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Five-fold increased risk of relapse following breaks in antipsychotic treatment of first episode psychosis

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ABSTRACT

Background: A key problem in the management of first episode psychosis is that patients are often reluctant to take antipsychotic medication, especially once their presenting symptoms have resolved. Clinicians may be tempted to trial a 'break in treatment' in such patients.

Aim: To assess the impact of interruptions in the antipsychotic treatment of first episode psychosis.

Method: Treatment adherence and clinical course were assessed during the 18 months following presentation in 136 consecutive patients with a first episode of psychosis in 2003–2005 by a systematic retrospective casenote review. Regression analyses were used to examine the time to remission and the risk of relapse in patients who had stopped antipsychotics for one month or more.

Results: There were breaks in antipsychotic treatment of ≥ 1 month in more than half of the patients ($n = 73$; 58%). When these occurred before they had recovered ($n = 22$; 17%), the time to remission was almost twice as long as in patients in whom treatment was continuous ($t = 2.9$, $P = 0.01$). Patients in whom treatment was interrupted were 5 times more likely to have relapsed than those in whom it was continuous ($p = 0.0001$, 95%CI 2.1–11). The mean time to relapse following an interruption in treatment was 3 months.

Conclusion: If the treatment of first episode psychosis with antipsychotic medication is stopped for a month or more, remission may be delayed and the risk of relapse following remission may be substantially increased.

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1. Introduction

Antipsychotic medication is the mainstay of treatment for first episode psychosis (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011; NICE, 2010). However, approximately half of first episode patients are poorly adherent with antipsychotic medication in the 12 months following the initiation of treatment (Lambert et al., 2010; Perkins et al., 2008). Paradoxically, the typically rapid resolution of symptoms in first episode psychosis can lead patients to believe that treatment is no longer necessary (Kane et al., 2013; Robinson et al., 2002). It is well established that complete discontinuation of antipsychotic treatment at this stage delays the time to first remission (Malla et al., 2006) and increases the risk of relapse after remission (Robinson et al., 1999). However, subsequent evidence suggests that even brief periods of non-adherence can also have an adverse effect on outcome (Subotnik et al., 2011).

In the present study, we examined the impact of interruptions in the antipsychotic treatment of patients with a first episode of psychosis on

their clinical course. We tested the hypothesis that even short breaks in antipsychotic treatment would a) delay remission and b) increase the risk of relapse following remission.

2. Methods

2.1. Design

This was a retrospective cohort study of 136 cases of first episode psychosis that presented consecutively to the Lambeth Early Onset (LEO) early intervention service in London, UK (Power et al., 2007b) between 2003 and 2005. Subjects were initially assessed at baseline, as previously reported (Power et al., 2007a) and for the current study were followed up 18 months after presentation by retrospectively examining the clinical notes at one month intervals between baseline and follow-up.

2.2. Inclusion and exclusion criteria

Inclusion required a diagnosis of first episode of psychosis, (ICD-10 F20-29) (World Health Organization, 2004), that the patient was 18–35 years old, and resident of the borough of Lambeth (population

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270,000). Psychosis was defined as more than one week of unremitting psychotic symptoms according to the Comprehensive Assessment of At Risk Mental States (Yung et al., 2005), and diagnosis was confirmed using an operationalized diagnostic classification system based on ICD-10, as previously published (Coentre et al., 2011). Patients with an affective or 'organic' psychosis were excluded. 10 patients were lost to follow-up at 18 months. For 9 cases out of those 10, no data were available for the parameters included in this study and hence were excluded from the analysis, leaving 127 cases. Participants provided written consent prior to the baseline interview for collection of follow-up data and the study was approved by a local ethics board.

2.3. Treatment

The type of treatment provided at presentation and over the following 18 months was determined by the patients' clinical team, an early intervention service that explicitly sought to maximize early detection, engagement and adherence with treatment in order to reduce duration of untreated psychosis (DUP) and to minimize adverse effects through the use of the lowest doses of antipsychotic medication that were effective (Power et al., 2007b). Management also involved (when necessary) admission to a specialised inpatient facility for first episode patients, and assertive community care, with involvement of family members and relatively frequent clinical contact – at least once per month including through periods of prolonged remission.

2.4. Data collection procedure

Patients were interviewed at baseline by trained research psychologists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Calgary Scale for Depression (Addington et al., 1993). Premorbid functioning was assessed using the Global Assessment of Functioning scale (GAF) (Jones et al., 1995), and insight was evaluated using a specialised rating scale (David et al., 1992). Baseline characteristics in the sample and aspects of study design and methodology have been previously described in detail (Power et al., 2007a).

