

# The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication

Dicapite, Suzanne; Upthegrove, Rachel; Mallikarjun, Pavan

DOI:  
[10.1111/eip.12385](https://doi.org/10.1111/eip.12385)

License:  
None: All rights reserved

Document Version  
Peer reviewed version

Citation for published version (Harvard):  
Dicapite, S, Upthegrove, R & Mallikarjun, P 2018, 'The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication', *Early Intervention in Psychiatry*, vol. 12, no. 5, pp. 893-899. <https://doi.org/10.1111/eip.12385>

[Link to publication on Research at Birmingham portal](#)

**Publisher Rights Statement:**  
Checked for eligibility: 04/10/2016

This is the peer reviewed version of the following article: Di Capite, Suzanne, Rachel Upthegrove, and Pavan Mallikarjun. The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication. *Early Intervention in Psychiatry* (2016)., which has been published in final form at: <http://dx.doi.org/10.1111/eip.12385>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



**The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication**

|                               |  |
|-------------------------------|--|
| Journal:                      | <i>Early Intervention in Psychiatry</i>  |
| Manuscript ID                 | EIP-2016-061.R1  |
| Manuscript Type:              | Original Article   |
| Date Submitted by the Author: | 12-Jul-2016  |
| Complete List of Authors:     | Di Capite, Suzanne; University of Birmingham, Department of Psychiatry Upthegrove, Rachel; University of Birmingham, Institute of Clinical Sciences ; Forward Thinking Birmingham, Early Intervention Service Mallikarjun, Pavan; University of Birmingham, Institute of Clinical Sciences / School of Psychology; Forward Thinking Birmingham, Early Intervention Service |
| Keywords:                     | Antipsychotics, first episode psychosis, Discontinuation, relapse rates, risk factors  |
|                               |  |

Review

# The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication

Suzanne Di Capite<sup>1</sup>, Rachel Upthegrove<sup>1,2</sup>, Pavan Mallikarjun<sup>1, 2,3\*</sup>

1. Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham
2. Birmingham and Solihull Mental Health Foundation Trust
3. School of Psychology, College of Life and Environmental Sciences, University of Birmingham

\*Correspondence

Pavan Mallikarjun

[p.mallikarjun@bham.ac.uk](mailto:p.mallikarjun@bham.ac.uk)

The Barberry, University of Birmingham, 25 Vincent Drive Edgbaston  
Birmingham B152FG.

Phone: 01213012355

## Acknowledgements

The authors would like to thank Dr Sayeed Haque for his statistical advice and to the Birmingham Early Intervention teams: North, East, South and West.

## Contributors:

PM had the original idea for the study. SDC, PM and RU designed the protocol. SDC conducted the data collection and the statistical analysis, and wrote the first draft. All authors undertook quality assessment and approved the final manuscript.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

## Abstract

---

**Aims:** To determine the “real world” relapse rate in patients with first-episode psychosis who had discontinued antipsychotic medication and identify socio-demographic and clinical factors associated with the risk of relapse. **Methods:** Quantitative data were obtained via case-note review on 63 patients with first-episode psychosis who had discontinued antipsychotic medication from Birmingham Early Intervention Service between 2012 and 2015. The follow-up period was until either: an occurrence of a relapse; end of 12 month study period; end of patient’s case-note record. Relapse was defined as a return of symptoms requiring: home treatment, hospital admission or was based on clinical teams’ decision as having a relapse. A pro-forma targeted pre-defined socio-demographic and clinical factors. Survival analysis was undertaken to estimate the 12 month relapse rate following discontinuation of antipsychotics and Cox regression performed to identify relapse predictors. **Results:** The Kaplan-Meier 12 month relapse estimate was 67% (95% confidence interval, 54%, 80%). Significant factors ( $P < 0.05$ ) independently associated with an increased risk of relapse following discontinuation of antipsychotic medication were: male gender, not being in education, employment or training (NEET) and number of previous psychiatric hospital admissions. **Conclusions:** Relapse is common after discontinuation of antipsychotic medication following recovery from a first-episode psychosis. It is important patients who wish to discontinue their medication are informed of the high relapse rates and the associated risks.

1  
2  
3  
4 Furthermore, male patients, patients with NEET status and those who have had  
5  
6 previous hospital admissions may require closer monitoring.  
7  
8  
9

10  
11 **Keywords:** antipsychotics, discontinuation, first-episode psychosis, relapse,  
12 risk factors.  
13  
14  
15  
16

## 17 **Introduction**

---

18  
19 Preventing relapse is one of the most important clinical targets in the  
20 management of first-episode psychosis (FEP); approximately 80% of patients  
21 treated following FEP, relapse within the first five years.<sup>1,2</sup> Relapse  
22 compromises the outcome of psychotic disorders, with each new episode  
23 significantly increasing the development of treatment resistant symptoms.  
24  
25 It has been well established that maintenance medication plays an important  
26 role in reducing the risk of relapse among FEP patients.<sup>3</sup> However, the optimum  
27 duration of maintenance medication is yet to be determined and published  
28 guidelines are not united in their recommendations. A recent systematic review  
29 of 14 guidelines for maintenance treatment after a first-episode of schizophrenia  
30 found that six were not opposed to discontinuing antipsychotics after one to two  
31 years, while two discouraged discontinuation<sup>4</sup>. In the remaining six guidelines,  
32 medication discontinuation was not mentioned.<sup>4</sup>  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

