Curr Psychiatry Rep. Author manuscript; available in PMC 2013 November 21.

Published in final edited form as:
Curr Psychiatry Rep. 2011 December ; 13(6): . doi:10.1007/s11920-011-0229-8.

Early Detection and Intervention in Bipolar Affective Disorder: targeting the development of the disorder

Oliver D Howes, MRCPsych PhD DM[*] and **Irina Falkenberg, MD**
Box 67, Institute of Psychiatry, Camberwell, London, SE5 8AF, UK

Abstract

The diagnosis of bipolar affective disorder (BD) is often delayed, and preceded by incorrect diagnoses and potentially harmful treatment, and the development of the disorder is associated with suicidal behavior and help-seeking. A number of clinical features have been linked to an increased risk of going on to develop BD, in particular attenuated symptoms of BD, personality traits such as cyclothymia, and general psychopathological symptoms. A number of these show high specificity, indicating that it may be possible to target detection and intervention on people at high risk of BD, and hopefully moderate the course of the illness and improve treatment outcome. This article summarises recent evidence on the characteristics of the prodrome to BD and discusses the potential value and challenges of early detection and intervention in BD.

Keywords

Bipolar affective disorder; at risk; high risk; prodrome; early intervention; early detection; mania; hypomania; depression; prevention; secondary disability

Introduction

Recent years have seen a paradigm shift in psychiatry from focusing on chronic established illness towards early detection and intervention. This has seen a revolution in the delivery of clinical care for patients manifested by the establishment of specialist early detection and interventions services in many countries around the world and underpinned by national programmes and government resources (eg: http://www.nmhdu.org.uk/nmhdu/). At the same time, there has been an explosion in clinical research into early detection and intervention and the development of international meetings and a journal (Early intervention in Psychiatry) dedicated to this area. The initial focus has been on psychotic disorders, predominantly schizophrenia, but there is no reason to suppose that early detection and intervention is only of value in psychotic disorders and attention has now shifted towards BD.

The value of early detection of bipolar affective disorder

BD is a chronic condition characterized by periodic episodes of mania and depression which causes considerable psychosocial impairment. Estimates of the lifetime prevalence of BD range between 1 and 6.5% [1-4]. BD is associated with significant psychosocial morbidity and elevated mortality, especially in patients with an onset during childhood or adolescence [5-7].

[*]corresponding author: oliver.howes@kcl.ac.uk, tel: 0044 208 383 3160, fax: 0044 207 701 9044 .

Disclosures: The authors report no conflicts of interest.

Europe PMC Funders Author Manuscripts

One of the reasons for the unfavorable outcome of BD is the diagnosis is often delayed. Latencies between the first experiences of symptoms and receiving a correct diagnosis can span up to ten years [8,9]. As a result, adequate treatment initiation is often considerably delayed [10-12]. Long duration of untreated illness is associated with greater subsequent morbidity[13,14] and lower response to mood stabilizer treatment [15]. Patients who developed BD during childhood or adolescence were found to be the ones that waited the longest for the correct diagnosis [16]. This might be due to the fact that early onset BD is mainly characterized by depressive symptoms, whereas later onset BD predominantly begins with manic episodes [17].

Although the correct diagnosis may be delayed by years, patients nevertheless present to clinicians for help early in their illness, and are often mis-diagnosed with other conditions [18]. High rates of mis-diagnosis have been reported- in one series over 50% of patients initially received a diagnosis other than BD when they sought medical attention and many of these received treatment with anti-depressant or antipsychotic drugs (19). Where mis-diagnosis leads to antidepressant treatment there is a risk of triggering manic switching and mood cycle acceleration [19-22]. This highlights one potential benefit of early detection- avoiding the risk of iatrogenic harm. Another potential benefit is the opportunity to prevent, or minimize, the secondary disability associated with the development of the disorder. BD disrupts patients' lives, and damages their work and social relationships (34). The prodromal phase of BD is thus a chance to engage patients and carers before secondary disability develops and maladaptive coping strategies are adopted- potentially preventing them from developing.

The risk of suicide early in the course of BD is another important argument for early detection. This is highlighted by the finding in one recent study that about one in ten patients reported suicide attempts in the year prior to the first onset of BD and that the risk was over two fold greater than in individuals experiencing a relapse of established BD (34). This indicates that suicidal behavior occurs in the prodromal phase. There is also evidence that patients want early intervention- patients at an early stage of BD are more likely to seek help for the distress they are experiencing and might therefore be more willing to utilize clinical services, intensified surveillance or specific treatment as compared to patients in later stages of the illness, where non-adherence and reduced insight might impair treatment strategies [23].

