

Manic symptoms in first-episode psychosis

The impact of manic symptoms in first-episode psychosis: findings from the UK

National EDEN study

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Abstract

Objective: The extant literature is inconsistent over whether manic symptoms in First Episode Psychosis (FEP) impact on its development and trajectory. This study addressed: 1) Does Duration of Untreated Illness (DUI) and Duration of Untreated Psychosis (DUP) differ between FEP patients with and without manic symptoms? 2) Do manic symptoms in FEP have an impact on time to remission over 1 year?

Methods: We used data from the National EDEN study, a longitudinal cohort of patients with FEP accessing early intervention services (EIS) in England, which measured manic, positive and negative psychotic symptoms, depression and functioning at service entry and 1 year. Data from 913 patients with FEP (639 without manic symptoms, 237 with manic symptoms) were analysed using both general linear modelling and survival analysis.

Results: Compared to FEP patients without manic symptoms, those with manic symptoms had a significantly longer DUI, though no difference in DUP. At baseline people with manic symptoms had higher levels of positive and negative psychotic symptoms, depression and worse functioning. At 12-months, people with manic symptoms had significantly poorer functioning and more positive psychotic symptoms. The presence of manic symptoms delayed time to remission over 1 year. There was a 19% reduced rate of remission for people with manic symptoms compared to those without.

Conclusions: Manic symptoms in FEP are associated with delays to treatment. This poorer trajectory persists over 1 year. They appear to be a vulnerable and under-recognised group for poor outcome and need more focussed early intervention treatment.

Keywords: Duration of untreated illness (DUI); Duration of untreated psychosis (DUP); first-episode psychosis; (FEP) Early intervention Services (EIS); mania, affective psychosis

Manic symptoms in first-episode psychosis

Significant Outcomes:

1	Manic symptoms in First Episode Psychosis are associated with a longer duration of untreated illness compared to First Episode psychosis without manic symptoms
2	Manic symptoms significantly delayed the time to remission over 1 year in people with FEP
3	First episode psychosis patients with manic symptoms need more focussed early intervention treatment

Limitations:

- 1) The YMRS assessed manic symptoms within a short time frame (i.e., 48 hours). Thus, it is unclear how far people experienced manic symptoms before presentation.

Data Availability Statement: Data is available on request subject to privacy/ethical restrictions

Manic symptoms in first-episode psychosis

Psychosis and bipolar disorder (BD) are connected, with the latter often being labelled as one aspect of the “affective psychosis” spectrum. In the UK, people newly presenting with psychosis are given a provisional diagnosis of first-episode psychosis (FEP) even if they meet criteria for bipolar disorder, meaning that they can access treatment via specialist early intervention services (EIS). It is estimated that 5–20% of EIS caseloads consist of patients with psychotic mania ¹ and in a UK epidemiological study, 25% of incident cases of FEP were bipolar disorder-related ². Mania is a core clinical feature of BD and is illness defining. During either a depressive or manic episode of BD, people can experience psychosis ³⁻⁵. This complex overlay and interplay of symptoms raises the possibility of whether the journey to services and outcomes for people with FEP with manic symptoms is different to those without manic symptoms. Understanding this could provide valuable insights to help provide optimal care for this group.

Duration of untreated psychosis (DUP) is known to impact outcomes, with shorter durations being linked to better outcomes⁶⁻⁸. Another measure of pathway to treatment is duration of untreated illness (DUI). Whilst having the same endpoint as DUP, DUI starts with the emergence of the first psychiatric symptom, thus taking into account affective or anxiety symptoms⁹, which occur much earlier in the genesis of psychosis. The specificity of these symptoms for affective or non-affective psychosis are largely unknown^{10, 11}.

Evidence to date suggests manic (or affective) symptoms in FEP are associated with a better outcome, for example, initial findings showed that affective psychosis had a better outcome than schizophrenia¹². Recent work has found people with affective psychosis to have better syndromal and functional recovery at 6 months, compared to people with schizophreniform disorders¹³ and a review highlighted that having non-affective psychosis, compared to affective, was associated with poorer outcomes¹⁴. To date, the largest UK study (N=557) to report relevant data is ÆSOP. In that ten-year longitudinal study of people with

Manic symptoms in first-episode psychosis

FEP, affective psychosis was associated with a shorter time to remission and improved symptomatic recovery^{15, 16}.