48 The question of how long to continue antipsychotic treatment after FEP is  
49 common among patients, and clinicians face difficulties convincing patients that  
50 indefinite treatment may be indicated. Premature discontinuation of medication  
51 is common among patients; a randomised controlled trial comparing atypical  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 antipsychotics in FEP patients reported 70% of patients discontinued before the  
5  
6 end of the 12 month study period.<sup>5</sup>  
7

8  
9 Given the high rates of discontinuation reported, clinical interest in the  
10  
11 relationship between relapse risk and discontinuation of medication in patients  
12  
13 with FEP has grown. Controlled trials of treatment discontinuation consistently  
14  
15 report higher relapse rates compared to maintenance treatment. However,  
16  
17 studies to date have yielded a range of relapse rates (between 41% and 80%)  
18  
19 following 12 months discontinuation.<sup>3,6-8</sup> A systematic review estimated a  
20  
21 weighted mean one-year relapse rate of 77% in six controlled trials.<sup>9</sup> However  
22  
23 the generalisability of these studies may be limited as patients required capacity  
24  
25 to consent for inclusion, and, as volunteers, reflected a research population.  
26  
27 Therefore, discontinuation relapse rates from a “real world” setting (i.e.  
28  
29 representing clinical practice) may differ considerably.  
30  
31

32  
33 In addition to the clinical importance of estimating relapse rates representative  
34  
35 of all patients who discontinue antipsychotic medication, it is also essential to be  
36  
37 able to predict relapse risk. To date, medication non-adherence has been the  
38  
39 only factor to robustly predict relapse in FEP patients, and is associated with a  
40  
41 four-fold increase in relapse risk.<sup>10</sup> The other risk factors associated with  
42  
43 relapse include persistent substance use disorder, carers’ critical comments  
44  
45 and poor premorbid adjustment<sup>10</sup>. Demographic and clinical variables such as  
46  
47 younger age at first onset psychosis<sup>11</sup>, duration of untreated psychosis<sup>12</sup> and  
48  
49 male gender<sup>13,14</sup> have been reported by some naturalistic studies to predict  
50  
51 relapse, although these have failed to be replicated in later studies.<sup>2,15-17</sup> It has  
52  
53 been proposed that there may be relapse predictors specific to patients who  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 discontinue medication.<sup>3</sup> It is imperative to be able to accurately predict relapse  
5  
6 in these patients in order to allow identification of those at higher risk.  
7  
8  
9

10 Thus, this study has two main objectives: first, to determine the “real world”  
11 relapse rate in patients with FEP who had discontinued antipsychotic  
12 medication, and second, to identify the socio-demographic and clinical factors  
13 associated with the risk of relapse.  
14  
15  
16  
17  
18

## 19 **Method**

---

### 20 **Study setting and population**

21  
22 The study population was drawn from patients under the care of the  
23 Birmingham Early Intervention Service (EIS) between 2012 and 2015. The EIS  
24 is responsible for the treatment of young people aged 16 - 35 with FEP. With a  
25 total caseload of approximately 700 patients, the service comprises five teams  
26 spanning the Birmingham and Solihull Mental Health Trust (BSMHFT); an area  
27 of diverse ethnic and socio-demographic communities.  
28  
29  
30  
31  
32  
33  
34  
35  
36

37 Patients were included on meeting the following criteria:

- 38 • discontinued antipsychotic medication for any reason
  - 39 • had a clinical diagnosis of FEP conforming to ICD-10 codes F20-29,  
40 F30.2, F31.2, F31.5, F32.3 and F33.3<sup>18</sup> (due to the diagnostic uncertainty  
41 during the early stages of psychosis, a broad diagnostic range was  
42 chosen)
  - 43 • experienced a significant reduction of symptoms as judged by the clinical  
44 team prior to discontinuing medication (i.e. had recovered)
- 45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4 Patients were excluded if they had i) discontinued antipsychotic medication for  
5  
6 less than four weeks, or ii) less than four weeks antipsychotic treatment prior to  
7  
8 discontinuation, (as these time periods were considered too short to be defined  
9  
10 as discontinuation or as an effective treatment episode). Patients with  
11  
12 insufficient case notes were also excluded.  
13  
14

### 15 **Study design**

16  
17 Quantitative data were obtained from retrospective electronic case-note review.  
18  
19 Case records were analysed from the point medication was discontinued. The  
20  
21 follow-up period was until: an occurrence of a relapse; the end of the 12 month  
22  
23 study period; or the end of the patient's case record if less than 12 month's  
24  
25 follow-up data (as this could be accounted for by statistical analysis). All data  
26  
27 were extracted by the author and were based on routine assessment by  
28  
29 clinicians as documented in BSMHFT electronic patient records.  
30  
31  
32

### 33 **Procedure**

34  
35 The study protocol was disseminated to all clinical teams within the Birmingham  
36  
37 EIS. Clinical teams identified patients who had discontinued medication  
38  
39 between 2012 and 2015. Case notes of eligible patients were subsequently  
40  
41 screened by the author using the eligibility criteria to determine the final sample.  
42  
43

