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Brief report

Prospective progression from high-prevalence disorders to bipolar disorder: Exploring characteristics of pre-illness stages

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ABSTRACT

Background: Identification of risk factors within precursor syndromes, such as depression, anxiety or substance use disorders (SUD), might help to pinpoint high-risk stages where preventive interventions for Bipolar Disorder (BD) could be evaluated.
Methods: We examined baseline demographic, clinical, quality of life, and temperament measures along with risk clusters among 52 young people seeking help for depression, anxiety or SUDs without psychosis or BD. The risk clusters included Bipolar At-Risk (BAR) and the Bipolarity Index as measures of bipolarity and the Ultra-High Risk assessment for psychosis. The participants were followed up for 12 months to identify conversion to BD. Those who converted and did not convert to BD were compared using Chi-Square and Mann Whitney *U* tests.
Results: The sample was predominantly female (85%) and a majority had prior treatment (64%). Four participants converted to BD over the 1-year follow up period. Having an alcohol use disorder at baseline (75% vs 8%, $\chi^2=14.1$, $p<0.001$) or a family history of SUD (67% vs 12.5%, $\chi^2=6.0$, $p=0.01$) were associated with development of BD. The sub-threshold mania subgroup of BAR criteria was also associated with 12-month BD outcomes. The severity of depressive symptoms and cannabis use had high effects sizes of association with BD outcomes, without statistical significance.
Conclusions and limitations: The small number of conversions limited the power of the study to identify associations with risk factors that have previously been reported to predict BD. However, subthreshold affective symptoms and SUDs might predict the onset of BD among help-seeking young people with high-prevalence disorders.

1. Background

Bipolar disorder (BD) is a leading cause of disability and morbidity (Whiteford et al., 2013). Early intervention and prevention efforts might help to decrease this morbidity, but such efforts require identification of precursor syndromes for BD. Familial high risk (Duffy et al., 2014; Egeland et al., 2012) and naturalistic cohort studies (Angst et al., 2005; Fiedorowicz et al., 2011) indicate that depression and anxiety symptoms might be precursor syndromes for BD. A longitudinal relationship is also evident between substance use disorders (SUD) and manic and hypomanic symptoms (Henquet et al., 2006; Manwani et al., 2006). The concept of high prevalence disorders such as depression, anxiety and SUD being precursor syndromes in some cases for lower prevalence syndromes such as BD, has received support in familial (Duffy et al., 2014), epidemiological (Beesdo et al., 2009) and clinical populations (Fiedorowicz et al., 2011). We prospectively examined factors associated with risk of developing BD over 12 months among young people seeking help for current depression, anxiety or SUD.

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2. Methods

2.1. Participants

A subsample was selected from a cohort of help-seeking young people aged 15–25 years attending a tertiary youth mental health service in Melbourne, Australia. For the primary study, 70 participants were selected from 559 help-seeking young people attending Orygen Youth Health (OYH) on the basis that they did not have threshold (hypo) mania or psychosis and consented to research follow up. The details of the selection criteria have previously been described (Bechdolf et al., 2014). Of these participants, a sub-group was selected on the basis of meeting at-risk criteria for BD (Bipolar At-Risk or BAR) (Bechdolf et al., 2010). The BAR criteria were: (i) age between 15 and 25 years; (ii) sub-threshold manic symptoms; and (iii) sub-threshold depression in combination with either a) cyclothymic features or b) family history of BD. Subthreshold mania was defined as Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) criteria for hypomania but for a shorter duration (between 2 and 4 days) and at a lower threshold for Criterion B symptoms (two associated with elation and three with irritability), and without consideration of criteria C through E. Subthreshold depression was defined in line with the criteria for Major Depressive Episodes in DSM-IV, but for a shorter duration of 1 week and with a requirement for a lower number of primary symptoms (three including the major criteria) and excluding criteria B through E. Among the participants followed up for 12 months, the current report examines a subgroup of 52 with one or more baseline DSM-IV diagnoses—of major depressive disorder (MDD), an anxiety disorder or a substance use disorder using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID IV-I/P) (First et al., 2002). Consistent with the DSM 5 (American Psychiatric Association, 2013), substance abuse and dependence was combined as a single diagnosis of SUD. The Melbourne Health Human Research Ethics Committee approved the research project [No: 2008.613].

