Tapering of SSRI treatment to mitigate withdrawal symptoms

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All classes of drug that are prescribed to treat depression are associated with withdrawal syndromes. SSRI withdrawal syndrome occurs often and can be severe, and might compel patients to recommence their medication. Although the withdrawal syndrome can be differentiated from recurrence of the underlying disorder, it might also be mistaken for recurrence, leading to long-term unnecessary medication. Guidelines recommend short tapers, of between 2 weeks and 4 weeks, down to therapeutic minimum doses, or half-minimum doses, before complete cessation. Studies have shown that these tapers show minimal benefits over abrupt discontinuation, and are often not tolerated by patients. Tapers over a period of months and down to doses much lower than minimum therapeutic doses have shown greater success in reducing withdrawal symptoms. Other types of medication associated with withdrawal, such as benzodiazepenes, are tapered to reduce their biological effect at receptors by fixed amounts to minimise withdrawal symptoms. These dose reductions are done with exponential tapering programmes that reach very small doses. This method could have relevance for tapering of SSRIs. We examined the PET imaging data of serotonin transporter occupancy by SSRIs and found that hyperbolically reducing doses of SSRIs reduces their effect on serotonin transporter inhibition in a linear manner. We therefore suggest that SSRIs should be tapered hyperbolically and slowly to doses much lower than those of therapeutic minimums, in line with tapering regimens for other medications associated with withdrawal symptoms. Withdrawal symptoms will then be minimised.

Introduction

Many medications are associated with withdrawal syndromes, most commonly those that act on the cardiovascular system and CNS.[1] All major classes of antidepressants—monoamine oxidase inhibitors, tricyclic antidepressants, SSRIs, and SNRIs—are associated with withdrawal symptoms on cessation.[2,3] The term discontinuation syndrome was coined to refer to the withdrawal syndrome related to antidepressants.[4] SSRI discontinuation syndrome, as outlined in DSM-5,[5] and captured in the Discontinuation-Emergent Signs and Symptoms checklist,[6] comprises a wide variety of somatic and psychological symptoms (figure 1).

SSRI withdrawal symptoms can, in part, resemble the symptoms of anxiety or depression for which the medication was originally given.[5] However, the withdrawal syndrome can be distinguished from a relapse or recurrence of the underlying disorder by its quickness of onset (days rather than weeks),[3,7,8] rapid response to reintroduction of the SSRI (generally within hours, certainly within days),[3,7,9] and the presence of somatic and psychological symptoms quite distinct from the original illness (including dizziness, nausea, and shock-like sensations).[7,10] The withdrawal syndrome can be misdiagnosed as depressive recurrence, leading to prolonged treatment for patients who might not require it,[11–13] but it is not clear how often this occurs.[14]

SSRI withdrawal symptoms occur in many patients, with reported incidence varying from 42% to 100% for paroxetine,[6,15–18] and from 9% to 77% for fluoxetine,[6,15,17,18] with a mean rate of 53·6% for SSRIs across 14 studies that examined antidepressant withdrawal.[13] The incidence and severity appear to be influenced by half-life and receptor affinities, treatment duration and dose, method of tapering, and individual patient characteristics, potentially including anticipation effects.[3,9,19] A systematic review identified five studies that evaluated the severity of withdrawal effects and reported that nearly half of participants who had experienced withdrawal effects chose the most extreme option in the scale offered to them to describe the severity of those effects.[13] The discontinuation period (14 days after cessation) is also associated with a 60% increase in suicide attempts compared with previous users of antidepressants (the increased risk therefore attributed to the process of withdrawal and not to being untreated).[20]

SSRI withdrawal syndrome can last substantially longer than the period of 1–2 weeks[13] that has been previously suggested.[4] In one study, withdrawal symptoms generally lasted for up to 6 weeks, with a quarter of patients reporting symptoms that lasted more than 12 weeks.[18] Another study reported that for 86·7% of respondents the syndrome had lasted at least 2 months, for 58·6% it had lasted at least 1 year, and for 16·2% it had lasted for more than 3 years.[21] Case reports identify symptoms lasting for a year or longer.[22,23]

The increasingly long-term use of SSRIs (with nearly half of the patients in the UK who take antidepressants [usually SSRIs] doing so for more than 2 years)[19,24] has arisen in part because patients are unwilling to stop due to the aversive nature of the withdrawal syndrome,[19,25] and a scarcity of information on how to mitigate the syndrome.[19,25] Doctors feel that there is not enough guidance on how to proceed with discontinuation.[19]

Tapering SSRIs

Guidelines recommend short tapers of SSRIs, rather than abrupt discontinuation, to avoid withdrawal symptoms. The National Institute for Health and Care Excellence,[26] the British Association for Psychopharmacology,[12] the Monthly Index of Medical Specialities,[27] and UpToDate[28] suggest tapering periods of between 2 weeks and 4 weeks, with linear reductions of dose down to the minimum therapeutic dose, or half of the minimum therapeutic

dose, before complete cessation. These guidelines suggest that fluoxetine does not require tapering,[28] or that, at high doses, it could be reduced over 2 weeks.[27] Drug manufacturer advice was found to be similarly "vague and non-specific" according to a systematic review.[29]