### 44 **Ethical approval**

45  
46 The study protocol was approved by BSMHFT Research and Innovation  
47  
48 department and by the BMedSc Population Sciences and Humanities Internal  
49  
50 Ethics Review Committee (IERC). In accordance with National Research Ethics  
51  
52 Service (NRES) guidelines for a study involving previously collected routine  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 clinical data, specific consent procedures were not required<sup>19</sup> and thus the  
5  
6 sample consisted of all patients who met the eligibility criteria.  
7

## 8 **Outcome measures**

### 9 **Relapse**

10  
11  
12 Relapse was defined as a return of symptoms requiring one of the following: home  
13  
14 treatment, an informal mental health admission to hospital, a compulsory admission  
15  
16 under the Mental Health Act (2007)<sup>20</sup>, or was based on the clinician's judgement of  
17  
18 having a relapse. This definition is representative of the BSMHFT EIS procedure to  
19  
20 detect a relapse of symptoms. Relapse evaluated was the first relapse following the  
21  
22 patient's FEP. The relapse status, definition and time to relapse were recorded.  
23  
24  
25  
26

### 27 **Predictor variables**

28  
29 A standard pro-forma targeted pre-defined socio-demographic and clinical  
30  
31 factors, and was developed from a systematic review that explored factors  
32  
33 associated with relapse in FEP.<sup>10</sup> Socio-demographic variables were evaluated  
34  
35 upon study entry and included: age, gender, ethnicity, marital status, education  
36  
37 level, accommodation, employment status and smoking status. Accommodation  
38  
39 status was categorised into settled versus not settled; not settled was defined  
40  
41 as being in supported housing or temporary accommodation.  
42  
43  
44

45  
46 Clinical variables were: clinical diagnosis, psychiatric co-morbidities, psychiatric  
47  
48 family history, number of previous psychiatric hospital admissions, substance  
49  
50 misuse, age at onset of psychosis, duration of untreated psychosis (DUP),  
51  
52 duration of untreated illness (DUI), duration of antipsychotic treatment prior  
53  
54 to discontinuation and type of antipsychotic medication (oral or depot). Due to  
55  
56 the sample only including FEP patients, previous psychiatric hospital  
57  
58  
59  
60

1  
2  
3  
4 admissions were evaluated prior to the patient's FEP. DUP was defined as the  
5  
6 period (in days) between first appearance of psychotic symptoms and the onset  
7  
8 of criterion treatment (defined as antipsychotic treatment for more than two  
9  
10 weeks). DUI was defined as the interval (in days) between the onset of non-  
11  
12 specific symptoms and the onset of criterion treatment. Both DUP and DUI  
13  
14 data were based on routine standardised clinical interview as recorded in case  
15  
16 notes.  
17

### 18 19 20 **Statistical analysis**

21  
22 A survival analysis was used to estimate the cumulative rate of relapse, with  
23  
24 censoring of data to account for differentiated duration of follow-up of study  
25  
26 subjects. Data were censored if no relapse occurred during follow-up.  
27

28  
29 Cox proportional hazards regression was used to identify predictors of relapse  
30  
31 by examining time to relapse and its relationship with independent variables.  
32

33  
34 Proportional hazard assumption was assessed graphically using log minus log  
35  
36 survival plots. Univariate Cox proportional hazards regression analysis was first  
37  
38 performed on each potential predictor. Variables with  $P \leq 0.1$  were entered into a  
39  
40 multivariate Cox proportional hazards model. A forward stepwise likelihood  
41  
42 ratio for variable selection was used in the multivariate model, with  $P < 0.05$  as  
43  
44 the entering criterion. Missing values were excluded from the analysis. A similar  
45  
46 analysis was conducted in patients who did not relapse despite stopping  
47  
48 medication to identify factors associated with non-relapse.  
49

### 50 51 52 **Results**

---

53  
54 A total of 133 patients were identified by the clinical teams' to have discontinued  
55  
56 antipsychotics. Following assessment of eligibility, 70 (52.6%) were excluded  
57  
58  
59  
60

1  
2  
3  
4 from the study for the following reasons: insufficient case notes (n = 29, 41.4%);  
5  
6 not meeting inclusion criteria (N=21, 30%) and discontinuation period of less  
7  
8 than four weeks (n = 20). For those excluded for not meeting the inclusion  
9  
10 criteria (n=21, 30%), 18 were due to partial non-concordance (i.e. not fully  
11  
12 discontinued medication) and the remaining 3 due to a reduction in symptoms  
13  
14 being deemed insignificant (as judged by the clinical team). Thus, data were  
15  
16 collected for 63 patients.  
17

### 18 19 **Sample characteristics**

20  
21 Table 1 summarises the socio-demographic and clinical characteristics of the  
22  
23 sample.  
24