2.2. Measures

In addition to the SCID-I/P and the BAR criteria, participants were assessed at baseline on dimensional measures of psychopathology including the Young Mania Rating Scale (YMRS, Young et al., 1978) as a cross sectional measure of manic symptoms and the Montgomery Åsberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979) and the Bipolar Depression Rating Scale (BDRS, Berk et al., 2007) for depressive symptoms. Brown scales for Attention Deficit Disorder (ADD) (Brown, 1996) were used as a self-report measure of dimensional ADD related pathology. The 69-item version of Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A, Akiskal et al., 2005) was used as a measure of temperament. Family history was assessed using the Family Interview for Genetic Studies (Maxwell, 1992). As with the SCID-I/P, the substance use diagnoses of dependence and abuse were combined to be a single diagnosis of substance use disorder among family members. The Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al., 2005) was used to identify those at Ultra-High Risk (UHR) of transition to psychosis. The Bipolarity Index (BI, Sachs, 2004)) was used as a composite measure of bipolar risk in addition to BAR criteria. In addition to the SCID IV-I/P, Additions Severity Index (McLellan et al., 1980) was used to quantify the number of days alcohol or cannabis was used in the month prior to baseline assessment. The subjective quality of life (QoL) was measured using the Modular System for Quality of Life (MSQoL, Pukrop et al., 1999). The socio-demographic details were collected using a proforma devised for this purpose. At the completion of the 12 month follow-up, the primary measure of conversion to BD was made using the Longitudinal Interval Follow-up Evaluation (LIFE) for DSM IV diagnoses (Keller et al., 1997).

2.3. Statistical analyses

The differences between the converters and non-convertors to BD were examined using chi-square tests for categorical variables and Mann–Whitney *U* tests for continuous variables. Effect sizes were also determined due to the risk of type II error, using Odds Ratios (OR) or Area Under the receiver-operating characteristic Curve (AUC). Corrections for multiple comparisons were not performed, as this was an exploratory study.

3. Results

At baseline, the sample was of a mean age of 19.7 years, predominantly female (85%) (Table 1) and were moderately unwell given 75% ($n=39$) had a previous suicide attempt, 64% ($n=33$) had previous psychiatric treatment and 32% ($n=16$) had a previous psychiatric hospitalization. At 12-month follow up, four participants (7.7%) had developed BD, all of whom were female. With respect to their DSM-IV diagnoses, three developed BD II and one developed BD not otherwise specified (NOS). Two of the four participants who converted to BD were prescribed an antidepressant at baseline and two were not. There were no significant differences between groups with respect to frequency of antidepressant or medication use. None of the participants were prescribed stimulants. Baseline predictors of developing BD were having an alcohol use disorder, or having a family history of SUD (Table 2). In addition, converters had significantly lower physical health QoL (converters $M=34.1$, SD=7.7, non-converters $M=44.5$, SD=6.7; $U=15.5$, $p=0.03$). Examination of the BI and BAR criteria indicated that subthreshold (hypo)manic symptoms or episodes were significantly associated with later development of BD. There were differences between the groups using the 'Episode Characteristics' subscale of BI, which measures subthreshold (hypo)manic symptoms, as a continuous measure [converters $M=5.0$,SD=0; nonconverters $M=2.4$ (SD=2.3); $U=30$, $p=0.02$] and using the subthreshold mania subgroup of BAR as a discontinuous measure [converters $n=2$, 29%; nonconverters $n=2$, 4%; $\chi^2=5.0$, $p=0.03$].

Table 1
Baseline clinical and demographic characteristics (N=52).

Characteristic at baseline	% (*N*)	Mean (SD)
Female gender	85% (44)	
Age, in years		19.7 (2.8)
Educational status[a]		
Year 10 or less	38% (20)	
Year 11 or 12	56% (29)	
More than year 12	6% (3)	
No history of migration	86% (45)	
Previous medical condition	29% (15)	
Previous suicide attempt	75% (39)	
Previous psychiatric hospitalization	32% (16)	
Current diagnosis		
Major depressive disorder	65% (34)	
Anxiety disorder	79% (41)	
Substance use disorder	37% (19)	
ADD diagnoses[b]	75% (39)	
UHR for psychosis	21% (11)	
BAR criteria at baseline	50% (26)	

ADD—Attention Deficit Disorder; UHR—Ultra-High Risk Criteria, based on the Comprehensive Assessment of At-Risk Mental States, BAR—Bipolar At-Risk.

[a] Enrolled or completed.

[b] Based on cut offs of 45 for adults and 60 for adolescents using the Brown ADD scale.