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A comprehensive review and model of putative prodromal features of bipolar affective disorder

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Abstract

Background—Identifying prodromal features that predate the onset of bipolar disorder (BD) may enable the prevention of BD and aid early intervention. This review addresses two key questions: Is there a bipolar prodrome? And, if there is, what are its characteristic features?

Method—A comprehensive search of databases (PubMed, MedLine, Embase, and PsychInfo) supplemented with hand-searches was used to identify studies of symptoms preceding the onset BD.

Results—Fifty-nine studies were identified, of which fourteen studies met inclusion criteria. Symptoms can predate the onset of BD by months to years and can be categorized as attenuated forms of BD symptoms, general symptoms common to a range of mental disorders, and personality traits, particularly cyclothymia. Two studies provided sufficient data to enable sensitivity and specificity to be calculated. Specificity of a number of the features was high (above 90%). However, sensitivity was generally low (all<60%). We propose a model based on the findings in the studies reviewed to illustrate the potential trajectory to BD and the points at which it may be possible to intervene.

Conclusions—Clinical features preceding the onset of BD can be identified. However, conclusions on whether there is a distinct prodrome to BD are restricted by the limitations of current evidence. The high specificity of some features suggests they may be useful in clinical practice. Large scale longitudinal studies are needed to validate these features and characterise their specificity and sensitivity in independent samples.

Keywords

bipolar disorder; affective disorders; prodrome; prodromal; identification; intervention; onset; symptoms; risk; risk factors; mania; hypomania; precursor; early

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Introduction

Bipolar disorder (BD) is a common condition, and ranked amongst the top ten causes of global disability amongst adults by the WHO (Murray and Lopez, 1997; McIntyre and Konarski, 2004). A major factor contributing to the burden of disease is the substantial delay between the first experience of symptoms and the initiation of treatment, which can be as long as 8-9 years (Baldessarini *et al.* 1999; Highet *et al.* 2004; McIntyre and Konarski, 2004). Delays in initiating treatment for BD are associated with greater subsequent morbidity (Franchini *et al.* 1999; Baldessarini *et al.* 2003), and the response to mood stabilizer treatment is better earlier in the course of the disorder (Swann *et al.* 1999).

The association between early treatment initiation and better outcome suggests that the early identification of BD may be useful (Mrazek D and Mrazek PJ, 2004). There is an increasing movement towards early intervention in psychiatric illnesses (McGorry *et al.* 2003). One component of this approach is to identify, and offer intervention to, individuals who are in the prodromal phase that precedes the onset of frank illness (Yung and McGorry, 1996; McGorry *et al.* 2003).

The prodrome, by definition, can only be determined in retrospect. It constitutes a period of disturbance characterized by distinct features/symptoms leading up to the development of the full blown disorder (Conus *et al.* 2008). Prodromal features can, however, be used to identify individuals prospectively; although their clinical utility will depend on how specific they are to the illness in question.

The availability of specific treatments for bipolar disorder, and evidence that early intervention in BD is associated with a better outcome (Mrazek D and Mrazek PJ, 2004; Bauer *et al.* 2008), suggests that prevention could be effective in BD. However, it is as yet unclear whether a specific prodromal phase for BD can be identified. This comprehensive review provides a summary of the evidence evaluating the putative bipolar prodrome and addresses two key questions:

- **i.** Is there a bipolar prodrome?
- **ii.** If there is bipolar prodrome, what are its characteristic features and how long does it last?

The paper reviews studies of symptoms/clinical features prior to the first manic or hypomanic episode as it is at this point that the diagnosis for BD can be first made. Features linked to the subsequent development of BD in patients with other diagnoses are beyond the scope of this review and have been addressed elsewhere (Berk *et al.* 2004; Calabrese *et al.* 2006; Henin *et al.* 2007).

METHODS

Search strategy

The PubMed, MedLine, Embase, Embase Classic and PsychInfo databases were electronically searched to identify relevant studies (see supplementary methods for further details). The abstracts of the papers identified by the search were screened by OH, SL and GT to identify papers meeting the selection criteria set out below. The papers identified through this process were then reviewed in full to identify those that those that met the selection criteria.

Selection Criteria

The following inclusion criterion was used:

- Studies of clinical features preceding the onset of the first manic or hypomanic episode.

The following exclusion criteria were applied:

- Studies that did not report specific clinical signs or symptoms.
- Studies *purely* of diagnoses preceding the development of BD.
- Reviews and other papers not reporting original data.