25  
26 The sample was 73% male and the median age at discontinuation was 22 years  
27  
28 (IQR = 6). The largest ethnic group was Asian (n = 22, 35.0%), followed by  
29  
30 White (n = 17, 27.0%) and Black (n = 13, 20.6%). Two-thirds of the sample  
31  
32 were classified as not being in education, employment or training (NEET) (n =  
33  
34 42, 66.7%). The most common diagnosis categories were psychosis not  
35  
36 otherwise specified (NOS) (n = 24, 38.1%) and schizophrenia (n = 21, 33.3%).  
37  
38 Prior to discontinuation, the median duration of antipsychotic treatment was 8.5  
39  
40 months (IQR = 11.3; range 1-36), of which oral medication was the most  
41  
42 common type (n = 53, 84.1%). The median duration of follow up was 6 months  
43  
44 (IQR = 6 months).  
45  
46  
47

### 48 49 **Relapse**

50  
51 Out of the 63 patients, 36 relapsed (57%) by the end of the 12 months; of those  
52  
53 that relapsed, the majority resulted in either an informal or compulsory hospital  
54  
55 admission (n = 19, 52.8%), with a greater proportion of compulsory admissions  
56  
57  
58  
59  
60

(n = 11, 30.6%). Taking into account censoring, the Kaplan-Meier estimate of the proportion relapsed at, or earlier than 12 months was 67% (95% confidence interval (CI), 54%, 80%) (Figure 2). The median time to relapse was 8 months (95% CI, 6.03, 9.97).

Given the differentiated length of antipsychotic treatment prior to discontinuation, patients were grouped into:  $\leq 12$  months antipsychotic treatment (n = 42, 66.7%) and  $>12$  months treatment (n = 20, 31.7%). No significant differences were found in time to relapse in these two groups. ( $X^2 = 0.001$ , d.f. = 1,  $P = 0.978$ ).

### **Predictors of relapse**

Several of the socio-demographic and clinical variables explored were found to be statistically insignificant ( $P > 0.05$ ) in the univariate analysis, and were: age at discontinuation, marital status, education level, accommodation, diagnosis, age at onset of FEP, DUP, DUI, psychiatric co-morbidities, psychiatric family history, duration of antipsychotic treatment and type of antipsychotic medication.

Results of the relapse predictors in the univariate Cox model analysis with  $P \leq 0.1$  are shown in Table 2. Significant univariate predictors included male gender, NEET, number of previous psychiatric hospital admissions and substance misuse. Three independent predictors for relapse were identified from the multivariate Cox model analysis (Table 2). Patients who were male had a 3.7 times higher risk of relapse (Exp B = 3.72; 95% CI, 1.42, 9.78;  $P = 0.008$ ). NEET status was associated with a two-fold increase in relapse risk when compared to being in education, training or employment (Exp B = 2.24; 95% CI, 1.01, 4.97;  $P = 0.047$ ). The number of previous psychiatric hospital

1  
2  
3  
4 admissions was identified as a highly significant clinical predictor, with the risk  
5  
6 of relapse increasing by approximately two times with every one unit increase in  
7  
8 previous hospital admission (Exp B = 1.94; 95% CI, 1.31, 2.88;  $P = 0.001$ ).

9  
10 None of the identified risk factors were found to be statistically significant in  
11  
12 predicting non-relapse in this sample of patients with first episode psychosis  
13  
14 who had stopped their medication.  
15  
16

## 17 **Discussion**

---

18  
19 This study sought to address the “real world” relapse rate and to identify which  
20  
21 factors (socio-demographic and clinical) were associated with relapse in a  
22  
23 sample of FEP patients, who had discontinued antipsychotic medication.  
24  
25

26  
27 Approximately two-thirds of the sample relapsed within 12 months following  
28  
29 discontinuation of antipsychotics, with male gender, NEET and increasing  
30  
31 number of previous psychiatric hospitalisations being independently associated  
32  
33 with a higher risk of relapse.  
34

## 35 **Relapse**

36  
37 This study’s relapse rate of 67% is in keeping with the literature, reporting  
38  
39 between 41% and 80% of FEP patients who discontinue medication go on to  
40  
41 relapse within the first year.<sup>3,7-9</sup> The higher relapse rates reported  
42  
43 (approximately 80%<sup>7-9</sup>) may be explained by the use of symptom-based  
44  
45 definitions and the intensive follow up and monitoring that existed, allowing  
46  
47 detection of relapses earlier. The relapse criterion for this study was less  
48  
49 stringent, which was reflected by the high hospitalisation rate (52%) among  
50  
51 those that relapsed, in comparison to previous studies.<sup>6-8</sup> Nevertheless, it was  
52  
53 based on the normal stepwise procedure used by the EIS to detect a relapse,  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 therefore likely to be better representative of “real world” clinical practice.

