Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Rates and predictors of relapse following discontinuation of antipsychotic medication after a first episode of psychosis

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ARTICLE INFO

Article history:
Received 24 July 2017
Received in revised form 19 September 2017
Accepted 15 October 2017
Available online xxxx

Keywords:
Psychosis
Schizophrenia
Antipsychotic medication
Discontinuation
Relapse

ABSTRACT

Background: There is uncertainty about the required duration of long-term antipsychotic maintenance medication after a first episode of psychosis. Robust predictors of relapse after discontinuation are yet to be identified. The present study aimed to determine the proportion of young people who discontinue their antipsychotic medication after a first episode of psychosis, the proportion who experience relapse, and predictors of relapse.
Methods: A retrospective study of all individuals presenting to the Early Psychosis Prevention and Intervention Centre between 01/01/11 and 31/12/13 was conducted. A Cox regression analysis was conducted to identify predictors of relapse.
Results: A total of 544 young people with a FEP were included. A trial of discontinuation was undertaken by 61% of the cohort. Median duration of antipsychotic medication prior to first trial of discontinuation was 174.50 days. Amongst those trialing discontinuation, 149 (45.8%) experienced relapse in a median follow-up time post discontinuation of 372 days. On multivariate analysis, predictors of relapse were a diagnosis of cannabis abuse disorder (HR: 1.40), and longer duration of antipsychotic medication (HR: 1.05).
Conclusion: Antipsychotic discontinuation frequently occurs earlier than guidelines recommend. Individuals with a diagnosis of cannabis abuse are more likely to experience relapse and addressing this substance abuse prior to discontinuation could possibly reduce relapse rates.

1. Introduction

Antipsychotic medications are effective in treating the symptoms of psychotic disorders, especially positive symptoms (Leucht et al., 2009). With such treatment, symptomatic remission is achieved in as many as 80% of individuals affected by a first episode of psychosis (FEP) (Malhi et al., 2010). However, when used long-term, antipsychotic medications can carry significant morbidity and mortality implications (Correll et al., 2009). Potential physical health complications include weight gain, dyslipidemia and diabetes, and possible structural brain changes (Fusar-Poli et al., 2013). A FEP is a clinical presentation that warrants unique treatment guidelines. Those affected are typically young, drug naïve, require lower doses of antipsychotic medication, and are more sensitive to side effects (Alvarez-Jimenez et al., 2016). In recent years, significant questions have arisen around the necessity of long-term maintenance antipsychotic medication in this population (Murray et al., 2016).

Current clinical guidelines recommend maintenance medication for between a minimum of one to two years following remission after a FEP (Taylor et al., 2011). However, contrary to such guidelines, up to 70% of individuals disclose that they ceased their medications within less than twelve months of achieving remission (McEvoy et al., 2007). Interestingly, this practice appears to be supported by the majority of clinicians, with less than one third believing that antipsychotic medication should be continued for over a year after clinical remission (Thompson et al., 2016).

Whilst long-term use of antipsychotic medications pose potential risks, so too does discontinuation. Relapse rates vary across studies, but are consistently higher amongst those who discontinue antipsychotic medication and are reduced with maintenance treatment (Zipursky et al., 2014). Some believe that relapse may hinder or reverse the gains made in social and vocational functioning whilst on maintenance treatment (Kam et al., 2015). There are also concerns that individuals may not respond as effectively to antipsychotic medication following relapse as for the first episode (Lieberman et al., 1996). Yet,

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https://doi.org/10.1016/j.schres.2017.10.030
0920-9964/

not all those who discontinue maintenance medication will experience relapse.

Considerable research exists with respect the factors predictive of relapse after a FEP. However, most studies have been conducted amongst individuals who remain on maintenance antipsychotic treatment (Diaz-Caneja et al., 2015). Importantly, predictive factors may differ between those who continue medication, and those who discontinue (Hui et al., 2013). At present, there is a paucity of information to guide clinicians in either supporting or advising against medication discontinuation after remission following a FEP.

A trial of discontinuation after remission is a common request, and following discontinuation, some individuals are able to sustain remission (Gaebel et al., 2016; Wunderink et al., 2007). In order to guide clinicians in pre-discontinuation counseling, there would be utility in being able to identify those individuals for whom either relapse or sustained remission is likely. As such, the present study is an analysis of the demographic and clinical predictors of relapse following discontinuation of antipsychotics after a FEP.

The study aimed to determine: i) the proportion of young people with a FEP who undergo at least one trial of discontinuation of their antipsychotic medication during their episode of care; ii) the proportion of those who discontinue their medication and experience a relapse of psychotic symptoms; and iii) the demographic and clinical predictors of relapse following a first trial of discontinuation.

2. Methods

2.1. Materials and methods

The study involved a retrospective study of an epidemiological cohort of 544 individuals who received treatment with the Early Psychosis Prevention and Intervention Centre (EPPIC) and were diagnosed with a FEP.

