbolic pattern of dose decrements (so that dose reductions become smaller and smaller as total dosage gets lower); and
- taper to low doses before stopping, so that the final reduction to zero in not greater (in terms of effect on target receptors) than the reductions previously tolerated[3] (example for a generic drug shown in Figure 1.2).

In this section, we examine the practical aspects of tapering in clinical practice using receptor occupancy as a guide to enable tapering in a pharmacologically rational manner with the following steps:

- Step 1: estimate the size of the initial reduction and implement this;
- Step 2: monitor subsequent withdrawal symptoms;
- Step 3: make decisions about further dose reductions based on this experience; and
- Step 4: continue this iterative process through to discontinuation or partial reduction.

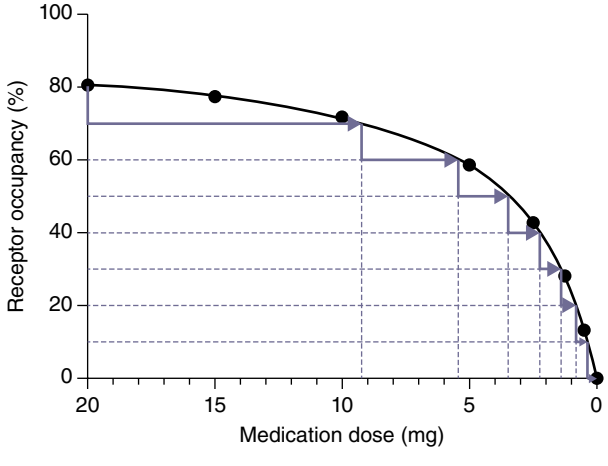

Figure 1.2 Example of hyperbolic tapering of a psychiatric medication. Dose reductions are shown on the x-axis, with increasingly small reductions producing equal-sized reductions in receptor occupancy (on the y-axis).

We also review the practical issues of making up small doses or doses that are intermediate between existing tablet dosages of psychiatric medications from liquid preparations, or alternatives, as well as some of the psychological issues encountered during tapering.

The neurobiology of tapering

As described previously, during long-term use of a psychiatric drug, the brain and body make adaptations to the drug to maintain homeostasis.[12,13] These adaptations are the key component of physical dependence.[13,14] The particular adaptations made in response to different psychiatric drugs depend on the receptor targets of the drug, and whether they are antagonists or agonists. There is evidence that these changes can persist for months or years after stopping in some patients,[15,16] a suggestion supported by findings in animal studies.[15,17]

Gradual tapering – theoretical aspects

These adaptations explain why when a psychiatric drug is stopped abruptly (as in Figure 1.3a), withdrawal symptoms are likely to occur. This action produces a large discrepancy between the level of drug the system 'expects' and the reduced level of actual drug action.[13,18] The duration of withdrawal symptoms is largely determined by the time required for adaptations to the presence of the drug to resolve (i.e. to re-adjust to the absence of the drug),[18] and not the time taken for the drug to be eliminated from the system.[15,19,20]

Alternatively, if the drug is reduced by small amounts and adequate time permitted before the next reduction in order for the brain to adjust to this lesser amount of drug (i.e. a new homeostatic equilibrium to be established), the risk of withdrawal effects (and their severity) is likely to be minimised (Figure 1.3b).[2] This can be thought of the difference between jumping from the top of a building to the ground (stopping a drug abruptly) versus going down storey by storey from the top of a building (tapering a drug).

Theoretically, lesser amounts of homeostatic disruption brought about by more gradual dose reductions result in reduced risk of severe (and, perhaps, long-lasting) withdrawal symptoms;[1,20] a principle which is now supported by some empirical studies.[21,22] Psychiatric drugs or formulations with longer half-lives may lessen withdrawal symptom risk further by minimising the degree of homeostatic disruption (e.g. drugs delivered in depot formulations).[23,24] Even smaller reductions of dose may further reduce withdrawal symptoms (Figure 1.3c) – analogous to taking even smaller steps down from the top of a building, allowing the brain to make small re-adjustments in its homeostatic equilibrium over a period of time.

Another useful analogy may be 'the bends' that is experienced by scuba divers when rising too quickly to the surface after a deep dive. Their bodies adapt to the greater depth and on rising to the surface of the water they experience uncomfortable symptoms called 'the bends'. The condition is prevented by slowly rising to the surface, allowing time for the body to adapt to the lower pressure conditions. The faster one rises the more likely 'the bends' are to occur. Successful prevention involves a stepped titration to sea-level pressure based on the person's response. If symptoms of 'the bends'