However, evidence to the contrary does also exist. In a 20 year follow-up of people with FEP (N=171, but data available for 80 at follow-up) those who had a non-affective psychosis had better outcomes (remission, clinical recovery, personal recovery and resilience)¹⁷. One issue is that people with manic symptoms are commonly investigated in a wider group labelled as having affective psychosis, but this affective psychosis group will usually include people with psychotic depression, schizo-affective disorder and even acute and transient psychotic disorders; all of which may have different outcomes and needs. Interestingly, in previous research when a group of people with FEP with manic symptoms have been specifically studied, that group were found to have a higher risk of relapses over a 5 year follow-up period among FEP patients (N=82)¹⁸, and also greater risk of hospitalisation (N=166) over 3 years¹⁹.

Given the inconsistent findings in the literature, a study utilising a larger sample of FEP patients, both with and without manic symptoms, is needed to better determine whether the trajectories into care and outcomes differ between these groups. Differences might indicate divergent underlying biological processes and/or service responses. Both could lead to advancements in the theory and practice of early intervention, with more individualised care depending on the presence or otherwise of affective symptoms.

Aims of the Study

The current study therefore aimed to answer two research questions: 1) Does DUI and DUP length differ between FEP patients with and without manic symptoms? and 2) Do manic symptoms in FEP have an impact on time to achieve remission over 1 year?

Manic symptoms in first-episode psychosis

Methods

Study design

The present study is an analysis of data from the National EDEN project; a longitudinal cohort study, which aimed to evaluate the implementation and effectiveness of Early Intervention Services (EIS) for people experiencing FEP. Full details of the study methods are provided in the baseline paper²⁰, but we summarise them here.

Setting

Participants were recruited from EIS located in five geographical areas across England: Birmingham, Cambridgeshire, Cornwall, Lancashire and Norwich. These EIS captured individuals with a broad-spectrum of psychotic disorders, including schizophrenia, schizoaffective disorder, bipolar disorder with psychotic symptoms and delusional disorder. Ethical approval for the National EDEN study was granted by Suffolk Local Research Ethics Committee, UK (REC reference number: 05/Q0102/44) and local approval was granted by each of the respective research sites. Participants gave written informed consent.

Participants

Eligibility criteria for entry into EIS specified that individuals must be aged between 14–35 years old and be presenting with FEP. There were no exclusion criteria, other than being unable to consent to the study. The participant sample was comprised of referrals to EIS from August 2005 to April 2009. Most participants were referred from home treatment teams or hospital inpatient services and the minority from primary care²⁰. Participants completed assessment measures at baseline, 6 months and 12 months after entry into the EIS. We however focus on the baseline and 1 year data in this study as we wished to investigate the impact of manic symptoms on 1 year remission. All follow-up assessments were completed

Manic symptoms in first-episode psychosis

by research assistants, independent from the EIS who were not involved in the patients' clinical care. All interviewers had extensive training and were experienced in carrying out standardised psychiatric assessments. Inter-rater reliability of interview-based assessments was assessed regularly by members of the research team.

Measures

Socio-demographic details: Data on sex (male/female), age at psychosis onset (in years), highest level of education achieved (primary, secondary and tertiary) and ethnicity (coded as Non-white vs White) were used.

Diagnosis: The OPCRIT (Operationalised Criteria_ computerised diagnostic system) procedure was used in order to assign diagnosis at baseline. This uses a symptom checklist and involves a researcher reviewing clinical records of a patient.

Onset of psychosis: the onset of psychosis was regarded to have occurred if patients presented with one symptom at level 4 or above from the Positive and Negative Syndrome Scale (PANSS)²¹ of psychosis, or several psychotic symptoms (e.g., conceptual disorganisation, delusions or hallucinations) at a total rating of 7 or more on the PANSS scale (excluding 'absent' scorings). These symptoms needed to be present for up to 2 weeks or more to satisfy the onset of psychosis.