2.2. Context and setting

The EPPIC program offers a comprehensive service to young people aged 15 to 24 years experiencing a FEP. Treatment duration is an average of eighteen months and a maximum of twenty-four months (except for those under the age of 18, who can continue to receive service beyond two years until their 18th birthday). The EPPIC catchment area covers the northwestern regions of Melbourne, Australia, which represents more than one million people, sees approximately 400 cases at any one time and has between 150 and 200 new referrals per year. The service therefore ascertains a treated epidemiological sample of individuals affected by a FEP.

2.3. Case identification and eligibility criteria

Individuals included in this study were assessed over the period from the 1st January 2011 to the 31st December 2013. In total, 555 individuals presented to EPPIC during the study period. Criteria for inclusion within the present study were a diagnosis of FEP according to DSM-IV criteria, and residence within the catchment area at the time of presentation. Individuals with co-morbid substance misuse or dependence, co-morbid personality disorders, and intellectual disability were included. Six individuals were excluded because of a non-psychotic diagnosis at discharge and five files were unavailable. Thus, data was collected for the remaining 544 eligible individuals.

2.4. Data sources, measures and definitions

2.4.1. Medical records

During treatment with EPPIC, individuals received outpatient services and were eligible for inpatient admissions where clinically indicated. In the first three months of treatment, individuals were typically seen weekly and then this was extended to fortnightly, or more frequently where clinically indicated. Clinical notes were documented by the case-manager, treating registrar or consultant psychiatrist. For each individual, information collected during the episode of care was recorded and stored in a single file.

An instrument was developed to facilitate extraction of quantitative data concerning pre-treatment and baseline characteristics, as well as treatment course and outcome measures. Case files were analysed from the time of registration with OYH. The follow up period was twenty-four months or until discharge from the EPPIC service. The author (MB) and four other researchers (LD, KT, SE and MBW) extracted all data by accessing components of each individual's file.

2.4.2. Predictor variables

The following demographic factors were analysed as potential predictors of relapse: age at service entry; sex; and a family history of psychotic disorders in a first or second-degree relative. The following clinical factors were analysed as potential predictors of relapse: a diagnosis of schizophrenia spectrum disorder; an affective as compared to a non-affective diagnosis; cannabis abuse; amphetamine abuse; the severity of positive and symptoms negative symptoms at service entry; the duration of antipsychotic medication treatment prior to the first trial of discontinuation; medication non-compliance; and the occurrence of relapse prior to a first trial of discontinuation.

Diagnoses of psychosis and co-morbidities, including a diagnosis of substance abuse, were made by the treating consultant psychiatrist at three months after service entry and reviewed at discharge according to DSM-IV classification of mental disorders. Some individuals disengaged from the service before a longitudinal assessment and adequate diagnosis could be made. These individuals were given a generic diagnosis of FEP.

The severity of psychotic symptoms were assessed and rated at baseline, and at three monthly intervals thereafter. Positive and negative symptoms were rated as per the short form SAPS and SANS (Alonso et al., 2008). Routinely, case managers and psychiatrists conduct and document mental state examinations in the clinical notes (Gottlieb, 1974). These were used as the basis from which to assess and rate psychotic symptoms using SAPS and SANS criteria. At the conclusion of data collection, all researchers (MB, LD, KT, SE and MBW) participated in inter-rater reliability testing through independently completing five ratings performed across five individual files.

Inter-rater agreement was assessed for the five assessors across five different participants. The level of agreement on all of the individual positive psychotic symptoms items ranged from 80 to 100%. The individual items of the SAPS were scored from 0 to 5 and there were no discrepancies between scores of greater than one unit difference. In regards to determining levels of remission, there was one case which had a symptoms rating of 2 (which corresponded to remission of symptoms) and there was 100% agreement on this item. One of the cases had a symptoms rating of 3 and there was 80% agreement on this item.

For each antipsychotic medication prescribed, the date of commencement, date of cessation and compliance were recorded. Compliance was ranked as compliant, whereby the individual reported taking 75%–100% of prescribed doses, partially compliant, 25%–74% of prescribed doses, or non-compliant, whereby <25% of prescribed doses were reported taken (Donohoe et al., 2001). Within the clinical file, reports by either the young person or their clinical team were used as the basis from which to assess compliance.

2.4.3. Outcome measures

Outcome measures were the first trial of antipsychotic discontinuation and the occurrence of relapse. A trial of antipsychotic discontinuation was defined as ceasing one antipsychotic and not commencing another, or as greater than one-week duration between ceasing one antipsychotic medication and commencing another. Discontinuation covered all all-causes for discontinuation. Remission was defined as positive psychotic symptoms of severity less than or equal to two on the short form SAPS for a period of at least twelve weeks. Relapse was

Please cite this article as: Bowtell, M., et al., Rates and predictors of relapse following discontinuation of antipsychotic medication after a first episode of psychosis, Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.10.030