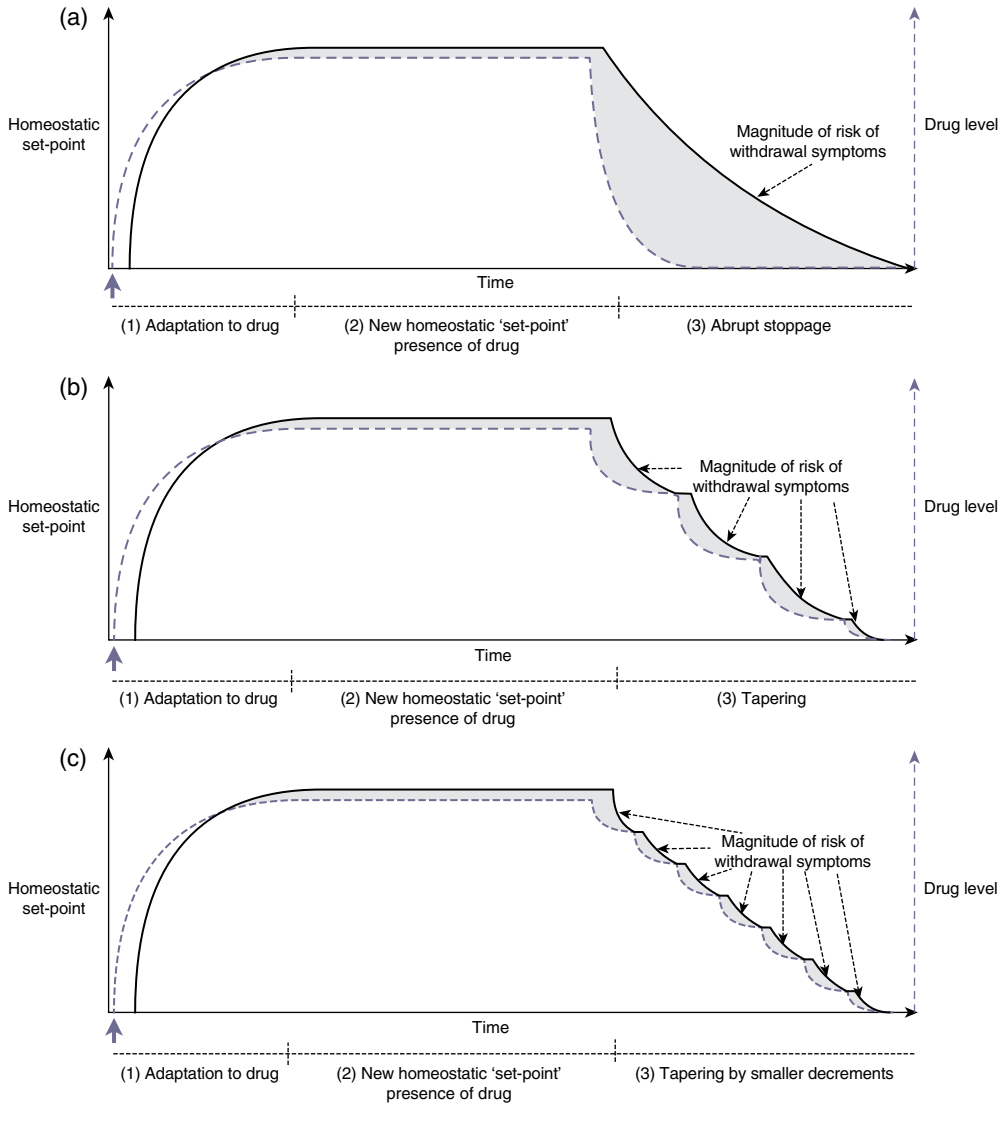

Figure 1.3 The neurobiology of tapering. In this diagram, the homeostatic 'set-point' of the brain is shown in black and psychiatric drug levels are shown in purple dashed lines. Adapted from Horowitz and Taylor (2021).[2] The shaded grey regions represent the degree of risk of withdrawal symptoms: the larger the area the greater the risk of withdrawal. (a) (1) and (2) The brain adapts to levels of a drug used over time. (3) The medication is abruptly ceased and plasma drug levels drop to zero (exponentially, according to the elimination half-life of the drug). This difference between the homeostatic set-point (the 'expectations' of the system) and the level of drug in the system (dashed purple line) is experienced as withdrawal symptoms. (b) (3) Tapering: when a drug is reduced step-wise, drug levels reduce exponentially to lower levels. At each step, there is a lag as the system adapts to a new level of drug, causing withdrawal symptoms (dashed arrows), but of lesser intensity (shaded area under the small, cupped curves) than the abrupt discontinuation shown in (a). A new (lower) homeostatic 'set-point' is established before further dose reductions are made. Drugs with longer half-lives may lessen withdrawal symptoms further by minimising the difference between the shifting homeostatic 'set-point' and plasma levels. (c) (3) An even more gradual step-wise reduction, with even smaller risk of withdrawal symptoms (shaded area under the smaller, cupped curves). With permission of Elsevier.

do occur the treatment is increasing pressure again and making even more gradual reductions subsequently. Similarly, for psychiatric drug withdrawal the more abrupt the change in level of drug the more pronounced the symptoms. An ounce of prevention is also worth a pound of cure because once significant disruption to the system is produced it is more difficult to reverse. If unpleasant symptoms arise, returning to a higher dose followed by more gradual dose reductions is generally the best approach.

Empirical support for gradual tapering

The evidence for gradual tapering for specific drug classes will be explored more closely in the relevant chapters, but, generally, in studies in which psychiatric drugs are stopped more slowly, there is a smaller risk of relapse. Many of these analyses were performed by Baldessarini and colleagues: they demonstrated that relapse rates are higher for patients who stop their antidepressants, mood stabilisers or antipsychotics abruptly or rapidly compared to those who stopped them more slowly.[25,26] For example, patients tapered off antidepressants rapidly had higher relapse rates than those tapered more gradually.[26] These findings are supported by more modern studies that find that relapse rates are lower in people who taper off a variety of psychiatric drugs more slowly.[3,4,27,28] For example, in one meta-analysis, a small number of studies found that the relapse rate in people who taper off antidepressants over several months is no different to the relapse rate in people who maintain antidepressants, while it is increased in those who taper off over weeks.[28]

These studies tell us two things: the first is that tapering more slowly seems to produce better outcomes. The second is that withdrawal effects must contribute to the reason that relapse rates are different when the rate of drug tapering is different. If relapse was simply the consequence of unmasking the untreated natural history of a patient's underlying condition, the rate at which a drug was stopped would be immaterial.[2] The rate at which, say, insulin is stopped has no bearing on relapse rates. For psychiatric drugs the nature of the process of discontinuation itself must be causally related to relapse.[29] If it is agreed that it is not plausible that rate of tapering can worsen an underlying condition, it is therefore more likely that rapidly stopping induces withdrawal effects (including effects on sleep, appetite, mood, anxiety and other psychiatric symptoms) which register on symptom rating scales as deterioration and are detected as relapse.[2,29–31] In addition to this, and perhaps at the same time, abrupt withdrawal can de-stabilise an individual, leading to genuine relapse.[25]

Overall, tapering more gradually is likely to reduce the relapse rate, if only because withdrawal symptoms are minimised. This notion is strengthened by findings that more gradual tapering can reduce the risk of withdrawal effects with a number of psychiatric drug classes.[3,13,32] The probability that withdrawal effects are contributing to an increase in apparent relapse rate is also supported by the pattern of relapses that occur in discontinuation studies where a disproportionate number of relapses occur in the first few weeks after stopping drugs.[30,33–35] As there should be no intrinsic reason why patients should relapse at the same time (they would each presumably have their own idiosyncratic periodicity of relapse), the early disproportionate preponderance of relapses suggests a withdrawal effect (withdrawal being most likely to occur at an early time point).[30,33–35] Gradual tapering may therefore minimise withdrawal effects and risk of relapse.

Hyperbolic tapering – theoretical aspects

In addition to the speed of tapering, the pattern of dose reduction is also likely to be important when trying to minimise withdrawal effects, and perhaps relapse, because of the pharmacology of psychiatric drugs.[2–4] The law of mass action dictates that when few molecules of a drug are present, every additional milligram of the drug will have large additional effects, because of the large number of unoccupied receptors to act upon, whilst when larger amounts of the drug are present, receptors are increasingly saturated and so each additional milligram of the drug will have smaller and smaller incremental effects.[36] This leads to a typical hyperbolic relationship between the dose of a psychiatric drug and its effect on target receptors, as revealed by PET imaging of various psychiatric drugs: GABA-A occupancy in benzodiazepines, D_2 dopaminergic blockade in antipsychotics and SERT occupancy for antidepressants. A generic relationship between a psychiatric drug and its target receptor is shown in Figure 1.4. The relationship between the dose of a psychiatric drug and its effect on its target receptors is very steep at small doses, with the curve flattening out at higher doses (often corresponding to the doses commonly employed clinically).

This hyperbolic relationship between the dose of a psychiatric drug and the effect on its major target receptors is not restricted to a single receptor target but applies to all targets of psychiatric drugs, including noradrenergic, dopaminergic, cholinergic, histaminergic and serotonergic receptors (which may each be responsible for the pathogenesis of some withdrawal effects),[37] as the law of mass action dictates the nature of the effect on all these receptors.[36,38] This relationship is sometimes obscured in textbooks and academic papers by plotting dose–response relationships with drug dose on a logarithmic axis, giving the impression of a linear relationship between drug dose and effect, especially at intermediate doses.[36,39] For some classes of drugs, including antipsychotics, antidepressants and benzodiazepines, clinical effects – such as on symptom scores and adverse effects – have also been demonstrated to follow this hyperbolic relationship with dose.[40–42] This is mirrored in cellular processes – for example, extracellular

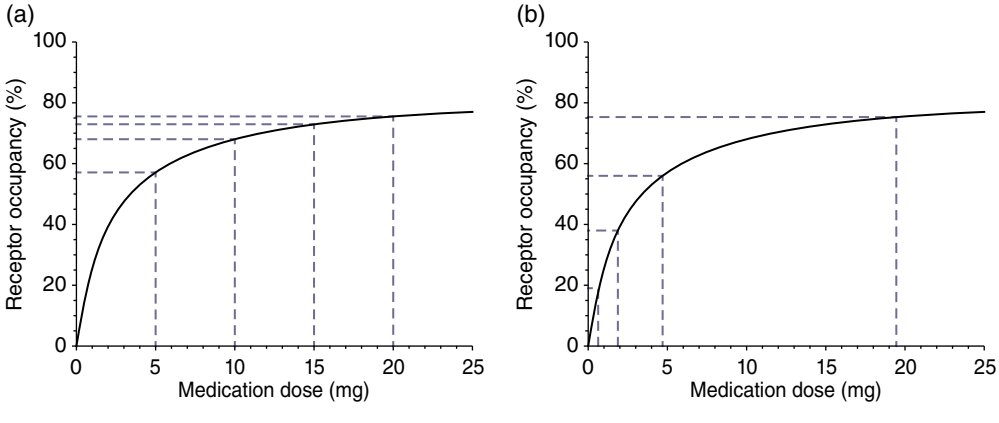

Figure 1.4 Linear versus hyperbolic tapering (a) Linear reductions of dose cause increasingly large reductions in effect on receptor targets, possibly associated with more withdrawal effects. (b) 'Even' reductions of effect at target receptors requires hyperbolic dose reductions. The final dose before stopping will need to be very small so that this step down is not larger (in terms of effect on the brain) than previous reductions.

serotonin levels show a hyperbolic relationship with dosage of antidepressants[43] as do GABA-gated currents in response to diazepam in cellular models[44] – suggesting that the effects of psychiatric drugs from the molecular level to the clinical level are all similarly hyperbolic in pattern.

