

A Method for Tapering Antipsychotic Treatment That May Minimize the Risk of Relapse

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The process of stopping antipsychotics may be causally related to relapse, potentially linked to neuroadaptations that persist after cessation, including dopaminergic hypersensitivity. Therefore, the risk of relapse on cessation of antipsychotics may be minimized by more gradual tapering. There is converging evidence that suggests that adaptations to antipsychotic exposure can persist for months or years after stopping the medication—from animal studies, observation of tardive dyskinesia in patients, and the clustering of relapses in this time period after the cessation of antipsychotics. Furthermore, PET imaging demonstrates a hyperbolic relationship between doses of antipsychotic and D₂ receptor blockade. We, therefore, suggest that when antipsychotics are reduced, it should be done gradually (over months or years) and in a hyperbolic manner (to reduce D₂ blockade “evenly”): ie, reducing by one quarter (or one half) of the most recent dose of antipsychotic, equivalent approximately to a reduction of 5 (or 10) percentage points of its D₂ blockade, sequentially (so that reductions become smaller and smaller in size as total dose decreases), at intervals of 3–6 months, titrated to individual tolerance. Some patients may prefer to taper at 10% or less of their most recent dose each month. This process might allow underlying adaptations time to resolve, possibly reducing the risk of relapse on discontinuation. Final doses before complete cessation may need to be as small as 1/40th a therapeutic dose to prevent a large decrease in D₂ blockade when stopped. This proposal should be tested in randomized controlled trials.

Keywords: discontinuation/withdrawal/schizophrenia/D2 occupancy/hyperbolic/dopaminergic hypersensitivity

Introduction

In an era of waning paternalism and shared decision-making, patient preference is increasingly emphasized. In practice, this preference often includes requests to reduce or stop antipsychotic medication from people with psychotic disorders.¹ Indeed, patients often do stop their medication abruptly,² and they may be more likely to do so when their preferences are not considered by their physicians.¹ Abruptly stopping antipsychotic medication is the method most likely to induce relapse and withdrawal symptoms.^{3,4}

These concepts are germane to the broader context of the practice of deprescribing in medicine, as part of high-quality prescribing practice, aiming for an optimal balance of benefits and harms in the use of medication. The practice originally derives from geriatric medicine, with its concerns around polypharmacy and the uncertain balance between risks and benefits in drugs prescribed over many years; some of these concerns are relevant to psychiatric practice.

Although evidence for the benefits of antipsychotic medication in short-term treatment is established,⁵ there is an ongoing debate about the need for and benefit of prophylactic long-term antipsychotics in every person with schizophrenia.^{6,7} In the context of adverse effects of long-term antipsychotic medication (movement disorders, such as tardive dyskinesia (TD), metabolic effects, and effects on brain structure)^{6,8,9} and, importantly, patient preference,¹⁰ it may be reasonable to attempt reduction or cessation of antipsychotics in people with nonaffective psychotic illnesses who have remitted after treatment,⁶ guided by psychiatrists. There is currently

significant uncertainty about what proportion of patients might be able to stay well without antipsychotics, with numerous antipsychotic discontinuation studies in progress, but some suggest it may be up to 40%.^{6,11} It has been proposed that patients on long-term antipsychotics could have them carefully reduced to minimum effective doses, which for some might be zero, without negatively affecting clinical outcome and potentially improving social functioning in some patients.^{6,12} Importantly, when asked, patients often prioritize social functioning over symptom reduction.¹³ Here, we explore what is known about reducing and discontinuing antipsychotics, including withdrawal syndromes, and put forward some principles for reducing and discontinuing antipsychotics in a manner that minimizes the risk of relapse.

Withdrawal Syndromes

Withdrawal syndromes occur with many medications,^{14,15} including all classes of psychotropics.^{16–20} Indeed, withdrawal syndromes are so common that it has been said that drug discontinuation effects are a predictable aspect of the pharmacology of any drug that is eliminated more quickly than the time taken for established adaptations to the drug to resolve.¹⁵

Receptor antagonists reduce the activation of target receptors and, as a result, receptors may be upregulated (increased in sensitivity and/or number).²¹ When the antagonist is abruptly withdrawn, physiological levels of the receptor’s ligand can cause overstimulation of the sensitized receptors, leading to withdrawal or rebound symptoms.^{22,23} For example, abrupt removal of beta-blockers can cause adrenergic rebound, characterized by increased

blood pressure and heart rate, anxiety, headache, and even myocardial infarction.²⁴

Antipsychotic Withdrawal Syndrome

Although not widely recognized, withdrawal symptoms can occur on the cessation of both first- and second-generation antipsychotics (FGAs and SGAs).^{17,20,23} These symptoms can be grouped into somatic symptoms (nausea, sweating, etc.), motor symptoms, and psychological symptoms (including psychosis; **figure 1**).^{17,20,23}

Autonomic and somatic symptoms that occur on cessation generally start within days of dose reduction and resolve within weeks.^{23,25,26} They are attributed to the abrupt removal of the antagonistic cholinergic, adrenergic, serotonergic, and histaminergic effects of antipsychotics.^{17,20} For example, after only 4 weeks of clozapine treatment, 13% of patients stopping the drug abruptly experienced moderate to severe symptoms of nausea, vomiting, and diarrhea, with 40% experiencing mild symptoms.²⁷ These symptoms have been attributed to cholinergic rebound following the induction of cholinergic hypersensitivity during clozapine treatment.²⁷ Notably, the cholinergic rebound can also be characterized by agitation, fear, and hallucinations, which may be mistaken for psychotic relapse.²⁰

Motor symptoms occur most commonly with the withdrawal of FGAs but also with SGAs^{17,20} and consist of dyskinesia, parkinsonism, and neuroleptic malignant syndrome (NMS). Symptoms develop over weeks following withdrawal and can persist for months or longer.^{23,28} Motor withdrawal symptoms have a reported incidence of 31%–50% after abrupt FGA