Data Extraction

Data were extracted independently by S.L. and G.T. and agreement confirmed by O.H. For each study the following variables were recorded: a) the year of publication, b) study design, c) sample characteristics, d) measurement scales used, e) frequency of putative prodromal features, f) criteria used to diagnose BD and g) time period from onset of putatively prodromal features to the onset of BD.

Method of analysis

It was not possible to combine the results for statistical analysis as the studies used different scales to assess putative prodromal features, and reported findings in a variety of ways. Rather we appraise and synthesise the data to address the key questions and calculate the sensitivity and specificity of putatively prodromal features for BD (see supplementary methods).

Results

Three hundred and eighteen studies were identified by the searches. The screening process is described in the supplementary methods and shown in supplementary figure 1. Following screening fourteen studies were identified for inclusion in the review. These have been divided according to methodology into retrospective and prospective studies and are summarized in tables 1 and 2 respectively.

Is there a prodrome to bipolar disorder?

The seven retrospective studies used a variety of methodologies to collect data from bipolar individuals and/or their carers about clinical features that predated the onset of the disorder (Lish *et al.* 1994; Egeland *et al.* 2000; Fergus *et al.* 2003; Berk *et al.* 2007; Correll *et al.* 2007; Rucklidge, 2008; Conus *et al.* 2010). These studies clearly indicate that there are symptoms that commonly precede the onset of frank BD in many patients. However, they have a number of methodological limitations, in particular the possibility recall bias has influenced the findings, and, in three studies, the lack of a validated assessment to determine the diagnosis (Lish *et al.* 1994; Fergus *et al.* 2003; Berk *et al.* 2007).

The seven prospective studies are less susceptible to recall bias and all use validated diagnostic assessments, indicating that they are likely to be more reliable sources of evidence. The case series by Thompson *et al.* (2003) describes the prospective assessment of cases using validated diagnostic instruments and rating scales. Consequently, one can be confident that the patients in this small case series did not meet diagnostic criteria for BD at initial assessment, and that the symptoms reported were not influenced by recall bias.

Three studies examined high risk clinical groups- either children/adolescents with unipolar depressive (Kochman *et al.* 2005), youths with brief psychotic episodes (Correll *et al.* 2008), or the relatives of individuals diagnosed with BD who were referred to a specialist clinic with suspected early signs of the condition (Akiskal *et al.*1985). All three studies report

clinical features preceding the onset of BD, providing clear evidence of symptoms/clinical features preceding the onset of BD. However, these studies and the case series by Thompson *et al.* (2003) are in select samples, and so the findings may not be representative of the general population.

Data on putatively prodromal features of BD in general population community samples are provided in three studies (Angst *et al.* 2003; Blechert and Meyer, 2005; Tijssen *et al.* 2010a). Of these, the outcome in the study by Blechert & Meyer (2005) was a manic symptom dimension, rather than a diagnosis of BD, and so, whilst informative, it is less specific to the prodrome of BD than the other studies. The studies by Angst *et al.* (2003) and Tijssen *et al.* (2010a) are noteworthy in recruiting large community samples and in conducting follow-up assessments for up to fifteen and ten years respectively. The outcome in Angst *et al.* (2003) was bipolar spectrum disorder or BD-II, rather than a BD-I diagnosis. Angst *et al.* (2003) enriched their sample by identifying high risk subjects (those with high scores on the Symptom Checklist-90R, whom they hypothesized would be more likely to subsequently develop BD) and, importantly, included a control group- a random sample of average scorers on the same checklist. The study by Tijssen *et al.* (2010a) recruited its sample of adolescents/young adults at random from the population register for the Munich area so the sample is likely to be representative of the general population. Other strengths of this study are the exclusion of symptoms that were directly attributed to alcohol or drug use, and excluding subjects with a past or current diagnosis of BD at baseline. Subjects were assessed at two intermediate time points before the final assessment so the persistence of symptoms over time could also be evaluated. Both studies provide evidence of clinical features/ symptoms preceding the onset of BD. Tijssen *et al* (2010a) report that over 70% of the subjects who subsequently developed BD had previously experienced at least two manic/ hypomanic and/or depressive symptoms, whilst Angst *et al.* (2003) found that over 40% of subjects who developed BD-II had previously experienced mood lability.