Early detection can be considered at several time points in the development of a disorder from a pre-symptomatic stage, through the development of prodromal features, to the first point at which the clinical manifestation meets diagnostic criteria (the first manic or hypomanic episode in the case of BD). Pre-symptomatic screening raises a number of technical and ethical issues- not least the absence of reliable biomarkers for BD- that are likely to limit its use for some time. In contrast, by the point at which diagnostic criteria are first met, there may already have been so much disruption to a patient's work and social relationships that they cannot return to them. The prodromal phase may thus be where there the most clinical traction can be obtained- individuals are distressed by symptoms and seeking help, but secondary disability has not yet occurred.

The term "prodrome" implies an inevitable progress into full blown illness. Therefore, a prodromal syndrome can only be identified in retrospect [24]. This is, of course, of little benefit to patient or clinician. It is, however, possible to identify symptoms and other clinical features that are associated with the prodrome to BD. Such prodromal features may thus help identifying individuals at risk of developing BD prospectively and guide early intervention. "Prodromal" can also be used to refer to the initial sub-clinical phase preceding

the relapse of an established disorder- this is also an active area of research in BD but beyond the remit of this review.

Early detection also has particular value for understanding the neurobiology that underlies BD. Studies of people in the prodromal phase, and particularly longitudinal studies through to the onset of the first clinical episode, have the potential to identify the critical processes that underlie the disorder, as has been the case for schizophrenia [25-27]. This research will be critical to developing accurate biomarkers for BD, and identifying new molecular targets for intervention.

Challenges for targeting the prodrome to bipolar disorder

Targeting the prodrome to BD raises several challenges. One challenge, common to targeting the prodrome to any condition, is being able to discriminate patients who truly are in the prodrome to BD from those who are not so that intervention can be correctly targeted on those who will benefit. This may be further complicated by co-morbidity- alcohol/drug abuse, or ADHD, for example- or differentiating understandable reactions to life events from early prodromal symptoms. Where the specificity of the features used to identify individuals potentially in the prodrome is low, there will be a high false positive rate and, if intervention is offered, a large number of individuals will receive treatment unnecessarily. The risk-benefit analysis in the prodrome is crucial, and depends on the intervention to be offered- it may be acceptable to offer treatments with a low risk of adverse events even if the likelihood that a patient is really at risk (and so will potentially benefit) is low. Sensitivity, on the other hand, is important for the targeting of scarce resources- if only a small proportion can be identified in the prodrome resources may be better directed at the first episode of disorder.

Another challenge is that BD has fluctuating clinical manifestations, and, not surprisingly, prodromal symptoms of BD also seem to fluctuate over time. In our experience this leads to some individuals dropping in and out of care as their prodromal symptoms fluctuate. A consequence of this is that services need to be flexible- keeping contact where possible, and allowing individuals to refer themselves again after dropping out. Furthermore, whilst the diagnosis of BD can only be made after the first hypomanic/manic episode, many patients will have experienced one or more prior depressive episodes. The role of prior depressive episodes as a risk factor needs further evaluation, but in our clinic also raises diagnostic challenges as there is often not a contemporary diagnosis because the individual did not seek help at the time. Whilst a retrospective diagnosis may be made in these instances, the reliability of such retrospective diagnoses is not known.

The reliability of the clinical assessment used to identify an individual at risk of BD is also important. This is particularly the case as some symptoms preceding the onset of BD might fall along a continuum with normal personality characteristics [28]. One key issue highlighted in our systematic review of the studies to date was the lack of data on the inter or intra-rater reliability of the measures used to identify individuals at risk of BD [49].

Current evidence of prodromal features

There have been a number of retrospective studies [e.g. 16, and see 29 for review] which have found that the majority of BD patients experience symptoms such as episodic mood changes, irritability or impulsivity before the onset of the first episode of BD. However, whilst these findings certainly supports the existence of a prodromal phase, these studies may have been influenced by recall bias.