Therefore, although tapering psychiatric drugs by linear amounts (for example, 20mg, 15mg, 10mg, 5mg, 0mg) seems intuitively appealing (and practical, through splitting tablets), however, because of the hyperbolic relationship between dose of psychiatric drug and effect on its receptor targets, this linear pattern of tapering will produce increasingly large reductions in effect on the target receptors (Figure 1.4a).

Whilst it is true that the relationship between dose of psychiatric drugs and effect on target receptor occupancy has not yet been shown to have a direct relationship to withdrawal effects, such a relationship remains highly plausible because all studied biochemical and clinical effects follow a hyperbolic relationship with psychiatric drug dosage. This is also consistent with patient accounts, who report that withdrawal effects worsen as the total dose becomes lower.[1,45] Given the pharmacology of psychiatric drugs, it is difficult to put forward a rationale for linear tapering.

It makes more sense to reduce the drug in such a way that produces an 'even' amount of reduction in effect on target receptors – which entails hyperbolic dose reductions (Figure 1.4b). In this figure reductions of 20 percentage points of receptor occupancy are shown. It can be seen that reducing in a manner that produces the same-sized reductions in receptor occupancy requires making dose reductions by smaller and smaller amounts. Note how small the final doses are required to be so that the final 'step down' from the lowest dose to zero is not larger (in terms of effect at target receptors) than the prior reductions in dose that have been tolerable for the patient (in Figure 1.4, this is 0.6mg). This is comparable to the manner in which planes land: they follow a hyperbolic pattern of descent, flattening out the angle of descent as they approach the ground to enable a soft landing.

Note: A percentage point means one point on a scale. For example, 80% receptor occupancy when reduced by 20 percentage points will produce 60% receptor occupancy. This is distinct from reducing 80% by 20% which will give 64% receptor occupancy.

The reduction regimens shown in the chapters dedicated to individual drugs follow this pattern of hyperbolic reductions, with more or less widely spaced steps in between doses. For each suggested regimen, the difference in receptor occupancy is preserved between the given steps, producing a pharmacologically rational regimen. This can be thought of as similar to the bellows on an accordion – where the steps are equally spaced apart but can be compressed (analogous to tapering more quickly) or dilated (analogous to tapering more slowly) according to the degree to which the patient tolerates the withdrawal process.

To taper at an 'even' rate, dose decreases are made such that the degree of receptor occupancy is reduced by the same number of percentage points of receptor occupancy at each step of the reduction regimen.

Empirical support for hyperbolic tapering

Although there has been limited research into tapering practice, there is some empirical support for tapering according to this hyperbolic pattern of dose reduction for some psychiatric drugs using 'tapering strips'.[32,46] 'Tapering strips' are composed of compounded tablet formulations of small doses of psychiatric medication – for example 5mg, 2mg, 1mg, 0.5mg, 0.2mg and 0.1mg of a drug – packaged into plastic pouches (similar to the way in which different change is made up by small denominations of coins) in such a way as to produce very gradual dose reductions (with the reductions slowing down at lower doses): for example 20mg, 19mg, 18mg, 17mg ... 1mg, 0.7mg, 0.5mg, 0.2mg, 0mg. These tapering strips are arranged in a hyperbolic pattern so that reductions are made by smaller and smaller amounts as total dosage gets lower. Several studies have now demonstrated that many patients on long-term antidepressants who have been unable to taper using conventional approaches are able to stop their antidepressants when following this pattern of hyperbolic dose reduction[32,46,47] and are able to remain off their medication at long periods of follow up (1–5 years).[47]

Other studies have shown that the risk of relapse when reducing dose of antipsychotic follows a hyperbolic pattern – when dose reductions are made from high doses there is only a minor increase in risk of relapse, but as doses become lower the risk of relapse increases hyperbolically, mirroring the receptor occupancy of antipsychotics.[48,49] This suggests that tapering of antipsychotics that adjusts for this effect (i.e. tapering hyperbolically) might minimise the risk of relapse. Some evidence for this suggestion exists in an antipsychotic reduction study performed with exponential reductions (i.e. reducing by one-quarter of the most recent dose every 6 months), which showed many patients were able to reduce their dose of antipsychotic by half or three-quarters without an increased risk of relapse.[50]

In the UK, NICE recommends tapering according to a proportionate pattern – that is, by a proportion of the most recent dose, so that the size of dose reductions becomes increasingly smaller as the total dose gets lower, a simple approximation of hyperbolic tapering – for several psychiatric medications, including antidepressants, benzodiazepines, and z-drugs, as well as opioids.[51]

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Practical options for prescribing gradually tapering doses

The dose forms available for psychiatric drugs are those marketed for therapeutic use, not for hyperbolic tapering. For many drugs, it is therefore difficult to find dose forms that are anywhere near small enough for such tapers. The smallest available tablets produce high receptor occupancy such that going from this tablet (or even a quarter of the smallest available tablet) to zero would cause a very large reduction in effect, producing substantial withdrawal symptoms for some patients.[1,2] NICE guidance on stopping antidepressants recommends, for example, 'if once very small doses have been reached, slow tapering cannot be achieved using tablets or capsules, consider using liquid preparations if available'.[3] The Royal College of Psychiatrists' guidance on 'Stopping antidepressants' provides examples throughout involving splitting tablets or using liquid versions of antidepressants to make up doses that cannot be made up by splitting existing tablet formulations.[4] This approach can be usefully applied to other psychiatric drugs as well.

To prepare dosages that allow steps in between or lower than doses widely available in tablet formulations, one or more of the following licensed methods can be used to facilitate gradual tapering:

- splitting tablets using a tablet cutter
- using manufacturers' liquid preparations

There are also off-licence methods that many patients use to make up these small doses including:[5–8]

- custom compounding of medications into tablets, capsules or liquids
- opening capsules to count or weigh beads
- dispersing (or sometimes dissolving) medication available in tablet or powdered (in capsules) form in water or other diluents

Every-other-day dosing

As current tablet formulations of many psychiatric medications do not permit pharmacologically informed tapering regimens as outlined above it is tempting to make dose reductions by having patients take their dose every other day or every third day so that their average dose each day is reduced. However, this method is not recommended for most psychiatric drugs, other than those with long elimination half-lives.[5,9] The half-lives of many psychiatric drugs are 24 hours or less, so dosing every second day will cause plasma levels of the drug to fall to one-quarter, or less, of peak levels before the next dose. It is widely recognised that skipping doses can induce withdrawal effects from psychiatric drugs,[10,11] something which patients routinely report,[5] and every-other-day dosing to taper has similar consequences. Some exceptions to this rule, such as drugs with longer half-lives (or metabolites with longer half-lives), for example, fluoxetine or diazepam, are discussed in the relevant chapters.

Splitting tablets using a tablet cutter

Many tablets can be easily divided into halves (or quarters if they are round) using cheaply available tablet cutters.[12] Using tablet cutters is more accurate for dividing tablets than either splitting by hand (for scored tablets), cutting with scissors or using a

kitchen knife (for unscored tablets).[13] Although in older methods of manufacturing, active medication was not evenly distributed throughout a tablet, this is no longer the case.[14] Tablet splitting is widely employed with almost one quarter of all drugs administered in primary care being split.[15] Although there are concerns that the splitting process may not be completely accurate,[16] this can be mitigated by storing the remainder of the tablet fragment to be used over subsequent days, meaning that the correct dose will be received over 2 or 4 days. Tablet cutters have the advantage of closing as they are used and so retain both halves of the tablet being cut.