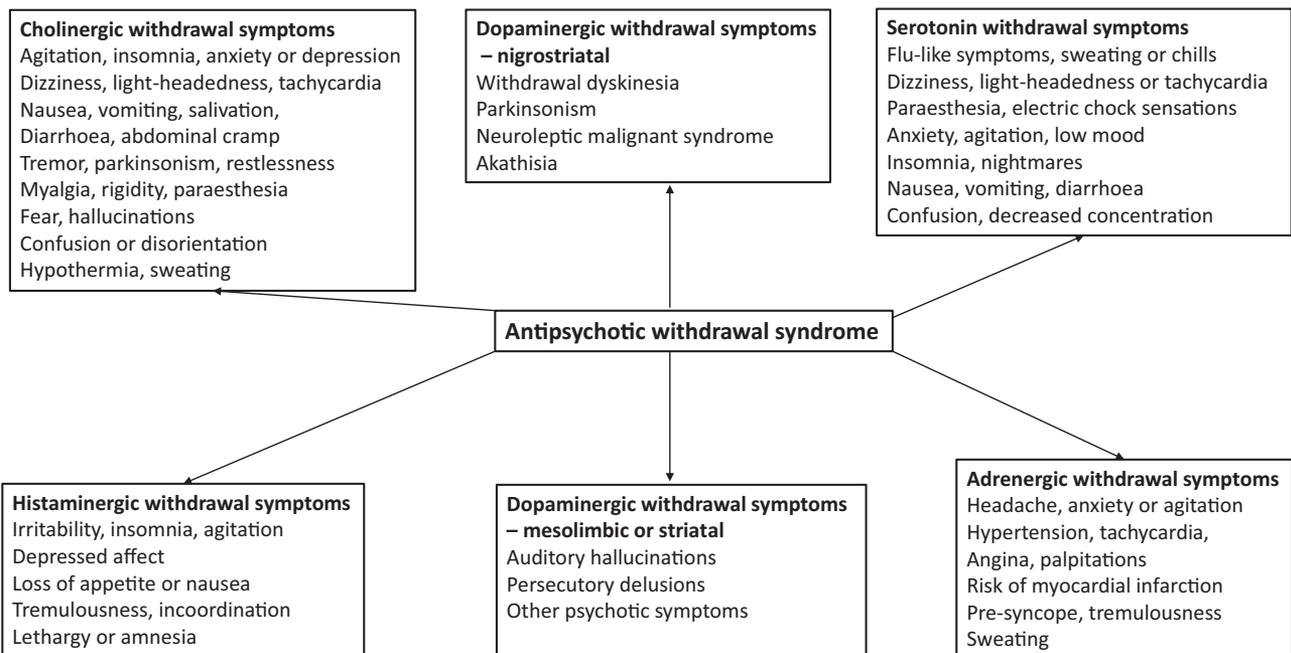


Fig. 1. Symptoms of the antipsychotic withdrawal syndrome, adapted from Chouinard et al.²³

withdrawal, following long-term treatment.^{29–31} SGAs, including risperidone³² and aripiprazole,³² can also be associated with dyskinesia upon cessation, but no formal studies looking at incidence rates have been conducted. NMS has been noted to occur on the abrupt withdrawal of antipsychotics, particularly clozapine,³³ although no systematic study of incidence has been performed.

Neurobiology of Antipsychotic Withdrawal Syndrome

Motor withdrawal effects have been attributed to dopaminergic hypersensitivity arising in nigrostriatal pathways caused by antipsychotic treatment.^{17,34} When antipsychotics are abruptly withdrawn, sensitized dopamine receptors are exposed to physiological levels of dopamine, which could cause increased striatal dopaminergic activity.^{20,34} Withdrawal dyskinesia has been interpreted as evidence of an intermediate form of dopaminergic hypersensitivity, unmasked by the removal of dopaminergic antagonists, as compared with TD where hypersensitivity is present to a degree evident even during treatment.²³

In animals, dopaminergic blockade leads to dopaminergic hypersensitivity.^{35,36} In one study, the administration of antipsychotics for 2 weeks gave rise to dopaminergic hypersensitivity in rats, as evidenced by the waning ability of antipsychotics to suppress amphetamine-induced behavioral effects.³⁵ D₂ receptor number also increased 20%–40%, alongside a 2- to 3-fold increase in highly sensitive dopamine receptors.³⁵ In another study in rats, 9 months of haloperidol led to a 2- to 3-fold increase in D₂ receptors.³⁶ Receptor numbers stayed high (and even increased) over the 2 months following haloperidol withdrawal.³⁶ This time period in rats has been suggested to be equivalent to more than a year for humans.³⁷

There is also evidence that dopaminergic hypersensitivity occurs in humans. Meta-analysis of molecular imaging studies in schizophrenia found increased D₂/D₃ receptor availability only in those subjects who had been exposed to antipsychotic medication but not in antipsychotic-naïve patients.³⁸ One study quantified this increase as 30% relative to antipsychotic-naïve patients.³⁹ Longitudinal studies confirm this effect: one patient demonstrated a 10% increase in D₂/D₃ receptor availability over 2 months when treated with very large doses of chlorpromazine⁴⁰; another study demonstrated an increase in D₂/D₃ receptor availability in some brain regions after 2–3 weeks of treatment with low-dose antipsychotics.⁴¹

Withdrawal-Associated Psychosis

Dopaminergic hypersensitivity has been proposed to contribute to early relapse into psychosis after antipsychotic cessation.²³ Dopaminergic hypersensitivity observed in nigrostriatal pathways may also be present in

other dopaminergic pathways,^{23,42} including the associative striatal pathways, now centrally implicated in schizophrenia.⁴³

People with no history of psychosis who develop psychotic symptoms on abrupt cessation of dopamine antagonists used in a non-psychiatric context (eg, breast milk stimulation or treatment of nausea) provide support for this hypothesis (table 1). Eight case reports describe psychotic symptoms arising in 13 patients with no history of psychosis after the abrupt withdrawal of dopamine antagonists (table 1). These cases manifested cardinal symptoms of psychosis, such as auditory hallucinations, persecutory, nihilistic, and Capgras delusions, and, in some instances, were only terminated by the re-introduction of a dopamine antagonist.^{44,45} In one case, the dopamine antagonist was not recommenced and symptoms persisted for 10 months⁴⁶: the same duration as the initial treatment course. These cases have been attributed to dopaminergic hypersensitivity,⁴⁷ although, of course, they represent a tiny fraction of those non-psychotic individuals treated with dopamine antagonists. However, Seeman suggests that such reactions may be underreported.⁴⁶ These observations are consistent with reports that the severity of psychotic psychopathology following clozapine withdrawal exceeded that in the illness before clozapine treatment.^{48,49}