In randomised studies, tapering for up to 14 days showed either no[16] or minimal[30] reduction in withdrawal symptom severity compared with abrupt discontinuation.[31] It has generally been concluded from these studies that longer tapering regimens are required.[3,32] Indeed, studies using tapering periods of months in duration[33–35] have shown better outcomes (table 1). In one study, reduction of paroxetine by 10 mg every 2 weeks lowered withdrawal incidence from 33·8% to 4·6%.[33] When the patients who had withdrawal symptoms in this study were recommenced on medication and then tapered at 5 mg every 2–4 weeks, withdrawal symptoms were successfully avoided.[33] In another study, patients who tapered their SSRI dose over up to 4 months had 5·1 Discontinuation-Emergent Signs and Symptoms events, compared with 11·7 events for patients who discontinued abruptly.[34]

In another study with paroxetine, patients who tapered their dose over an average duration of 38·6 weeks (range, 2–197 weeks), titrated to the individual, had a 6·1% incidence of withdrawal syndrome, compared with 78·2% for abrupt discontinuation (table 1).[35] Tapering strips for antidepressants, which reduce the medication to small fractions of the minimum therapeutic dose (eg, 0·5 mg for paroxetine and citalopram), have shown favourable outcomes; 71% of 895 patients, 97% of whom had experienced withdrawal previously, were able to discontinue their medication over a median of 56 days (IQR 28–84 days).[14] Several case studies also support the improved efficacy of slower tapering.[36–38] In one instructive case, several months of tapering down to an average dose of 6·25 mg of sertraline per day was required to avoid withdrawal symptoms in one man, whose withdrawal-induced orthostatic hypotension allowed objective measurement.[36]

Two studies from 2018 confirm that shorter tapering regimens, as advised by guidelines, are not effective. One study found that tapering over 4 weeks was not feasible, with 60% of patients (51 of 85) tapering their medications over 4 months.[39] Another study that used largely linear reductions, with final doses equal to minimum therapeutic doses (or half that value) found that only 37% of patients (26 of 71) were able to discontinue their medication.[40] A large study involving 400 patients showed a significantly lower risk of relapse if antidepressants were tapered gradually (>14 days) rather than rapidly (1–7 days).[41]

Neurobiology of withdrawal and its management

The strategy of tapering SSRIs is based on the rationale that biological systems will have more time to adapt to reductions in available ligand, thus reducing the intensity of withdrawal symptoms.[3,12,32,42] Receptors that are activated by a medication are often downregulated, or exhibit reduced sensitivity, to maintain homoeostasis.[43] Abrupt removal of medication disturbs the homoeostatic equilibrium, resulting in reduced stimulation, which is experienced as withdrawal symptoms that are often opposite in nature to the original effect of the drug.[43] For example, the withdrawal syndrome from tricyclic antidepressants, which have strong anticholinergic actions, is typified by cholinergic effects.[44] Adaptation to medication is more likely in the case of long-term and high-dose use.[45,46] Medications with shorter half-lives produce withdrawal symptoms with greater incidence, greater severity, and quicker onset than medications with longer half-lives, probably because their withdrawal is associated with more rapid decreases in the amount of available ligand.[45,47,48] Withdrawal symptoms can usually be eliminated by reintroduction of the discontinued agent, returning the system to homoeostatic equilibrium.[43]

The principal approach to mitigate withdrawal symptoms is to reduce the rate at which this equilibrium is disrupted, allowing time for adaptation of the system to lowered levels of ligand, thus limiting withdrawal symptoms to tolerable severity.[45] This process is achieved either by substitution of a longer-acting medication before tapering, or slow tapering of a drug with a short half-life.[45,48]

Notably, decreasing medication by constant amounts (linear tapering) tends to cause increasingly severe side-effects over time.[45,48,49] This effect is probably a consequence of the hyperbolic dose-response relationship between a drug and receptor, following the law of mass action,[50] as typified by the effect of diazepam on its target receptor, γ-aminobutyric-acid A (GABA-A, figure 2A). Consequently, tapering recommendations for benzodiazepines advise increasingly small decreases in dosage as it approaches zero,[45,48,49] or "stop slow as you go low".[1]