5  
6 Additionally, previous research conducted by Chen *et al.*<sup>8</sup> estimated a more  
7  
8 pragmatic relapse rate (69%) based on information from case notes, including  
9  
10 only relapses deemed clinically significant, which is comparable to the relapse  
11  
12 estimated in this study.  
13

14  
15 The high hospitalisation rate among those who relapsed demonstrated that this  
16  
17 study captured clinically significant relapses. This highlights the need for closer  
18  
19 follow-up of patients once they are known to discontinue medication in order to  
20  
21 identify relapses earlier before pronounced deterioration occurs. It would be  
22  
23 useful for future studies to not only quantify relapse rates but also evaluate the  
24  
25 clinical impact of the relapses.  
26  
27

28  
29 An important finding was that relapse was not found to be related to the  
30  
31 duration of previous antipsychotic medication (which ranged from 1 month to 36  
32  
33 months; median treatment duration being 8.5 months). This is concurrent with  
34  
35 research by Chen *et al.*<sup>8</sup> Furthermore, from previous discontinuation trials, there  
36  
37 is no apparent indication of reduced relapse risk with longer treatment periods.  
38  
39 Discontinuation after 3, 12 and 24 months in three separate trials all reported 12  
40  
41 month relapse rates of around 80%.<sup>7,8,21</sup> This has implications for clinical  
42  
43 practice, and suggests that lengthening treatment after a FEP does not reduce  
44  
45 the relapse risk. However, the optimum point in time at which medication can  
46  
47 safely be discontinued has yet to be established.  
48  
49

### 50 51 **Predictors of relapse**

52  
53 The strongest predictor was male gender, which was associated with  
54  
55 approximately a four-fold increase in risk of relapse. Previous studies have  
56  
57  
58  
59  
60

1  
2  
3  
4 been mixed with regards to the relationship between gender and relapse, with  
5  
6 some suggesting an association<sup>13,14</sup> while others have failed to show any  
7  
8 association.<sup>3,12</sup> Nonetheless, generally in FEP patients, gender effects have  
9  
10 been reported with regards to functional outcome; male patients have been  
11  
12 shown to have poorer functional outcome after a first-episode, suggesting  
13  
14 males may have an increased vulnerability to relapse.<sup>13</sup> Noteworthy, male  
15  
16 gender has been reported to be a predictor of medication discontinuation<sup>22</sup> and  
17  
18 so the high proportion of males in this sample may have enhanced the apparent  
19  
20 difference in relapse risk. Nevertheless, this higher proportion of males to  
21  
22 females is compatible with the gender split seen in this EIS.<sup>23</sup>  
23

24  
25 NEET was associated with an approximately two times increase risk in relapse  
26  
27 compared to those in employment, education or training. This finding ties in with  
28  
29 a FEP follow-up study reporting early vocational recovery to be associated with  
30  
31 longer term recovery.<sup>24</sup> Early vocational recovery is considered a key  
32  
33 component of recovery and it has been observed that those who only have one  
34  
35 episode and recover fully are less likely to be NEET.<sup>24</sup> NEET could be used as  
36  
37 a broad measure of poor functional outcome and suggests the importance of  
38  
39 interventions facilitating vocational recovery.  
40  
41  
42

43  
44 The association between previous number of psychiatric hospital admissions  
45  
46 and increased relapse risk is concurrent with studies examining predictors of  
47  
48 hospital readmission in schizophrenia.<sup>25,26</sup> It has been shown that a history of  
49  
50 hospitalisation is associated with a higher chance of earlier rehospitalisation in  
51  
52 patients with schizophrenia.<sup>27</sup> Although in this study previous psychiatric  
53  
54 admissions related to admissions prior to the patients' FEP diagnosis,  
55  
56  
57  
58  
59  
60



1  
2  
3  
4 hospitalisation typically indicates a higher level of symptom severity  
5  
6 experienced by patients. Therefore, it could suggest patients with previous  
7  
8 psychiatric admissions (prior to FEP) go onto have a more unstable illness.  
9

### 10 11 **Strengths and limitations**

12  
13 The diverse ethnic sample, the inclusion of all-cause discontinuation and  
14  
15 patients not limited to those with motivation and capacity to consent allowed an  
16  
17 estimate of relapse which is perhaps more generalisable to typical clinical  
18  
19 practice.  
20

21  
22 However, these findings must be interpreted in light of a number of limitations.

23  
24 The method used to determine the sample likely introduced recall and selection  
25  
26 biases. The method involved clinicians identifying patients who had  
27  
28 discontinued medication; clinicians are more likely to recall those patients who  
29  
30 had previously discontinued medication which resulted in a relapse, likely  
31  
32 inflating the relapse estimate. Furthermore, patients who discontinued  
33  
34 medication covertly and those who had successfully discontinued may have  
35  
36 been less likely to have been identified. These biases perhaps could have been  
37  
38 reduced through screening a random selection of patients, stratified by  
39  
40 demographic and clinical factors, within the EIS using the eligibility criteria.  
41  
42 Plasma antipsychotic levels monitoring would be the ideal way to establish  
43  
44 adherence to medication, which was not available in this study due to the  
45  
46 design constraints.  
47  
48

49  
50 The reliability of the relapse and predictor estimates were further limited by the  
51  
52 small sample size. The sample size may have been insufficient to detect  
53  
54 weaker predictors and was also restricted by the quality of the case notes: a  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 high proportion of the potentially eligible sample were excluded due to  
5  
6 insufficient case notes (41%) and it is possible a proportion of these might have  
7  
8 successfully fulfilled the eligibility criteria.  
9

10  
11 It is important to note that for inclusion, patients were judged as having  
12  
13 significant reduction in symptoms before discontinuation; however, the time  
14  
15 period for the recovery was not specified, which could have been a factor  
16  
17 associated with relapse. Other potentially important relapse factors were not  
18  
19 captured, such as level of insight and past adherence. Larger sample sizes and  
20  
21 prospective longitudinal studies are required to be able account for these  
22  
23 limitations.  
24