This technique may be helpful for the first few steps of a reduction regimen but may not be suitable after this stage as the doses required will be smaller than one-quarter of the smallest available tablet for some medications. Small variation in dose from day to day whilst at higher doses of medication is unlikely to cause withdrawal issues for most people (although these differences can become more critical at lower doses). Sustained-release, and extended-release tablets can also be split, with the understanding that splitting these types of tablets to some extent compromises their sustained-release properties, and may in some cases convert them to immediate-release formulations, which may need to be taken in divided doses two (or three) times a day, depending on their elimination half-lives.[8]

Solutions and suspensions

The difference between solutions and suspensions should be noted. When a substance is soluble enough in a solvent it will dissolve and form a solution. The substance will be evenly distributed in the solution once it is completely dissolved. An example is sugar in hot tea. When a substance is not very soluble in a solvent it will form a suspension, which is a heterogenous mixture of a fluid (usually called a 'vehicle') with solid particles spread throughout. An example is fine particles of sand suspended in a bucket of water. The particles will eventually settle if it is left to sit long enough. The speed of settling depends upon the size of the particles and the viscosity of the vehicle. Often suspensions are made with a viscous vehicle, like syrup (e.g. Ora Plus), as this slows down the process of settling.[6] Psychiatric drug tablets will often form suspensions in water as they are often only partially soluble.[7] In this case there may be visible material in the suspension, composed of both tablet filler and active medication. Vigorous shaking of such a suspension will cause the suspended drug particles to be more evenly distributed throughout the suspension so that each given volume contains equal amounts of drug. This is why it is so important to vigorously shake suspensions before any manipulation – such as removing a volume, or diluting it further – and before consuming a portion. Drug molecules will not be damaged by vigorous shaking.

Manufacturers' liquids

The most widely available option for making up doses that are smaller than those available in tablets is liquid versions of a drug. For some psychiatric drugs, liquid versions are available. These bottles of liquid usually contain a fixed amount of drug in 5mLs of liquid but sometimes come with a droplet mechanism which generally provide small drops (often 0.1mL) when the bottle is held upside down. This droplet mechanism allows only specific doses to be given – for example, 2mg per drop, so multiples of 2mg can be administered, but

half drops cannot. Alternatively, the droplet mechanism from these bottles is removable, and this allows the use of a small oral syringe to draw up small amounts of liquid, giving greater precision (for example, using a 1mL syringe, with 0.01mL gradations).

Some – but not all – liquid formulations are more expensive than tablets. For those liquid formulations that are more expensive, short-term use of this formulation might lead to a reduction in aversive effects from the discontinuation process and longer-term savings if the medication is successfully ceased[17] as well as a reduction in the burden of adverse effects to the patient and healthcare system.[18]

Off-licence options for making small doses of medications

Regulatory authorities approve formulations of drugs on the basis that these formulations provide a precise and accurate dosage and are stable, both chemically and biologically, over the period indicated by the stated expiry or expiration date. Any alteration to these approved formulations renders use 'off-label'. This includes the crushing of tablets and dilution of liquid formulations. It is important to note that dose precision and stability often cannot be formally guaranteed by the manufacturer in these situations. However, some manufacturers do assure stability for some situations and in other cases research has confirmed chemical stability.

Whilst it may represent an unlicensed ('off-label') use to open capsules, crush tablets or make extemporaneous suspensions, the General Medical Council (GMC) guidance on this matter states that doctors are permitted to prescribe medications off-licence when 'the dosage specified for a licensed medicine would not meet the patient's need'.[19] In the UK, for example, a medical practitioner can authorise the use of unlicensed medication (according to the Medicines Act 1968).[7] This is echoed by the NHS Pharmaceutical Quality Assurance Committee in their *Handbook of Extemporaneous Solutions*: 'some patients have special clinical needs that cannot be met by licensed medicinal products or by a viable alternative option. In these circumstances it would be inappropriate to curtail the patient's treatment, as this would have a detrimental effect on their condition'.[6] In the USA, such usage is also considered 'off-label' or 'unapproved' use by the FDA, which, however, explains that 'healthcare providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient'.[20]

Dilutions of manufacturers' liquids

The manufacturers' liquid versions of some psychiatric drugs are often quite concentrated – for example citalopram comes as a 40mg/mL solution.[21] As greater errors are found when measuring less than 20% of the labelled capacity of a syringe[22] and the smallest syringe widely available is a 1mL syringe, the smallest dose that could be measured accurately with a syringe is 8mg (0.2mL). This means that dilution of these liquids is often necessary to make the small doses needed by some patients. Citalopram, for example, can be diluted in water or juice according to their Summary of Product Characteristics (SmPC) approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.[21] The FDA also recommends that sertraline liquid is diluted in water or juices before administration.[23] This allows formulation of

Box 1.1 Steps required to measure out a small dose of a psychiatric medications, by diluting a manufacturer's oral solution. Other doses can be made following similar rules. Pharmacists will be a useful source of advice on these issues.

To deliver a psychiatric drug at a dose of 2mg from a liquid concentration of 40mg/mL made by the manufacturer:

- First verify the biological equivalence between the liquid version and the tablet version of the drug as sometimes different salts are used.
- In the case of equal bio-availability 2mg of liquid drug is equivalent to 2mg of drug in tablet form (otherwise a bio-equivalence calculation should be made).
- Volume of liquid drug required = mass/concentration = 2mg/ (40mg/mL) = 0.05mL.
- The smallest volume that can be accurately measured with a 1mL syringe is 0.2mL; therefore a dilution is required.
- Most liquid drugs (which are dissolved in water) can be mixed with water, or juice.[21]
- 0.5mL of this solution can be mixed with 4.5mLs of water to produce a solution with a concentration of 4mg/mL (a 1 in 10 dilution).
- Concentration = mass/volume. Therefore, volume = mass/concentration.
- Volume of this diluted solution required = 2mg/ (4mg/mL) = 0.5mL (which can be measured accurately with a 1mL syringe).
- Many drug labels for liquid versions of drugs recommends that this solution is consumed 'immediately',[21] which might be interpreted as meaning within an hour of preparation.

the very small doses suggested to facilitate tolerable tapering of different psychiatric medications (Box 1.1). The SmPC and FDA guidance both advise that such dilutions be consumed 'immediately', which may be interpreted as within an hour of preparation.[21,23]

It is likely that this recommendation is based on the remote possibility that chemical stability is compromised by dilution. Studies have found that there was less than 5% degradation over 8 weeks for fluoxetine solution in fruit juice, or other common diluents, as assessed by high-performance liquid chromatography.[24] Similarly, citalopram solution in water showed no significant degradation over 30 days when stored in the dark.[25]

The biological stability (referring to a drug's susceptibility to microbial contamination) of psychiatric drug dilutions has not been formally evaluated but this is likely to be unproblematic if solutions are stored in a refrigerator for several days. Some of the manufacturers' labels do not specifically state that a solution of a psychiatric drug can be diluted in water but if these drugs are dissolved in water, further dilution in water should be acceptable in terms of drug solubility.

Custom compounding of individualized dosages

Compounded liquids (e.g. 'Specials' in the UK)

For some psychiatric medications that are not made by their manufacturer into liquid formulations, liquid versions can be compounded at specialist pharmacies (for example, some psychiatric medications are available as prescription 'Specials' in the UK).

Compounded capsules or tablets

Some pharmacies are able to make up custom-made doses of medication in tablet or capsule form. Sometimes this will remove slow-release characteristics of the medication, which will have to be taken in immediate release form, sometimes necessitating dosing more than once a day. This should be verified with the pharmacy.

One such option is pre-packaged customised formulations of tablets that allow gradual reductions, made by a Dutch compounding pharmacy that produces 'tapering strips', as an unlicensed medication.[26,27] As mentioned above, these 'tapering strips' involve making up smaller formulations of many psychiatric medications than are currently available in tablet form, for example, 0.1mg or 0.5mg of a medication and preparing pouches of medication that contain a number of small tablets in order to make up hyperbolically decreasing dose regimens that are able to go down to very small final doses before stopping (e.g. 0.1mg of citalopram). Additionally, this compounding pharmacy also allows doctors to order customised reduction regimens, which facilitate any desired reduction trajectory.

