Implementing gradual, hyperbolic tapering of long-acting injectable antipsychotics by prolonging the inter-dose interval: an *in silico* modelling study

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Abstract: Gradual, hyperbolic tapering has been proposed as a method to reduce the risk of withdrawal effects and potential relapse of an underlying condition by minimising disruption of existing equilibria. We applied hyperbolic tapering principles *in silico* to long-acting aripiprazole to generate regimens for withdrawal in clinical practice. We derived thresholds for taper rates using existing studies and consensus. Using pharmacokinetic data for aripiprazole long-acting injectable antipsychotic (ALAI), we conducted *in silico* modelling to examine the impact of abrupt cessation of long-acting injectable antipsychotic (LAI) medication and the effect of prolonging inter-dose interval on plasma aripiprazole levels and consequent D_2 occupancy. We also modelled transitions from LAI medication to oral medication. Regimens were designed to afford a rate of reduction between 5 and 12.5 percentage points of D_2 occupancy per month. Abrupt discontinuation of ALAI was shown to lead to a maximal D_2 occupancy reduction of 16.8 percentage points per month; prolongation of the inter-dose interval of ALAI produced a slower reduction. Specifically, hyperbolic tapering was afforded by prolongation of a 400 mg ALAI inter-dose interval from 4 to 7 weeks, before reducing the dose to 300 mg ALAI. This could then be administered at up to 4-week (for 6% maximal D_2 occupancy change), 6-week (9% change) or 7-week (11% change) intervals. Switching to oral medication – 5, 2.5 and 1.25 mg for the three regimens, respectively – is required for ALAI to complete full cessation to prevent too rapid a reduction in D_2 occupancy. Oral medication should probably be maintained at a consistent dose for 3–6 months before further reductions to account for residual LAI being concurrently eliminated. Hyperbolic dose tapering is possible with ALAI through prolongation of the inter-dose interval and may reduce the risk of relapse compared to abrupt discontinuation of LAI medication.

Keywords: antipsychotic withdrawal, depot tapering, discontinuation, hyperbolic tapering, long-acting injectable antipsychotic, pharmacokinetic, stopping

Background

It has been observed that up to 40% of patients with psychotic conditions may be able to stay well without antipsychotic medication.[1] A substantial proportion of psychiatrists indicate a willingness to reduce antipsychotic medication in people who have experienced a single episode of psychosis, with a smaller but still sizeable proportion willing to reduce for people with multiple episodes of psychosis.[2] Several studies examining antipsychotic dose reduction and discontinuation are currently in progress around the world.[3,4]

Antipsychotic discontinuation studies have generally demonstrated that patients who stop their medication are more likely to relapse than those who are maintained on medication.[5,6] However,

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these studies mostly examine abrupt or rapid discontinuation.[7,8] In one influential meta-analysis, most studies compared abrupt discontinuation of oral medication with either stopping depot medication abruptly or tapering oral medication over 4 weeks on average.[5] The risk of relapse has been shown to markedly reduce when a more gradual approach is taken in reducing dosage, but even when antipsychotics are withdrawn over a period of months, this has been found to still lead to around a third of patients relapsing over the observational period.[9,10] In a similar way, prolongation of inter-dose intervals for long-acting injectable antipsychotics (LAIs) in a pharmacologically uninformed manner has been found to increase the risk of relapse.[11,12]

It has been proposed, however, that if antipsychotics are reduced according to their hyperbolic pattern of effect on target receptors (including but not limited to D_2 dopaminergic receptors), then reduction or discontinuation may be more successful than quicker linear tapers.[13] Hyperbolic tapers afford a linear reduction in receptor activity; linear tapers, in contrast, cause receptor activity to fall by ever-increasing degrees. There is some empirical support for this notion as the relationship between dose and effect on symptom scores is hyperbolic[14] and relapse also occurs according to a hyperbolic pattern on dose reduction,[15] suggesting a relationship with receptor occupancy.[16] One open-label randomised cohort study of hyperbolic antipsychotic dose reduction in psychotic disorders found no increased relapse rate compared to maintenance treatment with some patients who reduced their dose by more than half, with better clinical outcomes and quality of life.[17] A French study has currently been funded to explore hyperbolic dose reductions in people with psychotic disorders, but findings are yet to be published.

The rationale for the reduction or cessation of antipsychotic medication is that not all patients benefit from their use, whilst a variety of adverse effects are common; these include metabolic complications[18–20] and probable brain shrinkage, even on top of any effect attributed to the condition of schizophrenia itself.[21] Adverse effects can lead to service user dissatisfaction and increased risk of patient-led discontinuation of medication,[22–24] compromising the therapeutic relationship between clinician and patient. One randomised controlled trial demonstrated that reducing and stopping antipsychotic medication has been shown to improved long-term prognosis by increasing the likelihood of recovery through symptomatic and functional remission in people with psychotic conditions.[25]

Prescribing any medication should centre around the principles of using the lowest required dose for the shortest duration of time.[24] Therefore, clinicians should always consider when medications, including antipsychotics, can be reduced in dose and eventually discontinued. While the risk of relapse can be high if dose reductions are performed too rapidly, a meta-analysis of randomised controlled trials suggests that this risk is reduced when tapering takes place over months.[10]

There is limited current guidance on how to effectively discontinue antipsychotics while minimising significant withdrawal effects or destabilisation of the underlying condition. Withdrawal effects might either imitate psychotic relapse or precipitate a genuine relapse, perhaps as a consequence of withdrawal symptoms like insomnia or anxiety. A strategy has been proposed for reducing oral medications with progressively decreasing dosing differences.[13] However, no such work has been conducted into how to effectively discontinue LAIs, colloquially known as 'depots'. Compared with oral counterparts, there are limited available forms of these LAIs, leading to a reduced scope for tailoring dosage to individual patients as has been suggested for oral medication.[13]

LAIs, by definition, have a much longer elimination half-life than oral antipsychotics.[26] As such, it has previously been regarded that stopping LAIs abruptly may not lead to withdrawal symptoms or destabilisation of mental state because the change in plasma levels would be slow enough to mitigate any withdrawal effects.[27,28] However, changes induced by exposure to medication, such as dopaminergic hypersensitivity, for example manifesting as tardive dyskinesia, can take years to improve.[13] Therefore, tapering may need to take place over such a time scale to allow the brain to slowly re-adapt to lower levels of the drug to reduce the risk of relapse.[25] In this case, the abrupt cessation of LAI may produce too rapid reduction in dopamine occupancy.

