Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis

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Abstract

Importance: Psychosis and mania share conceptual, genetic, and clinical features, which suggest the possibility that they have common antecedents. Participants identified to be at-risk for psychosis might also be at-risk for mania.

Objective: We aimed to identify the rate and predictors of transition to mania in a cohort of youth at clinical high-risk for psychosis.

Design: Five to 13-year longitudinal follow-up study

Setting: Tertiary mental health service for young people in Melbourne, Australia

Participants: Among a cohort of 416 young people at clinical high-risk for psychosis defined using the Ultra-High-Risk (UHR) criteria, 74.7% were followed up between 5 and 13 years from their baseline assessment.

Exposures: Clinical characteristics and risk factors at baseline included i) the presence of threshold or subthreshold manic and depressive symptoms ii) medications and substance use iii) the severity of depression, anxiety, overall symptomatology, and positive and negative psychotic symptoms, iv) psychosocial functioning and v) family history.

Main outcomes and measures: Transition to mania, the outcome of interest, was determined using either a structured clinical interview, or diagnoses from a state-wide public mental health contact registry. The presence of subthreshold symptoms, syndromes and treatments were established using the Structured Clinical Interview for Diagnosis as well as clinical notes. Family history was established using the Family Interview for Genetic Studies. Severity of depression, anxiety and general psychopathology were determined using Hamilton Depression and Anxiety Rating scales as well as the Brief Psychiatric Rating Scale. Functioning was measured using the Global Assessment of Functioning scale. These

measures were compared between those who transitioned to mania and a subgroup of comparison participants who were individually matched on age, gender and baseline study.

Results: Eighteen participants developed mania (UHR-M, 4.3%). In comparison with participants matched on age, gender and baseline-study who developed neither mania nor psychosis, ~~more~~ UHR-M participants had more subthreshold manic symptoms, more antidepressant use, and had lower psychosocial functioning at baseline.

Conclusions and Relevance: In addition to the UHR criteria, additional features such as subthreshold manic symptoms and antidepressant use may help identify broader at-risk groups that predict the onset of mania in addition to transition to psychosis.

Keywords: mania, psychosis, at-risk, bipolar disorder, sub-threshold, antidepressants, functioning, ultra-high risk, depression.

Comment [SJ1]: This is not clear what it is!

Introduction

Prediction of the onset of mania may assist in prevention efforts and help to decrease the disability associated with this disorder [1]. Early or preventive interventions [2] may also help prevent the possible decline in neurocognition [3] or the risk of recurrence [4] associated with onset of one or more manic episodes. Hence, methods to define clinical at-risk stages for bipolar disorder (BD) before the onset of frank manic episodes are important. A number of findings point to a relationship between psychotic symptoms and risk of development of BD. First, there are indicators of a genetic overlap between schizophrenia and BD in genome-wide association studies [5]. Second, there are common therapeutic agents for treatment of mania and psychosis, such as atypical antipsychotics, suggesting that similar pathophysiological processes underlie the expression of these disorders. Lastly, these two groups overlap considerably regarding biomarkers, including structural and functional brain changes, cognition and peripheral markers [6]. Psychosis-at-risk samples may, thus, represent one of the common at-risk stages for BD, or more specifically, mania.

Previous studies in at-risk cohorts for psychosis [7] have been limited by the lack of information on characteristics such as sub-threshold mood symptoms, which may represent a useful risk identification approach prior to the onset of mania [8]. Further characterisation of pre-manic states may help identify a sub-group of participants within psychosis-at-risk clinical services. Additionally, such characteristics may add to the understanding of clinical prodromal characteristics for manic episodes.

Thus, the aims of this study were: (i) to determine the rate of transition to mania; and (ii) identify the clinical risk factors associated with the onset of mania, among help-seeking

Comment [SJ2]: Really the rate, or just the numbers who convert?

youth aged 15-30 years who were at ultra-high-risk (UHR) for psychosis. As the study was exploratory, no a-priori hypotheses were posited.