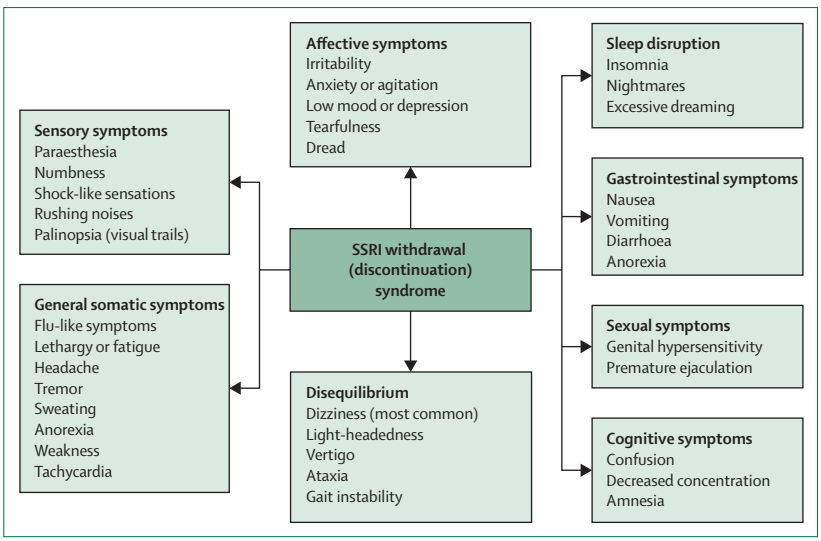

Figure 1: **Symptoms of SSRI withdrawal (discontinuation) syndrome**

	Number of patients	Medication	Tapering period	Lowest dose before zero	Outcome (% with discontinuation syndrome or DESS score)	Odds ratio AD versus taper	Comment
Groot and van Os (2018)[34]	895; antidepressant use median 2–5 years	Paroxetine, venlafaxine	Median 56 days (IQR 28–84 days)	0·5 mg (paroxetine); 1·0 mg (venlafaxine)	71% able to cease	N/A	Included patients who had had severe withdrawal syndrome previously
Tint and colleagues (2008)[16]	28	SSRI, venlafaxine	3 days; 14 days	Unknown	46% (3 days); 46% (14 days)	N/A	No difference between 3 day and 14 day taper
Baldwin and colleagues (2006)[30]	249	Paroxetine (N=115) or escitalopram (N=134)	7 days; 14 days	10 mg (paroxetine); 5 mg (escitalopram)	DESS 5·4 (SD 8·3) for paroxetine; DESS 3·2 (SD 4·8) for escitalopram; no difference between 7 and 14 days	N/A	No difference between 7 day and 14 day taper (but both slightly better than AD when compared with other studies)
Himei and Okamura (2006)[33]	385	Paroxetine	AD (N=80); taper, reducing by 10 mg every 2 weeks (N=305)	10 mg	33·8% (AD); 4·6% (taper)	7·4	36 patients with withdrawal syndrome were recommenced on paroxetine and tapered at 5 mg every 2–4 weeks with no re-emergence of symptoms
van Geffen (2005)[34]	74	Fluvoxamine, fluoxetine, paroxetine, citalopram	AD (N=14); taper, 2 weeks–4 months (N=52)	Unknown	86% (AD); 52% (taper)	1·65	Significant reduction in withdrawal symptoms with tapering compared with AD
Murata and colleagues (2010)[35]	56	Paroxetine	AD (N=23); taper, average 38·6 weeks, range 2–197 weeks (N=33)	10 mg	78·2% (AD); 6·1% (taper)	12	Odds ratio of 55·8 by univariate logistic regression of tapering compared with AD

DESS=Discontinuation-Emergent Signs and Symptoms. AD=abrupt discontinuation. N/A=not applicable.

Table 1: **Studies that measured withdrawal symptoms in patients tapered off antidepressants**

Withdrawal guidelines for benzodiazepines recommend dose reductions that are proportional to the present dose (most commonly 10% reductions), yielding exponentially decreasing regimens, as opposed to linear reductions.[45,49,52] For example, tapering from 20 mg of diazepam at a rate of 10% a week would entail a 2 mg reduction in the first week. The second week's cumulative reduction would be 3·8 mg (a further 1·8 mg reduction), the third week's cumulative reduction would be 5·42 mg (a further 1·62 mg), and so on (figure 2B). These exponentially decreasing regimens produce approximately linear reductions of effect at the target receptor. Reductions are continued to doses well under the minimum therapeutic dose (that might appear miniscule) before complete cessation. This process is done to avoid a step down in action at the target receptor that is substantially greater than the size of steps previously tolerated. For example, the final dose of diazepam recommended by tapering guidelines is 1 mg[45] (equivalent to 4% GABA-A receptor occupancy).[52]

As withdrawal symptoms are thought to abate because of homoeostatic adaptations to reduced medication levels, a pause is recommended between dose reductions.[45,48,49] As the exact timing of these adaptations is not fully understood, most guidelines for withdrawal have been developed on the basis of clinical experience; a consensus suggests waiting 1–4 weeks between dose reductions, to allow withdrawal symptoms to resolve.[45,48] Most guidelines recommend individualisation of this process, given the variation in adaptation to changes in drug levels, and consequent severity and duration of withdrawal symptoms.[45,48]