Characteristics of the putatively prodromal features

Frequency and form of clinical features—Seven studies report the frequency of specific symptoms occurring within the putative bipolar prodrome, summarized in Table 3. The most commonly reported putatively prodromal features were mood lability/swings and depressive mood. In the study by Angst *et al.* (2003), one of the most methodologically sound studies, mood lability was the strongest risk factor for the subsequent diagnosis of a bipolar spectrum disorder (odds ratio, OR=14), greater even than a family history of mania (OR=7). Depressive mood was reported in five of the seven studies (jointly with mood swings in one study). However, even these relatively common features were not seen in all subjects. In addition, such symptoms were also reported to a lesser degree in control samples. Thus, depressed mood was reported in 5.8% of controls by Angst *et al.* (2003) and in 9% of controls by Egeland *et al.* (2003).

Although data for individual symptoms are not reported in the study by Tijssen *et al.* (2010a), they did find that the combination of greater persistence and greater number of symptoms was associated with the greatest risk of subsequent transition to BD. Thus, symptom load may be more important than specific symptoms.

Many of the putatively prodromal symptoms (see table 3) are seen in established BD, and are probably attenuated forms of symptoms seen in the frank illness, whilst others are also features of other psychiatric disorders (American Psychiatric Association, 2000), and so may show relatively low specificity for BD.

In seven studies cyclothymic features were identified as a precursor of BD (Akiskal *et al.* 1985; Egeland *et al.* 2000; Fergus *et al.* 2003; Angst *et al.* 2003; Kochman *et al.* 2005; Berk

et al. 2007; Rucklidge, 2008). However, these features are also seen in the well relatives of people with BD (Findling *et al.* 2005; Jones *et al.* 2006) so it is not clear if these features could be a correlate of risk status also seen in some relatives who do not go on to develop BD. Furthermore, it remains to be determined whether these features reflect premorbid personality characteristics or are part of a distinct prodrome to BD, an issue that could be usefully addressed in future research.

Only one report, by Fergus *et al.* (2003), included an analysis of the degree to which individual symptoms clustered together. The principal component analysis revealed four symptom dimensions associated with the later diagnosis of BD: depression, irritability/dyscontrol, mania and psychosis/suicidality. Together these explained about 50% of the variance.

Sensitivity and specificity of putative prodromal features—None of the studies give the sensitivity or specificity of the putatively prodromal symptoms for BD, and only two provided sufficient data to calculate these. We have calculated the sensitivity and specificity for the symptoms that were significantly associated with BD in these two studies (table 4).

Time course of putatively prodromal symptoms—Four studies provide data on the time lag between the onset of putatively prodromal features and the subsequent development of BD (see tables 1 and 2), although the mean duration of the prodrome to BD is only reported in two studies. It was 1.7 (SD=1.8) years in patients who developed psychotic mania, and 1.9 (SD=1.5) in those who developed non-psychotic mania (Correll *et al.* 2007), whilst in the other study, which was of patients with psychotic mania and schizo-affective disorder, it was 20.9 weeks (SD=16.4) (Conus *et al.* 2010).

There are also indications that distinguishing features may be present from very early on in development (Fergus *et al.* 2003; Shaw *et al.* 2005). Fergus *et al.* (2003) report when the incidence of the symptoms within each of the dimensions they examined was 10% greater in the BD children than in the comparator groups by age. The striking finding from this fine-grained analysis was that the irritability/dyscontrol symptom cluster differentiated the BD children from the comparator groups from age one onwards, a decade before the onset of BD. Symptoms from the other clusters differentiated the BD children from around age eight, four years on average before the onset of BD. The main caveat with this study is that the diagnosis of BD was not operationalised and is likely to have included children with a broad version of childhood BD, which favours the inclusion of subjects with marked irritability, rather than euphoria (Baroni *et al.* 2009).

Discussion

The existence of symptoms predating the onset of BD is a consistent finding across retrospective and prospective studies, and symptoms may be present in many patients for months to years before a definitive diagnosis of BD is made. This suggests that there may be a relatively prolonged prodrome to BD, contrary to previous ideas that it is brief (Kraepelin, 1921). We have identified a number of features that may comprise a putative prodromal phase of BD. These include attenuated affective symptoms, such as depressive mood and mood swings, and symptoms common to a number of disorders, such as higher levels of anger, irritability and dyscontrol. Thus, it may be possible to identify people with the prodromal signs of BD well in advance of the onset of the disorder. However, the extent to which people experiencing putatively prodromal symptoms of BD present to services requesting help is unclear. This highlights the need for further large scale population studies in this area.