## 25 26 **Conclusion**

27  
28  
29 Relapse is common in “real world” clinical practice following discontinuation of  
30  
31 antipsychotic medication following recovery from a FEP. It is important for  
32  
33 clinicians to inform patients who wish to discontinued their medication of the  
34  
35 high relapse rates, and should ensure closer monitoring of patients who  
36  
37 discontinue medication. Patients who are male, NEET status and have a history  
38  
39 of psychiatric admissions should be recognised by health care professionals as  
40  
41 having an increased risk of relapse, and suggests continued medication in  
42  
43 these patients. However, these findings need to be replicated in larger  
44  
45 independent samples. It may also be useful for future work to identify those  
46  
47 patients who can discontinue medication without risk of relapse through  
48  
49 investigating factors that may be protective. This will further aid clinicians’  
50  
51 decision-making when confronted with patients requesting discontinuation.  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: A 15-year followup of a dutch incidence cohort. *Schizophr Bull.* 1998; 24(1): 75-85.
2. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; 56(3): 241-247.
3. Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J. Fluphenazine vs placebo in patients with remitted, acute first episode schizophrenia. *Arch Gen Psychiatry* 1982; 39(1): 70.
4. Takeuchi H, Suzuki T, Uchida H, Watanabe K, Mimura M. Antipsychotic treatment for schizophrenia in the maintenance phase: A systematic review of the guidelines and algorithms. *Schizophr Res* 2012 ; 134(2-3): 219-225.
5. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: A randomized, double-blind 52-week comparison. *Am J Psychiatry* 2007; 164(7): 1050-1060.
6. Gaebel W, Riesbeck M, Wolwer W, Klimke A, Eickhoff M, Von WM. Relapse prevention in first episode schizophrenia-maintenance vs intermittent drug treatment with prodrome-based early intervention: Results of a randomised controlled trial within the german research network on schizophrenia. *J Clin Psychiatry* 2011; 72: 205.

- 1  
2  
3  
4 7. Gitlin M, Nuechterlein K, Subotnik KL, et al. Clinical outcome following  
5 neuroleptic discontinuation in patients with remitted recent-onset  
6 schizophrenia. *Am J Psychiatry* 2001; 158(11): 1835-1842.  
7  
8  
9  
10  
11 8. Chen EYH, Hui CLM, Lam MML, et al. Maintenance treatment with  
12 quetiapine versus discontinuation after one year of treatment in patients with  
13 remitted first episode psychosis: Randomised controlled trial. *BMJ* 2010; 341:  
14 c4024  
15  
16  
17  
18  
19  
20  
21 9. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with  
22 medication discontinuation in first-episode psychosis: A systematic review.  
23 *Schizophr Res* 2014; 152(2-3): 408-414.  
24  
25  
26  
27  
28  
29 10. Alvarez-Jimenez M, Hetrick A, Bendall SE, et al. Risk factors for relapse  
30 following treatment for first episode psychosis: A systematic review and meta-  
31 analysis of longitudinal studies. *Schizophr Res* 2012; 139(1-3): 116-128.  
32  
33  
34  
35  
36  
37 11. Haro JM, Eaton WW, Bilker WB. Predictability of rehospitalisation for  
38 schizophrenia. *Eur Arch Psych and Cl Neuro*. 2006b; 244:241.  
39  
40  
41  
42  
43 12. Johnstone EC, Crow TJ, Johnson AL, MacMillan JF. The northwick park  
44 study of first episodes of schizophrenia. I. presentation of the illness and  
45 problems relating to admission. *Br J Psychiatry* 1986;148:115-120.  
46  
47  
48  
49  
50 13. Angermeyer MC, Goldstein JM, Kuehn L. Gender differences in  
51 schizophrenia: Rehospitalization and community survival. *Psychol Med* 1989;  
52 19(2): 365-382.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 14. Tohen M, Stoll AL, Strakowski SM. The Mclean first-episode psychosis  
5 project: Six month recovery and recurrence outcome. *Schizophr Bull* 1992;  
6 18(2): 273-82  
7  
8  
9  
10  
11 15. Johnstone EC, MacMillan JF, Frith CD. Further investigation of the  
12 predictors of outcome following first schizophrenia episodes. *Br J Psychiatry*  
13 1990; 157: 182-89.  
14  
15  
16 16. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of  
17 cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophr*  
18 *Res* 2005; 77(1): 99-104.  
19  
20  
21  
22  
23  
24  
25  
26  
27 17. Lenior ME, Dingemans PMAJ, Schene AH. Predictors of the early 5 year  
28 course of schizophrenia: A path analysis. *Schizophr Bull* 2005; 31: 781-91.  
29  
30  
31  
32  
33 18. World Health Organisation. *The ICD-10 international classification of*  
34 *diseases and related health problems*. Tenth Revision ed. Geneva: WHO; 1992.  
35  
36  
37  
38  
39 19. NHS health research authority ethical approval requirements.  
40 <http://www.nres.nhs.uk/applications>. Accessed 12/10, 2014.  
41  
42  
43  
44 20. The mental health act 2007. <http://www.legislation.gov.uk/ukpga/2007>.  
45 Accessed 05/1, 2015.  
46  
47  
48  
49 21. Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom  
50 recurrence following intermittent treatment in first-episode schizophrenia  
51 successfully treated for 2 years: A 3-year open-label clinical study. *J Clin*  
52 *Psychiatry* 2012; 73(4): e541-7.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1. Sample characteristics (N=63)**