Pharmacological characteristics of SSRI withdrawal

Withdrawal or discontinuation syndrome from SSRIs has the same determinants as described previously. Withdrawal symptoms are more common when SSRIs are given in high doses,[53,54] or for long periods.[53] Medications with shorter half-lives, such as paroxetine, produce withdrawal symptoms with greater incidence,[6,15–18] quicker onset,[6,15–18] and greater severity[6,15–18] than medications with longer half-lives, such as fluoxetine.[6,15,17,18] Paroxetine produces withdrawal symptoms within 2 days,[55] whereas symptoms of fluoxetine withdrawal can be delayed by 2–6 weeks.[9,56]

As with withdrawal from other medications, the appearance of these withdrawal effects correlates with percentage reductions in plasma concentration.[55] Higher SSRI plasma levels before cessation[57] and just after cessation[58] predict increased withdrawal symptoms. Reintroduction of the discontinued SSRI generally resolves symptoms within 24 h.[3] Approaches have been trialled to diminish withdrawal symptoms by tapering of SSRIs,[9,12] or substitution for the longest acting SSRI, fluoxetine,[3,12] according to the approaches used for withdrawal from other agents. Individual factors, including genetics,[35] are thought to play a role in determining withdrawal effects.

Neurobiology of SSRI withdrawal

SSRIs are thought to produce their effect through an initiating step of inhibition of the serotonin transporter, leading to an increase in synaptic levels of serotonin,

thereby transducing increased responses at serotonergic receptors.[59,60] Serotonergic neurons also modulate other neurotransmitter systems, including noradrenaline, dopamine, and GABA.[47] Effects on neurogenesis, inflammation, and the hypothalamic–pituitary–adrenal axis, downstream of serotonergic actions, are also hypothesised in the antidepressant effects of SSRIs.[59,61,62] Although the details remain to be elucidated, SSRI withdrawal has been attributed to a relative deficiency of serotonin in the context of widespread adaptation of serotonergic receptors.[9,47,63] SSRI treatment has been shown to down-regulate the density of serotonergic receptors in rats.[64] It has also been shown in humans that even short-term SSRI administration reduces the sensitivity of cortical 5-hydroxytryptamine receptor 2A[65] and 5-hydroxytryptamine receptor 4.[66] The reversal of effects on neurotransmitters that are indirectly affected by SSRIs, including noradrenaline, glutamate, and GABA, among other targets, could also play a role in SSRI withdrawal.[9,47,63]

The role of serotonin in coordinating sensory and autonomic function with motor activity has been implicated in SSRI withdrawal syndrome.[42] Reduced stimulation of 5-hydroxytryptamine receptor 1A in the raphe nucleus, known to be involved in motion sickness,[47] is thought to be related to the dizziness, vertigo, nausea, and lethargy of the withdrawal syndrome.[47] Dysregulation of somatosensory functions could result in paraesthesia, whereas movement disorders (eg, dystonia) could be due to altered dopaminergic function.[47]

Aspects of SSRI withdrawal syndrome might also be attributed to neuronal changes in tissues outside the brain, given the presence of serotonergic receptors in sites such as the vasculature and gut.[67]

Pharmacological principles of tapering SSRIs

As with other withdrawal syndromes, a rational tapering regimen for SSRIs will entail step-wise reductions in their action at serotonin transporters, their principal receptor targets.[59] PET studies in which a radioligand was bound to serotonin transporters have shown that the dose-response curve between SSRIs and serotonin transporters conforms to the typical hyperbolic relationship, which arises as a consequence of the law of mass action (figure 3). The line of best fit for the dose-response curve, which corresponds to a Michaelis-Menten equation,[68] can be used to derive values for the percentage inhibition of SERT at different doses of citalopram (figure 3, table 2).[60] Notably, serotonin transporter inhibition drops off sharply for doses lower than the minimum therapeutic dose for SSRIs.

It is therefore likely that tapering regimens with linear dose reductions will cause increasingly severe withdrawal reactions, as the reductions in serotonin transporter inhibition become increasingly large (figure 4A). For example, reducing the dose of citalopram in 5 mg increments from 20 mg will produce hyperbolically enlarging decreases in serotonin transporter inhibition: an absolute decrease in serotonin transporter inhibition of 3% from 20 mg to 15 mg, 6% from 15 mg to 10 mg, 13% from 10 mg to 5 mg, and 58% from 5 mg to 0 mg. Even reductions from 2·5 mg (a quarter of the smallest available tablet) to 0·0 mg will produce an absolute reduction in serotonin transporter inhibition of 42·9%, and reduction from 1·25 mg (an eighth of a tablet) to 0·00 mg will produce a 28% reduction (larger than the change from 40 mg to 5 mg, which produces a 27·3% reduction). These large reductions in inhibition could account for the paucity of success of previous tapering regimens,[39,40] and particularly for the difficulties with withdrawal symptoms that patients have towards the end of their taper, at low doses.[14,36]