Limited literature is available on an optimal rate of discontinuation for LAI. Studies have found that reducing oral doses by 25%–40% every 6 months does not increase the risk of relapse compared with maintenance treatment.[29,30]

One method to facilitate hyperbolic tapering of antipsychotic depots may be to extend the dosing interval.[31] One study lengthened inter-dose interval of flupentixol from 3 to 4 weeks whilst keeping a consistent dose and found no effect on relapse of psychosis symptoms.[32] Increased intervals for olanzapine and zuclopenthixol LAIs were also tolerated, although individual injection dosages were increased slightly to compensate; dosage per week was still reduced by 20%–30% once the prolonged interval was accounted for Fleming *et al.*[32] The authors notably did not extend intervals for aripiprazole monohydrate, citing limitations in licensing arrangements. However, the manufacturers of aripiprazole monohydrate advise that whilst at steady state, dosing intervals can be as long as 6 weeks before oral re-titration is required.[33] It should be noted, however, that this is advice given for a single missed dose, which would not have a significant effect on reducing steady-state levels in the long term. Nevertheless, this manufacturer's advice aims to maintain a patient within steady-state plasma ranges; this would not be the intention in the case of dose reduction or discontinuation, and therefore, longer inter-dose intervals may be permissible to achieve this.

Numerous administrations of LAI at a consistent dose are required before a steady-state plasma level is achieved. This is due to recommended dosing intervals typically being shorter than the half-life of LAI, leading to a cumulative effect of additional doses on pre-existing drug levels in the body.[34] Once a steady state is achieved, dosing intervals are designed to maintain plasma levels within a certain range. Therefore, any lengthening of dosing intervals should have the opposite effect, in that a gradual reduction in plasma levels will occur with subsequent dosing.

Objectives

Our aim was to derive a regimen for antipsychotic depot reduction that might minimise the risk of withdrawal symptoms and the risk of psychotic relapse by following a hyperbolic pattern of reduction outlined previously.[13] This would be applicable to either patients who might switch to oral medication to continue reducing their medication after reaching the lowest possible depot dose or those patients who may not be suitable for such a switch, but for whom a lower dose of LAI is desirable.

Aripiprazole monohydrate, known by its brand name of Abilify Maintena©, is currently the third most commonly prescribed LAI medication in the UK,[33] being the most prescribed second-generation depot antipsychotic.[35] Forms of 300 and 400 mg are approved for use by the Medicines and Healthcare Products Regulatory Agency[36] and are widely available within the UK at present.[37] A different formulation of aripiprazole LAI with a longer half-life, aripiprazole lauroxil, is also available[38] but our model has not included this LAI in analysis due to distinct differences in pharmacokinetic properties.

We aimed to establish acceptable rates of D_2 dopaminergic occupancy reduction based on existing studies and knowledge of the variation in plasma levels during steady-state depot maintenance treatment. We also aimed to determine the rate of reduction in D_2 dopaminergic occupancy in the case of abrupt discontinuation, and when inter-dose intervals were prolonged for aripiprazole long-acting injectable (ALAI). This was conducted through pharmacokinetic analysis of plasma levels and associated D_2 dopaminergic occupancy for ALAI. We also sought to establish an effective conversion from LAI to oral medications to allow for continued reduction and discontinuation of antipsychotic medication through the same *in silico* modelling of plasma levels and D_2 occupancy. Overall, this allowed us to generate reduction regimens for people on LAI according to three different speeds.

Methods

Overall and maximal reduction in D_2 blockade

The relationship between plasma levels of an abruptly ceased LAI medication, and time as the level falls from peak levels to zero, is logarithmic, determined by the elimination half-life of the LAI [see Figure 1(a)].[39] The relationship between plasma levels and D_2 dopaminergic is hyperbolic [see Figure 1(b)].[40] These relationships combine to produce a sigmoid-shaped decrease in D_2 blockade following abrupt discontinuation of LAI [Figure 1(c)], with a progressively faster rate of decrease over the first half of the period of elimination. For the majority of LAI medications, the rate of decrease will continue to accelerate over months, typically reaching a peak between 4 and 6 months, depending on half-life. Therefore, during the initial stages of drug elimination, the
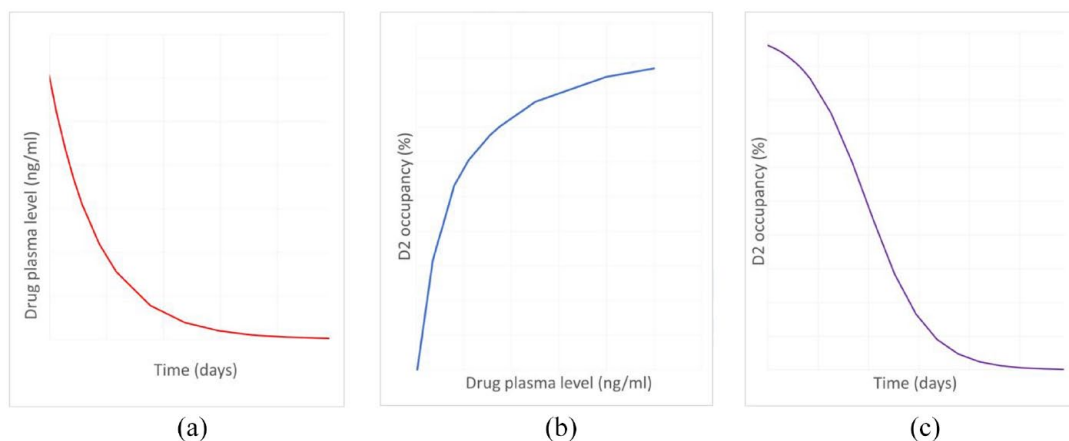
Figure 1. Graphs demonstrating (a) the elimination of LAI medication from plasma peak levels (time = 0) following abrupt cessation, (b) the effect that increasing the plasma level of medication has in occupying D_2 receptors and (c) the combined effects of the phenomena illustrated in part labels a and b which demonstrates the decrease in D_2 occupancy as LAI medications are eliminated from plasma.
LAI, long-acting injectable antipsychotic.