For the present study, follow up data were collected from a systematic review of the complete clinical case notes covering an 18 month period following first presentation. For each month during this period, clinical status, treatment engagement and medication adherence were rated by trainee psychiatrists (PBP, RS, MF) under the supervision of the senior consultant psychiatrist (PP) using operationalized criteria for 'Clinical status' (Table 1) and 'Adherence' (Table 2) derived from previous studies (Bebbington et al., 2006; Craig et al., 2004). Adherence was determined by combining a number of sources including case file notes, patient reports, carer reports, case manager reports of scripts and pharmacy records of medication dispensed. At each month the presence of potential adverse effects of treatment (subjective reports categorized in to sedation, weight gain and extra pyramidal symptoms, EPSE) and use of illicit psychoactive substances were also recorded. OPCRIT diagnostic evaluation (McGuffin et al., 1991) was undertaken retrospectively blind to outcome from the casefile notes by the follow-up evaluators (PBP, RS, MF) and senior consultant psychiatrist (PP) as previously described (Coentre et al., 2011).

2.5. Analysis of outcomes

We analyzed the impact of a 'Break in treatment' (not taking antipsychotics continuously for one month or more – yes/no) on two outcome variables, 'Time to remission from first episode' (in days) and 'Relapse' (yes/no). For the latter, both 'true relapses' and 'exacerbations' were grouped together.

We also examined the relationship between a set of Pre-treatment, Baseline and Follow-up potential explanatory variables (Table 2) with the clinical outcome and adherence variables.

Table 1
Definitions.

Definition of clinical outcomes	
Full remission	Complete remission of psychotic symptoms is achieved and maintained for two consecutive months.
Partial remission	<i>Full remission</i> is not achieved, however a sustained improvement in psychotic symptoms is reached and maintained for two consecutive months. This period must be free of moderately severe (or worse) psychotic symptoms.
Non-remission	Neither <i>full</i> nor <i>partial remission</i> has been achieved and moderately severe (or worse) psychotic symptoms persist.
True relapse	A period of at least two consecutive weeks of moderately severe (or worse) positive psychotic symptoms re-emerging after a period of <i>full remission</i> . The level of severity of symptoms is corroborated by an increase in the level of care (hospital admission; referral to crisis house/home treatment or crisis resolution team) AND/OR change in management (increase in clinical contact and/or medication) AND/OR decreased levels of social function.
Exacerbation	A period of at least two consecutive weeks of moderately severe (or worse) psychotic symptoms re-emerge after a period of <i>partial remission</i> . The level of severity of symptoms is corroborated by an increase in the level of care (hospital admission; referral to crisis house/home treatment or crisis resolution team) AND/OR change in management (increase in clinical contact and/or medication) AND/OR decreased levels of social function.
Definition of adherence outcomes	
Medication adherence	Expressed as a percentage of each monthly interval that the patient reported they took their prescribed antipsychotic medication. <i>Full adherence</i> = patient reported they took their medication 100% of the time.
Break in treatment	Not taking prescribed antipsychotic medication continuously for at least one month and restarted later on, at any point during 18 months.

2.6. Statistics

Statistical analysis was performed with SPSS 17 for Windows. Skewed data (DUP) were log transformed prior to analysis. Prediction of 'time to remission' by 'Break in treatment' was analysed by linear regression while the prediction of the binary outcome variable 'relapse' by 'Break in treatment' was analysed using logistic regression. 'Time to relapse from the time of remission' was then tested as a dependent variable using a cox-regression analysis generating a survival plot with 'Break in treatment' entered as a covariate of interest.

Analyses of Pre-treatment, Baseline and Follow-up potential explanatory variables against adherence and clinical outcome variables were performed with Chi-square testing for categorical variables and independent sample t-tests for continuous variables. Those variables

Table 2
Potential explanatory variables.

Pre-treatment variables	Baseline variables	Follow-up variables
<ul style="list-style-type: none"> Gender Ethnicity (BME/-Caucasian) Age at onset of psychosis (years) DUP (days) 	<ul style="list-style-type: none"> Age (in years) Substance use (cannabis, stimulants, alcohol, other) (yes/no) Symptoms scores; PANSS, GAF, Calgary depression score, Insight score 	<ul style="list-style-type: none"> Symptoms scores; PANSS, GAF, Calgary depression score, Insight score Antipsychotic type (Olanzapine, Quetiapine, Risperidone) Substance use (cannabis, stimulants, alcohol, other) (yes/no) Carer involved (yes/no) Side effects to medications (yes/no)

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