Manic symptoms: For the present study, total scores on the Young Mania Rating Scale²²(YMRS) were used to classify participants as having FEP either with or without manic symptoms. The YMRS is an 11-item scale, scored by a clinician, based on observations made during a clinical interview. It has good reliability, validity and sensitivity²². There is no

Manic symptoms in first-episode psychosis

widely agreed clinical cut-off threshold for the presence of manic symptoms using this scale. However, for the present study, consistent with previous work²³ patients who scored ≥ 9 were classified as FEP patients *with* clinically significant manic symptoms, and those with scores of ≤ 8 were classified as FEP *without* clinically significant manic symptoms.

Duration of untreated psychosis (DUP): DUP was defined as the number of days from the onset of positive psychotic symptoms to the initiation of the first pharmacological treatment for psychosis. To obtain DUP length in days, researchers combined retrospective PANSS scores, client-care records and pathways to care semi-structured interviews with patients, which focused on the source of care they accessed²⁰.

Duration of untreated illness (DUI): DUI was defined as the time period (i.e., days) between the onset of the first non-specific psychiatric symptoms (e.g., mood) and the onset of treatment⁹ for psychosis. Similar to the DUP assessment procedure DUI was assessed using a semi-structured interview (pathways to care) and client care records.

Depression: this was measured using the reliable and validated Calgary Depression scale²⁴ at baseline and 12 months

Functioning: this was measured by the General assessment of Functioning (GAF) scale²⁵ (total score) at baseline and 12 months with a higher score indicating better functioning.

Remission by 12 months: Remission status were recorded monthly over 12 months. Each monthly status (i.e., full remission, partial remission, non-remission or inadequate evidence) was classified using a reliable and valid method using the method of Bebbington et al²⁶ and as previously used²⁷. This method involved reviewing clinical case notes and conducting interviews with patients, doctors, case workers and other individuals attending to the patient's

Manic symptoms in first-episode psychosis

care, to assess whether there was any attenuation or deterioration in positive psychotic symptoms, functioning or social circumstance. A patient was considered to have entered a period of remission, when there was evidence from two separate consecutive months, indicating the absence of psychotic symptoms present (i.e., full remission), or that there is evidence of improvement of psychotic symptoms (i.e., partial remission).

Statistical analysis

All analyses were conducted using SPSS (Version 25). To address missing data, we used complete case analysis in the form of listwise deletion, removing missing data only from the exposure and outcome variables of interest, depending on the research question. Thus, research question 1 utilised a sample size of $N = 907$, whereas research question 2 used a sample size of $N = 913$.

To address the first research question: whether DUP and DUI length was different between in FEP patients with and without manic symptoms, we conducted separate independent *t*-tests. Here, manic symptoms were the exposure variable and DUI and DUP was the outcome variable. An independent *t*-test was conducted to analyse differences in DUI and DUP length between groups ($N=907$).

To address the second research question, whether time to reach a period of remission was different in FEP patients with and without manic symptoms, we used survival analysis ($N=913$) to calculate the time taken to reach a period of remission, by manic group (with vs without manic symptoms). Kaplan Meier analyses and Cox Proportional Hazard regression models were employed to examine the relative hazards of remission during the period from baseline (i.e., entry into EIS) until the end of their first remission period (e.g., remission: end date of the two consecutive months in either full or partial remission). Here, the “event” was remission, with “time” classified as the number of days from baseline until the end of their

Manic symptoms in first-episode psychosis

first remission. Patients who did not reach a period of remission within the 12-month study period were censored.

Firstly, an unadjusted univariable cox regression model was conducted to examine whether the presence of manic symptoms (with vs without manic symptoms) significantly predicted survival time to remission. Next, we adjusted this model, to account for socio-demographic confounding variables that had been found to be significantly different between the groups on univariate tests. We also conducted exploratory data analysis investigating manic symptoms (i.e., YMRS scores) as a continuous measure. Initially, we conducted a univariate separate cox regression model to examine whether YMRS scores significantly predicted time to remission, and then a further model adjusting for gender and ethnicity.