velocity of D_2 occupancy change will be greater than the average overall reduction as the inter-dose interval is prolonged.

In analysing the rate of reducing D_2 occupancy, two rates of decrease are examined. The first is the rate of decrease overall from administration ('overall' reduction), as well as the rate of reduction in the final stages of the measured period. For this project, 'terminal' reduction looked at the rate of reduction over the most recent 7 days, which would be the 'maximal' reduction over the course of the inter-dose interval. These concepts are depicted in Figure 2.

Although it has often been considered that relapse occurs when a certain threshold of D_2 occupancy is breached, it has been proposed recently that the process of dose reduction itself may induce withdrawal effects that mimic or precipitate relapse.[13] This would be expected to occur at the point of greatest rate of change in D_2 occupancy, as this would produce the greatest disruption to the equilibrium. As a result, we focused on maintaining the 'terminal', or 'maximal' reduction in D_2 occupancy within the constraints imposed by our guide for appropriate regimes.

Pharmacokinetic characteristics for ALAI
Pharmacokinetic characteristics for ALAI were obtained from two previous pharmacokinetic studies.[41,42] Figures were obtained for the time taken after injection to reach peak concentration

(t_{max}), the elimination half-life for a drug formulation ($t_{1/2}$), the maximum concentration observed post-injection (C_{max}) and the minimal level of drug detected in plasma levels immediately prior to the next injection (C_{min}). Demographics of studied samples were similar in both studies, predominantly assessing overweight males of black ethnicity in the fifth decade of life.[41]

Both pharmacokinetic studies[41,42] were used to determine figures for C_{ss}, t_{max} and $t_{1/2}$ of 400 mg ALAI dosing once at steady-state plasma levels (see Table 1). Both assessed pharmacokinetics after five injections of 400 mg long-acting aripiprazole. Collated means and standard deviations could be calculated for C_{ss} values. However, results from Mallikarjun *et al.*[41] were used alone for t_{max} and $t_{1/2}$, again due to either a lack of precision or unavailable data in Raoufinia *et al.*[42]

For the 300 mg injection, no pharmacokinetic studies were found assessing an increase in plasma level from an initial injection without previous administrations of LAI. However, Mallikarjun *et al.*[41] determined figures for C_{ss}, t_{max} and $t_{1/2}$ which are listed in Table 2.

There is a great difference in recorded elimination half-life between 300 and 400 mg doses at 4-weekly steady-state from the above pharmacokinetic studies. This could be due to multiple factors, including differences in particle size of the drug formulations, differences in drug release characteristics and inter-personal biological variation. To
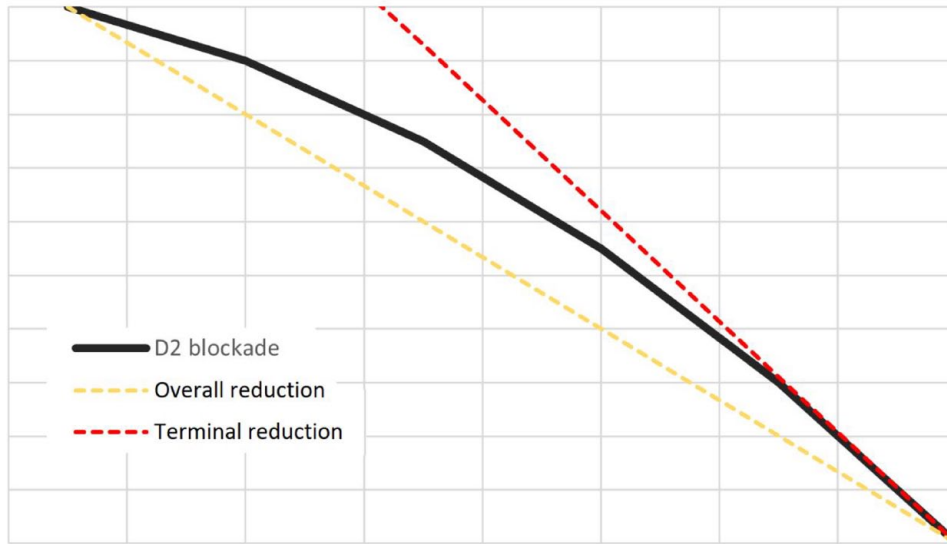
Figure 2. Pictorial representation of how the rate of decreasing D_2 occupancy was assessed, in terms of both overall and terminal reductions.

Table 1. Pharmacokinetics following injection of 400 mg ALAI on top of steady-state plasma levels. Results are displayed as mean (SD) for $C_{max,ss}$, $C_{min,ss}$ and $t_{1/2}$, and in the form of mean (range) for t_{max}.

