VIEWPOINT

Tapering Antipsychotic Treatment

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Antipsychotics are recommended for long-term treatment of schizophrenia because they reduce risk of relapse. However, antipsychotics have many adverse effects, including metabolic complications, tardive dyskinesia, and probable brain volume reduction.[1] Patients may ask to reduce or stop their medication or do so abruptly without professional support, sometimes with dire consequences. As there is some evidence that not all patients need lifelong antipsychotic treatment and some may have improved social functioning when taking less or no antipsychotic,[1] cautious deprescribing should be a component of high-quality prescribing practice. To our knowledge, there are currently no published guidelines on reduction or cessation of an antipsychotic; we propose principles relevant when deprescribing is thought appropriate.

Relapse Related to Withdrawal

Relapse often occurs when antipsychotics are withdrawn. This has been widely thought to represent an unmasking of the underlying chronic illness, but the nature of the process of withdrawing antipsychotics may itself be associated with relapse. This is evidenced by the occurrence of psychotic symptoms in people without a psychotic disorder who abruptly stop taking antipsychotics used to treat other conditions, such as nausea or lactation difficulties.[1] Likewise, it is one possible reason for the marked preponderance of relapses soon after abrupt antipsychotic cessation in patients with schizophrenia in discontinuation trials. In one meta-analysis,[2] 60% of all relapses over 4 years occurred within 3 months of drug cessation.

Underlying Neurobiology

Withdrawal-associated relapse has been attributed to neural adaptations to long-term antipsychotic treatment (dopaminergic hypersensitivity) that persist after antipsychotic cessation. Indeed, molecular imaging studies in individuals with schizophrenia have found increased D_2/D_3 receptor availability in those who had been exposed to antipsychotic medication but not in antipsychotic-naive patients.[3] This hypersensitivity to dopamine may render patients more susceptible to psychotic relapse when D_2 blockade is diminished by antipsychotic dose reduction.

There are converging lines of evidence that suggest that the neuroadaptive effects of antipsychotic treatment can persist for months or years after stopping. Dopaminergic hypersensitivity in animals persists for the equivalent of a human year after treatment is stopped.[4,5] Tardive dyskinesia—attributed to dopaminergic hypersensitivity—can persist for years after antipsychotic medication has been ceased. There is also evidence that patients who have discontinued antipsychotics have increased rates of relapse for 3 years compared with people who maintain antipsychotic treatment, after which relapse rates converge,[6] suggesting that adaptations may have resolved by this point.

If we are to accept these observations, then it follows that the risk of relapse on cessation of antipsychotics might be minimized by more gradual dose tapering because these neuroadaptations would then have time to resolve during the tapering process and the rate of decline of blockade is more modest. Indeed, a small meta-analysis found that tapering over 3 to 9 months halved the rate of relapse compared with abrupt discontinuation.[2] Tapering over 4 weeks showed no difference from abrupt discontinuation.[6]