Schizophrenia is attributed to increased presynaptic dopaminergic synthesizing capacity (DSC)⁵⁴; a recent study found that treatment with antipsychotics does not appear to alter DSC.⁵⁵ However, the effects of D₂ blockade may result in what starts as a presynaptic disorder being complicated and amplified by antipsychotic-induced postsynaptic effects. Upon the removal of blockade, persistently increased baseline presynaptic DSC in patients with schizophrenia may interact with elevated postsynaptic sensitivity to increase the likelihood of relapse.^{7,23}

Withdrawal-Associated Psychosis in Patients With Schizophrenia

Distinguishing withdrawal-associated relapse from the endogenous relapse of a psychotic illness is difficult.⁷ Withdrawal-associated relapse has been thought to be characterized by early onset following the elimination of medication^{7,15} and association with other evidence of withdrawal, including motor symptoms.^{7,20,23}

The strongest evidence for the existence of withdrawal-associated relapse is the preponderance of relapses that occur in the weeks and months following cessation.^{3,56–59} That is, relapses are not distributed evenly across time but tend to occur predominantly around the point of drug cessation. This is distinct from the natural history of the disease in which relapses in people with schizophrenia are evenly distributed across time, as seen in the early Northwick Park studies, which examined people with schizophrenia

Table 1. Case studies reporting psychotic symptoms following abrupt cessation of dopamine antagonists prescribed for reasons other than treating psychosis in patients with no history of primary psychotic symptoms

Study	Subject	Drug dose and duration	Description of psychopathology following the cessation of medication
Kent and Wilber ⁵⁰	Woman with no psychiatric history	Reserpine (dopamine depleting agent) for hypertension for 20 years	Euphoric, visual hallucinations, hyperactivity, and pressured speech Only extinguished by recommencement of reserpine
Witschy et al ⁵¹	26 M BPAD with brief DIP and no other psychotic symptoms	Fluphenazine for acute drug-induced psychosis	Paranoia, disconnected thoughts, and sense of personal disintegration Distinct from any previous experience Extinguished on recommencement of fluphenazine (did not reoccur when medication was tapered over several months)
Steiner et al ⁵²	5 pts with BPAD with no psychotic symptoms	First-generation anti-psychotics used as mood stabilisers for 2–8 years	Paranoid delusions, auditory, and visual hallucinations Irritability, insomnia, dysphoria, and poor concentration None of these symptoms had been present prior to AP use
Lu et al ⁴⁷	2 men with no psychiatric history	Metoclopramide for gastro-intestinal complaints for 3–6 months	Auditory hallucinations, persecutory delusions, ideas of reference, 12h and 3 days after abrupt cessation
Roy-Desruisseaux et al ⁴⁴	Elderly woman, with dementia but no mental health history	Domperidone for gastroesophageal reflux disorder for 10 years	Capgras and persecutory delusions, disorganized thought form, suicidal (no evidence of delirium) Responded to risperidone
Jacob et al ⁴⁵	17 F with depression and emotional dysregulation but no history of psychotic symptoms	Ziprasidone for emotional dysregulation for 2 years	Pt experienced visual and tactile (“bugs crawling” on her) hallucinations after she ran out of her prescription. Symptoms resolved within 24 h of recommencing ziprasidone
Bastiampillai et al ⁵³	28 M with moderate intellectual impairment but no history of psychotic symptoms	Thioridazine for behavioural management for 15 years	When thioridazine was switched to risperidone, pt experienced persecutory delusions and auditory hallucinations for the first time in his life
Seeman ⁴⁶	Woman, lawyer, no psychiatric history	Domperidone for breast milk stimulation for 10 months	Akathisia, severe anxiety, depression, nihilistic delusions (“putrefying inside”); cognitive and memory problems Disorganized in behavior, amotivated, suicidal

AP, antipsychotic; BPAD, bipolar affective disorder; DIP, drug-induced psychosis; F, female; M, male.

treated with placebo (thereby revealing the natural history of the disease), in which a similar proportion of patients relapsed each month.⁶⁰ This pattern is understandable because there should be no systematic correlation between the times at which different patients relapse.

Some have suggested that the reason that relapse rates are higher in the first few months following drug cessation, and then gradually reduce, is because there are fewer patients “available” to relapse as time goes on because they have already relapsed. However, the marked increase in relapse rates that occur following drug discontinuation cannot be explained by simple attrition of patients over time: the clustering of relapses around the point of discontinuation is of a much larger magnitude. For example, in the 2 studies with more than 2 years follow-up after treatment discontinuation, one found 43% of the original cohort of patients relapsed in the first year, 21.5% in the second year, and just 3.7% a year in each of the 5 years following^{57,61}; the other found that 56.5% of patients relapsed in the first year (41.3% in the first 6 months), 8.7% in the second year, and 2.2% per year thereafter.⁵⁸ This rebound pattern is evident in other discontinuation trials^{59,62,63} and is not consistent with simply attrition over time.

Meta-analyses also support this apparent “rebound” effect.^{3,56,64} One reported that 48% of relapses occur in the first 12 months after antipsychotic discontinuation (40% in the first 6 months), with only 2% per year after this.³ Meta-regression found that relapse rates for maintained and discontinued patients converge at 3 years after discontinuation, though higher in discontinued patients before that point.⁵⁶ It appears that relapse rates are raised in the discontinuation group for 1–3 years following a switch to placebo, before converging with relapse rates of medicated patients thereafter.^{3,56–59}

This period of increased relapse following antipsychotic cessation may be due in part to the effect of withdrawal-associated relapse. This temporary increase in relapse rate has been referred to as a “rebound” effect and is consistent with the concept of neuroadaptations that take months or years to resolve following discontinuation; these may increase the susceptibility to relapse during this period by exaggerating the increased sensitivity to life events and other triggers, hypothesized as the pathogenic mechanism for psychotic illness.^{6,23} Persisting neuroadaptation may lower the threshold for psychosis but only give rise to relapse in the context of relevant triggers, explaining why

not all relapses occur straight after drug discontinuation but may be increased for the period of time for which the neuroadaptations persist. This time period of 1–3 years is consistent with the period of time for which TD can persist, as outlined below.