Results

The DUP and DUI for people with FEP with manic symptoms vs. those without is shown in Table 1. DUP was approximately 1 year for both groups and DUI was around 2-3 years for both groups. Analysis revealed that FEP patients with manic symptoms have a significantly longer DUI length, compared to FEP without manic symptoms. However, no significant difference was found for DUP length.

-Table 1 about here-

At baseline the diagnostic makeup of the 913 sample was: Unspecified psychosis (68%); Schizophreniform disorders (13.4%); Drug induced psychosis (5.8%); data not captured (7%); Bipolar affective disorders (4.3%) and Schizoaffective disorders (1.5%). Table 2 outlines socio-demographic and clinical details of participants (N = 913), whose data

Manic symptoms in first-episode psychosis

was used for the survival analysis. Figure 1 shows how this final sample was derived. Both groups demonstrated a similar mean age and the proportion of male and female patients within each group was also similar. Compared with FEP patients without manic symptoms, those with manic symptoms were more likely to identify as being White, whereas those without manic symptoms were more likely to be Non-White. The overall 1-year remission rate in our sample was 89.1% (814/913). The 1-year remission rate for those in the manic symptom sub-group was 86.9% (n = 212/244) compared to 90% (602/669) for those in the non-manic group ($\chi^2 = 1.777$, $p = 0.183$ (df = 1)).

At baseline, FEP patients with manic symptoms demonstrated a significantly greater severity of psychotic and depressive symptoms and poor psychological functioning (i.e., lower scores on GAF indicate poorer functioning). To assess this further we used MANOVA to investigate differences in psychosocial functioning, depressive, positive and negative psychotic symptoms at baseline, between the FEP with manic vs without manic symptom groups. This showed a significant effect for group (F's >124.19; $p < .001$), with greater symptom severity and poorer psychosocial functioning being reported by the FEP with manic symptoms vs without manic symptom group. When controlling for DUI the group differences remained (F's > 19.08; $p < .001$) suggesting that group symptom and functioning differences at baseline are not due to DUI. Further, at 12-months, those with manic symptoms demonstrated significantly poorer functioning and greater positive PANSS scores.

-Figure 1 about here-

Kaplan-Meier analyses, using the log rank test, revealed a significant difference in the survival distributions between the two groups (manic vs no manic) $\chi^2(1) = 8.93$, $p = .003$.

Manic symptoms in first-episode psychosis

The estimated median time in days to reach remission was 119 (95% CI 109.32 – 128.68) for FEP patients with manic symptoms, vs 93 (95% CI 85.83 – 100.17) in FEP patients without manic symptoms.

To understand whether the impact of manic symptoms on survival time of remission was independent of socio-demographic variables, Cox regression models were employed. The proportional hazard assumption was tested by visually inspecting the logarithm of the estimated cumulative hazards function for each variable. The lines for the two groups were parallel, indicating that the proportional hazards assumption was met for the variables of interest. Firstly, a univariate Cox regression model was conducted (Table 3; model 1). Only the presence of manic symptoms (with vs without manic symptoms) was entered as the exposure variable and time to remission (i.e., days) was entered as the outcome variable and the presence of manic symptoms was a significant predictor of time to reach remission. FEP patients without manic symptoms demonstrated a 26% increased rate of remission compared to those with manic symptoms. The association slightly attenuated when an adjusted Cox regression analysis was conducted to control for ethnicity and DUI length (which were significantly different between groups at baseline) (Table 3; model 2). The adjusted results indicated there was a 19% increased rate of remission for FEP patients without manic symptoms, compared to those with manic symptoms. The survival curve is shown in Figure 2. Lastly, these results were further supported by exploratory data analysis, whereby YMRS scores were entered as a continuous predictor of time to remission. In the adjusted model we found YMRS scores significantly predicted time to remission (HR = 0.98, 95% CI .97-.99, $p = 0.008$)