To produce a linear reduction of pharmacological effect, a hyperbolically decreasing pattern of dose reduction is required (figure 4B). Rather than decreasing the dose by fixed amounts, the dose should be decreased according to fixed intervals of biological effect, for example, 10% reductions of serotonin transporter occupancy (20% reductions are shown in figure 4B). A tapering regimen that would produce approximately 10% reductions in serotonin receptor occupancy with each citalopram dose reduction would be: 20 mg, 9·1 mg, 5·4 mg, 3·4 mg, 2·3 mg, 1·5 mg, 0·8 mg, 0·4 mg, and 0·00 mg (table 2). Further SSRI examples are shown in the appendix. These

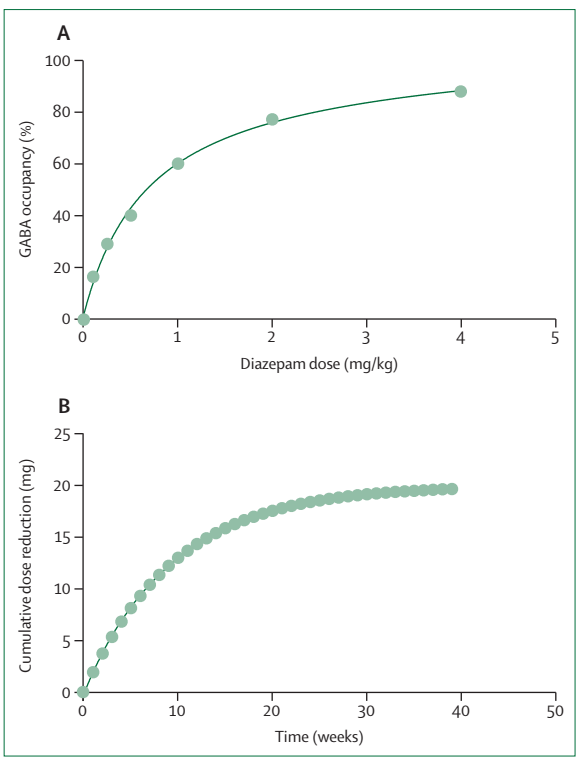

Figure 2: **Recommended tapering regimen for diazepam based on its dose-response relationship**
(A) Relationship between dose of diazepam and action at GABA-A receptors in non-human primates. Adapted from Brouillet and colleagues.[51] (B) Reductions in diazepam dose recommended by tapering guidelines for 20 mg diazepam (10% dose reduction per week).[45-49] GABA=γ-aminobutyric-acid.

See **Online** for appendix

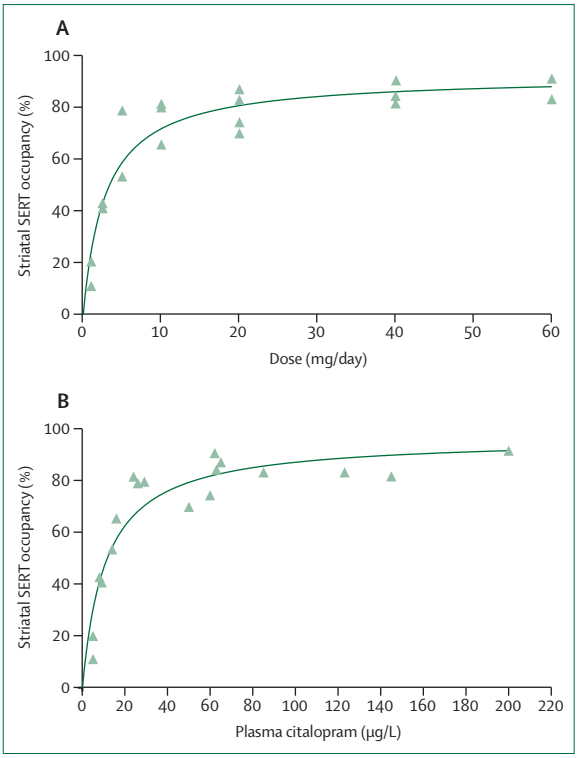

Figure 3: **Hyperbolic relationship between SERT and dose or plasma concentration of citalopram**
(A) Relationship between dose of citalopram and SERT occupancy (%). (B) Relationship between plasma level of citalopram and SERT occupancy (%). SERT=serotonin transporter. Reproduced from Meyer and colleagues,[60] by permission of the *American Journal of Psychiatry*.

Citalopram dose (mg)	SERT occupancy (%)
60·0	87·8%
40·0	85·9%
20·0	80·5%
19·0	80·0%
9·1	70·0%
5·4	60·0%
3·4	50·0%
2·3	40·0%
1·5	30·0%
0·8	20·0%
0·37	10·0%

SERT occupancy was calculated using the Michaelis-Menten equation of best fit derived by Meyer and colleagues.[60] Common clinical doses and doses corresponding to 10% decrements of SERT inhibition are displayed. These doses could be produced by a combination of tablets and liquid formulations. Approximations might be necessary. SERT=serotonin transporter.