400 mg steady state	N	$C_{max,ss}$ (ng/ml)	$C_{min,ss}$ (ng/ml)	t_{max} (days)	$t_{1/2}$ (days)
Raoufinia *et al.*[42]	39	328 (133)	239 (133)	3.95 (0–27.9)	ND
Mallikarjun *et al.*[41]	10	316 (160)	212 (113)	7.1 (3–11.2)	46.5 (10.8)
Collated	49	325.5 (137.2)	233.5 (128.5)	4.6 (ND)	46.5 (10.8)

ALAI, aripiprazole long-acting injectable; ND, not determinable.

Table 2. Pharmacokinetic data for injection of 300 mg ALAI. Results are displayed as mean (SD) for $C_{max,ss}$, $C_{min,ss}$ and $t_{1/2}$, and in the form of mean (range) for t_{max}.

300 mg steady state	N	$C_{max,ss}$ (ng/ml)	$C_{min,ss}$ (ng/ml)	t_{max} (days)	$t_{1/2}$ (days)
Mallikarjun *et al.*[41]	8	269 (128)	156 (67.7)	6.5 (0–21.2)	29.9 (8)

ALAI, aripiprazole long-acting injectable; ND, not determinable.

apply a stricter safeguard to the modelling, the shorter half-life determined for the 300 mg cycle was applied for any periods longer than the standard 4-weekly cycle of 400 mg.

Plasma concentrations with doses of oral aripiprazole

Data regarding the relationship between oral aripiprazole dose and plasma concentrations were obtained from a systematic review of five separate studies.[43] However, the lowest aripiprazole dose studied in adults for this sample was 10 mg, and the available trendline did not intercept at zero. The dose of medication and plasma concentrations correlate in a linear fashion for aripiprazole.[43,44] Therefore, to extrapolate corresponding plasma concentrations for doses between 0 and 10 mg, an intercept of zero was added to the trendline and the overall line-of-best-fit was adapted to accommodate this. This resulted in an equation of $d = 12.18c$, where 'd' represents the dose of oral aripiprazole in milligrams, and 'c' represents serum concentrations of aripiprazole in nanograms per

millilitre. This was then compared with data from a study analysing oral doses between 2 and 10 mg,[44] and there was good compatibility ($R^2 = 0.8754$).

Modelling of plasma concentrations

Plasma concentrations were modelled *in silico* using Microsoft Excel software (version 2209, 64-bit). The model was based on a hypothetical patient already established on 400 mg ALAI who had achieved steady-state plasma levels. We explored the effect of alterations to the dose intervals of the depot on overall plasma level over time, using the pharmacokinetic figures derived from the literature. The remaining proportion of the drug at varying lengths of half-lives was obtained using an online free-to-use half-life calculator.[45]

Modelling D_2 dopaminergic receptor occupancy

Receptor occupancy curves follow E_{max} equations, which when applied specifically to occupancy curves are referred to as Michaelis–Menten equations, in the form:

$$\text{Occupancy (\%)} = \frac{E_{max} \star \text{dose}}{\text{dose} + EC_{50}}$$

where E_{max} is the calculated maximal occupancy of receptors, and EC_{50} is the plasma concentration of the drug required to generate 50% of maximal occupancy.[44,46] These characteristics of aripiprazole were obtained from published striatal neuroimaging of aripiprazole using the nuclear imaging ligand [18[F]] fallypride. Point data from these curves were analysed using a least-squares mean difference approach,[47] to derive the best fit E_{max} and EC_{50} for aripiprazole with respect to D_2 occupancy. This yielded figures of 100.208 for E_{max} and 17.24 ng/ml for EC_{50}.

Plasma levels were transformed into the corresponding D_2 occupancy using data derived from pharmacokinetic modelling and the Michaelis–Menten equation.

Determining acceptable rates of D_2 blockade reduction

It is not known what rate of tapering antipsychotics might minimise withdrawal effects or minimise the risk of relapse. However, a recent theoretical paper has suggested reductions of 10 percentage points of D_2 blockade made at intervals form a pharmacologically rational tapering regimen.[13] Another consensus document recommended reductions of 2.5 percentage points of D_2 occupancy every 6–12 weeks, equivalent to a 1–1.5 percentage point reduction every month.[48] Recent papers have also found that antipsychotic dose reductions between 25% and 40% of the most recent dose (so that the size of the reductions becomes smaller and smaller as the total dose is decreased) every 6 months in patients with stable, chronic psychotic disorders do not precipitate relapse for most patients.[29] Such proportionate reductions would roughly equate on average to a 1–2 percentage point decrease in D_2 occupancy per month.

Regimens for oral regimes might be suggested to correspond arbitrarily to 10 (fast), 5 (moderate) and 2.5 (slow) percentage points of D_2 occupancy, producing regimes that would take 9, 18 and 36 months, respectively, if reductions were made each month.[13] However, reductions in ALAI dosage may permit greater reductions in receptor occupancy than reduction in oral medication, as the change in occupancy is spread over a prolonged period due to the greater elimination half-life. This is supported by the observation that, for example, the normal pharmacokinetic variation in D_2 blockade during a 300 mg aripiprazole monohydrate cycle (5.8%/month, see Table 3) is greater than some of the reduction targets outlined above per month.

Due to the more gradual reduction in plasma levels, and subsequently receptor occupancy, produced by reductions in depot dose, we reasoned that the addition of the usual monthly variation in occupancy during stable 400 mg ALAI administration (2.4%/month, see Table 3) to the proposed rates of reduction for the oral medication (2.5, 5 and 10) would be justifiable. This yields approximate rates of change between 5 and 12.5 percentage point reductions in D_2 occupancy per month. We aimed to derive regimens that would correspond to these rates of change using known pharmacokinetic properties.

Results

Examination of abrupt discontinuation of ALAI

As shown in Figure 3(b), the maximal change from abrupt discontinuation of ALAI would occur 3–5 months after the last injection and would lead to a rate of D_2 change of 16.8%/month. This rate

Table 3. Comparison of plasma concentration levels during the steady state for both 300 and 400 mg ALAI, and how this impacts on occupancy of D_2 receptors.