Methods:

We used a prospective case-control design nested within a larger cohort study of help-seeking young people at ultra-high risk (UHR) of developing psychosis [9,10]. All participants were part of a cohort of 416 young people aged 15 to 30 years, who were help-seeking and met criteria for being at UHR for psychotic disorder. The participants were recruited from a specialist clinic – the Personal Assessment and Crisis Evaluation (PACE) clinic – in a publically funded youth mental health service in Melbourne, Australia. The referral characteristics of the PACE clinic [11], and the UHR features for psychosis [9], have been previously described. Briefly, all participants had one or more of the following criteria: (i) attenuated psychotic symptoms; (ii) brief limited intermittent psychotic symptoms; and/or (iii) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) along with deterioration in functioning or chronic low functioning. The exclusion criteria for entry to PACE clinic included a previous psychotic episode, an organic cause for presentation, and past total antipsychotic exposure equivalent to a haloperidol dosage of more than 15 mg. A detailed description of the cohort has been previously published [12,13]. In addition, participants with full threshold BD I or II at baseline were excluded from the examination of incident mania in this study. Participants included in this study were recruited from five baseline studies [12] including two intervention studies (involving lithium and risperidone). The lithium intervention was not aimed at (sub)threshold manic or affective symptoms, but was an open label intervention for attenuated psychotic symptoms related to UHR status. Assessments in these studies were conducted by trained research assistants. The

Comment [SJ3]: Can you reference the trial here?

studies associated with this project were approved by the Melbourne Health Human Research Ethics Committee, and all participants provided written informed consent.

Baseline Measures and risk factors/variables: The baseline data on subthreshold symptoms, use of substances or antidepressants and family history were extracted by the first author (AR, a consultant psychiatrist) from a number of sources including: (i) the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I/P, [14], including additional notes made by baseline assessors; (ii) Family Interview for Genetic Studies FIGS, [15]; and (iii) patients' clinical files. In case of discrepancies across these sources, these were resolved using clinical judgment of the primary author (a psychiatrist). BD I or II at baseline were excluded as possible diagnoses for all participants in the current study using SCID-I/P.

Comment [SJ4]: Is this the same person as the 'first author' above?

The clinical risk factors examined at baseline included:

i. *subthreshold mania* (equivalent to Other Specified BD in Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition DSM-5, [16] and subthreshold manic symptoms, defined as two or more mania symptoms at threshold/sub-threshold severity (rated 2 or 3 on the SCID-I/P) coded within the Current or Past section of mania or hypomania in SCID-I/P;
ii. *depression* documented in SCID-I/P as major depressive episodes or minor depressive episodes;
iii. *family history* of bipolar disorder, schizophrenia and/or psychotic disorders, and depression noted on the FIGS or in clinical files;
iv. *substance use*, primarily alcohol, cannabis and stimulants, as recorded in the Substance Use Questionnaire [17]. This was supplemented by information from clinical

records. Cannabis and alcohol use severity was measured as the frequency of use in the preceding month as well as lifetime use;

v. *symptom severity* measured using the Brief Psychiatric Rating Scale - total score (BPRS~~,~~ [18]), Scale for Assessment of Negative Symptoms (SANS~~,~~ [19]), Hamilton Rating Scale for Depression (HRSD~~,~~ [20]) ~~,~~ and the Comprehensive Assessment of At-Risk Mental States (CAARMS~~,~~ [21]). The different domains of the CAARMS included disorders of thought content, perceptual abnormalities, conceptual disorganization, motor disturbances, disorders of concentration/attention/memory, disorders of emotions and affect, subjectively impaired energy and impaired tolerance to normal stress;

vi. *functioning* as measured by the Global Assessment of Functioning scale (GAF~~,~~ [22]) ~~scale~~ and Heinrich's Quality of Life Scale (QLS~~,~~ [23]).

