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Chronic Use of Antipsychotics in Schizophrenia: Are We Asking the Right Question?

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There is an ongoing debate about the potential risks and benefits of long-term antipsychotic treatment in schizophrenia. The data for and against the chronic use of these medicines is mostly indirect, either from observational studies potentially exposed to reverse causation bias or randomized controlled studies that do not cover beyond 2–3 years. We propose that perseverating on the question of what positive or negative outcomes are causally associated with chronic antipsychotic treatment may not lead to better answers than the limited ones that we have, given the limited feasibility of more conclusive studies. Rather, we argue that addressing the research question of the risks and benefits of antipsychotic discontinuation from a perspective of personalized medicine, can be more productive and meaningful to people living with schizophrenia. To this end, research that can quantify the risk of relapse after treatment continuation for a given individual should be prioritized. We make the case that clinically feasible neuroimaging biomarkers have demonstrated promise in related paradigms, and that could be offering a way past this long debate on the risks and benefits of chronic antipsychotic use.

Keywords: antipsychotic/treatment discontinuation/relapse

> "If I had an hour to solve a problem and my life depended on the solution, I would spend the first 55 minutes determining the proper question to ask…"
>
> Albert Einstein

Most psychiatrists treating individuals in the early phase of schizophrenia have been asked by patients and or families: "When can I stop taking this medicine?" This question has triggered a vast literature on the topic, with a contentious debate between those who advocate for and are against long-term antipsychotic treatment.[1–3] Here, we argue for the need to reformulate the core question of this debate, and to generate novel and actionable data for patients and clinicians.

No one challenges the data on the efficacy of antipsychotic medications for relapse-prevention in schizophrenia, at least in the short to mid-term. This question was tested in a seminal meta-analysis,[4] which yielded a number needed to treat of 3 for antipsychotics preventing relapse in schizophrenia. This benefit is superior to that of diuretics in delaying mortality in congestive heart failure.[5] However, since there are no controlled data for antipsychotics vs. placebo beyond 3 years of follow-up, there is some degree of uncertainty about the long-term effects of these drugs, positive and negative.

Long-term naturalistic cohorts, as well as cohort studies of untreated individuals, have been used as indirect data on the long-term consequences of antipsychotic use in schizophrenia. The association between lower antipsychotic doses and better clinical outcomes (ie, recovery, employment, etc.) has been recurrently reported in large naturalistic cohorts such as the Chicago cohort,[6] the Northern Finland cohort,[7] or the OPUS cohort.[8] However, since those with the most severe illness presentations are the most likely to be prescribed greater doses of antipsychotic medication, it is generally unwise to conclude that lower antipsychotic doses cause better outcomes (ie, reverse causation). A special case of this type of design is the MESIFOS study, which randomized to dose reduction/treatment discontinuation vs maintenance treatment over 2 years of treatment,[9] and then

reported outcomes for 5 years after the controlled study ended.[10] The results during the controlled phase favored maintenance treatment over treatment discontinuation. However, the outcomes 5 years after ending the study showed better recovery outcomes for those who had initially been assigned to treatment discontinuation. Although these results have been used to warn against chronic antipsychotic use,[3] we would caution against this interpretation. The reasons for this are that this cohort underrepresented those with worse prognosis, and that between years 2 and 7 those initially on dose reduction could increase their dose and vice versa, thus the treatment of the initial 2 years being poorly representative of the total antipsychotic exposure over the entire 7 years. Similarly, there is a literature linking chronic antipsychotic use to cortical thinning,[11,12] while other studies have suggested that greater adherence to antipsychotic medication during the early phase of the illness may be associated with neuroprotective effects, with a greater degree of intracortical myelination.[13] However, given the lack of randomized controlled data, it is impossible to disentangle the structural brain changes resulting from the illness itself vs. the direct effects of antipsychotic drugs on brain structure, either toxic or protective. Meanwhile, studies from individuals for whom antipsychotic treatment was withheld over the long-term show consistently a much worse course of illness compared to peers who were able to receive treatment.[14] Most importantly, large national registry studies with long-term follow-up periods have found consistent reductions in premature mortality associated with cumulative antipsychotic treatment, ranging between a 52% reduction in a follow-up of 62 250 individuals for up to 20 years in the Finnish national registry,[15] to a reduction of 40% to 25% in 21 492 in individuals followed up for 14 years in the Swedish national registry.[16]

In our opinion, despite some uncertainty, this body of literature leans in the direction of overall favoring chronic antipsychotic use for relapse prevention and reduction of premature mortality.[2] We may need to live with some questions unanswered, since longer controlled studies would be expensive, confounded by attrition and nonadherence, and likely unfeasible and unethical. Living with this uncertainty may be acceptable, though. In fact, is the question of whether chronic antipsychotic treatment is associated with a particular outcome the most appropriate? Not only it may be unanswerable with full certainty for longer timeframes, but also it may not be the most relevant anyway since most individuals with schizophrenia will interrupt treatment at least once within the first year of treatment.[17] We argue that a more actionable and relevant question is: Can we determine the risk of relapse after treatment interruption for a given individual? When patients inquire about when they can stop their medicine, they ask about their individual risk of relapse, not population averages. It has been well reported that about 10%–30% of individuals with schizophrenia may be able to stay relapse-free long-term without the need for ongoing antipsychotic treatment.[18,19] Thus, their question really is whether they belong to that ~10%–30%.