Dosage	T_{max} (days)	C_{max}		C_{min} (day 28)		Duration of C_{max} to C_{min}	Overall rate of D_2 occupancy difference (%/30 days)	Maximal rate of D_2 occupancy difference (%/30 days)
		Plasma concentration (ng/ml)	D_2 occupancy (%)	Plasma concentration (ng/ml)	D_2 occupancy (%)			
300 mg	6.5	269	94.2	156	90.2	21.5	5.5	5.8
400 mg	4.6	325.5	95.2	233.5	93.3	23.4	2.4	2.4
ALAI, aripiprazole long-acting injectable.								

would exceed the fastest arbitrary threshold that we have suggested in this paper (12.5%/month), and therefore abrupt discontinuation of ALAI might produce too rapid a change in D_2 occupancy to avoid an elevated risk of relapse.

Effect of prolongation of inter-dose interval for 400 mg ALAI

Plasma levels during stable administration of 400 mg ALAI 4 weekly were analysed to determine whether the inter-dose interval could be prolonged to reduce overall plasma levels to those of C_{min} levels at 300 mg ALAI steady state (to facilitate transition) and remain within the constraints of D_2 occupancy reduction defined above for different reduction regimens between 5 and 12.5 percentage points. This is demonstrated in Table 4.

Prolonged inter-dose intervals of 400 mg depots produced changes in D_2 occupancy that remained within the arbitrarily imposed constraints outlined above. Allowing an interval of 7 weeks after administration of a 400 mg dose would reduce plasma levels to those of C_{min} for 300 mg steady state (156 ng/ml, Table 3) and produce a maximal reduction rate of D_2 occupancy that approximately equates to the normal pharmacokinetic variation of a 300 mg ALAI cycle. Therefore, for the reduction regimens derived, this was applied universally to convert patients onto 300 mg dosing, due to its minimal impact on D_2 occupancy. It is worth noting that the pharmacokinetic variation experienced between 4-week intervals of 300 mg at steady state (5.7%/month) would be more substantial than the maximal reduction produced by extending the interval for 400 mg to 6 weeks (4.94%/month). This suggests that a 6-week interval following a 400 mg dose at steady-state would be as tolerable to patients as 300 mg ALAI administered stably at 4-week intervals. This arises because changes in plasma levels at lower doses will cause greater changes in D_2 occupancy, due to the hyperbolic pattern of the D_2 occupancy curve.

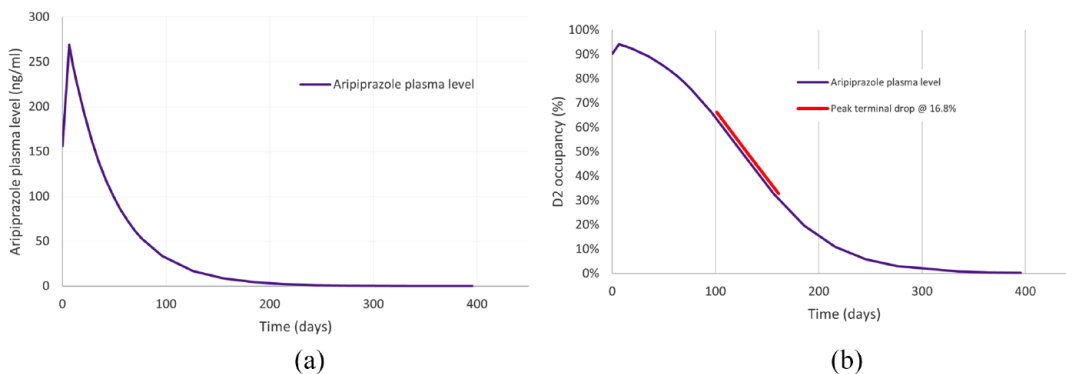

(a)   (b)

Figure 3. Effect of abrupt cessation of a 300 mg ALAI, in terms of both (a) plasma concentration levels and (b) occupancy of D_2 receptors.
ALAI, aripiprazole long-acting injectable.

Table 4. Comparison between varying lengths of inter-dose interval following administration of 400 mg ALAI at steady-state plasma levels.

Time	Plasma concentration (ng/ml)	D_2 occupancy (%)	Overall rate of reduction in D_2 occupancy (%/30 days)	Maximal rate of reduction in D_2 occupancy (%/30 days)
C_{max}	325.5	95.2	–	–
After 4 weeks	233.5	93.3	2.37	2.43
After 5 weeks	205.8	92.5	2.67	3.67
After 6 weeks	176.9	91.3	3.09	4.94
After 7 weeks	151.1	89.9	3.53	5.84
ALAI, aripiprazole long-acting injectable.				

Effect of prolongation of inter-dose interval for 300 mg ALAI

The impact of prolonging the inter-dose interval following a 300 mg dose at a steady state was also investigated, including an examination of the impact that this would have at the D_2 receptor level. This is demonstrated in Table 5.

The figures above demonstrate that the impact of prolonging the inter-dose interval between 300 mg doses leads to far greater reductions in D_2 occupancy than with 400 mg dosing. This is due to receptor occupancy changing more markedly at lower plasma concentrations, and so a longer inter-dose interval may not be tolerable at a lower dose.

Longer inter-dose intervals will also inevitably lead to a greater peak-to-trough ratios. However, C_{max} and C_{min}, and subsequently the peak-to-trough ratio, will eventually reach a steady state after approximately five doses. Prolonged inter-dose intervals will lead to lower C_{max} and C_{min} values than standard 4-week intervals, and lower values of C_{max} and C_{min} will result in greater rates of changing D_2 occupancy as trough levels are approached.