Table 2: **Derivation of SERT occupancy from citalopram dose using the Michaelis-Menten equation of best fit**

regimens allow pharmacologically informed application of the withdrawing principles outlined above ("stop slow as you go low").[1,49] The tapering regimen described above uses doses that are close to those that have been used successfully in trials involving tapering strips,[14] and in case studies involving difficult withdrawal syndromes.[36]

Limitations

There are potential limitations to interpreting the dose-response curve of the PET study presented.[60] The number of participants in each group is relatively small, perhaps limiting the ability to capture individual variation. However, the shape of the dose-response curve (ie, hyperbolic) should be the same for each individual, suggesting hyperbolic dose reduction regimens should be universally applicable.

SSRIs might also exert neurotrophic, anti-inflammatory, and neuroendocrine effects;[61,62] however, these are thought to be downstream of effects on serotonin transporters and consequent to changes to the serotonergic system,[59,61,62] indicating that serotonin transporter occupancy is likely to be a key indicator of biological response to SSRIs.

It is difficult to determine whether serotonin transporter inhibition will linearly correspond to withdrawal effects. Serotonin transporter binding is related to the antidepressant effects of SSRIs; the ratio of serotonin transporter binding between terminal regions and the median raphe nucleus has been shown to predict treatment response to SSRIs.[69] It is theoretically possible that a minimum threshold of serotonin transporter inhibition is required before a clinical effect is seen, with levels lower than this having minimal effects;[60] this could also correspond to withdrawal effects. However, withdrawal effects from other medications do not observe threshold effects,[45,48] and withdrawal effects have been observed at many doses during tapering of SSRIs,[9,35] suggesting that withdrawal is likely to be a continuous entity. Furthermore, a hyperbolic relationship exists between dose of SSRI and reduction in depressed mood, as shown in a mega-analysis;[70] a hyperbolic relationship has also been shown between dose of SSRI and risk of withdrawal symptoms.[55] These findings indicate that the hyperbolic relationship between dose and serotonin transporter inhibition could also extend to withdrawal effects, suggesting that serotonin transporter inhibition could be approximately linearly related to withdrawal effects.

Another potential limitation to interpreting the dose-response curve from Meyer and colleagues[60] is that serotonin transporter occupancy was measured in the striatum, which might not have direct relevance to antidepressant actions. However, this and a subsequent PET study[71] showed that SSRIs cause similar serotonin transporter inhibition in brain regions relevant to SSRI action (eg, subgenual cingulate, amygdala, and raphe nuclei), with a similar hyperbolic relationship between dose of SSRI and serotonin transporter occupancy at all regions examined.[71] Therefore, it seems reasonable to conclude that SSRIs, like most pharmacological agents, have a hyperbolic relationship between dose and biological effects, and that this could be relevant in generating rational discontinuation regimens.

Practical application of hyperbolic dose reduction

There are likely to be individual differences in experiences of SSRI withdrawal effects.[3] We suggest that a personalised rate for withdrawal could be established by an initial trial reduction of SSRI dose, equivalent to a reduction of 10% serotonin transporter occupancy (or 5% if being cautious), with subsequent monitoring of the severity and duration of withdrawal symptoms. An initial 10% reduction in serotonin transporter occupancy is suggested because this would result in approximately halving the dose from the therapeutic minimum dose (eg, from 20 mg to 10 mg of citalopram), which is tolerated well by most patients. If the patient's Discontinuation-Emergent Signs and Symptom score were to have returned to baseline 1 month after the initial reduction, then a rate equivalent to 10% reduction of serotonin transporter occupancy per month could be prescribed. This process should be subject to ongoing monitoring, with the rate titrated to patient tolerance.

The SSRI should be tapered such that the final reduction to zero is equal to (or less than) the size of reduction previously tolerated by the patient. This should be when the dose is equivalent to approximately 10% serotonin transporter occupancy. Notably, this will be a very small dose—eg, 0·4 mg for citalopram. However, studies have reported tapering regimens that have been successful only when they taper to similar doses of SSRIs.[14,36] The use of liquid formulations of SSRIs might be necessary to achieve these small doses.

