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Invited Letter Rejoinder

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Long-term effectiveness of antipsychotics

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We welcome the comments by Drs Pierre et al. and Aftab regarding the Chicago Follow-up Study, especially in relation to our most recent publication in Psychological Medicine, 'Twenty-year effects of antipsychotics in schizophrenia and affective psychosis' (Harrow, Jobe, & Tong, 2021). By way of introduction we should provide some background regarding our study, which is a prospective naturalistic observational study of 20 years duration that includes six follow-up evaluations, having been funded almost continuously for over a 35 year period, 25 of those years by the National Institute of Mental Health, NIMH, in addition to 5 years of funding by the MacArthur Foundation and 4 years by the Center of Excellence in Mental Health. Our findings bring into question the current standard of practice that emphasizes long-term maintenance treatment with antipsychotic medication in patients with schizophrenia as the optimal strategy in all cases (American Psychiatric Association, 2020).

First with reference to Dr Pierre et al.'s comments regarding the problem of reverse association, the proverbial chicken and egg question, we would point out that this kind of confound is difficult to control because the relevant variables are unanticipated and often discovered long after a study is completed (Carvalho et al., 2020; Marquis, Habicht, Lanata, Black, & Rasmussen, 1997). As a prospective long-term naturalistic study over 20 years, the Chicago Follow-up Study has made extraordinary efforts to sufficiently consider patients' heterogeneity and minimize biases.

Our research design helped control for confound by indication. The design control feature was the administration of a battery of premorbid prognostic indicators at index hospitalization that allowed us to distinguish outcomes in good *v.* poor prognosis groups for those prescribed and those not prescribed antipsychotic medication, and because the battery assessed many background variables, confound by indication could be assessed by comparing treatment outcomes in different prognostic groups over the 20 year period.

In order to minimize biases, we developed a study design that sustained full independence between the research data gathering process and the treatment process over a 20 year period in order to distinguish clinical course, which was measured whether the subject was in treatment or not, from treatment exposure. Each follow-up interview involved many structured instruments to measure a multitude of variables but also open dialog between the examiner and research subject about life events that occurred between the follow-up periods, which not only provided structured measurements for potential confounding factors' adjustment but also generated a natural temporal sequence for certain measurements.

For example, the medication status is a measurement between the follow-up periods whereas the recovery status is an evaluation right on each follow-up time point. That is, recovery is always after medication at each follow-up, which indicates temporality. One might argue that patients might discontinue medication some time before the follow-up evaluation time period because they are already recovered or they might continue medication until the evaluation time period because they are not recovered, which can make it look like that patients without medication are more likely to recover. To explore this possibility, we counted the number of events (n_1) that patients are on medication and recovered at a follow-up time point and the number of events (n_2) that patients are no longer on medication at the next time point. Our data show that $n_1 = 17$ and $n_2 = 0$, which indicates that the possibility for recovered patients to discontinue medication is very low although not necessarily zero.

This design strategy, in which patients were followed up as they moved in and out of treatment, led to the paradoxical discovery, published in multiple previous papers, that individuals who dropped out of treatment, even in cases with worsening symptoms in which illness morbidity led to non-adherence of medication and leaving treatment, often had better long-term outcomes than patients who stayed under treatment. Studies that are treatment based, meaning that providers are also the research data collectors, lose research subjects who drop out either because the experimental drug exposure is not effective, or the subject is experiencing negative effects, or untoward side-effects, thus biasing the drug arm of the study in a positive direction because these subjects who choose to remain in the study are experiencing a positive response (Deaton & Cartwright, 2018). Most randomized controlled trials (RCTs) in psychopharmacology are of this type resulting in substantial biased differential dropout rates or attrition, often as high as 60%, which leads to an over reliance on missing variable analysis based on questionable assumptions regarding those who dropped out such as the assumption that

the dropouts are random in nature (Bell, Kenward, Fairclough, & Horton, 2013; Hróbjartsson, Emanuelsson, Skou Thomsen, Hilden, & Brorson, 2014; Krauss, 2018). Future antipsychotic medication studies should include genetic and non-genetic biomarkers for the potential to develop antipsychotic-induced dopamine supersensitivity psychosis, aiDSP and treatment resistance, and various forms of oxidative stress and genetic metabolic responses, which may affect dropout rates, side effect profiles, and outcomes more generally. It is now possible to track long-term antipsychotic side effects such as cognitive decline and metabolic syndrome more precisely (Bar-Yosef et al., 2020; Cem Atbaşoglu, Schultz, & Andreasen, 2001; Joshi et al., 2021; Scaini et al., 2018). We, therefore, recommend that researchers follow biomarker adaptive antipsychotic medication clinical trial designs, in order to control for a myriad of molecular confounders and long-term side effects (Perkovic et al., 2017).