Follow-up:

Among the participants initially assessed between 1993 and 2006, 74.8% (311) were followed up between 5 and 13 years later. The participants included in the study were followed up in two waves; first from October 2007 till May 2009 and the second from August 2012 till December 2013. In each follow-up wave, we contacted the participants and reassessed them using the SCID-I/P via face-to-face or telephone interviews. If the participants ~~were~~ could not ~~able to~~ be contacted, the state-wide mental health registry was examined to determine if there had been contact with public mental health services and the diagnoses provided if such contact had occurred. Given the accessibility of public mental health services for significant episodes of mental illness in Victoria, requirements of the local mental health legislation, limits of private practice services in Australia, and the high

reliability of clinical diagnoses of BD I disorder diagnoses in general [24,25], it was considered that recorded manic episodes in the state-wide mental health registry were likely to be accurate.

Two subgroups were derived from the cohort of participants who were followed up. The first subgroup were those who later developed a manic episode after the baseline assessment according to DSM IV [26] criteria or equivalent (termed UHR –Manic transition or UHR-M). The second subgroup comprised participants individually matched on age and gender but who did not develop mania *or* threshold psychosis over the follow-up period (UHR- Non transitioned or UHR-NT). Threshold psychosis was defined as a week or more of one or more positive psychotic symptom at full severity/intensity, as per previous research [12].

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Matching: For each included participant who developed mania, a control participant was chosen by serially selecting the next participant in the individual baseline study on the basis of their gender being the same and their baseline age being no more than 3 years apart. When participants were prescribed lithium or risperidone as part of the baseline study, the medication prescribed was also matched. Participants with baseline diagnosis of BD I or II were excluded.

Analyses:

Baseline information was described using basic descriptive and inferential statistics. The included participants were compared with those who were not included using Mann Whitney U tests and chi-square (χ^2) tests. Due to the relatively small numbers of participants in individual groups, ~~the~~ parametric assumptions were not met. Within the included sample (n=

36), we performed McNemar's tests for categorical variables and Wilcoxon signed rank tests for continuous variables to compare the baseline differences between the group that developed mania and those who did not. Effect sizes were calculated as the *r* score for the Wilcoxon-test obtained by dividing the z score by the square root of the total number of observations [27] and when possible, the weighted-average Odds Ratios (OR) for categorical variables.

Results:

Eighteen participants developed mania over the follow up period (4.3%, UHR-M). The same number of individually matched participants was selected (UHR-NT). The sample that was included (n= 36) did not differ from those who were not included (n=380) based on their age (z= -1.5, p= 0.12), gender (χ^2=0.88, df= 1, p=0.35) or baseline educational status (χ^2=6.75, df= 5, p=0.24). The mean length of follow-up for the included participants was 9.6 years (SD=2.2) and did not differ significantly between UHR-M and UHR-NT (p=0.92) groups (Table 1). One participant developed BD I within 6 months from baseline assessment but completed suicide in the month after this follow-up assessment.

--- Table 1 about here.

No participant was recorded as having used prescribed psychostimulant medication. The prevalence of daily cannabis use in the previous month was not different between those who later developed mania (50%) and those who did not (42.86%). Relatively few participants (twelve) were reliably assessed as having minor depression in the absence of major

Comment [SJ5]: Previous to baseline or follow-up?

depression or prior to the onset of major depression from case records or from SCID notes. The different domains of CAARMS were not different across the two groups, including those of energy or the quality of emotions measured in terms of their frequency or intensity of symptoms.

--- Table 2 about here---

Comment [SJ6]: I think you need to describe the analyses in this table a bit, particularly the difference in mania symptom frequency

*OR*s could not be computed for the significantly different variables between groups such as subthreshold manic symptoms and antidepressant use due to low cell numbers (zero pairs). The difference in global functioning (r=0.34, p=0.04) and severity of depression (r=0.29, p=0.31) between the two groups was of small effect.

Although there was no association between rates of antidepressant use and subthreshold mania symptoms among all participants at baseline, whether such sub-threshold mania symptoms were in the context of antidepressant use could not be established. This was primarily because the information on subthreshold mania symptoms was mostly obtained from SCID-I/P notes and antidepressant use mostly obtained from clinical files.

Discussion

In a sample of help-seeking youth with a clinical high-risk state for psychosis, the numbers making a transition ~~rate~~ to mania over the 5 to 13-year follow-up period was low. Subthreshold manic symptoms, antidepressant use and lower functioning were associated with later episodes of mania.

