Psychological Medicine

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Cite this article: Pierre JM, Zito MF, Yang YS, Marder SR (2023). Antipsychotic discontinuation and recovery: chicken or egg? *Psychological Medicine* **53**, 1134–1135. https://doi.org/10.1017/S0033291721001872

Received: 21 April 2021
Accepted: 23 April 2021
First published online: 24 June 2021

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CAMBRIDGE UNIVERSITY PRESS

Antipsychotic discontinuation and recovery: chicken or egg?

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We read with interest Harrow, Jobe, and Tong's (2021) study on the long-term effects of antipsychotic medication on patients with either schizophrenia or affective psychoses. The article concludes that those who are 'not prescribed antipsychotic medication are more likely to experience episodes of recovery' and that 'after 2 years, antipsychotics no longer reduce psychotic symptoms and participants not on antipsychotics perform better' (Harrow et al. 2021). The suggestion that antipsychotic medications worsen the course of schizophrenia in the long run has been proposed by others (Whitaker, 2012), but such assertions are nearly always based on uncontrolled, naturalistic studies and clinical vignettes. We are concerned that generalizing the findings from these interesting studies to larger populations of patients is misleading, and for some individuals, harmful.

Although several previous longitudinal, naturalistic studies have suggested an association between poorer outcomes and antipsychotic medication compared to antipsychotic discontinuation (Harrow, Jobe, & Faull, 2012, 2014; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013), both a causal relationship and the direction of causality remain uncertain in the absence of randomized trials (RCTs). Harrow et al. (2014, 2017, 2021) have attempted to address this limitation by noting that the association persists regardless of baseline prognostic indicators and that antipsychotic discontinuation is also associated with better subsequent work functioning, but without knowing when and why antipsychotic medications were discontinued or deprescribed, we are left with a 'chicken *v.* egg' debate that risks conflating cause and effect. The choice of the phrase 'effects of antipsychotics' in the title of Harrow et al.'s (2021) paper notwithstanding, it is unclear whether antipsychotic discontinuation results in a better chance of recovery or conversely whether, or when, recovery leads to justifiable antipsychotic discontinuation. It is important to emphasize that we agree with Harrow et al. and others that there are patients who will benefit from having their antipsychotic medications discontinued or the dose reduced. Our concern is that the identification of this group of individuals should not be used as a treatment principle to be applied uniformly across the larger population of patients in long-term treatment.

A significant amount of evidence points away from Harrow et al.'s (2021) conclusions. A recent review of 37 studies supports the interpretation that better social functioning and fewer previous relapses increase the chances of successful antipsychotic discontinuation (Tani et al., 2018). Conversely, RCTs of antipsychotic discontinuation demonstrate that those who stay on antipsychotic medications tend to have lower rates of relapse compared to those who do not (Gilbert, Harris, McAdams, & Jeste, 1995; Hui et al., 2018; Wunderink et al., 2007). Harrow et al.'s reference to the 'supersensitivity psychosis' hypothesis (Chouinard et al., 2017) that argues that clinicians mistake relapse for medication rebound effects is unsupported by empiric evidence and is contradicted by a time course of relapse that often takes weeks to months as well as equivalent relapse rates with abrupt and gradual antipsychotic discontinuation (Emsley et al., 2018; Hayes, Osborn, Lundin, & Dalman, 2019; Leucht et al., 2012).

We acknowledge the increasing body of literature that indicates a complex risk-benefit ratio in the long-term treatment of schizophrenia. Antipsychotics have well-documented, common adverse effects like metabolic syndrome and tardive dyskinesia. In addition, many imaging studies have revealed an association between antipsychotic exposure and cerebral volume loss (Haijma et al., 2013), although controlled trials suggest that volume reduction and other structural abnormalities might be better attributed to known effects of disease process rather than medication effects (Chopra et al., 2021; Goff et al., 2017; Xiao et al., 2018). Similarly, while it is theoretically possible that antipsychotics could worsen the long-term course of schizophrenia, the effects of disease morbidity on medication prescribing and discontinuation remain major confounds within naturalistic, non-randomized study designs. If we imagined similar long-term studies of medications like anti-hypertensives or sulfonylureas, we would not be surprised if illness morbidity was greater among those who had to remain on medication due to illness severity, and we would not be led to invoke a medication toxicity effect.

It seems likely that some patients with chronic schizophrenia benefit from long-term antipsychotic treatment, whereas some who have recovered from psychosis could be harmed by unnecessary drug continuation and might benefit from careful and gradual discontinuation.

The question to be answered is how to distinguish between the two populations prospectively rather than through the kind of retrospective self-selection observed in long-term naturalistic studies like that of Harrow et al. (2021). Future RCTs of antipsychotic discontinuation in first-episode psychosis may help to clarify causal effects on recovery (Begemann et al., 2020; Moncrieff et al., 2019), but must be designed carefully to avoid diagnostic confounding by cohort (Pierre, 2020). In addition, clinical trials that test hypotheses about individual factors that might predict the ability to safely discontinue antipsychotic medications are sorely needed, as well as RCTs that go beyond 2 years. Of note, Harrow et al.'s cautionary findings could be explained by a cohort of patients with early course psychosis, whereas other naturalistic studies of patients with more clearly established chronic schizophrenia favor antipsychotic treatment (Ran et al., 2015). Indeed, both Harrow et al.'s Chicago cohort and the cohort in the widely-cited Wunderink studies (Wunderink et al., 2007, 2013) are diagnostically heterogeneous first-episode samples, limiting their strict applicability to schizophrenia populations.

Until studies such as the prospective RTCs proposed above are done, we recommend inviting the patient and their family to have a discussion of the risks, their counterbalancing benefits, and possible alternative strategies to indefinite antipsychotic usage. In some cases, the patient's preferences or clinical scenario may favor dose reduction or discontinuation, and these strategies ought to be seriously considered by providers. In the meantime, a large body of evidence from RCTs still supports maintenance antipsychotic therapy for most patients with chronic schizophrenia, and the risks can be partially balanced by thoughtful clinical care.

Financial support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest. No fees were accepted for preparation of this manuscript. Drs Pierre, Yang, and Zito report no conflicts of interest related to this manuscript. Dr Marder is a consultant and advisory board member for Roche, Merck, Boehringer-Ingelheim, Acadia, Lundbeck, receives research support from GW pharma and Boerhringer-Ingelheim, and receives royalties from Uptodate and Oxford Press.

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