Journal of Affective Disorders 152-154 (2014) 427–433

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

# Characteristics, symptomatology and naturalistic treatment in individuals at-risk for bipolar disorders: Baseline results in the first 180 help-seeking individuals assessed at the dresden high-risk project

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ARTICLE INFO

*Article history:*
Received 16 September 2013
Received in revised form
4 October 2013
Accepted 4 October 2013
Available online 12 October 2013

*Keywords:*
Bipolar disorder
Early recognition
Prodrome
Staging
Intervention

ABSTRACT

*Background:* Considering results from the early recognition and intervention in psychosis, identification and treatment of individuals with at-risk states for the development of bipolar disorders (BD) could improve the course and severity of illness and prevent long-term consequences. Different approaches to define risk factors and groups have recently been published, data on treatment options are still missing.
*Methods:* Help-seeking persons at the early recognition center in Dresden, Germany, were assessed with a standardized diagnostic procedure including following risk factors for BD: familial risk, increasing mood swings, subsyndromal (hypo)manic symptoms, specific sleep and circadian rhythm disturbances, anxiety/fearfulness, affective disorder, decreased psychosocial functioning, increasing periodic substance use, and attention-deficit/hyperactivity disorder. Based on symptomatology and current and/or life-time psychiatric diagnosis, subjects with an at-risk state were offered individual treatment options.
*Results:* Out of 180 referred and screened persons, 29 (16%) met criteria for at-risk state for BD. Altogether, 27 (93%) at-risk individuals fulfilled criteria for a current and/or life-time mental illness other than BD; 14 (48%) had received pharmacological and/or psychotherapeutic treatment in the past. Treatments recommended included psychoeducation (100%), psychotherapy alone (62%), pharmacotherapy alone (17%), and psychotherapy + pharmacotherapy (14%).
*Conclusions:* To identify at-risk states for BD, a multifactorial approach including all known risk markers should be used. As most at-risk patients meet criteria for other mental disorders, the short- and long-term impact of different treatment strategies on symptomatic, functional and diagnostic outcomes requires detailed investigation.
*Limitations:* Small sample size of at-risk individuals, lack of sufficient prospective data and control groups.


## 1. Background

Considering the success of early recognition and intervention programs focusing on prodromal syndromes for psychosis (Correll et al., 2010; Fusar-Poli et al., 2013; McGorry et al., 1996; McGorry et al., 2009; Schultze-Lutter et al., 2008), related, yet different approaches were developed recently to identify prodromal states of bipolar disorders (BD) (Bechdolf et al., 2010; Brietzke et al., 2012b; Conus et al., 2008; Correll et al., 2007b; Leopold et al., 2012).

The diagnosis of bipolar I or II disorder is defined by at least one (hypo-)manic episode. However, in the period prior to the first (hypo)mania, almost all patients suffer from depressive episodes, other psychiatric disorders or unspecific symptoms, including anxiety, sleep disturbances and mood swings (Duffy et al., 2010; Egeland et al., 2000; Goldstein and Levitt, 2007; Ozgurdal et al., 2009; Rucklidge, 2008; Skjelstad et al., 2010). First symptoms and episodes of BD emerge in youth and early adulthood (Lish et al., 1994; Perlis et al., 2004). Usually, however, there is a long lag before the correct diagnosis is established, and treatment is often delayed for many years (Hirschfeld et al., 2003; Lish et al., 1994; Morken et al., 2009; Oedegaard et al., 2009; Perlis et al., 2004; Pfennig et al., 2011; Post et al., 2008). Delayed treatment and an increasing number of illness episodes have been associated with a decreased probability of response to treatment (Berk et al., 2011) and an adverse course of illness (Post et al., 2010; Post et al., 2012). Therefore early detection and intervention in patients with BD provides an opportunity to improve outcomes. The identification

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http://dx.doi.org/10.1016/j.jad.2013.10.009

and treatment of at-risk subjects could have a preventive effect, besides alleviation of acute symptoms and preservation or improvement of psychosocial functioning.

For the identification of bipolar prodromal symptoms different approaches have been used. In retrospective studies, information regarding symptoms prior to manifestation is collected from patients with BD (Correll et al., 2007a; Fergus et al., 2003). In addition, in prospective studies of at-risk populations, e.g., offspring (Duffy et al., 2010) or patients with unipolar depressive disorder (Akiskal et al., 1995), factors were identified that could potentially predict the manifestation of BD. These include anxiety, sleep disorders, major mood disorders, substance use disorders and mood lability. Furthermore, retrospective analyses in populations from early recognition and intervention centers focusing on risk for psychosis identified symptom constellations consisting of sub-threshold mania-like symptoms or depressive symptoms plus a positive family history of BD (Bechdolf et al., 2012) to define a prodromal state to mania. Instruments for the prospective identification of at-risk constellations for BD have been developed (Correll et al., 2013; Leopold et al., 2012) and are currently being validated.

Regarding early interventions, so far there are very few data on the effects of psychotherapeutic interventions in subjects with bipolar at risk (Miklowitz et al., 2011; Miklowitz, 2012; Miklowitz et al., 2013; Nadkarni and Fristad, 2010) and only four published studies on psychopharmacological treatment in subjects with an assumed bipolar prodrome (Chang et al., 2003; DelBello et al., 2007; Findling et al., 2007; Geller et al., 1998). None of these data allow clear conclusions about efficacy and safety of treatments in at-risk subjects for BD (Pfennig et al., in press; Hauser and Correll, 2013).