Dispersing tablets

When liquid formulations are not available, many tablets that are not enterically coated or sustained- or extended-release can be crushed to a powdered form and/or dispersed in water, as indicated by guidance for patients with swallowing difficulties.[7,28] The contents may sometimes taste bitter and some drugs may have a local anaesthetic effect on the tongue.[7] Crushing and dispersing will not greatly alter these medications' pharmacokinetic properties (their rate of gastrointestinal absorption will be increased as they are more easily absorbed), according to the FDA medication guide[8] and the Royal Pharmaceutical Society (RPS) guidance on crushing, opening or splitting oral dosage forms.[12]

Many immediate-release tablets will simply disperse in water after a few minutes, aided by stirring or shaking.[29] Some formulations of psychiatric medications come as orodispersible tablets, such as mirtazapine or olanzapine. These tablets are designed to rapidly disintegrate on the tongue without the need for water. However, guidelines for people who have swallowing difficulties, like the NEWT guidelines in the UK,[7] and similar guidance in the USA[30] indicate that they will also disperse in water (generally quickly) and the suspension formed can be used to administer the drug to the patient.[7]

The Specialist Pharmacy Service in the NHS provides instructions on how to administer antidepressants to people with swallowing difficulties, recommending that citalopram, escitalopram, paroxetine and sertraline can all be crushed and/or dispersed in water and that fluoxetine capsules can be opened and dispersed in water.[28] Crushing can be performed with a spoon or a mortar and pestle and will help the drug to dissolve more quickly. For example, application of the above principles for gradual tapering could involve dispersing a 10mg tablet in 100mL of water (by shaking or stirring) and then discarding 5mL of the suspension with a syringe to administer a dose of 9.5mg when the remaining 95mL is consumed.

As some psychiatric medications are poorly soluble in water, it should be noted that mixtures made by dispersing a tablet in water are often suspensions (not solutions). Flakes or particles visible in a suspension are a combination of excipients (or 'fillers')

and active drug. Care should be taken to vigorously shake a suspension to ensure even dispersion of drug.[29] Some sustained-release and extended-release drug forms contain a binder that will thicken when added to liquid and so cannot be crushed and dissolved in an aqueous solution. If an enteric coating, which protects a drug from the acidic environment in the stomach, is removed by crushing the tablet, the in vivo drug degradation will increase, with less drug available to produce the desired clinical effect.[12] Issues regarding specific drugs are discussed in subsequent chapters.

Opening capsules to count beads

The extended-release forms of various psychiatric drugs, when delivered as gelatine capsules filled with tiny beads, may be opened and the beads emptied out, as suggested by guidelines for patients with difficulty swallowing tablets or capsules.[7] The pharmacokinetic properties of beads are retained if the capsules are opened and the beads are exposed to air for medications like duloxetine and venlafaxine.[31,32] These drugs can then be tapered by progressively removing more beads at designated intervals to gradually reduce the dose. This method requires some amount of manual dexterity and so will not be appropriate for all patients. The beads can be weighed or counted. This should be done with clean and dry hands (or using an instrument like a ruler or pair of tweezers). The number of beads to be taken will need to be placed back into the original capsule or another gelatine capsule bought from a pharmacy or online. The beads should not be swallowed without a capsule as there are some reports of throat irritation occurring.[33]

Each capsule contains the same weight of drug but, because the beads vary in size, they may have different numbers of beads. The average number of beads in three capsules might be used to estimate the number in each capsule. Doses in milligrams can then be converted into the number of beads required. For example, if a 30mg capsule contains, on average, 250 beads, then to achieve a dose of 6mg 50 beads are needed. Beads can be kept in a suitable container for a couple of days as their enteric coating is stable in air.[34] This is an off-label use of the drug.

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Psychological aspects of tapering

Tapering off psychiatric drugs can be a difficult process, leading to numerous withdrawal symptoms described in subsequent chapters, as well as risking relapse. Although there are ways of coping with specific distressing withdrawal symptoms, which will be discussed, it is generally best to avoid overly distressing symptoms because they can impair social and professional functioning, precipitate relapse and cause a patient to become fearful of the process of reducing their medication or of ever stopping it.[1] Although there may be exceptions, most people do not do well by 'white-knuckling' through the process of very severe withdrawal effects. Furthermore, while there has been limited research in the area, it seems to be the case that more severe withdrawal symptoms arising from rapid reductions may increase the risk of a protracted withdrawal syndrome in the long run.[1–3]

Many people cannot tolerate severe withdrawal effects and will return to a full dose of medication, or seek other medications to manage their symptoms, and occasionally severe withdrawal effects can lead to hospital admissions or suicidality because they are so aversive.[4–6] So the main approach to manage withdrawal symptoms during the process of discontinuing psychiatric medications should be to reduce the dose gradually enough to avoid severe withdrawal symptoms in the first place. Generally, if symptoms are too severe, the reduction schedule should be halted until these symptoms resolve. In the case of intolerable withdrawal symptoms then the dose should be increased and held there until the symptoms resolve, before progressing at a more gradual rate (with smaller dose reductions, and/or longer periods between dose reductions).

There are several techniques that may be helpful to cope with withdrawal symptoms – derived from both the academic literature and extensive patient experience.[1,7–9] There are a few interventions which have some evidence in supporting patients during tapering – for example mindfulness based cognitive therapies in antidepressant withdrawal.[9,10] While these forms of therapy, especially mindfulness, seem to be helpful with the process of discontinuation, it is unlikely that any psychological therapy can substitute for gradual tapering titrated to the ability of the individual patient to tolerate the process,[1] as evidenced by some negative findings for these interventions.[11,12]

Many patients report that it is useful to be clear, and to be reminded, that the symptoms that are experienced during the withdrawal process are of a physiological origin due to decreasing the drug rather than conferring on these symptoms an existential weight they do not merit.[7] In peer-led withdrawal communities these symptoms are referred to as 'neuro-emotions', denoting emotions that arise because of withdrawal-associated neurological processes, as distinct from 'endogenous' emotions that relate to events in the person's life.[1] This may be thought of as similar to the negative emotions that are well recognised to occur in withdrawal states from recreational substances.[1,13] A guide book for therapists on how to support patients undergoing psychiatric drug withdrawal suggests to therapists that they 'suspend customary assumptions about the source of distress and associated interventions (i.e. emotional processing or analysis) for the duration of withdrawal'(p.95).[7] Other coping techniques are outlined in Box 1.2.

This advice relates to patients without significant risk of harm to themselves or others and in cases where these risks are unmanageable in the process of withdrawal then sensible clinical management should be followed. Clinicians need to stay vigilant for genuine relapse as well, using guides outlined in subsequent chapters for how to distinguish withdrawal effects from relapse. A previously agreed-upon plan for how to approach relapse with the patient is useful in such circumstances.

Box 1.2 Coping techniques during tapering.

- Often patients will require some preparation for psychiatric drug tapering. This might include devising a list of existing coping skills for dealing with difficult emotions and sensations.
- Patients may also consider developing new coping skills before or during tapering. For example, mindfulness based cognitive therapy (MB-CT) appears helpful in the process of stopping antidepressants.[9]
- Sometimes practical arrangements for reducing work or family duties can be worth exploring.
- Patients may require more psychological support during the process; professional or otherwise.[7] This could be via more frequent contact with a physician, nurse, counsellor or peer group.
- Some patients will find monitoring their symptoms to be helpful in giving them some perspective that symptoms come and go, often with a predictable pattern after dose reductions. This can help to counter fears about relapse and help people to plan their lives around withdrawal symptoms.
- Patients may benefit from being directed to useful written or online resources.[8]
- For difficulties with sleep, which are common during withdrawal, maintaining a fixed sleep–wake cycle, avoiding light for an hour or two before bed (especially electronic equipment) or using different means to restrict blue light from devices, exposure to bright light in the morning, avoiding caffeine in the afternoon and exercise (more than 3 hours before bed ideally) can be helpful.[14]
- There are a number of other coping techniques that people report are useful summarised in a guidebook for therapists[7] as well as other sites.[8] They include:
  - Acceptance/non-resistance – maintaining a non-resisting attitude involving staying with painful experiences rather than struggling with them or attempting to stop or fix them
  - Breathing exercises – one form of intentional relaxation
  - Exercise – if tolerable and appropriate to the person's capacity
  - Healthy distraction
  - Keeping a diary – can help patients to get a sense of how reductions in dose affect their symptoms
  - De-catastrophising – trying to avoid worst case scenario thinking

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Tapering psychiatric drugs in practice

The practical steps for deprescribing are similar across different classes of psychiatric drugs, although there will be wide variation on the details depending on the medication type and the patient's pre-existing condition.