Fortunately there have been prospective studies, which avoid recall bias. Two general approaches that have been adopted- either focusing on clinical groups who are likely to be at high risk of BD, or large general population community samples. The clinical groups have been identified by the presence of psychiatric symptoms such as depression, brief psychotic episodes, anxiety, mood swings or sleep disturbances and/or biological loading [30-34]. Individuals in these samples have, however, already been introduced to clinical services. Therefore, they might not be representative of prodromal individuals in the general population. Hence, prospective studies using samples from the general population are likely to provide a more representative reflection of the processes involved in the development of BD in general.

Several studies have provided data from general population community samples [35-37]. Blechert & Meyer [36] applied measures of hypomanic personality, impulsive nonconformity and rigidity to a sample of 114 individuals who were followed up for two years after an initial screening. None of the measures was found to predict depressive symptoms. The scale for hypomanic personality was, however, found to predict (hypo-) manic symptoms, although BD was not registered as an outcome after two years. Therefore, this study does not allow conclusions on the specificity of hypomanic personality to the prodrome of BD.

The studies by Angst et al. [35] and Tijssen et al. [37] provide clearer evidence of the clinical features preceding the onset of BD. In addition to subjects from the general population, high-risk subjects (high-scorers on the Symptom Checklist 90-R (SCL-90-R [38]) and a control group (subjects scoring low on the SCL-90-R) were included in the study by Angst et al. [35]. Tijsen et al. [37] excluded symptoms that were directly related to alcohol or drug use in young adults and did not study subjects with a previous diagnosis of BD. Angst et al. [35] found that previously experienced mood instability was the strongest risk factor for bipolar disorder and Tijssen et al [37] found that more than 70% of the individuals who later on developed BD had experienced at least two hypomanic/manic and/or depressive symptoms previously.

Overall the retrospective and prospective studies reveal a pattern of putatively prodromal symptoms, of which mood lability/mood swings and depressive mood are the most commonly reported. Out of these common symptoms, mood lability looks likely to be the strongest risk factor for the subsequent diagnosis of a bipolar spectrum disorder (odds ratio (OR) 14, [35]). A positive family history of mania was found to be an additional risk factor, though less influential (OR 7). Apart from mood lability and depression, the putative bipolar prodrome is also characterized by more general psychiatric symptoms such as anxiety, racing thoughts, irritability and physical agitation, although these appear less specific for BD.

Symptoms relating to personality aspects such as cyclothymia have also been identified prior to the onset of BD [16,31,33,35,39]. As these features, however, were also found in healthy relatives of patients with BD [40,41], they may constitute an endophenotype for BD.

Sensitivity and specificity of prodromal features

Our systematic review found that none of the studies to date reported both the sensitivity and specificity of clinical features and only two provided the data to enable these to be calculated. Based on the sensitivity data we were able to derive from these studies, a number of individual features had high specificities- approaching or above 90%. Sensitivity values were lower: the only features with sensitivities above 70% were elevated/irritable mood, grandiosity, and mood swings. Nevertheless, the high specificity values indicate that it

should be possible to selectively target individuals who are likely to be in the prodrome to BD.

Combining factors

As discussed above, a number of different symptoms are evident prior to the development of BD and there is no single pathognomic symptom or clinical feature. Thus different 'state' features may be evident in different individuals. Furthermore, trait factors including family history of BD and cyclothymic personality traits have also been linked to a higher risk of developing BD. Thus a combination of state features and trait risk factors may be most useful to identify people at high risk of being in the prodrome to BD. Bechdolf et al. [42] have recently developed clinical criteria for identifying people who are at incipient risk of developing first episode mania, and thus are likely to be in the prodrome to BD. This uses the same 'close-in' approach that has previously been used for psychotic disorders- that is focusing on symptomatic individuals who are distressed by their symptoms and help-seeking. Ultra-high risk criteria for BD were proposed and validated on the basis of previous studies on putative prodromal symptoms and experience with the ultra-high risk concept in psychosis [43,44]. UHR criteria were defined as follows: age between 15 and 25 years and meeting criteria for at least one of the following three categories within the last 12 months: (1) Sub-threshold mania (2) depression + cyclothymic features (3) depression + genetic risk. After a mean follow-up duration of 265 days in a specialized early intervention service, conversion to mania occurred in 22.8% (5 of 22) of those who had fulfilled the UHR criteria, compared to 0.7% in the group of those who had not fulfilled the criteria. This study was a preliminary evaluation, and the sample was relatively small (only 6 patients developed BD in total). Nevertheless, the findings indicate that this combination of state and trait factors can be used to identify during the prodromal phase to BD, although the proposed criteria need to be further evaluated in prospective clinical studies.