Overall, the association with subthreshold manic symptoms points to the utility of the prodromal approach for mania particularly in staging models for severe mental disorders [28]. Previous prospective studies [29,30] have also identified the occurrence of subthreshold manic symptoms prior to threshold manic episodes. The higher prevalence of antidepressant use may point to their potential contribution in switch from depression to mania [31]. Alternatively, this may also indicate that persons with greater severity of depression ~~may be~~are more likely to be prescribed antidepressant medication, consistent with clinical practice guidelines. Greater severity of depression has been previously ~~identified to be~~ associated with transition to mania among adolescents [32].

The identified association with lower functioning may point to the possibility of this being associated with the incipient risk of transition to psychosis [33], which occurred in a majority of the UHR-manic sample. Thus, lower functioning could represent a clinical phenotype that has greater risk of transition to BD with psychosis, as outlined in staging models for this disorder [34]. This has been supported by the finding of lower psychosocial functioning in people with comorbid psychosis in the months following an acute mood episode in BD [35].

Limitations: The small number of conversions to mania in the cohort limited the power to detect smaller differences between groups. However, the small number of conversions to mania is itself indicative of the possibility that samples with standard UHR criteria for psychoses may be relatively less useful in prevention paradigms for mania. This may be consistent with the low rate of incident BD reported in a large cohort of UHR participants from North America, though the length of follow-up in that study may have been lower [36]. The confounding effect of the risk for psychosis in the sample is also an important consideration. A comparison group that later developed schizophrenia may have facilitated

Comment [SJ7]: 'like predicts like', not surprising really!

Comment [SJ8]: Don't understand this sentence

Comment [SJ9]: But I don't think you mean the lower functioning is specific to BD onset. So what are you getting at? Lower functioning is a risk for poorer outcome…

examination of factors more specific for BD. However, given the high genetic and/or clinical loading for psychosis at baseline for all participants, as well as the large proportion that also transitioned to psychosis by follow-up, it was not possible to parse out the risk for psychosis in the current sample. Determination of diagnosis of eight control participants and two manic participants using non-interview based means (i.e., mental health registries) may be another limitation. However, it is unlikely that significant episodes of mania were missed, as these usually lead to contact with public mental health services. The lack of availability of some data particularly with respect to substance use both at baseline and in the intervening time points before the onset of mania limits the ability of the study to control for these confounding variables. However, substance-induced manic episodes were excluded using SCID interviews. Lack of blinding and or extraction of data by independent raters may have increased the risk of observation and expectancy bias.

Comment [SJ10]: This sentence is odd because it's obvious that we do have a group who later developed schizophrenia

Comment [SJ11]: I think you might need to explain a little more – do you just mean that everyone has the same apparent psychosis risk in this sample?

Significance for pre-onset identification and interventions: This study validates the sub-threshold symptom approach in predicting the onset of mania. The identified characteristics may help improve risk prediction tools [37,38] for the onset of mania among help-seeking young people with an at-risk mental state for psychosis but possibly also other help-seeking young people with clinical symptoms, distress or family history. The Bipolar At-Risk (BAR) criteria are an example of such a risk prediction tool [38], which have been associated with prospective transition risks of 11% within one year of follow-up [39]. These criteria incorporate concepts of subthreshold mania, cyclothymic features, depression and genetic risk among youth at a similar age group as those with UHR criteria. Incorporation of reduced functioning in such criteria may be important given the association with transition to mania and/or psychosis. This finding also points to the possible trans-diagnostic significance of deterioration in functioning prior to the onset of severe mental disorders. The trans-diagnostic enriching of

these disorders is also indicated by the finding that those with UHR criteria and baseline BD were at a greater risk of transition to psychosis in short to medium term follow-up [40], a finding that was not identified with non-bipolar depressive mood disorders or anxiety disorders. The association with antidepressant use may be of clinical relevance in considering the risks of prescription of these medications for help-seeking young people when other risk factors of latent bipolarity such as subthreshold manic symptoms or family history of severe mental disorders are present. Future well-powered cohort studies with cross-diagnostic outcomes will help clarify the predictive power of these risk factors.