These steps are explored in more detail for each relevant drug class in subsequent chapters, but some general principles are outlined below.

Considerations before tapering

Education about benefits and harms of continuing or stopping medication

- Discuss the patient's circumstances and motivation for reducing or stopping. More stable life circumstances are generally more conducive towards reducing medication. Patients who are ambivalent about the process may benefit from more information.
- Patients should be informed about the risks and benefits of reducing or stopping their psychiatric drug. The major risks are withdrawal and relapse. The risk of relapse might be mitigated by slowly tapering the medication, and by alternative means for managing an underlying mental health condition. For some patients a past stressor will have resolved such that relapse is less of a concern. For other patients with a greater number of risk factors or severe conditions relapse will be a much greater concern. The risks and benefits of medication continuation are outlined in subsequent chapters.
- Some patients may have queries about prescribing decisions made previously. Explain that our understanding of the balance of risks and benefits of a medicine can change over time.
- The adverse effects of being on a psychiatric drug need to be weighed against the potentially aversive consequences of stopping a psychiatric drug too quickly. If the adverse effects of a psychiatric medication are life-threatening or severe, then this will need to take precedence over slow tapering. In other circumstances the risks will need to be balanced for each individual case.[1] Most of the advice below relates to patients who do not have life-threatening or urgent adverse effects.

Addressing potential barriers and facilitators

- Recognise that patients may have fears and concerns about stopping their psychiatric drugs (both relapse and withdrawal effects) and will need support to withdraw successfully, particularly if previous attempts have been difficult. Details for online or written resources may be useful[2] as will increased support from a clinician or therapist (for example, check-in phone calls, more frequent appointments and specific advice about major hurdles that might arise, such as insomnia).[3]
- If possible it is useful to engage support networks in the process – including family and friends, and other professionals involved in care.[4,5] These people can have strong opinions regarding continuing or stopping medication that can be barriers or facilitators of the process. Much of the information given to patients about withdrawal effects, the distinction from relapse, and the harms and benefits of continuing versus stopping medication can be useful for these stakeholders as well.

- Existing beliefs about medication should be explored including the patient's understanding of the role of medication, and alternative options.[4,6] For example, in an intervention designed to help patients to stop unnecessary antidepressants, one element was educating patients that there is no evidence that antidepressants correct an underlying chemical imbalance in depression, identified as an important barrier to stopping medications.[6]

Education about withdrawal symptoms and their management

- All patients should be informed of the risk of withdrawal symptoms on reducing the dose or stopping any psychiatric drug.[1] These symptoms arise because the brain has become accustomed to the medication and when the drug dose is lowered, the difference between what the brain expects and what input the drugs provide is experienced as withdrawal symptoms, as for many other substances like caffeine, or nicotine.
- In order that patients do not mistake withdrawal symptoms for a return of their underlying condition, it is useful to inform patients which withdrawal symptoms they might experience. Specific symptoms for each class of medication are provided in subsequent chapters. For all classes of psychiatric drugs withdrawal symptoms can manifest as both psychological and physical symptoms because of the myriad effects of the medications on different bodily systems. It is the psychological symptoms of withdrawal that cause the most confusion regarding relapse, as there is much overlap in these sets of symptoms.
- Reassure the patient that although there seems to be an intimidating list of symptoms these symptoms are most likely to occur or to be severe when people stop their psychiatric drugs abruptly or too quickly. The entire process outlined below is aimed to minimise the chance of experiencing these unpleasant withdrawal symptoms.
- Explain that it is not fully understood what factors determine risk of withdrawal symptoms for an individual. However, there is evidence that the risks are increased for longer term use, higher doses, specific drugs (for example, short-acting drugs or those with specific receptor targets, such as paroxetine and venlafaxine). People who have experienced withdrawal symptoms previously when tapering or on forgetting their dose are more likely to experience withdrawal symptoms in the future.
- The patient's past experience of stopping should be explored as this can be informative for predicting which symptoms may arise again on tapering. Careful exploration of past attempts to stop may detect withdrawal symptoms being mis-diagnosed as relapse (e.g. by the presence of dizziness, electric 'zaps' or symptoms quite distinct from the original condition for which the drug was prescribed).
- Explain that withdrawal symptoms often occur within a few days of reducing or stopping psychiatric drugs, although they can be delayed in onset, especially with medications with a long half-life like fluoxetine, which can take several weeks to arise.[7] For reasons that are not completely understood (but may relate to the time taken for drug levels in the brain to calibrate to peripheral plasma levels), medications with shorter half-lives can also have delayed onset of withdrawal symptoms, sometimes by several weeks, or longer.[8–10]

- Withdrawal symptoms vary greatly in duration and severity. Some people experience minimal withdrawal effects that last for a few days, but severe withdrawal effects are also possible, although there has been little research into what proportion of patients may experience this.[10]
- Withdrawal symptoms are thought to be more severe and long-lasting when psychiatric drugs are stopped quickly and lessened when they are stopped more gradually.[9,11,12] Withdrawal symptoms can last for months or years in some cases.[10] Long-lasting withdrawal symptoms are often termed post-acute withdrawal symptoms (PAWS). Patients should therefore be warned not to stop psychiatric drugs abruptly. This is ample reason to approach the rate of taper cautiously; if there are no withdrawal symptoms the rate of taper can always be increased.
- Patients should also be made aware that if they experience unpleasant psychological and physical symptoms during withdrawal, this does not necessarily indicate that they need the drug, but rather it may be withdrawal symptoms that instead indicate the need to taper the drug more slowly (after a period of stabilisation).[10] Patients often report that withdrawal symptoms they have experienced in the past have been perceived as relapse.[13,14] Familiarity of the patient and the prescriber with the wide variety of withdrawal symptoms may help to mitigate unnecessary anxiety when symptoms arise.

Outline the process of reducing and/or stopping the medication

- Reassure patients that the some of the negative consequences of tapering can be managed by regular and frequent monitoring. If withdrawal symptoms become too severe then the taper can be halted, or the dose increased. Withdrawal symptoms will then normally resolve over time and the rate of taper can be slowed down to prevent further symptoms arising.[9,15,16]
- Tapering according to a pattern that matches the action of the drugs on the brain might also minimise withdrawal effects. A clinician may explain to the patient that the relationship between the dose of a psychiatric drug and its effect on the brain is hyperbolic, meaning that at small doses, every extra milligram of drug has a large additive effect, whereas at commonly used doses every extra milligram has less and less additive effect. It is thought that this can inform the process of tapering, where patients can reduce their dose by greater amounts when at higher doses but need to reduce by smaller and smaller decrements as they get down to lower doses. Tapering according to a hyperbolic pattern down to low final doses before completely stopping can reduce the risk of withdrawal symptoms.[15,17]
- Patients often find it helpful to see a picture of the relationship between their drug and its effect on the brain so that they understand the rationale for tapering in a hyperbolic manner. On seeing the relationship between the dose of their medication and its effect on target receptors some patients may understand why past attempts were not successful as they stopped at doses that produce high receptor occupancy, leading to significant withdrawal symptoms. These graphs are presented for many commonly used psychiatric drugs in the drug-specific chapters.