Limitations of the evidence

Our review has highlighted a number of methodological factors that limit the interpretation of the findings and the comparison across studies. Retrospective studies are useful in highlighting features that may be significant. However, such studies are limited by the possibility that subjects actually met diagnostic criteria for BD at an earlier stage, and that the results may be significantly affected by recall biases. The more methodologically robust prospective studies have in the main recruited subjects from selected populations, limiting generalisability and comparison across studies. However, two prospective studies have recruited from general community samples (Angst *et al.* 2003; Tijssen *et al.* 2010a). A further issue is that some of the studies were of childhood onset BD and/or use a broad definition of BD- conclusions based on studies of childhood onset BD may not be applicable to adult onset BD, and vice versa. Differential diagnosis is controversial in childhood onset BD, but a more narrow definition of BD may be more appropriate (Baroni *et al.* 2009). Future studies comparing putatively prodromal symptoms in childhood and adult onset BD would help address this issue.

Specificity and sensitivity

Whilst the literature has identified a number of putatively prodromal features, it is striking that none of the studies reviewed provided both their specificity and sensitivity, and only two (one a relatively small retrospective study) gave sufficient data to allow these to be calculated. This highlights the need for future studies to include specificity and sensitivity. Where we were able to calculate these variables, our key finding was that while the specificity of many of the prodromal symptoms is high, their sensitivity is relatively low. However, the balance between the competing needs for specificity and sensitivity depends on the risks associated with false negative or false positive cases. In the case of the bipolar prodrome, high specificity may be useful if the risk of a false positive is considered substantial- in this case the risks are those associated with initiating treatments such as mood stabilizers in people who are unlikely to benefit from them. However, other potential interventions, such a psychoeducation or life-style advice, are likely to be associated with a lower risk of adverse events- in which case sensitivity may be considered relatively more important than specificity. Nevertheless the high specificity of some of the features indicates they may have potential to identify patients in the prodrome to BD.

Future directions

As no single prodromal feature has been identified in all subjects, the BD prodrome may be best defined by a cluster of features. One approach for future studies would be to evaluate which combination of the symptoms listed in table 4 provides the highest predictive accuracy for a subsequent diagnosis of BD.

An alternative strategy is to focus on other risk factors, such as family history or personality traits, possibly in combination with the putatively prodromal symptoms, as used in the criteria for the prodrome to psychosis (Yung *et al.* 2005). The high rate of BD spectrum disorders in people with cyclothymia suggests that this is a promising candidate risk feature to be included. The two approaches may be combined to complement each other. This combinatorial approach was used in the study (Akiskal *et al.* 1985) that showed the highest proportion of subjects that subsequently developed BD- suggesting that this approach might be most useful in clinical practice. Focusing on youths/young adults is likely to give the highest yield as this is the peak period for onset of BD- the risk of developing a first manic/hypomanic episode may decrease sharply after age 21 years old (Tijssen *et al.* 2010b).

Studies that included a psychiatric comparator group indicated that many of the putatively BD prodromal features may also be seen in other psychiatric disorders (Angst *et al.* 2003;

Fergus *et al.* 2003; Rucklidge, 2008). One key outstanding question is thus whether the putative prodrome to BD can be reliably identified in a distinct, stable enough form to permit specific intervention, as appears to be the case in psychosis, or whether it is manifest as an 'at risk mental state' that gradually develops into one of a number of disorders, including BD. The specificity of putative BD prodromal features needs to be determined with respect to the prodrome of other psychiatric conditions, particularly schizophrenia and recurrent unipolar depression. Furthermore, the existence of childhood traits, such as cyclothymia, as well as the later development of frank symptoms suggests that there may be 'early' and 'late' prodromal features, as has been described for the prodrome of schizophrenia (Hambrecht *et al.* 2002).

Finally it is also evident from our review that there has been little investigation of the neurobiology of the BD prodromal phase, beyond a study of its relationship to alterations in sleep (Jones *et al.* 2005). Neurobiological markers may be used in people at risk on the basis of clinical features to enhance sensitivity and specificity of identifying the prodrome- an approach that has been tried in psychosis (McGuire *et al.* 2008).