Our ability to respond to this question is currently limited. There is a literature on clinical factors associated with successful treatment discontinuation,[19,20] but unfortunately, these have shown poor replicability.[21] Indeed, studies need to move from identifying group associations, to generating individual estimates that allow classifying individuals based on their relapse risk. These patient-level estimates will need to demonstrate internal and external validity, as well as acceptable levels of predictive accuracy (ie, sensitivity and specificity) that justify their clinical usefulness.[22] The development of biomarkers for related purposes seems promising. For individual prediction of treatment response, neuroimaging biomarkers have demonstrated predictive accuracy of ~ 80%, with replication in independent samples.[23] These individual predictions are more accurate than those possibly generated with clinical data only.[24] The application of a similar biomarker paradigm to the problem of prediction of relapse upon treatment discontinuation could be promising and deserve further attention.

New data will be necessary to demonstrate that biomarkers can predict outcomes of interest that result from antipsychotic continuation or discontinuation. For instance, measuring the risk of recurrence of psychosis after discontinuation of antipsychotic medication for a given individual is relevant to informing the decision about whether to continue pharmacological treatment. This patient-level information could be used in addition to other relevant patient-centric outcomes, such as residual symptoms, side effects, quality of life, and social functioning, to inform the patient's decision to discontinue treatment according to their needs and preferences. Other outcomes, such as relapse despite ongoing treatment may be relevant too,[25] to determine the optimal duration of maintenance treatment. Furthermore, other aspects of non-pharmacological treatment such as social or psychological interventions should be accounted for in this line of research, so that individuals can incorporate non-pharmacological treatment strategies, regardless of their decision to continue or interrupt maintenance pharmacological treatment.

Although we get there, what is an acceptable answer to the question of when to discontinue treatment? In our opinion, it first must be acknowledged that the vast majority of those who stop treatment will relapse, as opposed to those who continue treatment, and that we cannot reliably tell our patients whether they will be among the minority for whom antipsychotics can be interrupted safely. Second, the side effect burden of treatment should be weighed against the potential consequences of relapse when considering the decision to discontinue. The course, context, and consequences of previous acute psychotic

episodes should be used as a reference for what could happen if there is a recurrence of symptoms. In addition, it should be considered that progress made towards recovery could be quickly undone if for example an individual gets sick again and loses their job, or if the social gains they made during recovery of acute psychosis are lost by recurrence of unusual behavior or psychiatric hospitalization. In addition, it should be considered that in the event of relapse, there is the possibility that antipsychotic drugs will be less effective upon their reintroduction than what they were previously, given the growing data indicating a progressive loss of treatment efficacy with each relapse.[26,27] Third, if there is a decision to interrupt maintenance treatment at the expense of increased risk of relapse, mitigating strategies should be discussed. These should include non-pharmacological interventions for relapse-prevention, such as family psychoeducation or increased patient contact.[28] Prescribers should also recognize that it is not well understood yet what the rate for the dose reduction should be. Some argue for extremely long tapers mainly based on theoretical models,[29] while most data suggest no differences in relapse risk between abrupt and progressive tapers.[4] It is probably recommendable to base the pace of dose reduction on factors such as patient preference or illness history. And finally, clinicians must acknowledge that many individuals with schizophrenia spectrum disorders may not be able or feel comfortable bringing up this conversation.[30] As clinicians, we must respect this, while at the same time being proactive about discussing the risks and benefits of interrupting treatment for a given individual.

Clinical Vignettes

A is a 23-year-old man who experienced unusual preoccupation about being tracked on social media 18 months ago. This preoccupation worsened over time, he became more isolated from family and friends and his thought process became vaguer and more circumstantial. After 6 months of symptoms, he was brought to a psychiatrist who after demonstrating tolerability with oral risperidone, initiated treatment with a long-acting injectable (LAI) of paliperidone palmitate 156 mg monthly. During this time, his psychiatrist has done a Brief Psychiatric Rating Scale (BPRS) at least quarterly, with all psychotic items persistently scoring <4. Also, A has gained 5 kg since treatment onset, and has become worried about some mild breast enlargement. Upon A's request, they decide to start a taper of treatment, since there is full remission of symptoms in the presence of some side effects. After a careful discussion of the potential risks, benefits, and expectations for the following months (including the circumstances that would lead to resuming antipsychotic treatment), they decrease to a lower dose of the LAI each month until they stop. During this time the frequency of clinical assessments has increased, given the greater risk of relapse. One month after completely stopping the medicine, A's speech becomes again vaguer and starts again isolating from his family, which led to reintroducing paliperidone palmitate to treat recurring psychosis.

B is a 29-year-old woman who has been in outpatient care for the last 4 months. She has a history of 3 previous hospitalizations for wandering in the context of worsening psychosis, last one 4 months ago. She is currently on treatment with oral olanzapine 20mg, which was initiated in the inpatient setting and which has led to the remission of positive symptoms, with mild to moderate cognitive and negative symptoms, according to quarterly Brief Psychiatric Rating Scale (BPRS) assessments. B complains of gaining 8kg since olanzapine and disliking how this medication makes her feel, and for this reason requests to stop it. The psychiatrist is concerned that despite positive symptom remission, there is a high risk of relapse given her history of recurrent relapses, some of which have resulted in imminent danger to herself. The focus of the intervention of the psychiatrist is to provide psychoeducation on the high risk of relapse and potential consequences of another relapse, as well as in optimizing current treatment by switching to a regimen with a LAI with a better tolerability profile.

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