---

22. Kampman O, Laippala P, Vaananen J, et al. Indicators of medication compliance in first-episode psychosis. *Psychiatry Res* 2002; 110(1): 39-48.
23. Kam.S.M., Singh SP, Upthegrove R. What needs to follow early intervention? predictors of relapse and functional recovery following first episode psychosis. *Early Interv Psychiatry* 2015; 9(4): 279-83
24. Alvarez-Jimenez M, Gleeson JF, Henry LP, et al. Road to full recovery: Longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychol Med* 2012; 42(3): 595-606.
25. Mortensen PB, Eaton WW. Predictors for readmission risk in schizophrenia. *Psychol Med* 1994; 24(1): 223-232.
26. Swett C. Symptom severity and number of previous psychiatric admissions as predictors of readmission. *Psychiatr Serv* 1995; 46(5): 482-485.
27. Olfson M, Mechanic D, Boyer CA, Hansell S, Walkup J, Weiden PJ. Assessing clinical predictions of early rehospitalization in schizophrenia. *J Nerv Ment Dis.* 1999; 187(12): 721-729.

| Socio-demographic variables |                               | N (%) or Median (IQR) |
|-----------------------------|-------------------------------|-----------------------|
| Gender                      | Male                          | 46 (73.0)             |
|                             | Female                        | 17 (27.0)             |
| Age (years)                 |                               | 22 (6)                |
| Ethnicity                   | White                         | 17 (27.0)             |
|                             | Asian                         | 22 (35.0)             |
|                             | Black                         | 13 (20.6)             |
|                             | Mixed/Multiple                | 6 (9.5)               |
|                             | Other                         | 5 (7.9)               |
| Marital status              | Single/separated/divorced     | 56 (88.9)             |
|                             | Married/cohabiting            | 7 (11.1)              |
| Accommodation               | Settled                       | 58 (92.1)             |
|                             | Not settled                   | 5 (7.9)               |
| Employment status           | NEET                          | 42 (66.7)             |
|                             | In education/training         | 12 (19.0)             |
|                             | Employed                      | 9 (14.3)              |
| Education level             | Education to 16 only          | 46 (73.0)             |
|                             | Education to 18               | 9 (14.3)              |
|                             | Higher education              | 8 (12.7)              |
| Smoking status              | Non smoker                    | 34 (54.0)             |
|                             | smoker                        | 29 (46.0)             |
| Clinical variables          |                               | N (%) or Median (IQR) |
| Age at onset of FEP (years) |                               | 21 (5)                |
| Diagnosis                   | Schizophrenia                 | 21 (33.3)             |
|                             | Delusional disorder           | 2 (3.2)               |
|                             | Schizoaffective disorder      | 4 (6.3)               |
|                             | Acute and transient psychosis | 2 (3.2)               |
|                             | Psychosis NOS                 | 24 (38.1)             |
|                             | Mania with psychosis          | 9 (14.3)              |
|                             | Depression with psychosis     | 1 (1.6)               |

|   |                               |            |
|---|-------------------------------|------------|
| DUP (days)†   |                               | 55 (112)   |
| DUI (days)‡   |                               | 270 (619)  |
| Psychiatric co-morbidities  | Yes                           | 14 (22.2)  |
|   | No                            | 49 (77.8)  |
| Psychiatric family history  | Yes                           | 29 (46.0)  |
|   | No                            | 34 (54)    |
| Number of previous psychiatric hospital admissions (prior to FEP)§      |                               | 0 (1)      |
| Number of previous psychiatric hospital admissions (prior to FEP)¶      | 0                             | 41 (65.1)  |
|   | ≥ 1                           | 22 (34.9)  |
| History of substance misuse   | Yes                           | 30 (47.6)  |
|   | No                            | 33 (52.4)  |
| Duration of antipsychotic treatment prior to discontinuation (months) # |                               | 8.5 (11.3) |
| Type of antipsychotic medication  | Oral                          | 53 (84.1)  |
|   | Depot                         | 10 (15.9)  |
| Relapse   | Yes                           | 36 (57.0)  |
|   | Home treatment                | 4 (11.1)   |
|   | Informal hospital admission   | 8 (22.2)   |
|   | Compulsory hospital admission | 11 (30.6)  |
|   | Clinical team decision        | 13 (36.1)  |

FEP=first-episode psychosis; Psychosis NOS=psychosis not otherwise specified; DUP=duration of untreated psychosis; DUI=duration of untreated illness; N=number; IQR=inter-quartile range.

† 2 data missing.

‡ 7 data missing.

§ continuous variable.

¶ categorical variable.