It is difficult to establish the optimal time interval between dose reductions. In the absence of studies evaluating the rate at which neuroadaptation can occur, several aspects can provide guidance. For all SSRIs except fluoxetine, pharmacokinetic properties predict that they will achieve steady state between 5 days and 14 days after dose reduction (table 3).[72] As outlined above, discontinuation symptoms have been detected in patients for varying periods of time, from a number of days,[9] to weeks and months,[18,21–23,73,74] and, in some cases, for more than a year.[21,22,73,74] These records have generally been derived from patients who abruptly cease their medication; it is possible that with more cautious reductions, the discontinuation symptoms will last for shorter periods. The clinical effects of SSRIs can be delayed by weeks following their commencement,[59,70] whereas side-effects arise in days.[75] It is unclear whether withdrawal symptoms are likely to follow the temporal pattern of antidepressant effects, or side-effects. It might be prudent to allow 4 weeks after a reduction in SSRI to observe for delayed withdrawal effects. This would also allow for observation of recurrence of underlying symptoms as a result of the decrease in SSRI dose. However, the best guide might be the interval required for the patient's Discontinuation-Emergent Signs and Symptoms score to return to baseline after a test reduction.

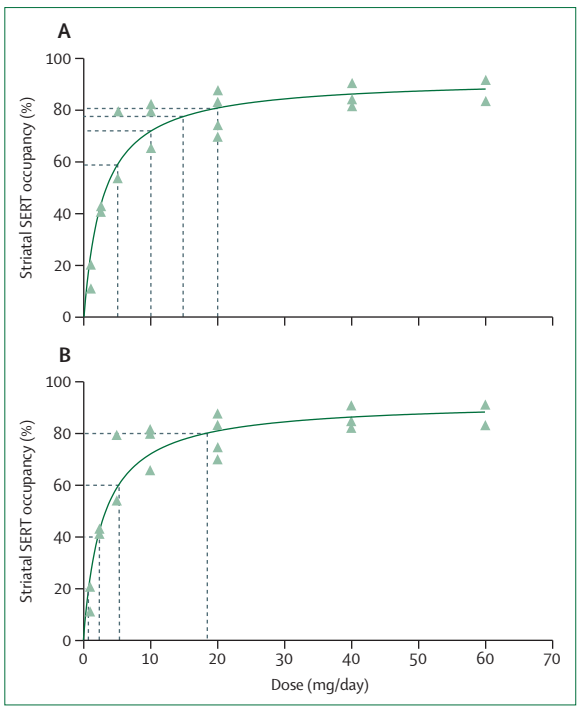

Figure 4: **Effect of linear and hyperbolic citalopram dose reductions on SERT occupancy**
(A) Linear dose decrements of citalopram (eg, intervals of 5 mg) produce exponentially increasing changes in SERT occupancy. (B) Hyperbolic dose decreases of citalopram produce linear changes in SERT occupancy (eg, intervals of 20% SERT occupancy). SERT=serotonin transporter. Reproduced from Meyer and colleagues,[60] by permission of the *American Journal of Psychiatry*.

Other determinants of withdrawal symptoms from SSRIs

Other drug and patient characteristics are likely to affect the severity of withdrawal syndromes from SSRIs. Paroxetine and fluoxetine are both metabolised by cytochrome P450 2D6 and inhibit their own metabolism, resulting in non-linear kinetics.[76] This predicts disproportionate declines in plasma concentrations during drug withdrawal. Although this effect might not be clinically significant for fluoxetine because of its long half-life, it is likely to be significant for paroxetine.[47] Paroxetine might produce a more severe withdrawal syndrome than other SSRIs because it has pronounced muscarinic antagonist effects and moderate norepinephrine transporter inhibiting effects.[47,63] It is also likely that patient factors, such as presence of different cytochrome enzymes, serotonin transporter sensitivity to inhibition, and psychological factors, could contribute to the risk of withdrawal symptoms. Further understanding of these factors, and testing of plasma levels of SSRIs, might be instructive in designing personalised tapering regimens.

Practical consequences of hyperbolic dose reduction

The model above resolves an uncertainty often raised by patients and treating physicians, which is whether to use a

	Daily dose (mg)	Half-life	Time to reach steady state	Linear kinetics	Cytochrome P450 inhibition
Fluoxetine	20–80	1–4 days	5–11 weeks	No	2D6
Norfluoxetine	..	7–15 days	..	..	2D6, 3A4
Fluvoxamine	50–300	15 h	10 days	No	1A2, 2C19
Paroxetine	20–50	20 h	7–14 days	No	2D6
Sertraline	50–150	26 h	5–7 days	Yes	Minimal
Citalopram	10–60	36 h	6–10 days	Yes	Not relevant
Escitalopram	5–30	27–33 h	7–10 days	Yes	2C19, 2D6, 3A4

Adapted from Hiemke and colleagues.[72]

Table 3: **Pharmacokinetic characteristics of SSRIs and their clinically active metabolites**