Until steady-state levels are reached, C_{min} values will continue to decrease. As such, a patient who has tolerated a prolonged inter-dose interval for one cycle of depot administration may not be able to tolerate subsequent cycles. However, steady-state levels are achieved in a logarithmic fashion,

Table 5. Comparison between varying lengths of a single inter-dose interval following administration of 300 mg ALAI at steady-state plasma levels.

Time	Plasma concentration (ng/ml)	D_2 occupancy (%)	Overall rate of reduction in D_2 occupancy (%/30 days)	Maximal rate of reduction in D_2 occupancy (%/30 days)
C_{max}	269	94.2	–	–
After 4 weeks	156	90.2	5.49	5.83
After 5 weeks	132.6	88.7	5.78	6.66
After 6 weeks	112.8	86.9	6.13	7.54
After 7 weeks	95.9	84.9	6.52	8.52
After 8 weeks	81.5	82.7	6.94	9.52
ALAI, aripiprazole long-acting injectable.				

meaning that changes in plasma level will become less pronounced with each administration. New steady-state values for C_{min} after five consistent administrations of ALAI are shown in Table 6.

Arbitrary rate thresholds between 5% and 12.5% per month suggest that tolerable 300 mg ALAI intervals permissible would be between 4 weekly and 8 weekly, respectively. Of interest, there are clinical reports of some patients experiencing a worsening of their mental state or withdrawal symptoms as they approach the end of their typical 28-day inter-dose interval. This may indicate a group of patients sensitive to changes in D_2 occupancy of 5.8% who would be least likely to tolerate faster reductions of dose.

Switching to oral medication

If patients are switched to oral medication to continue reductions, clinicians should be mindful of residual drug present in the blood for months after the last administration as it is progressively excreted. This should be accounted for when deciding what oral dose to prescribe as the rate of reduction in residual depot medication will have implications for the rate of D_2 occupancy decline. For example, if a patient is switched onto an oral regime that is reduced by 5% D_2 occupancy monthly, the additional reduction in levels caused by the elimination of the residual LAI will contribute to a much more rapid rate of occupancy reduction. Therefore, any dose of oral medication should be maintained for 3–6 months (approximately 5 half-lives) following a switch from ALAI to accommodate the steady excretion of residual

drug in the system, acting as a partial form of self-tapering. Figure 4 illustrates how maintaining a constant oral dose of medication in combination with naturally reducing residual ALAI medication will produce an approximately steady decline of D_2 occupancy (in this case about 2.5 percentage points per month).

Summary of dose reduction regimens for ALAI

Patients on 400 mg dosing should be able to tolerate a prolongation of the inter-dose interval to 7 weeks duration before administering 300 mg and still be within the constraints of D_2 occupancy imposed as detailed above. The further steps of discontinuation regimes that cohere to these constraints are outlined in Table 7. Regimes have also been demonstrated pictorially in Figure 5, for both plasma levels and D_2 blockade commencing from a steady state of 400 mg ALAI down to full discontinuation.[9]

Application of principles to other LAIs

This paper has focussed solely on aripiprazole monohydrate to explain the principles of discontinuing depots through prolonging inter-dose intervals. LAIs with longer half-lives may have the potential to be reduced further in their current forms before a transition to oral medication is required. Abrupt discontinuation of some LAIs with particularly long half-lives, for example aripiprazole lauroxil[49] and longer preparations of paliperidone palmitate[50,51] may produce maximal rates of D_2 occupancy reduction that are less than the constraints for 'fast' reductions in D_2 occupancy, and may therefore be tolerable.

Table 6. Comparison between the impact on plasma levels and D_2 occupancy following five administrations of 300 mg ALAI at various prolonged inter-dose intervals.

Weeks	Minimum plasma concentration (ng/ml)	D_2 occupancy at C_{min} (%)	Overall rate of reduction in D_2 occupancy (%/30 days)	Maximal rate of reduction in D_2 occupancy (%/30 days)
5	121.8	87.8	5.89	7.12
6	90.8	84.2	7.00	8.84
7	67.9	79.9	8.20	10.71
8	52.9	75.6	9.24	12.39

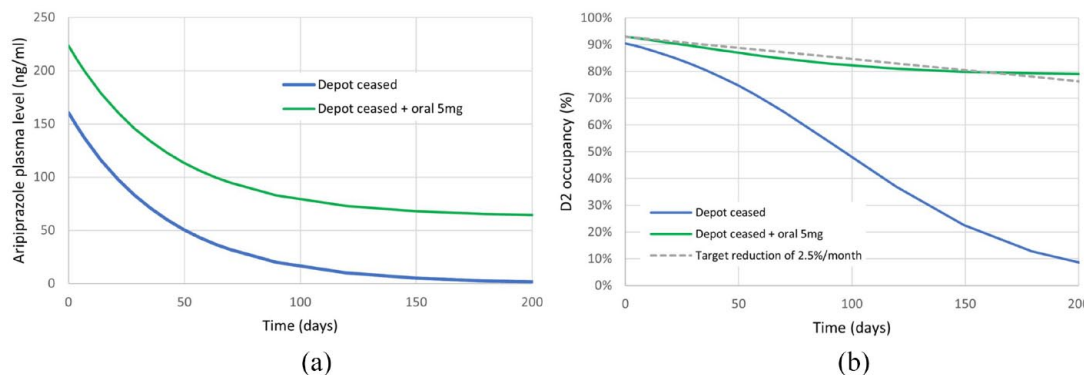ALAI, aripiprazole long-acting injectable.

Figure 4. Pictorial representation of how residual drug from previous ALAI administration affects the choice of dose for subsequent oral medications. This is reflected in both (a) plasma aripiprazole level and (b) the effect on changing D$_2$ occupancy.
ALAI, aripiprazole long-acting injectable.

Table 7. Suggested recommendations for three potential regimes involving prolonging inter-dose intervals for ALAI.