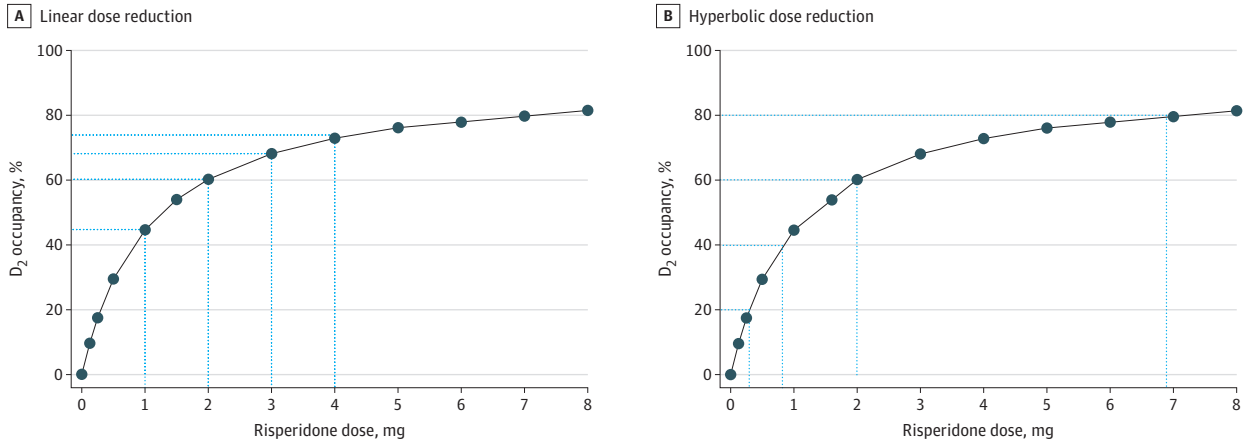
Pattern of Tapering

Positron emission tomography imaging demonstrates a hyperbolic association between dose of antipsychotic and D_2 receptor occupany.[7] This hyperbolic association applies to other receptor targets of antipsychotics as well (including histaminergic, cholinergic, and serotonergic receptors) because it arises from the law of mass action whereby each additional molecule of a drug has incrementally less effect as receptor targets become saturated. The nature of this association is often obscured by the habit of plotting dose-response curves on semilogarithmic axes. A hyperbolic association between dose of antipsychotic and its therapeutic effects (as measured by symptoms scales) has also been shown,[8] suggesting that clinical response mirrors the neurobiological pattern of effects.

This brings into question the rationale for a linear reduction of antipsychotic dose—for example, a reduction from 4 mg to 3 mg to 2 mg to 1 mg to 0 mg of risperidone. Although this regimen appears reasonable, the hyperbolic association between dose and effect on D_2 blockade dictates that these linear dose decreases will produce increasingly larger reductions of D_2 blockade (and the clinical consequences of this) (**Figure**, A). Indeed, the reduction of dose from 1 mg to 0 mg will produce a reduction in D_2 blockade (44.6%) larger than that produced by the reduction from 10 mg to 1 mg of risperidone (38.8%). These increasingly large reductions in D_2 blockade may be more likely to provoke relapse.

Linear or evenly spaced reductions in D_2 blockade require hyperbolically reducing doses of antipsychotic medication (Figure, B). These hyperbolic reductions are approximated by sequential halving of dose: for example, risperidone doses of 8 mg, 4 mg, 2 mg, 1 mg, 0.5 mg, 0.25 mg, 0.125 mg, and 0 mg produce roughly 10-percentage point reductions in the extent of D_2 blockade. This pattern of reduction may be less likely to provoke relapse because it avoids large increases in dopaminergic signaling. Preliminary support for this notion comes from a pilot trial in which an average 42% reduction of antipsychotic dose (slightly less than

Figure. Association of Linear and Hyperbolic Dose Reduction Regimens of Risperidone on D_2 Occupancy



A, Linear dose reductions of risperidone are associated with increasingly large reductions in D_2 dopaminergic receptor blockade. B, Linear reductions of D_2 dopaminergic occupancy (in this case, 20% reductions) correspond to hyperbolically decreasing doses of risperidone. The doses in this case correspond to 6.9 mg (80% D_2 occupancy), 2.0 mg (60% D_2 occupancy), 0.82 mg (40% D_2 occupancy), and 0.30 mg (20% D_2 occupancy). Data points indicate commonly used dosages of risperidone or those suggested for tapering at low dosages; the solid line indicates the line of best fit for the association between dose of risperidone and D_2 blockade, taken from a meta-analysis of positron emission tomography studies[7]; and dotted blue lines indicate the corresponding D_2 occupancies for linear reduction of dose in panel A and corresponding doses for linear reduction of D_2 occupancy in panel B.

halving) did not provoke any excess relapses over maintenance treatment.[9] However, numbers were small in this trial and so it should be cautiously interpreted. There was also an acute increase in relapses in another trial of gradual reduction,[10] although this was less than the large increase in relapses seen when antipsychotics were more quickly ceased.[6] Hyperbolically reducing regimens will produce roughly linear reductions at all receptor targets of antipsychotics, making it applicable to a wide range of antipsychotic medications.

Suggested Practice

We suggest that when antipsychotic medication reduction is appropriate, it should be done very slowly (over months or years) and in a hyperbolic manner. For example, the dose could be reduced by an amount calculated to reduce 10 percentage points of the drug's D_2 blockade (approximately equal to a reduction in half the last dose given) every 3 to 6 months. Final doses before complete cessation will need to be very small to prevent a large decrease in D_2 blockade. This may need to be as small as 2.5% the original therapeutic dose. Delivery of these small doses may require splitting tablets or using liquid formulations. Such a reduction regimen might reduce the risk of relapse on discontinuation. This proposal should be tested in randomized clinical trials comparing linear, rapid tapers with slow, hyperbolic tapers to assess the effect on relapse rates.

ARTICLE INFORMATION

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