Bipolar I versus bipolar II

Differentiating the prodrome to bipolar disorder type I (BD-I) from that to bipolar disorder type II (BD-II) may be useful both from a prognostic perspective, and to inform understanding of the neurobiology of the development of BD. However, we have not been able to identify any reports comparing the prodromal phase of BD-I to that of BD-II. Most studies combine data from individuals with BD-I and BD-II so it is not possible to determine if there are differences between the two, although there has been one study that specifically investigated the initial prodromal phase of BD-II [28]. This study used in-depth interviews of 15 patients and at least one relative or spouse to provide a collateral history. Two main categories of putatively prodromal symptoms prior to BD-II were identified: (1) affective symptoms (mood swings, depression-type symptoms, mania-type symptoms) and (2) general symptoms (anxiety, irritability/aggressiveness, sleep disturbances, other symptoms. Of these, anxiety and depression-type symptoms were the most frequent. Only a minority of the patients experienced mood swings (5 of 15) or mania-type symptoms (3 of 15), mainly at the final stage before the first major affective episode emerged. Mood swings may thus be a candidate to differentiate the prodrome to BD-I from that to BD-II. However, in the absence of studies directly comparing the prodrome to BD-I with that to BD-II, this clearly needs evaluating before it can be useful clinically.

Time course of the prodrome

There is evidence that some temperamental traits associated with the subsequent development of BD may be present from very early on in childhood, for example high irritability and dyscontrol has been reported in infants who went on to develop a bipolar spectrum disorder years later (see review [29]). Current data on the mean duration of the

prodrome varies considerably. Conus et al. [45] reported a mean duration of the prodrome of 20.9 weeks (SD=16.4) in patients with psychotic mania and schizoaffective disorder. Other findings suggested that the first symptoms usually occur years before the syndrome (with duration periods ranging from 1.8 to 7.3 years [46]). These diverging findings might be explained by differences in defining the onset (e.g. the first reported affective symptoms or unusual behavior) and the end of the prodromal phase (e.g. first admission to hospital), i.e. the transition to BD, as well as differences in the samples being studied.

Model of the development of bipolar disorder

Howes et al. [29] have proposed a model summarizing the features of the putative trajectory to BD based on the existing evidence on prodromal symptoms and the time course of their occurrence. According to this model, personality features such as cyclothymia are a vulnerability marker and may be present many years before the development of the frank illness [37,47], i.e. they form the pre-prodromal phase. Over the course of time these become more marked and attenuated BD and other symptoms become apparent, and are associated with significant distress. This exacerbation represents the prodrome to BD. This model highlights that there are several potential time points for prevention. Primary prevention could be targeted at the pre-prodromal phase, whereas secondary prevention could begin when life events or other triggers might prompt the beginning of the prodrome. The model proposes that the type of intervention should be tailored to the phase taking into consideration the features and that the balance between potential benefits and risks is likely to vary by phase. For example, treatments with a risk of significant side-effects, such as mood stabilisers, would be reserved for the later phases when symptoms are evident together with functional impairment, and there is a high risk of imminently developing BD, whilst interventions with a lower risk of side-effects, such as psychoeducation or psychotherapy, are used in the pre-prodromal phase. There is evidence that psychotherapy can be effective in people at risk of BD from a study of family therapy [48]. The study found family therapy was acceptable and associated with a reduction in symptoms and an improvement in functioning at one year. Whilst this is encouraging, the study was small (n=13), and lacked a comparator group. As such these results should be considered as preliminary, and further work is needed to determine the effectiveness and acceptability of early intervention.

Precipitating and protective factors

Although it is likely that life events have a role in the evolution of prodromal phase and triggering the first frank manic episode, as suggested in the model discussed above, the role of these and other factors in the development of BD has received relatively little attention. Identifying precipitating factors and those that may be protective against the development of BD, or associated with a more benign course, would be useful, both for factoring into the assessment of individuals who may be at risk of BD, and for developing interventions. A recent study does provide some preliminary evidence in this area [27]. The study used detailed life-charting to group patients based on whether they were high functioning or had evidence of neurocognitive impairment prior to the development of BD. The presence of neurocognitive deficits (either associated with ADHD (n=3) or specific learning difficulties (n=2) was associated with earlier age of onset of symptoms and a greater number of symptoms prior to the onset of BD than the high functioning group. The high functioning group was characterized as such based on scholastic achievements, social popularity/good adjustment, positive/agreeable attitude, and stable mood. Therefore, the presence of neurocognitive impairments might constitute a vulnerability marker of earlier transition, whereas the factors associated with the high functioning group might be protective. Whilst this study does have a number of limitations, not least that the neurocognitive impairment group confounds co-morbidity with neurocognitive difficulties, its relatively sample size,