- Although it is difficult to predict the exact period required for an individual to taper off their medication most patients take months or even years after long-term use,[1,17,18] depending on the characteristics of their medication use and the individual. This may help to set expectations. Suggested reduction regimens that span these time-lines are given for commonly used medications in later chapters. Some patients might find the prospect of long periods to taper off their medication unappealing, but will sometimes understand as the process unfolds that more gradual tapering gives them a better chance of reducing and stopping their medication in a sustainable manner. Generally, patients should proceed as fast as they can tolerate, but as slow as they need to balance the harm of staying on unnecessary medication against the harm of tapering too quickly.
- Often patients will require some preparation for tapering. This might include devising a list of existing coping skills that the patient possesses for dealing with difficult emotions and sensations, for example acceptance, breathing exercises, mindfulness, exercise, time with friends and family, hobbies, diary keeping and de-catastrophising (see previous section).
- Patients may require more psychological support during the process, which might be professional or otherwise. This could be in the form of a group or via more frequent contact with a physician, nurse, counsellor or peer group.[4,19]
- A plan should also be agreed upon for how to approach a deterioration in mental state, or early signs of relapse – ranging from pausing or slowing down the taper, to more targeted management including increased contact, non-pharmacological management, admission to hospital, or re-instatement of medication, depending on the preference of the patient, and the degree of past and present risk.

Choosing a medication in the case of polypharmacy

- In the case of polypharmacy, although there is limited research, it is generally best to start with a single drug first so that the process of tapering can be optimised before a second drug is also considered for tapering. In terms of selecting a specific drug, there is limited research[20] but there are several pertinent factors to consider. Perhaps the most important is which drug the patient feels is causing them the most pronounced adverse effects and the least benefit. In case the patient is unsure, more objective criteria such as those medications with the least favourable balance of recognised adverse effects and benefit for the patient's condition should be prioritised. Suggestions can be adapted from the STOPP (Screening Tool of Older Persons' Prescriptions) criteria, which although aimed at older people, espouses general principles applicable to other patient groups such as prioritising deprescribing of any drug without an evidence-based clinical indication, or a drug prescribed beyond its recommended duration, or where there is a duplication of prescription from the same drug class.[21] The patient's wishes and aims should be prioritised in any decision.
- Other considerations might be to choose the drug most recently started on the premise that this might be the most easily stopped as adaptation to the drug will be most limited for this medication. Related to this, the drug that the patient thinks might be the easiest to come off might be worth choosing, to build confidence in the process of stopping. Other commentators recommend postponing cessation of medications that can help with sleep in order that these drugs may help to minimise insomnia, which is a very common and sometimes troubling withdrawal symptom.[9]

The process of dose reduction

Once there has been agreement to reduce the dose of a medication, the key elements of a programme of tapering are:

- that it is flexible and can be adjusted so that the process is tolerable for the patient;
- that it involves close monitoring of withdrawal symptoms to facilitate timely adjustments to the rate of taper;
- that patients are provided with preparations of their medication to make the process of creating doses that are not easily able to be made with currently available tablet doses (e.g. access to liquid formulations of their medication or smaller formulations of tablets).

The actual process of tapering involves the following four steps (Figure 1.5):

- Step 1: estimation of risk of withdrawal for the patient and from this estimate the size of the initial dose reduction.
- Step 2: monitoring of the withdrawal symptoms resulting from this initial reduction.
- Step 3: determination of the size of the next reduction based on how tolerable this reduction was for the patient.
- Step 4: repetition of Steps 2 and 3 until a dose is reached that is small enough so that the reduction to zero is not a larger step down (in terms of effect on the brain) than the reductions that have been previously tolerated.

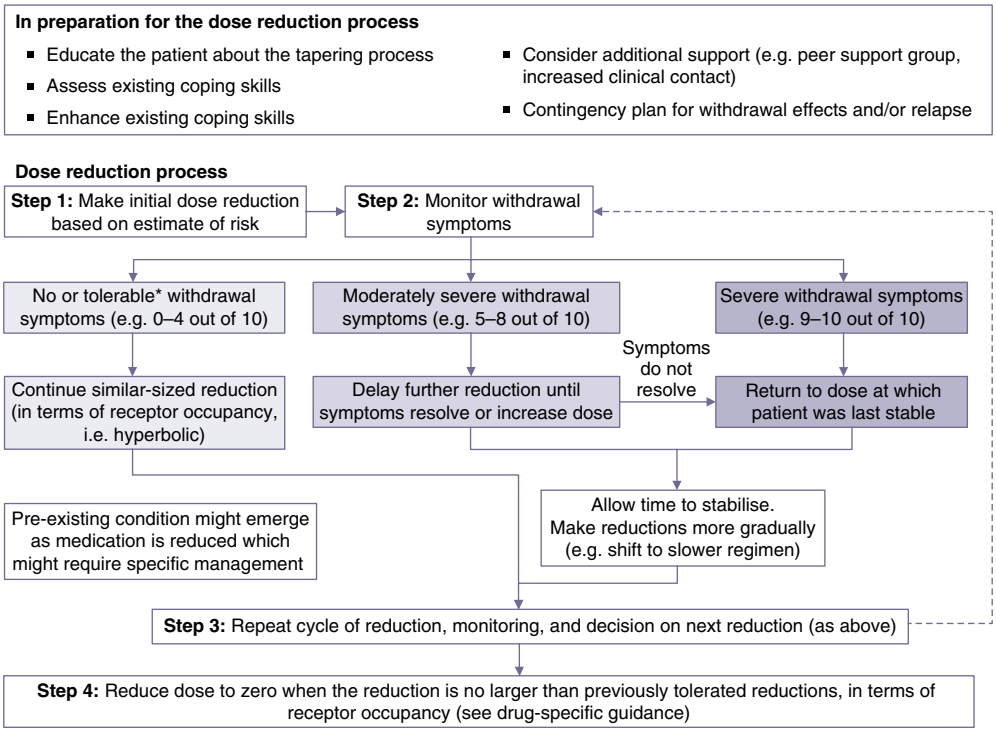

Figure 1.5 An overview of the process of tapering psychiatric drugs. *The definition of 'tolerable' will vary from patient to patient.

These steps are explored in greater depth in subsequent chapters (see Chapter 2), but, in general, a rate of reduction is selected based on the suspected risk of withdrawal effects, erring on the side of caution, but taking into account the patient's preferences (Step 1). There are several options provided for each medication in the drug-specific chapters.

After the first dose reduction patients should be monitored for symptoms of withdrawal. Common withdrawal symptoms can be found in each relevant chapter. Some patients will be aware of their distinctive withdrawal symptoms from previous reduction attempts. Monitoring should normally occur for a period of two to four weeks but may be longer in patients for which there is greater uncertainty about the response (Step 2). Based on the response to this first reduction the next reduction can be made according to a similar reduction in receptor occupancy (along the same reduction schedule), slowed down (or sometimes sped up) (Step 3). The next reduction should occur when withdrawal effects from the previous reduction have resolved or largely resolved.

This process should be repeated – involving repeated cycles of dose reduction, symptom monitoring and adjustment of the next reduction based on these symptoms (Step 4). As circumstances change and symptoms can vary, the trajectories suggested in subsequent chapters should not be seen as 'set-and-forget' regimens but require active monitoring and feedback with adjustment of the rate of taper in order to make the process tolerable. Many patients will find a rate of taper that they can tolerate around their lives. The drug can be stopped when a reduction to zero will not cause a greater decrease in effect (in terms of receptor occupancy) than previous reductions. Patients should be monitored after they have stopped medication for several weeks or longer in case of delayed-onset withdrawal effects or relapse, and these conditions managed appropriately.

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Further topics

Troubleshooting

If withdrawal symptoms become intolerable at any point – and risk is manageable – it is worth repeating that the best approach is to either hold the current dose for longer to allow symptoms to resolve, or increase to the last dose at which the symptoms were tolerable, remaining there until they resolve (which can sometimes take much longer than expected – weeks or months in some cases).[1] Sometimes patients will need to increase their dose further in order to stabilise after severe withdrawal effects. After this stabilisation, further tapering will need to be performed more gradually with smaller reductions and/or longer periods between them. Patients, and clinicians, are often surprised at how long a tolerable taper can take – sometimes more than a year and in some cases over several years.[1] Some patients find they cannot reduce at a rate quicker than that equivalent to a reduction of 1 percentage point of receptor occupancy every 4 weeks (equivalent to approximately 5–10% dose reductions every 4 weeks), or sometimes by even smaller amounts. Most people through some trial and error can find a rate that is tolerable for them. If a patient experiences distressing withdrawal symptoms, this does not necessarily indicate that they cannot stop a psychiatric medication, but might mean that they need to taper more slowly. If complete cessation is too difficult, being on a smaller dose may be a worthwhile goal as patients will be exposed to less adverse effects.