Proposed model of the development of BD

Overall our findings suggest key differences in the trajectory to BD from models of the prodrome to psychotic illnesses (Yung and McGorry, 1996). In particular, BD is a fluctuating condition, and, as shown in tables 3 and 4, many of the symptoms potentially predating it have a fluctuating nature. Moreover, the first manic episode may have been preceded by a major depressive episode, and the clinical picture may be further complicated by treatment for depression. This contrasts with psychotic illnesses such as schizophrenia, where the diagnosis can be made on the basis of the first episode of frank illness alone. The prodrome to BD is therefore harder to define than that to psychosis, as there may have been a prodrome to the first affective episode and residual symptoms from that episode. We have constructed an illustrative model (figure 1) that encapsulates features of the putative trajectory to BD based on our reading of the evidence in this review. This model is intended to highlight likely key aspects of the prodrome to BD that need to be considered by future studies. It is will undoubtedly need to be revised in the light of future evidence. The model has three components. Firstly features such as cyclothymic traits and/or manic/hypomanic symptoms may be apparent many years before the development of the frank illness (Fergus *et al.* 2003; Tijssen *et al.* 2010a), in a pre-prodromal phase (arrow 1). Secondly, over time, and possibly triggered by life events or other factors ((Mathew *et al.* 1994; Johnson *et al.* 2000) (arrow 2)), persisting and worsening symptoms become apparent that indicate a prodrome to BD (arrow 3) leading on to, thirdly, the first manic episode (arrow 4). Some patients will receive intervention for depression in the prodromal phase, although it may not be designed to prevent the later onset of BD and many BD patients do not receive intervention at this point (McIntyre and Konarski, 2004). The figure highlights that there are a number of potential points when preventive intervention could occur-primary intervention could be instituted during the period marked by arrow 1, and secondary prevention during the periods marked by arrows 2 and 3. Furthermore it is likely that intervention will need to be tailored to the phase- for example psychosocial interventions with proven benefit in BD (Sachs, 2008) could be beneficial in the pre-prodromal phase, whereas targeted cognitive behavioural therapy and/or medication may be used later once prodromal features are apparent.

Conclusions

Symptoms predating the onset of BD have been identified in a number of studies, but further work is required to determine if these represent a distinct prodrome to BD. These putatively prodromal features can be grouped as attenuated symptoms of BD, general

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psychopathological features, and cyclothymic traits. The specificity and sensitivity of these features to the putative prodrome of BD remains to be established, and will require longitudinal studies that include appropriate psychiatric controls to determine whether a prodrome to BD can be reliably identified. We have proposed a model of the trajectory to BD based on our reading of the evidence reviewed to illustrate the points at which it may be possible to intervene clinically. However, further work is required before it will be possible to determine the full potential for early and preventive intervention for BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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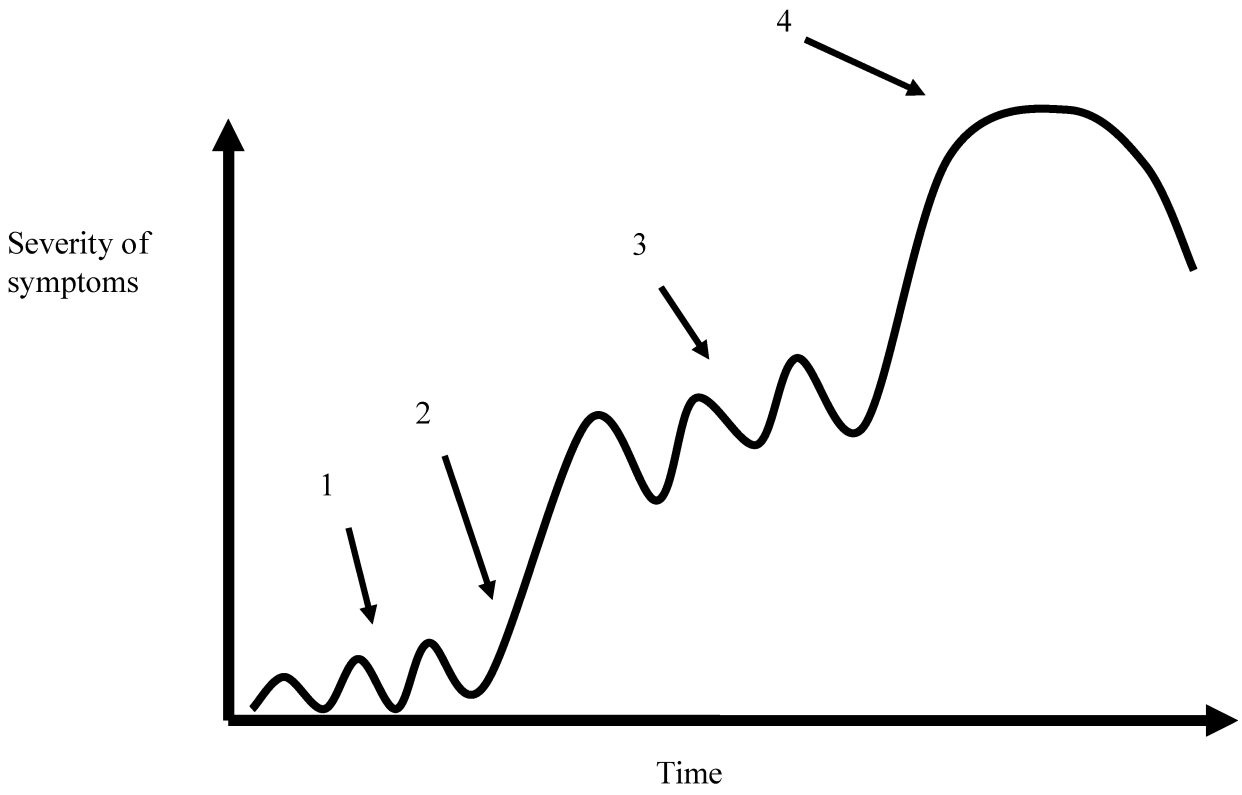

