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Long-term impact of antipsychotics: settling the controversy requires more clarity

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The long-term use of antipsychotic medications has generated significant controversy over the years, and this debate has been vital in moving the field away from a single-minded focus on lifelong administration of antipsychotic medications as the preferred treatment for schizophrenia. The notion that a substantial number of individuals with schizophrenia can achieve meaningful or sustained recovery without the long-term use of antipsychotic medications is gradually becoming more widely accepted, especially in the first-episode psychosis community.

A more disturbing prospect that is being debated, however, is the notion that long-term use of antipsychotic medications actively worsens the course of the schizophrenia, hinders recovery, and leads to poor outcomes (Harrow & Jobe, 2018). This possibility has been highly contested and remains without widespread acceptance of the scientific community (Goff et al., 2017). A major issue has been that much of the support for this hypothesis has come from observational studies, which have inherent limitations such as confounding due to a lack of randomization. Such limitations have been used to dismiss the findings from observational studies. However, that is not a position I wish to support here. As Ohlsson and Kendler (2020) have stated in a different context (psychiatric epidemiology), 'We need to avoid the extremes of overzealous causal claims and the cynical view that potential causal information is unattainable when RCTs are infeasible.'

I say all this as a preface to emphasize that I am an advocate of taking observational data seriously and using them to make reasonable inferences. Given the critical importance of determining optimal pharmacologic treatment for individuals who experience psychosis, it was with great eagerness that I read the latest report from Harrow, Jobe, and Tong (2021) in *Psychological Medicine* is investigating the effects of antipsychotics on the course of the illness in individuals with schizophrenia and bipolar disorder over a 20-year period. While this study is of great value, there appeared to be deficiencies in the reporting of important details and possible oversight of vital considerations which make it very difficult to interpret the results with meaningful clarity. This makes it difficult to accept the author's conclusions. In this correspondence, I will elaborate on these concerns, with the hope that Harrow et al., can offer clarification.

What exactly does antipsychotic use/antipsychotic prescription variable represent?

The manuscript switches between the language of individuals being 'on antipsychotics' and 'prescribed antipsychotics'. It is unclear what this means. Does it mean the individuals were prescribed antipsychotics and they were actively taking it? Individuals who were prescribed antipsychotic medications by their psychiatrists but decided not to take them, were they classified in the category of 'antipsychotics prescribed' or 'antipsychotics not prescribed'? A related variable of interested here, although this is not something the authors may have collected data on, is whether the individuals not prescribed antipsychotics were actively engaged in psychiatric care, and whether the discontinuation of antipsychotics had been recommended by the psychiatrist.

How was the recovery variable handled in statistical analysis?

It is unclear how exactly the relationship between antipsychotic medications and recovery status on follow-up visits was determined. While an association between antipsychotic medication use and recovery relating to the *same* follow-up visit is simple enough, how this association was determined for future recovery status is unclear. This lack of clarity emerges from the fact that 'recovery' is restricted to the follow-up year by study definition. Since there are six follow-up visits, it means that there are six instances in which an individual is categorized as being in recovery or not being in recovery. In their analyses and results, the authors talk about the likelihood of recovery ('participants not on antipsychotic medication were about six times more likely to recover than participants on medication') but since we are talking about six time points of recovery, readers are left to speculate as to what the 'likelihood of recovery' entails exactly. Does it mean subjects were more likely to be in recovery status on at least one follow-up visit (out of the total six follow-ups)? Or does it mean that

they were more likely to be in recovery in the aggregate? In the latter case, we are left to wonder as to how recovery has been weighted as a variable. Was each instance of recovery counted separately, such that if individual A was in recovery status on five follow-up visits and individual B was in recovery on one follow-up visit, individual A was determined to have five times more recovery than individual B?

How were missing values handled?

Missing values are alluded to, but no further information is provided.

Intermittent prescription of medication means the category of 'antipsychotic prescribed' is not stable

Per the article, 42% of individuals with schizophrenia were always prescribed antipsychotic medications, 24% were never prescribed, and 34% were intermittently prescribed. This suggests that individuals who were classified in the 'antipsychotic not prescribed' group at one follow-up may have been classified as in the 'antipsychotic prescribed' group at another follow-up. Given that the antipsychotic prescribed and not prescribed categories are *subject to change* from one visit to the next, how was this intermittent prescription of antipsychotic medication taken into account? How are we comparing the antipsychotic prescribed group at different time points when the constitution of this group is subject to change?