Our findings support the view that providers and recipients of mental health care should enter into a partnership to assess the unique cost benefit in each individual case of long-term antipsychotic treatment and make informed decisions from time to time regarding evidence based deprescribing when appropriate. Providers should be aware of the emerging field of evidence based deprescribing practices as well as the administration of clinical scales for evaluating the presence of aiDSP, and that aiDSP not only manifests as a rapid rebound psychosis after discontinuing but can also manifest long after tapering or completely stopping antipsychotic medication often when individuals are experiencing minor stressful events (Cooper, Mason, Calton, Richardson, & Moncrief, 2021; Fallon, Dursun, & Deakin, 2012; Gupta, Steingard, Garcia Aracena, & Fathy, 2018; Horowitz, Jauhar, Natesan, Murray, & Taylor, 2021; Le Bosquet, Barnett, & Minshull, 2019; Oda, Kanahara, & Iyo, 2015; Steingard, 2018).

We should also not lose sight of the fact that statistical studies, both RCTs and long-term naturalistic studies, generate associations between variables not measures of causality. To go a step further and make causal inferences that involve more than just weighing the strength of associations specific criteria are necessary. Indeed the gold standards for making causal inferences in statistical research are the Bradford Hill criteria. A statistical association must past the test of fulfilling these criteria to qualify as a measure of causality. With the advent of molecular biomedicine and precision medicine the Bradford Hill criterion of 'specificity', or the specific molecular mechanisms that have been found to underlie a strong statistical association, has assumed a dominant position in assessing causality. In the case of our study the association between long-term antipsychotic use and negative outcome is most likely based on the molecular mechanisms of aiDSP (Goff, Tsai, Beal, & Coyle, 1995; Howes et al., 2012; Samaha, Seeman, Stewart, Rajabi, & Kapur, 2007; Thompson, de Vries, & Sommer, 2020) and antipsychotic-induced brain shrinkage largely in fronto-temporal cortical areas due to oxidative stress and neuronal loss (Aderhold, Weinmann, Hägele, & Heinz, 2015; Dorph-Petersen et al., 2005; Fusar-Poli et al., 2013; Raudenska et al., 2013; Vita, De Peri, Deste, Barlati, & Sacchetti, 2015). It is ironic that the recent American Psychiatric Association recommendations for long-term antipsychotic use in patients with schizophrenia recommend switching to clozapine when patients stop improving on their initial antipsychotic medication, in that clozapine has been found to mitigate the molecular sensitivity reaction in the dopamine system aiDSP caused by the long-term use of antipsychotic medications, and also to reduce the long term mortality risk associated with all other antipsychotic medications.(American Psychiatric Association, 2020; Fava, 2020; Fedak, Bernal, Capshaw, & Gross, 2015; Kobayashi et al., 2020; Kose & Cetin, 2018; Oishi et al., 2018; Vermeulen, van Rooijen, van de Kerkhof, Sutterland, Correll, & de Haan, 2019).

As an introduction to our second commentator, Dr Aftab, we should take a page from the conceptual clarity school of the philosophy of psychiatry, which he has pioneered, by emphasizing the point that the myriad of brain changes that have been found to underlie much of the phenomenology of mental disorder, thanks to modern radioligand positron emission tomography (PET) studies, functional magnetic resonance imaging (fMRI), diffusion tensor imaging brain imaging, modern electrophysiology and single-cell recording, bioenergetics, epigenetics, neurosteroid research, genomic biomarkers, dendritic calcium imaging, connectomics, peripheral biomarkers, optogenetic analysis, focused ion beam/scanning electron microscopy (FIB-EM) etc. do not necessarily indicate pathological states of the brain because all behavior and all conscious and unconscious states, no matter how extreme, have potentially reversible neuronal correlates that may solely result from psychosocial stress and trauma (Carvalho et al., 2020; Schultze-Lutter, Schmidt, & Theodoridou, 2018). To count as a pathological brain lesion signifying a disease state requires another distinctive level of assessment as to whether the brain process in question constitutes a brain lesion such as is the case of prionopathy, a viral encephalitis, a tauopath, a case of ischemic hypoxic atrophy, a demyelinating disease, an hemorrhagic stroke, a neoplastic change, a genetic protein storage disease, etc. Although we cannot therefore be sure that the brain changes thought to be treated by antipsychotics, such as neuromodulatory bioenergetic, and neuroplastic imbalances, are true disease states, we can be reasonably sure that the iatrogenic brain changes that strongly correlate with underlay the long-term use of antipsychotics such as aiBS, antipsychotic induced brain shrinkage, aiDSP, tardive dyskinesia, tardive dystonia, tardive psychosis or dysmentia, neuroleptic malignant syndrome, derangement of glucose metabolism, etc. are diseased in nature (Wilson, Garbutt, Lanier, Moylan, Nelson, & Prange, 1983).