Challenges for early detection include the heterogeneity of at-risk groups because of the variety of risk constellations, the episodic illness course, multiplicity of subthreshold symptoms not yet fulfilling full (hypo)mania criteria, the symptomatic overlap with prodromal symptoms for psychosis, and the usually long time period from first symptoms to the first (hypo)manic episode (Hauser and Correll, 2013).

The aim of the presented study was to present prospectively collected data on characteristics, symptomatology and treatment approaches in a group of individuals with risk constellations for the development of BD from the early recognition center in Dresden, Germany.

## 2. Methods

The early recognition center at the university hospital in Dresden, Germany, was established for help-seeking young people from the age of 12 until 40 years. Individuals can also be referred to the center by psychologists, psychiatrists or primary care physicians in case of suspected development of BD or psychosis. After a first contact, subjects are assessed by clinical psychologists and psychiatrists with a standardized diagnostic battery, including psychiatric and medical history, psychopathological state and the German version of Structured Clinical Interview for DSM-IV (Wittchen et al., 1997). Subjects with any suggestion of prodromal psychotic symptoms, are assessed subsequently using the Structured Interview for Prodromal Syndromes (Miller et al., 2002) and the Schizophrenia Proneness Instrument Adult version (Schultze-Lutter et al., 2007). Individuals with mood swings, affective and/or anxiety symptoms, and/or positive family history for affective or psychotic disorders are assessed with the Early Phase Inventory for bipolar disorders (EPI*bipolar*) and the Bipolar Prodrome Symptom Scale-Prospective (BPSS-P) Mania Symptom Index (Correll et al., 2013).

The BPSS-P comprises an interview with sections rating subthreshold (hypo-)manic, depressive and general symptoms, and closely follows the structure of the SIPS (Correll et al., 2013). Subjects fulfilling at least moderate severity in two or more (hypo) mania items (counting inattention and increased psychomotor activity as one symptom) meet operationally defined criteria for a (hypo)mania prodrome.

EPI*bipolar* is a semi-structured interview comprising the categories disturbances in sleep and circadian rhythm, mood swings and affective lability, fearfulness and anxiety, psychosocial functioning, course of illness, anamnestic or current behavioral problems, and/or attention-deficit/hyperactivity disorder (ADHD) and substance use. Supplemented by information from the BPSS-P Mania Symptom Index, the SCID and information about family history, different risk constellations with main and secondary risk factors are defined. Main risk factors are comprised of (i) “Genetic” risk (family history of BD, major depressive disorders and/or psychosis), (ii) mania prodrome (at least moderate severity score in two or more (hypo)mania items), and (iii) increasing mood swings (increased duration, frequency and/or severity of mood swings over life-time). Secondary risk factors include (i) anxiety/fearfulness (current or life-time and independent from depressive episodes), (ii) decreased psychosocial functioning (work/school, social life, family and global), (iii) fulfilling diagnostic criteria for a recent or life-time affective disorder, (iv) specific sleep and circadian rhythm disturbances, (v) increasing, periodic substance use (alcohol or cannabis), and (vi) life-time or suspected diagnosis of ADHD. At-risk state for BD was defined as having at least one main plus one secondary risk factor. Subjects with the main risk factor “genetic” risk other than BD needed to fulfill criteria for another main risk factor or at least have specific sleep and circadian rhythm disturbances to be classified as at-risk. Finally, ultra-high risk (UHR) state for psychosis was defined according to convention as a rating of 3–5 (i.e., moderate to severe) on at least one of the five positive psychotic symptom items (Miller et al., 2002).

In the early recognition center in Dresden, individual treatment recommendations are communicated to the assessed persons based on the diagnosis and symptomatology. There is no defined treatment algorithm, but different pharmacological and psychotherapeutic treatment options are offered based on clinical need and best available evidence by personnel specially trained in the diagnosis and treatment of individuals with incipient and early-phase psychotic and bipolar disorders. Decisions are made in a shared decision making process.

## 3. Results

Between May 2009 and June 2012, 284 young individuals had at least one contact with the early recognition center. 180 (63%) individuals (mean age$=25.2\pm6.7$ years, 50% female) underwent diagnostic procedures because of undiagnosed but suspected, manifest and/or prodromal psychiatric disorder(s). Out of these 180 individuals, 29 (16%) met criteria for a bipolar at-risk state and completed the entire battery of the complex diagnostic procedures. Except for a significantly younger age in at-risk subjects for BD ($23.6\pm3.9$ vs $25.5\pm7.1$, $p=0.042$) and the number of diagnoses, the two groups did not differ on any demographic or clinical variable, including substance use, (Table 1).

Of the 29 persons with at-risk state for BD, five (17%) also fulfilled criteria for (U)HR for psychosis and 27 (93%) fulfilled DSM-IV criteria for a *current and/or life-time* mental illness other than BD. Diagnostic criteria for major depressive disorder were fulfilled in 23 (79%) at-risk persons, 12 (41%) of these had at least one additional comorbidity (six cases with anxiety disorders, two with substance related diseases, and one case each with ADHD,