Always *v.* intermittently *v.* never psychotic

As reported, 23% of individuals with schizophrenia were always psychotic, 20% were never psychotic (during the follow-up period), and 57% were intermittently psychotic. It is unclear if this variable was taken into account or controlled for in any way during the analysis? How did the use of antipsychotic medications influence functioning and outcomes within these subgroups? For instance, within the subgroup of individuals who were always psychotic, was not being on antipsychotic medication also associated with prospectively higher Global Assessment of Functioning (GAF) scores and a prospectively lower risk of hospitalization?

Were temporal relationships between recovery status, hospitalization, GAF, and antipsychotic use looked at?

The authors looked at how antipsychotic use predicts recovery, hospitalization, and GAF, but it is not reported whether these variables also predict antipsychotic use on prospective follow-up visits. Is a high GAF on one follow-up visit associated with an increased likelihood of not being prescribed antipsychotic medication on the next follow-up visit? Does being hospitalized predict a higher likelihood of being prescribed antipsychotic medication on the next follow-up visit? The existence of such relationships would be consistent with the possibility of reverse causality.

The interpretation of odd's ratio is ambiguous

In the body of the article, the authors write: 'For recovery, the coefficient of medication was 1.79 (OR 5.989, 95% CI 3.588–9.993), which indicated that participants not on antipsychotic medication were about six times more likely to recover than participants on medication.' The abstract states: 'The adjusted odds ratio of not on antipsychotic medication was 5.989 (95% CI 3.588–9.993) for recovery.'

These interpretations hint at two different things. The abstract seems to suggest that for individuals who were in recovery, the likelihood that they were not on antipsychotic medications (at the time of recovery? on one or more follow-up visits?) was six times compared to those who were not in recovery, while the text suggests that the individuals who were not on antipsychotic medications had a six times higher likelihood of recovery on follow-up (see question 2 above about quantifying recovery). These are quite different claims, but the article offers little clarity in discriminating between the two.

Given the controversial conclusions of the article which counter the prevailing scientific consensus, these deficiencies in reporting identified above are concerning. They also make the article more vulnerable to misinterpretation.

In addition to addressing the above queries, I would encourage the authors to go even further and make the data available to scientific researchers who are interested in critically evaluating and replicating the conclusions. This encouragement is not by any means specific to this article and is of broader relevance congruent with the open data movement. In this case, however, it would certainly help demonstrate to the satisfaction of critics that the conclusions can indeed withstand robust scrutiny.

Regardless of what the Harrow study does and does not demonstrate about the adverse long-term impact of antipsychotics, the study remains valuable because the results challenge the 'received wisdom' of the past psychiatric generations that the long-term use of antipsychotic medications is crucial to the recovery and well-being of individuals with schizophrenia.

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References

Goff, D. C., Falkai, P., Fleischhacker, W. W., Girgis, R. R., Kahn, R. M., Uchida, H., … Lieberman, J. A. (2017). The long-term effects of antipsychotic medication on clinical course in schizophrenia. *American Journal of Psychiatry*, *174*(9), 840–849. doi:10.1176/appi.ajp.2017.16091016.

Harrow, M., & Jobe, T. H. (2018). Long-term antipsychotic treatment of schizophrenia: Does it help or hurt over a 20-year period?. *World Psychiatry*, *17*(2), 162–163. doi:10.1002/wps.20518.

Harrow, M., Jobe, T. H., & Tong, L. (2021). Twenty-year effects of antipsychotics in schizophrenia and affective psychotic disorders. *Psychological Medicine*, 1–11. doi:10.1017/S0033291720004778.

Ohlsson, H., & Kendler, K. S. (2020). Applying causal inference methods in psychiatric epidemiology: A review. *JAMA Psychiatry*, *77*(6), 637–644. doi:10.1001/jamapsychiatry.2019.3758.

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