-Table 3 about here-

-Figure 2 about here-

Discussion

This study investigated whether DUI, DUP and remission over 1 year are influenced by the presence of manic symptoms in young people with FEP within EISs in England, UK. As far as we are aware, this is the largest study to date to examine trajectory into treatment and outcome among FEP patients both with and without high manic symptoms. Our findings are the first to demonstrate that DUI is significantly longer, approximately 3 years on average in FEP patients with manic symptoms, compared to those without manic symptoms (approximately 2 years on average). DUP is not statistically different but is also longer in people with manic symptoms. People with manic symptoms appeared to have higher levels of positive and negative psychotic symptoms, depressive symptoms and lower levels of functioning on admission, and therefore their presence may be one marker of greater illness severity. We also found, that compared to FEP patients without manic symptoms, those with manic symptoms were waiting longer to enter a period of remission at one-year follow-up (Median 93 days vs 119 days, respectively); a finding that is further supported when examining YMRS as a continuous predictor variable.

Our findings are framed by the existing evidence related to people with affective and non-affective psychosis. Whilst by no means definitive differences in grey matter volumes have been found in people with affective vs non-affective psychosis²⁸. At first episode, processing speed is significantly associated with functional outcome in people with schizophrenia, whereas visuospatial functioning is specifically linked to functional outcomes in people who do not have schizophrenia²⁹.

Our findings demonstrate that people experiencing manic symptoms alongside psychosis are ill for longer before obtaining treatment compared to those without manic symptoms. A proportion of this group will have BD and our results are consistent with

Manic symptoms in first-episode psychosis

literature related to the delays to diagnosis and treatment in BD. For example, a recent meta-analysis analysing data from 9145 patients found the interval between the onset of any type of bipolar symptoms and treatment had a pooled estimate delay of 5.8 years (standardised difference 0.53, 95% CI: 0.45-0.62)³⁰ though longer periods of over 9 years have been found in some studies³¹. Whilst the group of people with psychosis with manic symptoms will not exactly match those with psychotic bipolar disorder, previous work has found that among bipolar patients with psychotic symptoms, DUI, but not DUP, predicted treatment outcomes such as poorer functioning³². Thus, DUI length is an important marker among those with high manic symptoms and supports the notion that earlier recognition of affective psychosis and targeted treatment of affective as well as psychotic symptoms is key to improving outcomes for this clinical group.

Why the presence of manic symptoms is associated with delays to treatment access may have a number of different explanations. Firstly, it is possible that the emergence of manic symptoms is not easily or appropriately recognised as being a symptom of mental illness. Indeed, many people with hypomania do not present to mental health services, as they do not necessarily find their symptoms distressing or disabling. It is also possible that manic symptoms are mis-attributed as representing symptoms of substance misuse, either by individuals, family or by healthcare professionals. Psychotic symptoms may seem more abnormal, noticeable or distressing to a person and this may trigger help seeking rather than the experience of manic symptoms (e.g., changeable or elated mood or sleeplessness). Indeed, research shows that recognition and awareness of previous manic symptoms in people who have already had a diagnosis of BD is often poor³³ and frequently patients may even deny their manic symptoms or offer alternative explanations for them (e.g., seeing them as a pleasant non-distressing symptom, a time of productivity, or part of their personality)³⁴.

Manic symptoms in first-episode psychosis

Overall, this finding highlights the need for people to have a better understanding around the recognition and development of manic symptoms.

There is existing evidence that BD and other conditions under the “affective psychoses” rubric, generally have a more benign course of illness, compared to non-affective psychoses³⁵. However, our finding that FEP patients with manic symptoms compared to those without, experience a greater time to reach remission challenges this assumption, and previous evidence. It could be that this group obtain sub-optimal treatment within EIS. Affective symptoms could also simply be a marker of treatment resistance³⁶, though manic symptoms have not been identified as such in recent studies³⁷⁻³⁹. Whilst a recent expert review⁴⁰ suggested that people with first episode manic psychosis should be primarily cared for within EISs, our results offer some caution to this view, or at the least stimulate the necessity for changes that would support this case. Evidence indicates that EIS staff may not be confident or have the required knowledge or care packages needed for optimal treatment of people with manic psychosis⁴¹.