Europe PMC Funders Author Manuscripts

and its retrospective design, it does suggest these factors should be further evaluated. However it will be more clinically useful to study the role of factors that are potentially modifiable, such as psychosocial stress and sleep patterns, as these are potentially amenable to intervention.

Potential ethical concerns

Detecting and intervening in the development of BD raises several ethical issues. As there is no pathognomic feature for the prodrome to BD, there will be the risk of false positive cases who are not at risk of developing BD. There is thus a risk that individuals will be unnecessarily worried by being wrongly identified as 'at risk of BD', and, if intervention is offered, also receive treatment that is not needed. The treatment may also unnecessarily expose them to the risk of side-effects. This highlights the importance of ensuring that the identification of people at risk of BD is as accurate as possible, and that individuals fully understand the nature of their risk for BD as well as the potential risks and benefits of any intervention. Another concern for early detection is that even being correctly identified as at risk of BD may have undesirable consequence for the individual- for example, potentially making it harder to obtain work or health insurance. These issues would be of particular concern if community screening programmes were developed, but are likely to be less of an issue for most clinical settings where individuals self-present because they are distressed and seeking help and advice.

Conclusion

Many patients report distressing symptoms that predate the onset of BD by years in some cases. Furthermore this period is associated with significant levels of suicidal behavior and help-seeking, which suggests that there is a need and desire for medical attention, at least some individuals. Studies on the bipolar prodrome to date have predominantly identified mood-related symptoms such as depression, mood lability, irritability and personality characteristics, such as cyclothymia, to be associated with the phase leading up to the diagnosis of BD. These findings suggest that the majority of the symptoms of the putative bipolar prodrome may be conceptualized as attenuated symptoms of BD. High specificity (> 90%) but low sensitivity (< 60%) is evident in many of these prodromal features [29]. The high sensitivity is promising for the development of early intervention in BD as it suggests that intervention can be targeted on individuals who are likely to be in the prodrome to the illness. However, there are a number of challenges to targeting the prodrome to BD. Amongst these the major ones are probably the lack of data on the sensitivity and specificity of some of the putatively prodromal features identified to date, the fluctuating nature of symptoms and the long time lag between the emergence of prodromal features and clear-cut symptoms of BD. Once these challenges have been addressed it will be possible to develop and evaluate interventions to target the prodrome. Whilst preventing the onset of BD will be the ultimate aim, it is important to note that individuals experiencing the putatively prodromal symptoms are distressed by their symptoms and help-seeking, and alleviating symptoms and reducing suicide risk are also important end-points.

Attempts to identify prodromal features of BD have not yielded a single characteristic in all subjects, suggesting that the bipolar prodrome might be best considered in terms of a cluster of symptoms [cf. 42]. Other risk factors, such as genetic risk or personality characteristics (i.e. cyclothymia), might further increase the overall risk of developing the disorder. Preliminary evidence suggests that the combination of symptom combinations with high predictive accuracy for a later diagnosis of BD with other risk factors improves the identification of people at highest risk of imminently developing BD. The pattern of prodromal features that has been identified so far also includes symptoms seen in a number

Europe PMC Funders Author Manuscripts

of other conditions. Therefore, studies using adequate psychiatric control groups are needed to further clarify which prodromal features are most specific for BD. Furthermore, so far the impact of incipient prodromal symptoms on the life and the behaviour of the affected individuals has not been studied in detail. For instance, the percentage of individuals in the prodrome to BD who present to medical services, and the functional impact of the symptoms is unknown. Large scale studies of prodromal symptoms in the general population are needed to address these issues.

Whilst it is hoped that indicated prevention for BD will reduce morbidity and prevent the development of BD in vulnerable individuals, it remains to be established if this is possible. Being able to reliably identify people who are in the prodromal phase of BD is the first step, and good progress has been made towards this. The next step will be to evaluate whether interventions targeted on individuals with prodromal signs of BD can reduce symptoms and the risk of developing BD.