This pattern of early relapse, consistent with withdrawal-related effects from discontinuation, is not restricted to antipsychotics but also evident for antidepressants in anxiety,⁶⁵ as well as lithium and other mood stabilizers in bipolar affective disorder (BPAD),^{18,66} also persisting for months.^{18,65,66} On the cessation of lithium in BPAD, in patients with a mean cycle length (average period of euthymia between episodes) before treatment of 11.6 months, the time to a new episode following the abrupt cessation of lithium therapy was just 1.7 months.⁶⁶

Pharmacological Characteristics of Antipsychotic Withdrawal

There is evidence that patients with longer exposure to antipsychotics are more likely to have psychosis on withdrawal. One study, using a nationwide cohort, found a striking relationship between the length of antipsychotic treatment and the risk of relapse on discontinuation.⁶⁷ While patients who discontinued antipsychotic treatment soon after their first discharge had a small increased risk of relapse, this risk increased with the length of time patients had taken antipsychotics: the risk doubled after 1–2 years of exposure, tripled after 2–5 years of exposure, and increased 7 times after 8 years of antipsychotic exposure.⁶⁷ It has been suggested that this finding might be explained by the patients with more severe conditions being treated for longer—however, there is no clear consensus on what constitutes a reliable measure of “severity,” and, certainly, symptom scores do not predict the risk of relapse.⁶⁸ However, another paper found that longer treatment was associated with a smaller risk of relapse, after controlling for a wide variety of demographic and clinical variables, although the relapse rates of 2%–5% per year in these patients were unusually low, making extrapolation to other populations difficult.⁶⁹ Furthermore, patients who demonstrate greater evidence of tolerance to antipsychotics (increasing dose requirements, the development of treatment resistance, or TD) are more likely to have withdrawal psychosis.²³

Tapering Antipsychotics

Standard guidelines do not mention antipsychotic deprescribing,⁷⁰ or tapering,⁷¹ although some current guidelines encourage reduction to minimum effective doses without specifying how to do so.^{72,73} The principal means to mitigate withdrawal symptoms is to reduce the rate at which the equilibrium is disturbed, so allowing time for the reversal of underlying neuroadaptations to return to baseline.^{16,70,74} Gradual tapering of antipsychotics,

when cessation is the goal, is sometimes advised on this principle.^{56,70,74} Tapering may reduce the likelihood and intensity of withdrawal symptoms, including, potentially, the risk of withdrawal psychosis.^{70,74}

The persistence of TD, the most visible manifestation of dopaminergic hypersensitivity,⁷⁵ for a considerable time following cessation of antipsychotics, provides evidence that neuro-adaptations to antipsychotics persist for many years and supports the need for long tapering. An early review of studies found that it took 2–5 years for 60%–90% of symptoms of TD to resolve following antipsychotic cessation ([supplementary table S1](#)).⁷⁶ Another study found that 92.8% of patients achieved a 50% reduction in TD symptoms 46 weeks after discontinuing on average 10 years of antipsychotic treatment.⁷⁷ A more recent study examined patients with 1 year of TD in whom dopamine antagonists (including metoclopramide) were ceased after 5 years of exposure⁷⁴: in 13% of the patients, symptoms resolved completely (taking 2–4 years, average 2.3), and the number defined as moderate or severe decreased from 63% to less than 20%.⁷⁸ This suggests that TD (along with, presumably, dopaminergic hypersensitivity) can resolve when antipsychotics are discontinued but this process might, in some cases, take years^{75,76} and may be irreversible in some patients.⁷⁵

Tapering periods probably need to be similarly prolonged to minimize the risk of psychotic relapse in people who have been on these medications long term. This is consistent with the finding that relapse rates for discontinued patients tend to match those of maintained patients but only after 1–3 years.^{56,57,64} Prolonged tapering is not unreasonable given the duration of antipsychotic treatment in many patients, the long persistence of adaptations to antipsychotics in animals to antipsychotics,^{6,79} and the evidence that withdrawal from other medications like selective serotonin reuptake inhibitors (SSRIs) can be prolonged, lasting for months or years^{80,81} with months-long tapering most effective in minimizing withdrawal symptoms in some people.⁸²

Evidence for Prolonged Tapering

There is evidence to support the notion that longer tapering periods may lead to lower relapse rates compared with more rapid tapering periods.^{3,4,57,74,83,84} A meta-analysis of studies examining relapse comparing abrupt discontinuation with “gradual” discontinuation (average period of 4 weeks) found no significant benefits for this “gradual” discontinuation over abrupt cessation.⁵⁶ However, 4 weeks is a brief period and a more recent meta-analysis finds an inverse dose response between the duration of discontinuation and the rate of relapse over the next year: abrupt stopping led to relapse in 77% of patients; stopping over 1–2 weeks to relapse in 57%; 3–10 weeks to 47%; and stopping over longer than 10 weeks led to a relapse rate of 31%.⁴

Recent systematic reviews^{83,84} have included 10 tapering studies ($n = 1040$) with maintenance arms in people with first-episode psychosis (FEP), with one further study looking at a group with longer-term illness⁷⁴ (table 2). The discontinuation group showed more relapses than the maintenance group^{83,84} in all but 3 studies examined.^{57,74,85} These 3 studies were distinguished by either the longer length of their tapering process⁸⁵ or the longer length of their follow-up period,⁵⁷ or both⁷⁴ (however, this last study was not randomized, meaning selection bias is possible).