Figure 1.
Model illustrating the possible development of bipolar disorder over time. Potential points for preventive intervention are identified by arrows 1, 2 and 3.
1= fluctuating mood representing underlying cyclothymia or at risk mental state
2= life events precipitating transition to
3= prodromal phase and
4= first manic episode

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Table 1

Retrospective studies

Author	Sample	Source	Instruments	BD diagnosis according to:	Rating by	Size (n)	Gender (M=male; F=female)	Mean Age (SD) /yrs	Comparator group	Time Course: symptom onset to diagnosis
Lish *et al.* 1994	Adults with BD (subtype not specified)	Members of a BD support group	Bespoke self-report questionnaire	Self report	Patients	500	181 M 313 F (6 N/A)	N/A	None	% of sample in range: <6mth: 23% 6mths-5 yrs: 26% >5yrs: 51%
Egeland *et al.* 2000	Bipolar I adults admitted to hospital for the first time.	Single Amish community	Bespoke semi-structured rating scale of antecedent symptoms recorded in clinical notes	Research Diagnostic Criteria	Investigators	58	32 M 26 F	N/A	None	Range: 9 to 12 years.
Fergus *et al.* 2003	Children diagnosed with BD I and BD II	Recruited through adverts in local press	Bespoke symptom check-list rated for each year of life until diagnosis	Parental report of a diagnosis given by a community clinician.	Parents of children diagnosed with BD	78	34 M 34 F	13.7 (6.6)	Well children (n=82) and children with other psychiatric diagnoses (n=38).	N/A
Berk *et al.* 2007	Adults diagnosed with BD I or schizo-affective disorder	Recruited by adverts in local press and hospitals.	Bespoke semi-structured questionnaire	Not stated.	Investigators	218	125 F 93 M	41.8 (12.7)	None	Median time between first symptoms and first manic episode = 6.6 years (sd=n/a)
Correll *et al.* 2007	Children diagnosed with BD I	Subjects in a treatment trial	Bespoke semi-structured interview of patient or carer (BPSS-R)	KSADS criteria for n=33 and WASH-U-KSADS criteria for n=19	Investigators	48	27 F 25 M	16.2 (2.8)	None	Mean (sd) time between first symptoms and BD diagnosis= 1.8 (1.7) years
Rucklidge *et al.* 2008	Adolescents (13-17yrs) diagnosed with BD I or II	Recruited from an earlier study of neuro-cognitive function.	Bespoke symptom checklist of range of psychiatric symptoms.	DSM-IV-TR criteria for BD I or II based on WASH-U-KSADS	Filled in by parents of subjects.	25	10 M 15 F	15.71 (1.55)	Normal controls (n=28) and children with ADHD (n=29)	N/A
Conus *et al.* 2010	Adolescents/ adults diagnosed with a first episode of psychotic mania or schizo-affective disorder	Recruited from referrals to a specialist service for first episode psychosis	Bespoke questionnaire (IMPQ)	DSM-IV criteria for BD I plus YMRS score>19	Investigators	22	18 M 4 F	23 (2.9)	Nil	Mean (sd) time between first symptoms and diagnosis= 20.9 (16.4) weeks, range 2-49 weeks.