# 1 data missing.

**Table 2.** Predictors of relapse in univariate and multivariate Cox proportional hazards regression analysis.



| Factors   | Univariate model* |       |         | Multivariate model |       |                |
|---|-------------------|-------|---------|--------------------|-------|----------------|
|   | Exp B (95% CI)    | Wald  | P       | Exp B (95% CI)     | Wald  | P              |
| <b>Socio-demographic</b>                          |                   |       |         |                    |       |                |
| <b>GENDER</b>                                     |                   |       |         |                    |       |                |
| Female  | 1                 |       |         |                    |       |                |
| Male  | 3.10 (1.20-8.01)  | 5.47  | 0.019** | 3.72 (1.42-9.78)   | 7.10  | <b>0.008**</b> |
| <b>ETHNICITY</b>                                  |                   |       |         |                    |       |                |
| White   | 1                 |       | 0.066   |                    |       | 0.419          |
| Asian   | 0.49 (0.19-1.25)  | 1.18  | 0.135   | NA                 |       | 0.127          |
| Black   | 1.75 (0.73-4.22)  | 2.25  | 0.214   |                    |       | 0.429          |
| Other   | 1.71 (0.46-2.97)  | 1.56  | 0.740   |                    |       | 0.301          |
| <b>EMPLOYMENT STATUS</b>                          |                   |       |         |                    |       |                |
| In education/training/employment                  | 1                 |       |         | 1                  |       |                |
| NEET  | 2.55 (1.18-5.48)  | 5.70  | 0.017** | 2.24 (1.01-4.97)   | 3.94  | <b>0.047**</b> |
| <b>SMOKING STATUS</b>                             |                   |       |         |                    |       |                |
| Non smoker  | 1                 |       |         | NA                 |       |                |
| Smoker  | 1.89 (0.98-3.68)  | 3.56  | 0.059   |                    |       | 0.724          |
| <b>Clinical</b>                                   |                   |       |         |                    |       |                |
| No. past psychiatric hospital admissions (1 unit) | 1.96† (1.30-2.96) | 10.41 | 0.001** | 1.94† (1.31-2.88)  | 10.94 | <b>0.001**</b> |
| <b>SUBSTANCE MISUSE</b>                           |                   |       |         |                    |       |                |

|     |                  |      |         |    |       |
|-----|------------------|------|---------|----|-------|
| No  | 1                |      |         |    |       |
| Yes | 2.22 (1.23-4.35) | 5.35 | 0.002** | NA | 0.773 |

NEET=not in employment, education or training; NA=not applicable; Exp B=hazard ratio; CI=confidence interval.

† Exp B (hazard ratio) represents relative increase in hazard with one unit increment in variable.



\*=predictors with P-value  $\leq 0.1$  in univariate analyses were entered in multivariate analysis.

\*\*=significant at 5% level.

For Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figure 1.** Kaplan-Meier survival analysis for time to relapse following discontinuation of antipsychotic medication. , survival function:  censored. N=63. Cumulative relapse rate = 67%. Median time to relapse = 8 months.

For Peer Review

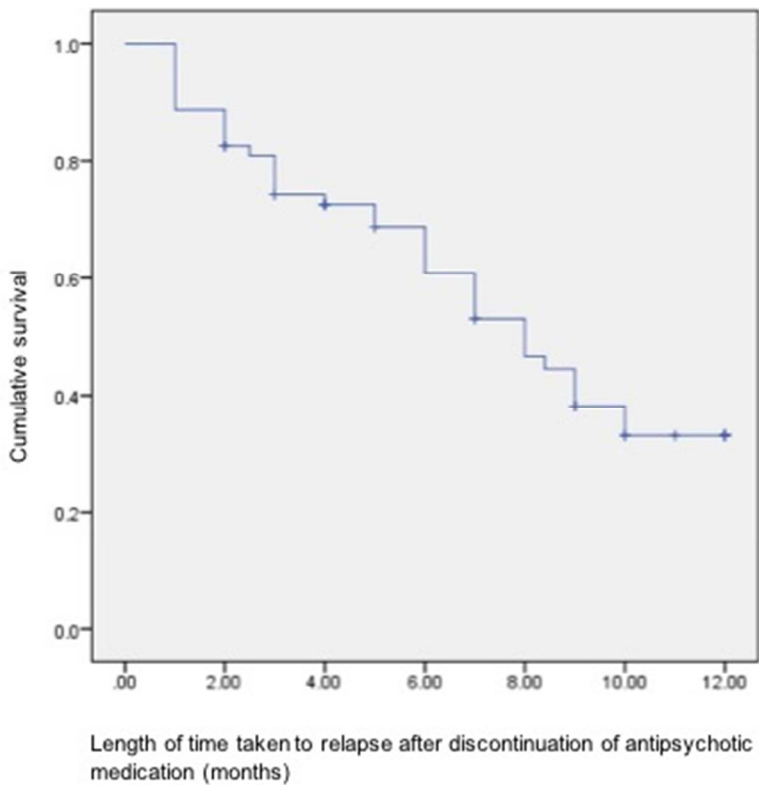


Figure 1: Kaplan-Meier survival analysis for time to relapse following discontinuation of antipsychotic medication. + censored. N=63. Cumulative relapse rate = 67%. Median time to relapse = 8 months.

137x141mm (72 x 72 DPI)

view

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60