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Letter to the Editor

Is a higher dose of antipsychotic medication required to treat a relapse following discontinuation in first episode psychosis?

Dear Editors,

Antipsychotic medications are effective in treating positive psychotic symptoms (Leucht et al., 2009) and preventing relapse (Leucht et al., 2012). Yet, prolonged exposure is associated with adverse effects (Young et al., 2015). Clinicians should use the minimum dose for the minimum duration in order to achieve and sustain recovery. However, it is currently not possible to predict the necessary dose or duration for each individual. Unnecessarily prolonged use of antipsychotics may increase adverse effects, while trials of discontinuation may lead to relapses.

There is concern that individuals who relapse may not achieve subsequent remission (Emsley et al., 2013) or may require a dose increase in order to do so. Therefore, unsuccessful discontinuation may inadvertently result in an increased exposure to antipsychotic medication. Dosing comparisons between first and multi-episode individuals have been used to support this claim. Significant symptomatic improvements have been demonstrated amongst first episode individuals at doses much lower than those required by multi-episode individuals (McGorry et al., 2011). Yet, evidence directly correlating relapse with dose increase is absent from the literature.

The present study compared the dose of antipsychotic medication required to achieve initial remission to the dose required to achieve remission following relapse. It also aimed to identify demographic and clinical characteristics associated with requiring a dose increase.

This study was conducted at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia. The EPPIC service is a component of Orygen Youth Health, a specialist youth mental health service for individuals aged 15 to 24 residing in the northwestern regions of Melbourne, Australia.

This study included individuals aged 15 to 24 presenting with a FEP over a three-year period (01.01.11–31.12.13). An FEP was defined as a DSM-IV psychotic disorder encompassing both affective and non-affective psychoses, drug induced psychosis, and psychosis not otherwise specified. Further inclusion criteria were: a trial of antipsychotic discontinuation post initial remission; relapse; and post relapse follow up data of at least three months duration.

This was a longitudinal cohort study. Information was obtained retrospectively from each individual's clinical file. Positive symptom severity was quantified at service entry and at three monthly intervals thereafter until discharge using the Short Form SAPS (Alonso et al., 2008). Remission was defined as positive symptoms of severity rating less than or equal to two for at least twelve weeks. Relapse was defined as the return of positive symptoms of severity greater than a rating of two for at least one week. Discontinuation was defined as the cessation of one antipsychotic without commencing another, or as greater than one-week between ceasing an antipsychotic and commencing another. This study received ethical approval from the Royal Melbourne Hospital Human Research and Ethics Committee.

For the purposes of this study, the Defined Daily Dose (DDD) method of calculating dose equivalence across antipsychotics was chosen. Olanzapine was used as the standardized benchmark. Conversions were performed using data from Leucht et al. (2015) (Supplementary Data; Table 3). Before conversion to olanzapine equivalents, depot medications were converted to oral equivalents using either the manufacturer guide or the Maudsley prescribing guidelines (Taylor et al., 2015).

The Wilcoxon signed rank test was used to determine whether there was a difference in the dose of antipsychotic medication required to achieve initial remission and the dose required for subsequent remission. Pearson Chi-Square test was used to determine whether categorical variables were associated with dose increase (Table 1).

During the study period, 544 individuals presented with a FEP. Of these, 332 (61%) had a trial of discontinuation of whom 113 (34%) experienced a relapse within a median follow up of 372 days (IQR 183.5–536.0 days). Of these 113 individuals, ten were discharged, six were lost to follow up, one was deceased, and data was missing for ten. Therefore, data was available for 86 individuals (76.1%, $N = 86$). These individuals were more likely to be older and female (Supplementary Data; Table 2).

For those with data, 91.9% ($N = 79$) achieved remission, while seven (8.1%) continued to experience positive psychotic symptoms. Of those who achieved symptomatic remission, 88% ($N = 68$) recommenced antipsychotic medication. Over half of the cohort (55.9%, $N = 38$) required a higher dose to achieve remission, while 29.4% ($N = 20$) achieved remission on a lower dose, and 14.7% ($N = 10$) achieved remission on the same dose.

The median olanzapine equivalent dose prior to discontinuation was 8.00 mg (IQR 5.25 mg–14.38 mg) compared to 12.90 mg (6.87–20.00) at remission post relapse ($Z = -3.191$ $p = 0.001$). No demographic or clinical factors were associated with a higher dose of antipsychotic medication being required to achieve remission following relapse (Table 1).

The majority of individuals who experienced a relapse following discontinuation required a higher dose to achieve subsequent remission and not all individuals experienced remission within the follow-up period. No demographic or clinical factors were found to be associated with a higher dose being required.

There are a number of potential explanations for these findings. First, this was a naturalistic observational study and it is possible that clinicians prescribed a higher dose based on the assumption that a higher dose is required after relapse. While there are specific guidelines for the treatment of a first episode of psychosis that advise 'start low and go slow,' such guidelines do not exist for relapse and as such, medications may be resumed at higher doses or titrated up quickly. Alternatively, there may be tolerance to dopamine blockade following treatment of the initial episode and relapse. Finally, the requirement for a higher dose may be associated with illness progression.

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Table 1
Predictors of dose increase.

Factor		Higher dose		Lower or same dose		Significance
		N	%	*N*	%	
Sex	Male	28	56.0	22	44.0	0.71
	Female	11	61.1	7	38.9	
1st degree family history	Present	6	60.0	4	40.0	0.86
	Absent	33	56.9	25	43.1	
Migrant status	Born in Australia	26	51.0	25	49.0	0.07
	Not born in Australia	13	76.5	4	23.5	
Co morbid substance abuse	Present	27	56.3	21	43.8	0.78
	Not present	12	60.0	8	40.0	
Cannabis abuse	Present	26	56.5	20	43.5	0.84
	Not present	13	59.1	9	40.9	
Diagnosis	Affective	15	50.0	15	50.0	0.28
	Non-affective	24	63.2	14	36.8	

The findings must be considered within the limitations. First, there was missing data for a proportion of individuals who experienced a relapse following discontinuation. Second, data was obtained retrospectively from the clinical file and therefore is susceptible to bias and is limited to what was documented.

Individuals who wish to discontinue must be counseled about the significant risk of relapse, but also the risk of non-remission and the necessity of dose increase. At present, it is not possible to identify which individuals may be more likely to require dose increase after relapse.

Conflict of interest
The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.07.032.

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