* The authors have also published a report of an earlier follow-up of the same cohort

SADS= Schedule for Affective disorders and Schizophrenia. CDRS= Children's depression rating scale YMRS= Young Mania Rating Scale GAF= Global Assessment of Functioning scale. PGBI= Parent General Behavior Inventory CBCL=Child Behavior Checklist DSM-IV= Diagnostic and statistical Manual, 4th edition. SSAS=Schizophrenia for School-Age Children, WASH-U-KSADS= Washington University in St Louis Schedule for Affective Disorders and Schizophrenia. BPSS-R= Bipolar Prodrome Symptom Scale-Retrospective. HAMD12= Hamilton Depression Rating Scale, CGI-BP= Clinical Global Impression Scale-Bipolar Version, CDME= Current Major Depressive/Manic Episode Checklist. RDC=Research Diagnostic Criteria. K-SADS-PL= Schedule for Affective Disorders and Schizophrenia for School Age Children; Present and Lifetime version. CRS= Conners' Rating Scales, CBC= Child Behavior Rating Checklist, IMPQ= Initial Mania Prodrome Questionnaire, YMRS= Young Mania Rating Scale.

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Table 2

Prospective studies

Author	Sample	Source	Instruments	BD diagnosis according to:	Rating by	Size (n) of risk sample	Gender (n)	Mean Age (years old)	Comparator Group	Duration of study period.
Akiskal *et al*. 1985	Relatives of BD	Referrals to a specialist outpatient clinic because of possible early signs of BD	Bespoke questionnaire categorizing sub-syndromal mood symptoms based on a clinical interview	Feighner Schema based on DSM-III criteria	Investigator	68 (n=39 developed a BD spectrum disorder)	39 males, 29 females	N/A (all <25 years old)	68 older onset BD patients (all 25 years or older at onset)	Mean=3 years (sd=n/a; range 1-8 years)
Thompson *et al*. 2003	3 patients referred to a specialist clinic for people at high risk of psychosis	PACE (Personal Assessment and Crisis Evaluation) clinic in Australia.	DSM-IV SCID BPRS YMRS	DSM-IV criteria	Investigator	3 (all developed BD)	3 females	21	None	12 months
Angst *et al*. 2003	High scoring adults on the SCL-90-R	General community sample	Social variables and emotional and vegetative lability measured using the SCL-90-R	DSM-IV criteria for bipolar spectrum disorders	Investigator	591 (n=127 developed a BD spectrum disorder)	Total sample: 299 females 292 males	N/A (range 19-20 at recruitment)	A random sample of subjects scoring below the SCL-90 high score cut-off (n=261)	15 years
Blechert and Meyer. 2005	Adolescents scoring above a cut-off on the hypomanic personality scale	Pupils at selected schools in Germany	HYP, RIG, IMP, EPI-Lie	DSM-IV criteria for BD II using a SCID inter-view.	Teacher, Investigator	114 (n=15 developed BD II)	69 females 45 males	19. 9 (sd=1.3)	Adolescents scoring below a cut-off on the hypomanic personality scale (n=35)	2 years
Kochman *et al*. 2005	Children with major depression	Consecutive children admitted to a hospital in France	K-SADS, CHT, CDI, YMRS, CGAS, OAS	DSM-IV criteria	Investigator	Total=80 (n=35 developed BD)	N/A	N/A (range: 7-17)	Subjects who did not develop BD (n=45)	Mean=26.6 (sd=9) months
Cornell *et al*. 2008	Youths presenting with psychotic NOS or brief psychotic episode	Referrals to an early intervention service for psychosis.	K-SADS, SIDP-IV, SOPS, BDI, BAI, CDI	DSM-IV criteria	Investigator	26 (n=4 developed BD)	2 males, 2 females	15.1 (sd=1.6)	Referrals who did not develop BD (n=22)	Mean=22.8 (sd=19.4) months
Tijssen *et al*. 2010a	Adolescents/young adults with no prior DSM IV diagnosis of BD or prior use of mental health services.	Random population sample drawn from government registers for a geographic area.	DIA-X/M-CIDI	DSM-IV criteria (for manic/ hypomanic episode).	Investigator	1902 (n=21 developed the outcome)	Total sample: 1025 males, 877 females	18.3 (sd=3.3). (range 14-24)	All subjects (n=1881) who had not developed BD by the study end	Mean=8.3 years (sd=0.7; range 7.4-10.6 years)