One of these studies was in people with FEP with a tapering period of 10–40 weeks and found no significant difference in relapse rates between withdrawn patients and patients who were maintained on antipsychotics.⁸⁵ Tapering over months and years (by 25%–30% reductions of original dose every 3 months) also demonstrated no significant difference in relapse rates between patients who continued or discontinued antipsychotics.⁷⁴

The final dose of medication before complete cessation may also be a predictor of relapse because it might represent a large “step down” in dopaminergic (or other target) blockade (table 2).¹⁶ However, this is a difficult value to establish, with most authors reporting that they used

either the smallest available tablet or half that value^{86,87} or that this value was not recorded.^{57,58}

Dose-Response Studies of Antipsychotics

The relationship between antipsychotic dose and effect at receptor targets may also be informative for tapering. Positron emission tomography (PET) studies demonstrate hyperbolic relationships between doses (or plasma level) of antipsychotic and D₂ receptor occupancy (figure 2).^{91,92} This relationship is typical of bimolecular interactions (one receptor and one ligand) that follow the law of mass action and is widely applicable to many medications and their receptor targets.⁹³ The nature of this relationship is often obscured by the habit of plotting dose-response curves on semi-logarithmic axes, giving the appearance of a linear relationship at intermediate doses.⁹³ Systems obeying these dynamics are described by E_{max} equations of the form $y = \text{maximal occupancy} \times x / (x + \text{ED}_{50})$ ⁹³ ($y =$ percentage receptor occupancy, $x =$ dose, $\text{ED}_{50} =$ dose required to achieve 50% of maximum occupancy of receptor target), which are used as lines of best fit in the graphs displayed and allow the calculation of receptor occupancy for given dosage.⁹¹

Table 2 Randomized controlled trials examining discontinuation (DS) groups vs maintained (MT) groups (n.s. = no significant difference; N/A = not available)

Study	Subjects	Tapering period (weeks)	Lowest dose before complete cessation (haloperidol equivalent mg*)	Follow-up period (years)	Difference in DS relapse rate c/w MT (absolute)
Kane et al ⁸⁸	28; MT = 11 DS = 17	0 (some IM)	5–20	1	41%
Crow et al ⁸⁹	120; MT = 54 DS = 66	4	> 1.5	2	18%
McCreadie et al ⁹⁰	15; MT = 8 DS = 7	0	18.8	1	57%
Wunderink et al ⁶¹	103; MT = 51 DS = 52	“tapering guided by symptom severity and patients’ preferences”	N/A	2	22%
Chen et al ⁵⁹	178; MT = 89 DS = 89	4–6	2.5mg	1	33%
Boonstra et al ⁸⁶	20; MT = 9 DS = 11	6–12	1-3mg	2	46%
Gaebel et al ⁸⁷	44; MT = 23 DS = 21	3–17 (median 10)	1mg	1	19%
Wunderink et al ⁵⁷	103; MT = 51 DS = 52	“tapering guided by symptom severity and patient’s preference”	N/A	7	–7.1%
Landolt et al ⁸⁵	325; MT = 274 DS = 51	10–40 (median 23.6)	N/A	1	0.6%
Mayoral-van Son ⁵⁸	46; MT = 24 DS = 22	Physician’s discretion	N/A	3	35.6%
Steingard 2018 ⁷⁴	58; MT = 26 DS = 32	Months/years	N/A	5	15.1% (n.s.)

*Dose equivalent calculated using Maudsley Prescribing Guidelines.⁷³

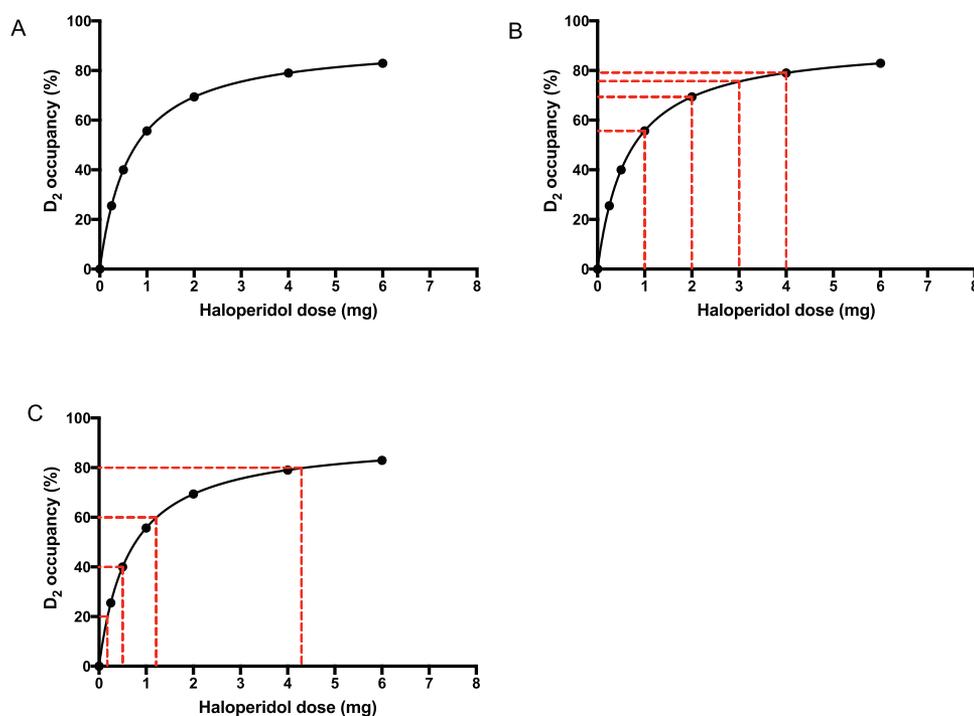


Fig. 2. The effect of linear or hyperbolic reductions of dose of antipsychotic on D₂ receptor occupancy. (A) Relationship between haloperidol dose and D₂ dopaminergic receptor occupancy (%) on PET, adapted from the equation for the line of best fit in Lako et al.⁹¹ (B) Linear dose reductions of haloperidol produce hyperbolically increasing changes in D₂ occupancy, with the largest decrease of 55.7 percentage points of D₂ occupancy occurring when the dose is reduced from 1 mg to 0. (C) Hyperbolically decreasing doses of haloperidol correspond to linear reductions in D₂ dopaminergic occupancy (in this case, intervals of 20 percentage points of D₂ occupancy). The doses in this case correspond to 4.4 mg (80% D₂ occupancy), 1.2 mg (60% D₂ occupancy), 0.50 mg (40% D₂ occupancy), and 0.18 mg (20% D₂ occupancy).