In response to Dr Aftab's thoughtful questions we have addressed each of his questions as listed and numbered below followed by our answers.

(1) What exactly does antipsychotic use/antipsychotic prescription variable represent? The manuscript switches between the language of individuals being 'on antipsychotics' and 'prescribed antipsychotics'.

The terms 'on antipsychotics' and 'prescribed antipsychotics' were used interchangeably throughout the manuscript and hold the same meaning in that the individual endorsed that they were taking their prescribed medications. Individuals who were in treatment and not taking antipsychotics had made that decision independently or partially independent of the advice of their prescribing psychiatrist. In many cases the individuals independently decided not to take their prescribed antipsychotic medications.

(1) How was the recovery variable handled in statistical analysis? It is unclear how exactly the relationship between

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antipsychotic medications and recovery status on follow-up visits was determined.

Both recovery and medication status have binary outcomes (yes/no) and are treated as longitudinal variables, which have a maximum of six observations at the six follow-up time points. The medication status was on and before each follow-up time point and the recovery status was evaluated right on each time point. Such a study design on a temporal sequence for progress on medication and recovery status can help to reduce the possibility of reverse causation (Hill, 1965). The major statistical method used in the analysis is logistic regression with generalized estimating equation (GEE). Since most of Dr Aftab's questions are related to the statistical models, we give an introduction on the logistic GEE model before answering further questions.

Logistic regression is one of the generalized linear models (GLMs) and is widely used in practice to model binary outcome variables (McCullagh & Nelder, 1989). Coefficients for risk factors are the major parameters of interest in logistic models. The odds ratio for a risk factor in a logistic model is the exponential of the coefficient for this factor. We will discuss odds ratios with more details in the next paragraph. The GEE is used to estimate the parameters in a GLM with a possible unknown correlation between outcome variables (Liang & Zeger, 1986). In our data, participants were followed up at a maximum of six time points which generated repeated measurements through time. Observations from the same individual tend to be correlated, which needs to be taken into account for a valid inference. The choice of logistic models with GEE in the paper is consistent with such features of our data (Ballinger, 2004).

An odds ratio is the ratio of two odds: $(p/(1-p))/(q/(1-q))$, where p is the probability of an outcome with a risk factor and q is the probability of the same outcome without this risk factor. An odds ratio of 1 indicates that this risk factor does not associate with the outcome; greater than 1 indicates that this risk factor positively associates with the outcome and higher odds ratio indicates stronger positive association; less than 1 indicates that this risk factor negatively associates with the outcome and lower odds ratio indicates stronger negative association. When p or q is small, the odds ratio approximately equals to the relative risk: p/q. The estimated odds ratio for a risk factor in a logistic model can be explained similarly as above by assuming that all the other factors are fixed at the same value. For example, an odds ratio of six for a risk factor indicates a positive association between the outcome and the risk factor, which is usually described as six times more likely/more often for an outcome to happen with this risk factor than without it. Although strictly speaking such a statement is statistically sound only when p or q is small enough, it is more widely accepted by practitioners than the statement on odds ratio itself. More explanations on odds ratios can be found in the book of McCullagh and Nelder (1989), as well as articles such as (1) The odds ratio: calculation, usage, and interpretation (McHugh, 2009), and (2) Explaining odds ratios (Szumilas, 2010).

More specifically, to answer Dr Aftab's question, data were NOT aggregated. There will be information loss and sample size shrinking during aggregation so it is not a good choice for us. In our fitted logistic models with GEE, the estimated odds ratio for the risk factor of antipsychotic medication (not on medication *v.* on medication) was 5.989 [95% confidence interval (CI) 3.588–9.993] for the outcome variable recovery. Therefore, the likelihood of recovery does NOT mean recovery on at least one follow-up visit or in some other aggregated way. Instead, it means that at any time point, two individuals A and B, assuming that A is on antipsychotic medication, B is not, and all the other risk factors for A and B are the same, then B is about six times more likely to be in the recovery status than A.