BAI= Beck anxiety inventory, BDI= Beck depression inventory, BIS/BAS=behavioral inhibition/ activation scale, CARE- Child and Adolescent Research and Evaluation interview, CDI=children's depression inventory, CHT=cyclothymic-hypersensitive questionnaire, CGAS=Clinical Global Assessment Scale, DSM-IV= Diagnostic and statistical manual version IV, EPI-lie= lie scale of the Eysenck Personality Inventory, HYP= Hypomanic Personality scale, IMP= Impulsive nonconformity scale, K-SADS= Schedule for Affective disorders and Schizophrenia for school age children, MSED=mood and self esteem diary, NOS=not otherwise specified, OAS= Overt Aggression Scale, PSQI=Pittsburgh Sleep Questionnaire, RIG= rigidity subscale of the Munich Personality Test, RSQ=response style questionnaire, SADS-L=Schedule for Affective Disorders and Schizophrenia-Lifetime version, SCL-90-R= Symptom Checklist-90-R, SIDP-IV=Structured interview for DSM-IV personality, SOPS= Scale of prodromal symptoms, YMRS= Young Mania Rating Scale. DIA-X/M-CIDI= Munich Composite International Diagnostic Interview.

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Table 3

Frequency of specific symptoms preceding BD

SYMPTOMS	Lish *et al.* 1994	Shaw *et al.* 2005	Angst *et al.* 2003	Fergus *et al.* 2003	Berk *et al.* 2007	Correll *et al.* 2007	Rucklidge *et al.* 2008
Depressive mood	32.8%	11%	Not reported	14.2%	90.3%	53.8%	60%
Mood lability/swings	12.8%	10%	32.6%	Not reported	90.3%	57.7%	72%
Anxiety	Not reported	13%	39.5%	Not reported	Not reported	43.1%	28%
Racing thoughts	Not reported	Not reported	Not reported	11%	Not reported	57.4%	60%
Irritability/anger	9.4%	7%	Not reported	14.1%	Not reported	61.5%	55.2%
Physical agitation	32.0%	Not reported	Not reported	14.1%	Not reported	48.1%	48%

Table 4

Sensitivity and specificity of symptoms for BD compared to a healthy control group

Symptoms occurring with onset aged 6-11 yrs old. Rucklidge *et al*. 2008	**Sensitivity**	**Specificity**
Elevated/ Irritable Mood lasting >1hour/day	56%	79%
Elevated/ Irritable Mood lasting >6hour/day	32%	95%
Depressed Mood lasting >1hour/day	32%	93%
Depressed Mood lasting >6hour/day *	24%	100%
Grandiosity	32%	82%
Racing Thoughts	24%	79%
Mood Swings	48%	77%
Symptoms occurring with onset aged 12-16 yrs old. Rucklidge *et al,*. 2008	**Sensitivity**	**Specificity**
Tantrums	52%	71%
Extremely Clingy	24%	91%
Excessive Anxiety and Worry	48%	82%
Anxiety causing impairment to Social Functioning	28%	89%
Marked Changes in Appetite	44%	79%
Elevated/ Irritable Mood lasting >1hour/day	76%	58%
Elevated/ Irritable Mood lasting >6hour/day *	60%	89%
Elevated/ Irritable Mood lasting >2days *	56%	93%
Depressed Mood lasting >1hour/day	60%	68%
Depressed Mood lasting >6h/day	56%	84%
Depressed Mood lasting >2 days	44%	89%
Suicidal Ideation	52%	82%
Self Harm	48%	84%
Often Awakes at Night	44%	79%
Very Rapid Speech	60%	72%
Racing Thoughts	60%	68%
Mood Swings	72%	53%
Takes Excessive Risks	28%	72%
Hears Voices	28%	96%
Grandiosity	72%	70%
Symptoms of bipolar *spectrum* illness. Angst *et al.* 2003	**Sensitivity**	**Specificity**
Mood lability	30%	89%

* incidence of symptoms differed significantly between subjects with BD and subjects with ADHD and controls.