It is not generally advisable to use other medications that can themselves cause physical dependence and withdrawal in order to manage withdrawal symptoms from psychiatric medications.[2] These medications include benzodiazepines, antidepressants, gabapentinoids, opioids and antipsychotics.[3,4] Use of these medications to manage withdrawal can lead to switching from one medication to another, rather than stopping the first medication. It is generally better to slow down a taper to produce tolerable withdrawal effects than substitute a different medication.

Psychological effects of psychiatric drug withdrawal

As mentioned, the withdrawal process per se can involve intense emotions, ranging from despair, to anger, anxiety, emotional lability, hypomania and suicidal thoughts, often unrelated or out of proportion to events or circumstances.[1,3,5] These can sometimes be familiar to the patient, and other times be quite novel, and can be distressing and confusing.[1] Like the physical symptoms of withdrawal, these can often come in intense waves.[1,6]

Sometimes withdrawal symptoms from psychiatric drugs can be difficult to distinguish from an underlying condition not just for the clinician but also for the patient.[1] The Royal College of Psychiatrists' guidance on 'Stopping Antidepressants' specifically cautions patients on this point, highlighting that 'Some withdrawal symptoms can feel like the symptoms you had before you started the antidepressant. The low mood and difficulty in sleeping of withdrawal can feel like the symptoms of depression.'[7] Although timing and associated physical symptoms can be helpful to discern this distinction the subjective similarity of symptoms to the original condition can be

confusing for some.[1] Such symptoms have been designated rebound withdrawal symptoms, because they involve the effects of withdrawal causing previously present symptoms to be exaggerated.[8]

Many patients go through a phase of shock when they contemplate the effects of withdrawal on their lives, including worries about the impact on their financial, work and personal affairs, involving feelings of regret, self-blame and anger.[1,9] They may feel unhappy that they were not properly informed about the difficulties in stopping medication. Another common emotional symptom in withdrawal is the opposite of intense emotion: rather it is the complete absence of emotions, sometimes referred to as 'emotional anaesthesia', or as anhedonia, numbness, apathy or 'dysthymia' following drug withdrawal.[1,3,10,11] This effect, like other withdrawal effects, seems to fade over time but can take months or years in some patients.[3]

There are patient support groups, in person or online,[6,12] that might provide helpful support for patients going through this process. Techniques such as distraction, acceptance and re-orientation to recognising these symptoms as temporary products of the withdrawal process that resolve in time like other symptoms can all be helpful.[1] Some patients find that learning to manage and cope with withdrawal symptoms, also translates to being able to manage better the mental health conditions that first prompted medication prescriptions.[1]

Approach to withdrawal akathisia

As mentioned, one of the worst outcomes of psychiatric drug withdrawal, generally when it is too rapid, is akathisia.[13–16] Although this has been more often associated with an adverse effect of antipsychotic exposure it can be induced by withdrawal from antidepressants and benzodiazepines.[13–16] Gradual tapering is thought to minimise the risk of this event, but there have been no trials looking specifically at this topic. As people can be agitated and quite disordered in their behaviour (pacing, restless, grimacing, etc.) it is often mis-diagnosed as mania, psychosis or agitated depression,[15,17,18] and can sometimes lead to suicide.[19,20] Once a patient is in such a state it is very difficult to treat. This state can be prolonged in some patients.[17]

Although there has been little in the way of research on this topic, the most successful approach to this condition is, as for other withdrawal symptoms, a return to the dose of the medication being tapered at which the patient was last stable. If this approach is unsuccessful, then other agents may be required. The drugs most commonly reported to be useful are beta-blockers like propranolol, $5HT_{2A}$ receptor antagonists (e.g. mirtazapine, cyproheptadine), anti-histamines and benzodiazepines (e.g. clonazepam and diazepam).[17] However, patient groups who advocate for greater awareness of akathisia report that even these medications, including benzodiazepines, antidepressants and antipsychotics can all exacerbate akathisia in some people.[19] Consequently, a cautious approach to treatment is recommended. This should involve exposure to one medication at a time, followed by close observation to assess response, with cessation if unhelpful, before trialling additional medication.[17,19] Some patient advocacy groups suggest that the best management may be conservative – that is, not introducing further pharmacological agents – allowing symptoms to resolve over time with minimal intervention, although this can sometimes be difficult for patients to tolerate.[19] Movement is widely

found to be helpful by patients, who often find that pacing somewhat lessens unpleasant sensations, with a (stationary) cycling intervention supported by a case study.[21]

Management of protracted withdrawal syndrome

Protracted withdrawal (sometimes called PAWS) occurs in an unknown proportion of patients after stopping psychiatric medications.[3,14,20,22] Its risk is thought to be minimised by gradual tapering.[23,24] Some patients may present for assistance in protracted withdrawal from previous rapid reductions. There is a dearth of research on the best management approach but two methods are suggested: conservative management or re-instatement of the original medication.

Limited research and clinical experience suggest people do recover spontaneously from protracted withdrawal without specific intervention, albeit over sometimes long periods. So, a conservative approach to management may be reasonable.[1,20] Patients often require reassurance that they will improve in time. They also need support, often including financial assistance, if such states are prolonged, as they can sometimes be debilitating.[1,14,20]

The second option is re-instatement of the original medication.[20] When re-instatement is performed shortly after cessation of a psychiatric drug, this almost universally leads to symptom resolution. However, when there is a longer delay in re-instatement after the onset of withdrawal effects (e.g. months or longer) the response is less certain. Re-instatement can still be successful. For example, in an analysis of patients with protracted withdrawal syndromes from antidepressants, it was found that re-instatement of the original drug was the most common approach trialled and was successful in about half of people who attempted it, even when it was initiated months or years after the drug had been stopped.[20]

However, there is great variation in response to re-instatement in people with protracted withdrawal syndromes. Some of these patients report improvement in their symptoms soon after re-instatement. Some report initial worsening of their symptoms, followed by improvement. Some report no discernible change and some patients report paradoxical worsening.[1] These responses have not been systematically studied and there is a poor understanding of the relevant factors. Paradoxical worsening is most well-recognised in re-instatement of benzodiazepines long after cessation.[1] These paradoxical responses have been linked to a process called kindling, involving sensitisation to the ceased medication, which is analogous to the kindling effect recognised in repeated cycles of exposure to and cessation of several psychoactive substances, especially alcohol.[1,25,26]

Given this uncertainty one suggested approach to mitigate the possibility of negative outcomes whilst trialling re-instatement is to re-instate a very small dose of the original medication (as small as 5% of usual doses).[1] This provides a test dose to monitor response, and can be successful in some cases of long-standing protracted withdrawal.[1,20] If this test dose has positive effects, a further increase in dose may be cautiously trialled;[1] if a negative response is produced the drug may be stopped.

Initiation of other medications is of mixed utility for most patients with this condition, perhaps because of increased sensitivity to psychoactive substances in this state (see subsequent section).[1,20] Response to the initiation of novel psychiatric medications

is somewhat unpredictable with some reported cases of improvement, as well as deterioration, but in the absence of clear factors allowing prediction of response.[1,20] Caution is recommended in the trial of any novel psychotropic medication in this population.

Sensitivity to other substances during withdrawal

Patients can become highly sensitive to neurologically active substances in the process of withdrawal, thought to be related to an increased sensitivity to stimuli secondary to the de-stabilisation produced by the drug withdrawal process,[1,27,28] though the mechanism is not fully understood. People can respond to a wide variety of substances with activation or other paradoxical effects, including alcohol, neurologically active antibiotics,[29] caffeine, St John's Wort, and sometimes even to specific foods, supplements and herbs,[1,30] in addition to sensitivities to light and sound, more generally recognised.[3] Exposure to these substances can exacerbate withdrawal symptoms, and in this case it can be useful to restrict exposure during the discontinuation process depending on the clinical circumstances.[1] These sensitivities can resolve or improve when the patient recovers from the withdrawal process.[1]

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