The misdiagnosis of BD as psychosis, might also explain our findings of a poorer course with EIS, at least for a proportion of cases. Indeed, studies show that BD is often misdiagnosed⁴² and the presence of psychotic symptoms can often lead to people with BD being misdiagnosed as having a schizophrenia spectrum disorder^{32, 43, 44}. This is particularly the case for people who are black or of non-white ethnicity, meaning their treatment is especially vulnerable to being sub-optimal⁴⁵. The under-recognition of manic symptoms in people of colour may be one explanation of why we found an ethnic difference in the FEP groups with and without manic symptoms, though of course this is a hypothesis that requires formal testing. Due to the complex symptom presentation, it is possible that clinicians find psychotic symptoms easier to detect than manic symptoms. Psychotic symptoms may ‘mask’ symptoms of mania, making them harder to detect. Also, it is likely that affective symptoms

Manic symptoms in first-episode psychosis

are generally being less targeted than frank psychotic positive symptoms, especially by the appropriate use of mood stabilisers. This aligns with the fact that other affective symptoms such as depression in psychosis are poorly understood and sub-optimally treated³⁶.

Implications

Our findings suggest manic symptoms disadvantage young people with FEP in accessing treatment and in delaying their time to remission. In line with efforts around the early detection of psychosis to address this, public health campaigns and clinical training workshops for clinicians within both primary and secondary level health services, could be delivered and is an area of further research. Improving people's understanding and awareness around mania will help these symptoms to be detected earlier and will ultimately promote early intervention and more personalized care for this group. Earlier detection of people with FEP with manic symptoms, many of whom are likely to have bipolar disorder needs development in the UK, and internationally, especially as earlier treatment is more effective⁴¹ and early symptoms such as cyclothymia can be predictive of early transition to BD⁴⁶.

This study offers support for EISs to offer more tailored early intervention for people with FEP with manic symptoms. Indeed, existing therapies or programmes may need to be modified or developed anew for this group as they may not be sufficiently helpful. For example social recovery therapy, whilst effective for FEP overall, is least effective for people with strong affective symptoms⁴⁷. Further research in this area should focus on exploring the mediators and pathways to accessing treatment among those presenting with manic symptoms, as well as the development of care packages that are bespoke for this group.

Strengths and Limitations

Manic symptoms in first-episode psychosis

A key strength to this study is the large representative sample analysed. The National EDEN cohort is the largest study to date to assess the impact of manic symptoms on FEP patients, both before presentation and longitudinally. Second, previous studies assessing DUI and DUP length have focused primarily on FEP diagnoses only, with little being known about how the presence of manic symptoms influences DUI or DUP length. Lastly, the use of survival analysis to examine how the presence of manic symptoms affects delays to remission is another strength and supports the notion that early intervention programmes for this group need further development.

In terms of limitations, firstly, the YMRS²² captures the presence of manic symptoms that are experienced within a relative short time frame (previous 48 hours). Therefore, it is unknown how far people experienced manic symptoms for a prolonged period of time before presentation. We used a cut-off for manic symptoms that may be distinct from other research, that is, a YMRS score of above 8 indicating at least “mild mania”. This was based on and consistent with previous work which indicates YMRS scores of above 8 were independently associated with functional disability in people with bipolar disorder²³ suggesting some validity for this approach.

The assessment of manic symptoms using the YMRS was at baseline study entry as opposed to at the onset of FEP. Therefore, the assessment reflects a cross sectional evaluation of manic symptoms that is potentially impacted by different variables, and we are unable to make substantive assertions related to psychosis onset. We did not investigate the extent to which manic symptoms were due to substance misuse. Whilst there is little evidence related to the onset of FEP, manic symptoms can be quite prolonged and intermittent before the first presentation of BD⁴⁶. It is possible that some patients with psychosis, who were considered to have a clear-cut diagnosis of BD at the time of presentation may have been excluded from

Manic symptoms in first-episode psychosis

EISs, and therefore our sample is likely to be biased towards individuals with higher levels of psychotic symptoms.