References

Papers of particular interest, published recently, have been highlighted

*Of importance

**Of major importance

1. Bauer M, Pfennig A. Epidemiology of Bipolar Disorders. Epilepsia. 2005; 46:8–13. [PubMed: 15968806]
2. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007; 64:543–52. [PubMed: 17485606]
3. Pini S, de Queiroz V, Pagnin D, et al. Prevalence and burden of bipolar disorders in European countries. Eur Neuropsychopharmacol. 2005; 15:425–34. [PubMed: 15935623]
4. Waraich P, Goldner EM, Somers JM, et al. Prevalence and incidence studies of mood disorders: a systematic review of the literature. Can J Psychiatry. 2004; 49:124–38. [PubMed: 15065747]
5. Brent DA, Perper JA, Moritz G, et al. Psychiatric risk factors for adolescent suicide: a case-control study. J Am Acad Child Adolesc Psychiatry. 1993; 32:521–9. [PubMed: 8496115]
6. Brent DA, Perper JA, Goldstein CE, et al. Risk factors for adolescent suicide. A comparison of adolescent suicide victims with suicidal inpatients. Arch Gen Psychiatry. 1988; 45:581–8. [PubMed: 3377645]
7. Craney JL, Geller B. A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. Bipolar Disord. 2003; 5:243–56. [PubMed: 12895202]
8. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J Affect Disord. 2001; 67:45–59. [PubMed: 11869752]
9. Hirschfeld RMA, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry. 2003; 64:161–74. [PubMed: 12633125]
10. Baldessarini RJ, Tondo L, Hennen J, et al. Latency and episodes before treatment: response to lithium maintenance in bipolar I and II disorders. Bipolar Disord. 1999; 1:91–7. [PubMed: 11252665]
11. Highet NJ, McNair BG, Thompson M, et al. Experience with treatment services for people with bipolar disorder. Med J Aust. 2004; 181:S47–51. [PubMed: 15462642]
12. McIntyre RS, Konarski JZ. Bipolar disorder: a national health concern. CNS Spectr. 2004; 9:6–15. [PubMed: 15529087]
13. Franchini L, Zanardi R, Smeraldi E, et al. Early onset of lithium prophylaxis as a predictor of good long-term outcome. Eur Arch Psychiatry Clin Neurosci. 1999; 249:227–30. [PubMed: 10591987]

14. Baldessarini RJ, Tondo L, Hennen J. Treatment-latency and previous episodes: relationships to pretreatment morbidity and response to maintenance treatment in bipolar I and II disorders. Bipolar Disord. 2003; 5:169–79. [PubMed: 12780871]
15. Swann AC, Bowden CL, Calabrese JR, et al. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry. 1999; 156:1264–6. [PubMed: 10450271]
16*. Berk M, Dodd S, Callaly P, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. Journal of Affective Disorders. 2007; 103:181–6. [PubMed: 17324469] This study found that there was a period of several years between the first onset of symptoms and the onset of the first affective episode, and a further delay before the correct diagnosis of BD was made.
17. Perugi G, Micheli C, Akiskal HS, et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry. 2000; 41:13–8. [PubMed: 10646613]
18. Berk M, Hallam K, Malhi GS, et al. Evidence and implications for early intervention in bipolar disorder. J Ment Health. 2010; 19:113–26. [PubMed: 20433320]
19. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry. 1995; 152:1130–8. [PubMed: 7625459]
20. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry. 2006; 163:313–5. [PubMed: 16449487]
21. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry. 2006; 163:232–9. [PubMed: 16449476]
22. Post RM, Altshuler LL, Frye MA, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. Bipolar Disord. 2001; 3:259–65. [PubMed: 11912569]
23. Berk M, Hallam K, Lucas N, et al. Early intervention in bipolar disorders: opportunities and pitfalls. Med J Aust. 2007; 187:S11–4. [PubMed: 17908017]
24. Conus P, Ward J, Hallam KT, et al. The proximal prodrome to first episode mania – a new target for early intervention. Bipolar Disorders. 2008; 10:555–65. [PubMed: 18657240]
25. Bramon E, Shaikh M, Broome M, et al. Abnormal P300 in people with high risk of developing psychosis. NeuroImage. 2008; 41:553–60. [PubMed: 18387827]
26. Howes OD, Montgomery AJ, Asselin MC, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Archives of general psychiatry. 2009
27. Howes O, Bose S, Turkheimer F, et al. Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. Mol Psychiatry. 2011 doi:10.1038/mp.2011.20.
28. Skjelstad DV, Malt UF, Holte A. Symptoms and behaviors prior to the first major affective episode of bipolar II disorder. An exploratory study. J Affect Disord. 2011 doi:10.1016/j.jad.2011.03.003.
29*. Howes OD, Lim S, Theologos G, et al. A comprehensive review and model of putative prodromal features of bipolar affective disorder. Psychol Med. 2010:1–11. In this systematic review we provide the frequency of symptoms and their specificity and sensitivity, as well as providing a framework for considering the prodrome to BD.
30. Thompson KN, Conus PO, Ward JL, et al. The initial prodrome to bipolar affective disorder: prospective case studies. J Affect Disord. 2003; 77:79–85. [PubMed: 14550938]
31. Kochman FJ, Hantouche EG, Ferrari P, et al. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. J Affect Disord. 2005; 85:181–9. [PubMed: 15780688]
32. Correll CU, Smith CW, Auther AM, et al. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. J Child Adolesc Psychopharmacol. 2008; 18:475–90. [PubMed: 18928412]