Taking the example of haloperidol (figure 2 and table 3a),⁹¹ it is notable that linear dose reductions from therapeutic doses of 4 mg produce increasingly large reductions in percentage points of D₂ dopamine antagonism: 3.5 percentage points (4 to 3 mg), 6.1 percentage points (3 to 2 mg), 13.7 percentage points (2 to 1 mg), and 55.7 percentage points (1 to 0 mg; figure 2b and table 3a). It is, therefore, likely that discontinuation studies employing linear dose reductions,^{74,83,84,86,87} as recommended in some older guidelines,⁹⁴ will be more likely to induce withdrawal reactions (including, potentially, withdrawal psychosis) because reductions in D₂ antagonism become increasingly large, causing greater likelihood of dopaminergic rebound.

Indeed, even reductions from 0.5 mg of haloperidol (the smallest available tablet) to 0 mg will produce a reduction in D₂ antagonism of 40.0 percentage points, and reduction from 0.25 mg (half the smallest tablet) to 0 mg will produce a 25.5 percentage point reduction (larger than the change from 20 to 2 mg [19.6 percentage points]); this may account for the relative ease of reductions at higher doses of antipsychotic and the difficulties in tapering at lower doses.^{45,51,74} In one recent study, there was no significant increase in relapse rate when patients reduced their dose by 40%⁹⁵ compared with the significant chance of early relapse when patients discontinue

their entire dose.⁵⁶ When interpreting PET data, it should be noted that there is a degree of individual variability in D₂ receptor binding and response across studies.⁹⁶

In this context, it is notable that a handful of studies have suggested that low doses of medication are effective in maintaining patients with psychotic disorders. For example, very low doses of depot antipsychotic (2.5–10 mg of fluphenazine decanoate every 2 weeks) were as effective in preventing a relapse as the standard recommended doses, 5–10 times that amount^{70,97}; in another study, 1 mg of haloperidol or less was effective in symptom reduction in FEP in the majority of patients.⁹⁸

Application to Tapering Antipsychotics

Given that reduced antagonism of D₂ dopaminergic receptors has been implicated in many of the withdrawal phenomena attributed to antipsychotics, including psychotic symptoms,^{17,20,23} we suggest that tapering regimes should aim to reduce D₂ receptor antagonism in a linear fashion with adequate time provided in between dose reductions to allow adaptation to lower doses of the drug, as this may produce more “evenly spread” perturbations to the system, which may minimize withdrawal-associated effects (figure 3).^{16,99} Linear decrements of, eg, 10 percentage point D₂ receptor occupancy from 90% for

Table 3. Relationship between the dose of haloperidol and D_2 occupancy: (A) commonly used doses of haloperidol and their D_2 occupancy, derived from E_{\max} equation⁹¹; (B) dosages of haloperidol corresponding to 10 percentage point decrements of D_2 occupancy from 90% D_2 occupancy

A	
Haloperidol dose (mg)	D_2 occupancy (%)
10	86.3
8	85.0
6	82.9
4	79.0
3	75.5
2	69.4
1	55.7
0.5	40.0
0.25	25.5
0	0
B	
Haloperidol dose (mg)	D_2 occupancy (%)
30.8	90
4.4	80
2.1	70
1.2	60
0.78	50
0.50	40
0.32	30
0.18	20
0.08	10
0	0

It is worth noting that there is a drop of 25 percentage points of D_2 occupancy when the last 0.25mg of haloperidol is stopped compared with a drop of 10 percentage points in occupancy when the last 0.08 mg is stopped (italicized for emphasis).

haloperidol require hyperbolic dose reductions (table 3b; decrements of 20 percentage points in figure 2c), with further medications shown in table 4 and supplementary tables S3–S11.

In the absence of direct data in humans of the time taken for dopamine D_2 receptor adaptations to resolve, we can be guided by observations that TD improves over 2–3 years, and this is the same time period over which relapse rates of patients discontinued from medication takes to converge with relapse rates of patients maintained on medication, suggesting that this may be a reasonable time period over which to taper patients who have received long-term antipsychotics.

There is some support for this time period for tapering in small studies examining tolerable rates of discontinuation. One study has investigated reducing antipsychotics in patients with remitted psychosis by 25% of the most recent dose every 6 months (a logarithmic pattern that closely approximates hyperbolic dose reductions), with 3 quarters of patients able to achieve between 25% and 71.4% dose reduction without relapse in the first year of

the study.¹⁰⁰ Another pilot study found that patients with chronic schizophrenia who, on average, achieved a 42% reduction in antipsychotic dose over 6 months demonstrated no difference in relapse rates from patients maintained on antipsychotics.⁹⁵ This suggests that many patients may tolerate dose reductions of 25%–50% of the most recent dose (corresponding approximately to 5–10 percentage point decrements of D_2 occupancy) every 3–6 months. Smaller reductions (such as 10% of the most recent dose) made every month may be more tolerable in the aim of producing more “evenly spread” perturbation to the equilibrium.

There is likely to be considerable interindividual variability in this process, with patients able to tolerate greatly varying rates of reduction: given the data on time for TD to resolve, some long-term treated patients may need longer periods, and some first-episode patients or those treated for briefer periods may tolerate shorter tapering periods.^{75,76,78,101} However, we suggest that, even in quicker tapering protocols, tapering should follow a hyperbolic course to “evenly spread” change at receptors. If the reason for discontinuation is pressing, such as a severe adverse reaction, such schedules may need to be much quicker, acknowledging the increased risk of withdrawal symptoms. In patients with poor compliance, such prolonged tapers will be challenging, although a reduced adverse effect burden and the possibility of discontinuation may enhance engagement with the process.¹⁰²

The tapering process should be conceptualized as finding a new minimum effective dose.^{70,74} The process could be individualized by observing patients for 3–6 months following an initial reduction of 5–10 percentage points of D_2 receptor blockade, and gauging response, to determine a tolerable rate of decrease thereafter. As outlined recently, it is possible that there would be an increase in symptoms following a dose reduction,⁷⁰ but it might be expected that these symptoms would resolve over time, as underlying adaptations resolve (though this can take weeks or even months); increased psychosocial support may be necessary to manage this period if risks are manageable.^{70,103}