(1) How were missing values handled? Missing values are alluded to, but no further information is provided.

Since our data include participants with four or more of the six follow-up evaluations with 91% of the participants studied at five or six follow-ups, and there was no significant difference in the number of follow-up evaluations, missing values were not a major concern in this study and were assumed missing at random.

(1) 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.

Since data were treated as longitudinal variables in the logistic GEE models, change of medication status or any other time-dependent variables is not a problem and can be handled separately and properly at each time point.

(1) 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?

The group classification of Always *v.* Intermittently *v.* Never psychotic is for initial exploration and intuitive understanding of the data. In the more comprehensive analysis with logistic GEE models, the psychotic status itself is already an outcome variable in the model. Thus, there is no need to control for such a group classification.

(1) Were temporal relationships between recovery status, hospitalization, global assessment of functioning (GAF), and antipsychotic use looked at?

Our major focus in this paper is to explore how antipsychotic use is associated with recovery, hospitalization, and GAF. How these variables predict antipsychotic use on prospective follow-up visits were not directly examined in this study and can be an interesting topic in future research. Answers to this question can strengthen our understanding on the complex progress process of psychiatry but won't affect our conclusions on the association between these variables and the antipsychotic use.

To date, the Chicago Follow-up Study has published seven papers focusing specifically on the topic of antipsychotic medication and have examined multiple outcomes and considered multiple confounds and in each study the findings '*highlight the importance of prescribers to work together in partnership with individuals with psychosis to continuously and consistently evaluate the need for antipsychotic medication*' this point is to stress that prescribers should not assume that antipsychotic medications are essential for continued stability (Harrow et al., 2021). Overall, our multiple antipsychotic focused studies have shown that

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'because there is considerable outcome heterogeneity in schizophrenia patients regardless of treatment employed, a more directed research agenda involving subgrouping according to response to treatment is needed…longitudinal studies indicate the importance of further research on how many schizophrenia patients profit from continuous administration of antipsychotics over a prolonged period, what factors identify and separate schizophrenia patients who do not need prolonged antipsychotic treatment, and whether or not prolonged use of antipsychotics is harmful for some or many patients. Overall discussion of the risk-benefit profiles for different subgroups of schizophrenia patients in different stages of illness seems warranted' and continues to be warranted (Harrow et al., 2021; Harrow & Jobe, 2007, 2013, 2018; Harrow, Jobe, & Faull, 2012, 2014; Harrow, Jobe, Faull, & Yang, 2017; Jobe & Harrow, 2010).

(1) The interpretation of odds 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'.

These two sentences are consistent. A more complete version for the sentence in the abstract would be: The adjusted odds ratio of not on antipsychotic medication (*v.* on antipsychotic medication) was 5.989 (95% CI 3.588–9.993) for (the outcome variable) recovery. Refer to response to Question (2) for more details on odds ratio explanations.

In closing, the Chicago Follow-up Study challenges current prescribing practices that operate under the precept that individuals with psychosis, specifically individuals diagnosed with schizophrenia, require life-time antipsychotic medications, especially at maintenance levels. Our data show that the individual course and trajectory is extremely heterogeneous and medication effectiveness, tolerability, side-effect profile is equally heterogeneous; that many individuals, for multiple reasons (asymptomatic or medication side-effects), with and/or without prescribers will intermittently discontinue antipsychotic medication treatment and maintain their recovery while some individuals will experience a relapse. We also show in this naturalistic study design study that a sub-group of individuals not taking antipsychotic medications can have better outcomes than individuals taking antipsychotic medications even when multiple confounds by indication were controlled for. Current studies are closing the translational research gap toward the development of medications that would mitigate some of the serious side effects of currently available dopamine blocking drugs, even including targeting increased dopamine synthesis directly rather than blocking dopamine D2 receptors specifically, providing a pathway to avoid the potential for developing aiDSP (Jauhar et al., 2017). Several trials are currently underway for non-dopamine blocking medications for both positive and negative symptoms that show encouraging results (Goff, 2020; Strauss et al., 2020).

Finally, we emphasis again, the importance for prescribers to not assume that medications are essential longitudinally for continued stability for individuals diagnosed with schizophrenia but rather to work together in partnership with individuals with psychosis to continuously and consistently evaluate the need for ongoing antipsychotic medication.

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Conflict of interest. I have listed and confirmed for all authors, that there is no financial involvement (including employment, fees, and share ownership) or affiliation with any organization whose financial interests may be affected by material in the manuscript, or which might potentially bias it.

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