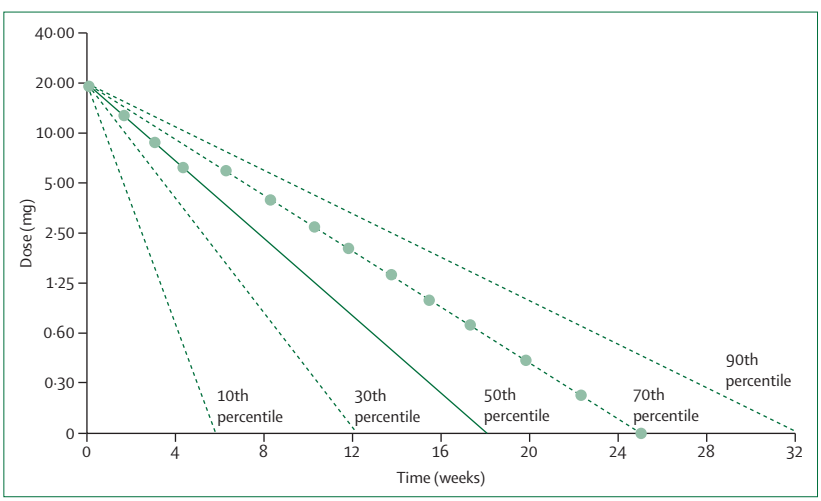

Figure 5: **Hypothetical nomogram for determining withdrawal rates for citalopram**
An example tapering regimen from 20 mg citalopram is indicated (semi-log scale for dose). The patient's results initially follows the trajectory for the 50th percentile, with dose reductions equivalent to 10% serotonin transporter occupancy every 4 weeks (20·0 mg, 9·1 mg, and 5·4 mg). She then experiences unpleasant side-effects (eg, Discontinuation-Emergent Signs and Symptoms score of >3). Her tapering shifts to the slower trajectory for the 70th percentile and she experiences no periods of intolerable withdrawal symptoms as she completes the taper.

micro-taper or mini-taper strategy. Micro-tapering involves miniscule decrements in SSRI medication every day or week. Mini-tapering involves larger, step-wise decrements, with longer intervals between decrements (generally intervals of weeks). Mini-tapering appears more sensible than micro-tapering. Withdrawal symptoms are reported to last for several weeks (or longer) after medication discontinuation in a large proportion of patients.[9,13] Consequently, micro-tapering presents the possibility of cumulative withdrawal effects being superimposed on one another. This process would make it difficult to establish which reduction (or set of reductions) was responsible for the symptoms experienced. It therefore seems prudent to decrease the dose of medication, then allow a substantial period of time to elapse while withdrawal effects resolve, before making the next decrement.

Fluoxetine

Substitution of short-acting SSRIs with fluoxetine has been suggested as a way to avoid intolerable withdrawal symptoms.[3,77] Fluoxetine has been routinely identified to cause less severe withdrawal effects than other SSRIs, which has been attributed to its longer half-life.[3,29,77] Fluoxetine takes 35–75 days to reach steady state,[47] which is likely to be responsible for observations that its withdrawal symptoms can arise weeks after cessation.[9,56] Therefore, it would be prudent to wait 3 months (35–75 days plus 4 weeks) to observe for late-arising withdrawal symptoms. Given this property of fluoxetine, which is similar to an in-built tapering system, it could be reasonable to reduce doses by the equivalent of approximately 30% serotonin transporter occupancy in each iteration, titrated to patient tolerance.

Nevertheless, we should be wary of the idea that fluoxetine is self-tapering, and can therefore be abruptly or rapidly ceased, as guidelines suggest.[29,78] Although its pharmacokinetic profile predicts a gradual decline in plasma level, a short reduction (eg, 2 weeks)[27] could still represent a rapid withdrawal schedule that exceeds a 10% decrease in biological effect per month.

Future directions for research

We have proposed a pharmacologically informed method for tapering SSRI treatment, the validity of which should be evaluated by randomised controlled trials. Withdrawal nomograms aggregating variation in responses to withdrawal could guide taper rates (figure 5). Risk determinants, such as plasma SSRI level, cytochrome enzyme status, PET measurement of serotonin transporter occupancy, and other genetic, metabolic, and psychological factors, could be incorporated into the nomogram as their effects are clarified. Pharmacological and non-pharmacological means to improve the tolerability of SSRI withdrawal also warrant research. Psychological interventions, such as preventive cognitive therapy, and other CBT approaches, have been found to reduce the risk of relapse in patients with recurrent depression and those tapering their antidepressants.[39,40]

We suggest that, in the absence of more robust evidence to guide tapering (especially where guidelines advise to taper gradually without specific instructions), the tapering regimen described here should be considered for adoption into clinical practice. There are few disadvantages of recommending slower tapers.[29] It should at least be recognised that tapering periods of 2–4 weeks are likely to be inadequate for reducing withdrawal symptoms for many patients, with longer periods of tapering, and regimens that include lower doses of medication, more likely to be effective. Further empirical study of tapering regimens, including the one proposed here, is urgently required, with a consequent update of formal guidelines.

Contributors
MAH conceived the manuscript idea, wrote the manuscript, and drew the figures. DT helped to develop the idea, and revised and edited the manuscript.

Declaration of interests
MAH declares no competing interests. DT reports personal fees from Lundbeck, and grants and personal fees from Janssen, outside the submitted work.

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