33. Akiskal HS, Downs J, Jordan P, et al. Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. Arch Gen Psychiatry. 1985; 42:996–1003. [PubMed: 4037989]
34. Olvet DM, Stearns WH, McLaughlin D, et al. Comparing clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome. Schizophr Res. 2010; 123:59–63. [PubMed: 20716479]
35. Angst J, Gamma A, Endrass J. Risk factors for the bipolar and depression spectra. Acta Psychiatr Scand Suppl. 2003:15–9. [PubMed: 12956808]
36. Blechert J, Meyer TD. Are measures of hypomanic personality, impulsive nonconformity and rigidity predictors of bipolar symptoms? Br J Clin Psychol. 2005; 44:15–27. [PubMed: 15826341]
37**. Tijssen MJA, van Os J, Wittchen H-U, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. The British Journal of Psychiatry. 2010; 196:102–8. [PubMed: 20118453] This prospective study mapped the development of BD in a large representative community sample at repeated time points over up t 10 years.
38. Derogatis, LR. SCL-90 Administration, scoring and procedures manual-I for the R (revised) version and other instruments of the psychopathology rating scale series. Johns Hopkins University School of Medicine; Chicago: 1977.
39. Azorin J-M, Kaladjian A, Adida M, et al. Baseline and prodromal characteristics of first-versus multiple-episode mania in a French cohort of bipolar patients. Eur Psychiatry. 2011 doi:10.1016/j.eurpsy.2010.11.001.
40. Findling RL, Youngstrom EA, McNamara NK, et al. Early symptoms of mania and the role of parental risk. Bipolar Disord. 2005; 7:623–34. [PubMed: 16403188]
41. Jones SH, Tai S, Evershed K, et al. Early detection of bipolar disorder: a pilot familial high-risk study of parents with bipolar disorder and their adolescent children. Bipolar Disord. 2006; 8:362–72. [PubMed: 16879137]
42. Bechdolf A, Nelson B, Cotton SM, et al. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. J Affect Disord. 2010; 127:316–20. [PubMed: 20619465]
43. McGorry PD, Yung AR, Phillips LJ. The “Close-in” or Ultra High-Risk Model: A Safe and Effective Strategy for Research and Clinical Intervention in Prepsychotic Mental Disorder. Schizophrenia Bulletin. 2003; 29:771–90. [PubMed: 14989414]
44. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry Suppl. 1998; 172:14–20. [PubMed: 9764121]
45. Conus P, Ward J, Lucas N, et al. Characterisation of the prodrome to a first episode of psychotic mania: results of a retrospective study. J Affect Disord. 2010; 124:341–5. [PubMed: 20085850]
46. Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. J Affect Disord. 2010; 126:1–13. [PubMed: 19883943]
47. Fergus EL, Miller RB, Luckenbaugh DA, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. J Affect Disord. 2003; 77:71–8. [PubMed: 14550937]
48. Miklowitz DJ, Chang KD, Taylor DO, George EL, Singh MK, Schneck CD, Dickinson LM, Howe ME, Garber J. Early psychosocial intervention for youth at risk for bipolar I or II disorder: a one year treatment development trial. Bipolar Disorders. 2011; 13:67–75. [PubMed: 21320254]