	'Slow' (6% maximal reduction)	'Moderate' (9% maximal reduction)	'Fast' (11% maximal reduction)
Step 1	400 mg 4 weekly	400 mg 4 weekly	400 mg 4 weekly
Step 2	Prolong interval to 7 weeks	Prolong interval to 7 weeks	Prolong interval to 7 weeks
Step 3	300 mg 4 weekly	300 mg 4 weekly	300 mg 4 weekly
Step 4	Continue 4-weekly injections until oral switch appropriate	300 mg 6 weekly	300 mg 7 weekly
Step 5	After 4 weeks (at trough level), commence 5 mg oral aripiprazole daily for 6 months minimum	Continue 6-weekly injections until oral switch appropriate	Continue 7-weekly injections until oral switch appropriate
Step 6	Reduce oral aripiprazole in a hyperbolic fashion corresponding to a 3% D$_2$ occupancy reduction	After 6 weeks (at trough level), commence 2.5 mg oral aripiprazole for 4 months minimum	After 7 weeks (at trough level), commence 1.25 mg oral aripiprazole for 3 months
Step 7		Reduce oral aripiprazole in a hyperbolic fashion corresponding to a 5% D$_2$ occupancy reduction	Reduce oral aripiprazole in a hyperbolic fashion corresponding to a 10% D$_2$ occupancy reduction

ALAI, aripiprazole long-acting injectable.

Summary of pharmacokinetic modelling

We have derived three possible regimens for aripiprazole which allow for cautious reduction in a patient's dose of antipsychotic, which might minimise the risk of withdrawal effects and relapse by adhering to different arbitrary rates of D$_2$ blockade reduction over time. These regimens could potentially be used for both patients who will switch to oral medication to make further reductions or to reduce the dose of a depot to the smallest possible dose in patients for whom oral medication may not be an appropriate option.

The overarching principle was to develop regimens that did not produce too rapid a reduction in D$_2$ occupancy to the minimise risk of withdrawal effects or excessive destabilisation leading to relapse. Given a lack of definitive studies on what rate of reduction is tolerable, the three devised regimens correspond to reductions that cohere to arbitrary constraints for oral doses which have been adjusted to allow for the self-tapering characteristics of depots. This is because the change in occupancy will be spread over a longer period than when reductions are made for oral medication.
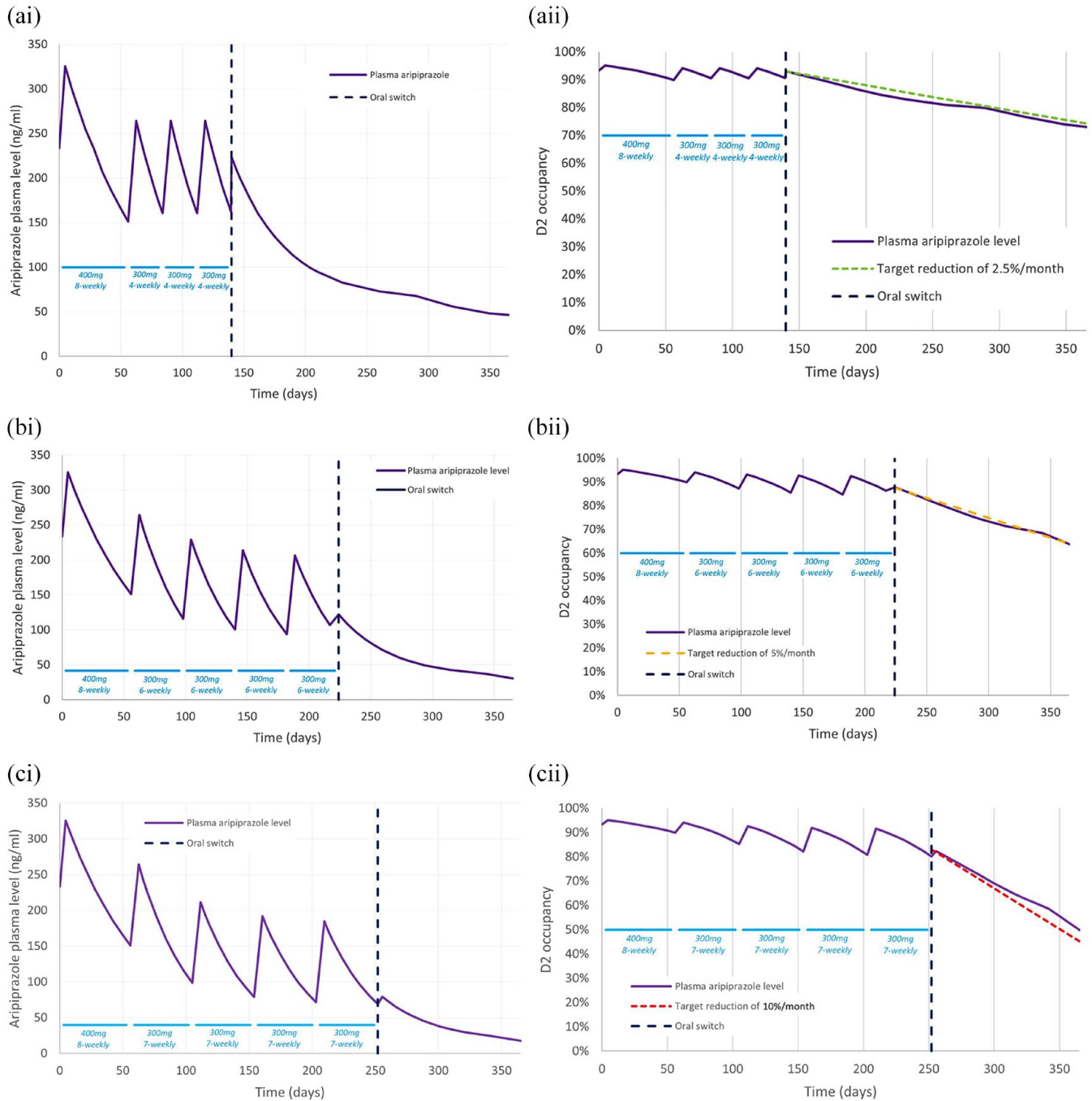
Figure 5. Pictorial representations of how the proposed (a) 'slow', (b) 'moderate' and (c) 'fast' regimes would affect both (i) plasma aripiprazole level and (ii) D_2 receptor occupancy.