An example tapering regime for haloperidol, taking into account ease of administration and D_2 occupancy, might be a reduction in dose from 4 to 3 to 2 to 1.5 to 1 to 0.75 to 0.5 to 0.375 to 0.25 to 0.125 to 0.06 to 0 mg, with tablet splitting and liquid formulations required for the lower doses (figures 2c and tables 3 and 4). The size of reductions may be decreased or the time between reductions increased if patients experience a significant increase in symptoms. Holding the dose for a prolonged period or increasing to a previously tolerated dose may be advisable if the patient experiences significant symptoms; some may be able to tolerate slower or more gradual reductions subsequently. Similar regimes for other antipsychotics are shown in table 4 (with further detail in the supplementary material). One of the major barriers to the pharmacologically informed tapering

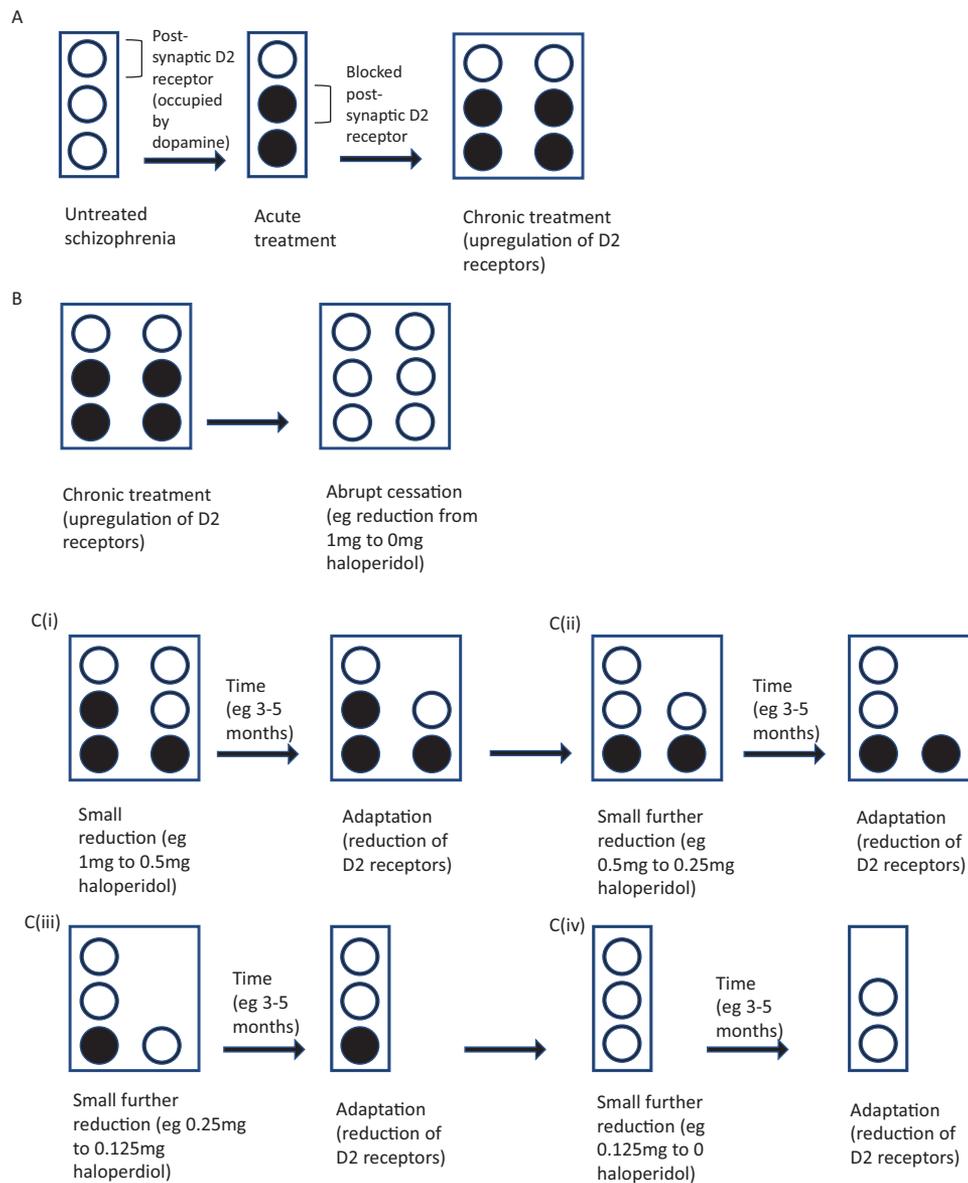


Fig. 3 Theoretical representation of abrupt vs gradual reduction of antipsychotic dose. (A) Untreated schizophrenia is represented by postsynaptic D₂ receptors (open circles). Antipsychotics cause blockade of D₂ receptors (filled in circles). Chronic treatment is hypothesized to cause the upregulation of D₂ receptors. (B) Abrupt cessation of antipsychotic causes a large increase in dopaminergic transmission in sensitized D₂ receptors, possibly associated with an increased risk of relapse. (C) (i) Gradual reduction in antipsychotic dose leads to incrementally increased dopaminergic transmission, possibly associated with a smaller increase in the risk of relapse or temporary increase in symptoms. Over time (likely months or years) D₂ upregulation starts to resolve. (ii)–(iv) Gradual antipsychotic dose reduction is repeated. Please note the time frames indicated here are theoretical, based on few small studies.^{95,100}

proposed is achieving doses intermediate between commonly available tablet formulations and the very small doses suggested at the end of the taper: tablet cutters can be helpful, some antipsychotics are available in liquid formulations, and “tapering strips” developed in Holland are another option, providing small formulations of tablets that can be combined to facilitate a wide variety of doses for incremental tapers.¹⁰⁴

Depot medications provide a useful option in tapering as their extended half-lives represent a form of “in-built” tapering (supplementary table S3). For example,