Importantly, we calculated remission using a validated method²⁶, which defined remission based on changes in *positive psychotic symptoms*. Thus, we did not directly investigate remission of *manic mood state*, only of psychosis; though it is likely they are connected. The sample under study were people with FEP with manic symptoms. We did not differentiate this group into people with schizo-affective disorder and BD, but previous evidence indicates people with the former diagnosis have poor functioning and are more symptomatic at 18 months⁴⁸. Therefore, our results can most validly be applied to FEP with manic symptoms as opposed to people with specific diagnoses.

In conclusion, people with FEP with manic symptoms are waiting longer to receive adequate treatment and enter a period of remission within EISs. Both of these findings offer support for the need to employ tailored early intervention treatments for this group to improve their outcomes.

Conflict of Interest: SM has attended educational events sponsored by Lundbeck, Sunovion and Janssen. All other authors declare no conflict of interest for the publication of this study.

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

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Manic symptoms in first-episode psychosis

Table 1: Duration of untreated psychosis and untreated illness for participants with FEP with and without manic symptoms

	FEP with manic symptoms (<i>n</i> = 245)	FEP without manic symptoms (<i>n</i> = 662)	<i>p</i>
DUP (days) <i>M(SD)</i>	319.62 (614.55)	285.76 (593.07)	0.45
DUI (days) <i>M(SD)</i>	1104.05 (1287.35)	838.42 (1071.04)	0.004

Table 2: Baseline and 12-month socio-demographic and clinical data for participants with FEP with and without manic symptoms (N = 913)

Variables	FEP with manic symptoms (<i>n</i> = 244)	FEP without manic symptoms (<i>n</i> = 669)	<i>p</i> (two-tailed)
Age (at onset) M (SD)			0.30
Sex % (<i>n</i>)	20.89 (5.59)	21.30 (5.02)	0.60
Male	67.21	69.06 (462)	-
Female	32.79 (80)	30.94 (207)	-
Ethnicity % (<i>n</i>)			<0.001
Non-White	16.80 (41)	30.79 (206)	<0.001
White	83.20	69.21 (463)	<0.001
Marital status % (<i>n</i>)			0.64
Married	7.79 (19)	7.32	-
Relationship	7.79 (19)	6.13 (41)	-
Single	84.43 (206)	86.55 (579)	-
Highest level of education achieved % (<i>n</i>)			0.73
Secondary	39.34 (96)	39.46 (264)	-
Tertiary	34.43	36.62 (245)	-
Receiving state benefits % (<i>n</i> = yes)	53.69	49.63 (332)	0.44
Employment % (<i>n</i>)			0.53

Manic symptoms in first-episode psychosis

Employed paid	20.90 (51)	18.24 (122)	-
Employed voluntary	0 (0)	1.35 (9)	-
Unemployed	56.15 (137)	57.40 (384)	-
Homemaker	2.46 (6)	2.09 (14)	-
Student	19.67 (48)	20.03 (134)	-
Other	0.82 (2)	2.46 (6)	-
Baseline scale scores <i>M(SD)</i>			
PANSS Positive Symptom	20.06 (5.43)	13.45 (5.09)	<0.001
PANSS Negative Symptom	16.70 (7.05)	14.28 (6.28)	<0.001
GAF	41.64 (16.49)	55.07 (15.25)	<0.001
CDSS	7.84 (6.06)	5.82 (5.08)	<0.001
12 month scale scores <i>M(SD)</i>			
PANSS Positive Symptom	11.94 (5.05)	10.80 (4.62)	0.006
PANSS Negative Symptom	11.77 (5.63)	11.73 (5.51)	0.93
GAF	59.89 (20.42)	64.20 (17.87)	0.004
CDSS	3.50 (4.37)	3.48 (4.35)	0.95

Manic symptoms in first-episode psychosis

Table 2. Cox proportional hazards regression models for time to reach remission

	HR (95% CI)	<i>p</i>
Model 1 unadjusted	1.26 (1.08 – 1.47)	0.004
Model 2 adjusted†	1.19 (1.02 – 1.40)	0.032

Note. Manic group is the reference category; HR= hazard ratio, 95 % CI = 95% confidence intervals; †Adjusted to control for ethnicity and DUI length

Manic symptoms in first-episode psychosis

Figure 1: Cox proportional hazards regression survival plot (n=913)

Figure 2: Procedural overview of final sample size