Abrupt stopping of depot medication

An important observation was that, although abrupt stopping of antipsychotics seems intuitively an appealing approach to gradual tapering,[27,28] the rate of D_2 occupancy reduction was larger than hypothesised maximum limits. It may therefore be advisable to reduce antipsychotic depots more gradually than abrupt stoppage. The above regimes offer potential solutions to tailor the dosage to individual patients, which might both

reduce the impact that antipsychotic medication can have on wider physical health[18–21,52] and also reduce the demands on healthcare professionals administering LAIs,[32] whilst potentially minimising the disruption caused by withdrawal effects or destabilising patients' mental states. Many studies examining the relapse prevention properties of antipsychotics have utilised abrupt stoppage of antipsychotic depots.[5,18] It is therefore possible that these studies may have produced unfavourable outcomes in the discontinuation arms because of excessively rapid reduction in antipsychotics, possibly causing withdrawal symptoms, therefore potentially exaggerating the relapse prevention properties of antipsychotics.[27]

Switching to oral medication

At lower plasma concentration levels, utilising depot medication alone does not offer appropriate control over plasma levels; this would result in marked variation in D_2 occupancy, greater than the determined maximal limits, which might lead to withdrawal symptoms and an increased risk of precipitating relapse. Therefore, for all proposed ALAI regimes, it is recommended that a switch to oral medication takes place to fully discontinue the medication.

From the point of switching to oral medication, the pre-existing level of residual aripiprazole from the ALAI should be considered. As a result, a much lower oral dose is required than what is accepted as the oral equivalent dose to convert to 300 mg ALAI. Due to the tapering effect of the residual depot being eliminated from the system acting concurrently with oral medication, the dose of oral medication should remain the same until the residual depot is sufficiently eliminated. From this point, for those patients appropriate to further reduce or discontinue medication, the oral aripiprazole dose could be progressively decreased in a hyperbolic fashion.[13]

Limitations

The main limitation of this modelling is that these regimes are based on arbitrary rates of decreasing D_2 occupancy based on theoretical reasoning and therefore have not yet been assessed in terms of clinical response or efficacy. These have been informed by some empirical studies[29,30] but should be seen as preliminary. These regimens could be tested in cohort studies or randomised trials seeking to minimise

withdrawal effects or relapse in people coming off antipsychotics, including plasma testing of antipsychotic levels. This may allow for further tailoring of regimes using real-world data. To truly gauge the wider impact that this regime would have on service users, such studies should account not only for psychiatric symptomatology and relapse rates but also for overall quality of life and adverse physical effects.

Another limitation of this modelling is that pharmacokinetic data were not available for initial 300 mg injections with no pre-existing serum drug. It is likely that the increase in plasma levels following a 300 mg dose would be more substantial at lower pre-existing plasma concentrations, as this was observed with 400 mg doses.[42] This could lead to a greater difference between $C_{max,ss}$ and $C_{min,ss}$ with longer inter-dose intervals. However, if this were the case, then the actual steady-state levels would be higher than the modelling has predicted and therefore have a reduced maximal reduction at $C_{min,ss}$. Therefore, the proposed regimes would, if anything, be more conservative.

Another limitation is that there are great interpersonal differences in pharmacokinetic response. We have modelled average data, but exact plasma level figures will vary widely for different patients. This could explain the varying tolerability of discontinuation for different patients. This also suggests that the best guide for any reduction regimen is a patient's symptoms which should take preference over strict adherence to the regimens we have outlined.

Notably, aripiprazole differs from other conventional antipsychotics in that aripiprazole is a partial D_2 agonist rather than an antagonist.[53,54] It has not been possible to reflect this different mechanism of action for aripiprazole, and the model has purely looked at D_2 occupancy rather than the resultant clinical effect through receptor affinity and strength of binding.[55] As a result of this differing mechanism of action, the inter-dose interval regimes suggested here may not be applicable to other psychotropics without further clinical analysis. Nevertheless, the literature suggests that the principles of steady reductions in dose, and therefore D_2 occupancy, might apply to all psychotropics.[13,53] Clinicians should closely monitor and supervise patients undergoing dose reductions to detect and account for any withdrawal symptoms.

Conclusion

In summary, this model suggests a novel use of LAIs by extending the interval between their dosing to implement dose reduction whilst observing the principles of gradual hyperbolic reduction outlined previously. The advantages of this approach are potentially multiple, including less frequent injections for service users, a progressive reduction in the physical health burden that antipsychotics can have on patients and allowing for greater clinician control and adaptability with a medicinal product that has previously been rigid in its dosing and frequency. This analysis also has suggested that abrupt stoppage of most LAI preparations, although generally considered to produce gradual tapering of antipsychotics, may produce a rate of reduction in D_2 blockade too great for many patients and a more gradual method of stopping may produce better outcomes. Lastly, this analysis suggests that when LAIs are converted to oral medications in the process of a supported reduction, the dose of oral medication required is far less than in the opposite conversion of oral medication to depot because of the presence of residual LAI for long periods.

Declarations

Ethics approval and consent for participate
This project did not involve any individual patient data, and as such did not require ethical approval or consent for publication.

Consent for publication
Not applicable.

Author contributions
James R. O'Neill: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft.

David M. Taylor: Conceptualization; Writing – review & editing.

Mark A. Horowitz: Conceptualization; Formal analysis; Supervision; Writing – review & editing.

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Availability of data and materials
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