Conclusions

Subthreshold symptoms of mania, antidepressant use as well as lower global functioning in UHR patients at baseline should raise clinical concern about the possibility of transition to manic episodes with or without comorbid psychosis. Incorporation of these factors into at-risk states for psychoses may help develop broader cross-diagnostic risk criteria among help-seeking youth.

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Table 1: Descriptive characteristics of participants who developed mania (UHR M, n= 18) and those who did not transition to psychosis or mania (UHR NT, n= 18) at follow-up

Characteristic		Developed Mania (UHR M) (*n*=18)	Did not develop mania or psychosis (UHR NT) (*n*=18)
Age, in years	M±SD	28.19±4.91	28.77±5.06
Gender	% (*n*)	55.56 (10)	55.56 (10)
Length of follow-up, years	M±SD	9.50±2.38	9.66±2.16
Diagnostic ascertainment of mania			
Structured assessment	% (*n*)	88.89 (16)	55.56 (10)
State-wide registry diagnosis	% (*n*)	12.11 (2)	44.44 (8)
Primary diagnosis on follow-up	*n*	Bipolar I disorder (*n*= 14) Schizoaffective disorder-manic type (*n* =4)	Major depressive disorder (*n*= 8) Substance use disorder (*n*= 2) Anxiety disorder (*n*= 2) Brief psychotic disorder (*n*=1) Dissociative disorder (*n*= 1) No formal diagnosis (*n* =4)
Transition to psychosis threshold	% (N)	77.78 (14)	0.00 (0)

Table 2: Baseline characteristics of youth who later developed manic episodes compared to a subgroup who did not develop mania or threshold psychosis (N= 36)

Characteristic	Measure	N (pairs)	Developed Mania (UHR-M)*	Did not develop Mania or psychosis (UHR-NT)[#]	Statistic	P-value
Age at baseline	*M (SD)*	18	19.89±3.89	19.39±3.48	Z=-0.28	0.777
Symptom domains						
Subthreshold (hypo)manic symptoms	*% (n)*	14	58.82 (10)	0 (0)		**0.008**
Subthreshold bipolar disorder^	*% (n)*	13	35.29 (6)	0 (0)		0.063
Major depression	*% (n)*	14	76.47 (13)	54.54 (6)		0.375
Cannabis use- Lifetime	*% (n)*	13	64.70 (11)	64.28 (9)		1.000
Antidepressant use- Lifetime	*% (n)*	12	76.47 (13)	38.46 (5)		**0.031**
Family history						
Family history of Bipolar Disorder	*% (n)*	17	23.52 (4)	0 (0)		0.125
Family history of Major Depression	*% (n)*	14	6.67 (1)	25.00 (4)		0.375
Family history of Schizophrenia spectrum disorder	*% (n)*	17	50.00 (9)	35.29 (6)		0.754
Family history of Bipolar or a Psychotic Disorder	*% (n)*	17	55.56 (10)	35.29 (6)		0.549

Functioning						
Global Assessment of Functioning	*M (SD)*	18	55.56±9.02	62.33±12.33	Z=-2.04	**0.041**
Heinrich's Quality of Life Scale	*M (SD)*	18	84.17±33.38	82.06±22.79	Z=-0.61	0.542
Symptom severity						
Scale for Assessment of Negative Symptoms	% (n)	18	17.50±10.59	13.94±9.67	Z=-0.96	0.338
Brief Psychiatric Rating Scale total	% (n)	18	45.72±7.81	45.72±10.03	Z=-0.02	0.981
Hamilton Anxiety Rating Scale	% (n)	11	17.64±9.27	14.18±8.72	Z=-0.98	0.327
Hamilton Depression Rating Scale	% (n)	12	25.00±15.69	18.25±12.81	Z=-1.02	0.307

^ Subthreshold Bipolar disorder was defined to be equivalent to 'Other specified Bipolar Disorder' in DSM 5;