3-monthly paliperidone depot takes 52 weeks to reach a steady state and may be tapered over 3 years by yearly dose reductions equivalent to approximately 30% D₂ occupancy (equivalent to reducing by 10 percentage points of D₂ occupancy every 4 months), with the time taken to reach a steady state providing time for neural adaptation. Very small doses of the depot would be required for final dosing (eg, 90 mg, equivalent to 30% D₂ occupancy). For drugs with short half-lives or “fast off” characteristics, like clozapine or quetiapine (supplementary table S12),¹⁰⁵ with reputations for quicker onset of psychosis following

Table 4. Pharmacologically informed tapering regimens for 6 antipsychotics

Steps	Haloperidol (mg)	Risperidone (mg)	Olanzapine (mg)	Clozapine (mg)	Quetiapine (mg)	Amisulpride (mg)
1	4.0	4.0	7.5	300	300	400
2	2.0	2.5	5.9	210	240	270
3	1.3	1.7	4.6	150	200	190
4	0.85	1.2	3.6	110	160	140
5	0.60	0.85	2.7	80	120	95
6	0.40	0.60	2.0	55	90	70
7	0.25	0.40	1.4	40	65	45
8	0.15	0.25	0.90	25	40	25
9	0.05	0.10	0.40	10	20	10
10	0	0	0	0	0	0

The starting dose for each antipsychotic represents the lowest dose recommended for multiple episodes of psychosis according to the Maudsley Prescribing Guidelines (clozapine is selected based on usual dosing regimens).⁷³ Steps below each drug represent 9 “evenly spaced” reductions based on D_2 occupancy down to 0% occupancy (note that because the D_2 occupancy of the minimum effective dose is not the same for each antipsychotic, the intervals are not evenly spaced across different antipsychotics). D_2 occupancy is presented based on the E_{\max} equation of best fit derived from meta-analysis of PET scanning of antipsychotics for those 6 antipsychotics for which the R^2 of the equation for the line of best fit explains at least 30% of variability in the data.⁹¹ Doses are rounded to 2 significant figures, with the last significant figure rounded to 0 or 5 for simplicity. Some patients will require intermediate steps between the values shown as these reductions will represent too large a reduction to easily tolerate, although others may be able to tolerate larger reductions. Reduction rate should be titrated to the ability of the patient to tolerate reductions.

withdrawal, more caution may be required and it may be necessary to reduce doses by 2.5–5 percentage points of D_2 (or cholinergic or histaminergic) occupancy every 6–12 weeks, depending on individual responses (see [supplementary material](#)). There is recent evidence that drugs like aripiprazole that are partial agonists at the D_2 receptor are less likely to induce dopaminergic hypersensitivity (as evidenced by very low rates of TD)¹⁰⁶ and, therefore, may be less likely to cause a relapse on discontinuation as supported by animal data,¹⁰⁷ but this has not yet been examined in clinical studies.

Limitations

There are potential limitations to the interpretation of the dose-response curves from PET studies. First, individual variation may not have been captured by the relatively small sample sizes.⁹¹ However, the shape of the dose-activity curve (ie, hyperbolic) should be the same for each individual,⁹³ suggesting that hyperbolic dose reduction regimes should be universally applicable. It should also be noted that there is some heterogeneity in the meta-analysis of PET studies⁹¹ indicating the likelihood of interindividual differences in receptor occupancy for a given dose, emphasizing the importance of individualized tapering guided by the patient’s response to reductions.

Second, it is difficult to determine whether D_2 occupancy will linearly correspond to withdrawal effects. There is a body of evidence that suggests that a minimum threshold of D_2 antagonism is required before a clinical effect or adverse effects are seen¹⁰⁸; this may also apply to withdrawal effects. However, a recent meta-analysis has found a continuous hyperbolic relationship between

antipsychotic dose and clinical response,¹⁰⁹ mirroring the relationship between dose and D_2 occupancy. One meta-analysis found evidence of a positive linear relationship between clinical improvement and D_2 receptor occupancy (when patients taking quetiapine and clozapine, thought to act through mechanisms other than D_2 antagonism, and outliers with very high dopaminergic blockade were excluded).¹¹⁰ Evidence of a linear relationship between D_2 antagonism and therapeutic effects may extend to withdrawal effects, but this requires further investigation.

Third, although the principal therapeutic effects of antipsychotics are attributed to D_2 antagonism, other receptor targets, including $5HT_2$ and $5HT_{1A}$, have also been thought relevant, and these receptors, and others, such as cholinergic receptors, may also determine withdrawal effects.²⁰ Therefore, tapering according to the binding affinity of receptor subtypes other than D_2 receptors¹¹¹ may be indicated with some antipsychotics. This limitation may apply particularly to clozapine because it acts partly through non-dopaminergic pathways, and it demonstrates the lowest correlation between plasma levels and D_2 occupancy of commonly used antipsychotics.^{110,112} However, dose reduction schedules using alternative receptor dose-response curves follow similar hyperbolically reducing dosing schedules because these relationships also follow the law of mass action.

Future Directions

This paper offers some pharmacological principles that may aid in withdrawing from antipsychotics. We anticipate that this regime might reduce relapse during and after discontinuation. At a minimum, it should

be recognized that tapering periods of weeks down to minimum or half-minimum therapeutic doses of medication are likely to be inadequate to avoid withdrawal symptoms, including early relapse. In those who have received antipsychotics over prolonged periods, tapering regimes over months and years down to small portions of drug doses are more likely to be effective. The hypothesis put forward in this paper should be tested in further tapering trials of antipsychotics, including slower tapering down to lower final doses before complete cessation, including the use of depot preparations. Establishment of formal guidelines for tapering antipsychotics is required.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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M.A.H. conceived the manuscript idea, wrote the manuscript, and drew the figures. D.T. helped develop the idea and revised and edited the manuscript. R.M., S.N., and S.J. helped to substantially revise and edit the manuscript.

Conflict of interest

M.H. declares no conflict of interest. D.T. reports grants and personal fees from Janssen and personal fees from Recordati and Lundbeck, outside the submitted work. R.M. reports honoraria for lectures from Lundbeck, Sunovian, Janssen, Otsuka, and Angelini, outside the submitted work. S.N. declares no conflict of interest. S.J. has received honoraria from Sunovian for educational talks he has given, and K.C.L. (his employer) has received funding for educational talks he has given for Lundbeck.

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