

Early Detection and Intervention in Bipolar Affective Disorder: Targeting the Development of the Disorder

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Abstract The diagnosis of bipolar affective disorder (BD) is often delayed, and preceded by incorrect diagnoses and potentially harmful treatment, while the development of the disorder is associated with suicidal behavior and help seeking. Several 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 psychopathologic symptoms. Several of these show high specificity, indicating that it may be possible to target detection and intervention in individuals at high risk of BD and perhaps moderate the course of the illness and improve treatment outcome. This article summarizes 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 · Development

Introduction

Recent years have seen a paradigm shift in psychiatry, from a focus on chronic established illness toward one of early detection and intervention. This has resulted in 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 programs and government resources (<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 toward bipolar affective disorder (BD).

The Value of Early Detection of Bipolar Affective Disorder

BD is a chronic condition characterized by periodic episodes of mania and depression that cause 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 onset during childhood or adolescence [5–7].

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 10 years [8, 9]. As a result, adequate treatment initiation is often delayed considerably [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 who waited the longest for the correct diagnosis [16]. This may be because early-onset BD is mainly characterized by depressive

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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 misdiagnosed with other conditions [18]. High rates of misdiagnosis have been reported: in one series, more than 50% of patients initially received a diagnosis other than BD when they sought medical attention, and many received treatment with antidepressant or antipsychotic drugs [19]. Where misdiagnosis 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 [23]. Thus, the prodromal phase of BD is a chance to engage patients and caregivers 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 1 in 10 patients reported suicide attempts in the year prior to the initial onset of BD, and that the risk was more than twofold greater than in individuals experiencing a relapse of established BD [23]. This indicates that suicidal behavior occurs in the prodromal phase. Evidence also suggests 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 therefore may be more willing to utilize clinical services, intensified surveillance, or specific treatment as compared with patients in later stages of the illness, during which nonadherence and reduced insight may impair treatment strategies [24].

Early detection can be considered at several time points in the development of a disorder, from a presymptomatic stage, through the development of prodromal features, and to the first point at which the clinical manifestation meets diagnostic criteria (the first manic or hypomanic episode in the case of BD). Presymptomatic screening raises several technical and ethical issues—not the least of which is 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 he or she cannot return to them. The prodromal phase thus may be where the most clinical traction can be obtained, as 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 [25]. This is, of course, of little benefit to patients and clinicians. It is, however, possible to identify symptoms and other clinical features that are associated with the prodrome to BD. Such prodromal features thus may help in identifying individuals at risk of developing BD prospectively, and guide early intervention. *Prodromal* also can be used to refer to the initial subclinical phase preceding the relapse of an established disorder. This is also an active area of research in BD but is beyond the scope of this review.

Early detection also has particular value for understanding the neurobiology that underlies BD. Studies of individuals in the prodromal phase, 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 [26–28]. 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 that is common to targeting the prodrome to any condition is being able to distinguish patients who truly are in the prodrome to BD from those who are not so that intervention can be correctly targeted to those who will benefit. This may be further complicated by comorbidity (eg, alcohol/drug abuse or attention-deficit/hyperactivity disorder) 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 thus 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, although 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 no contemporary diagnosis because the individual did not seek help at the time. Although a retrospective diagnosis may be made in these instances, the reliability of such retrospective diagnoses is not clear.

The reliability of the clinical assessment used to identify an individual at risk of BD is also important. This is particularly important, as some symptoms preceding the onset of BD may fall along a continuum with normal personality characteristics [29]. One key issue highlighted in our systematic review of the studies to date was the lack of data on the inter- or intrarater reliability of the measures used to identify individuals at risk of BD.

Current Evidence of Prodromal Features

Several retrospective studies [16, 30•] have found that most BD patients experience symptoms such as episodic mood changes, irritability, or impulsivity before the onset of the first episode of BD [16, 30•]. However, while these findings support the existence of a prodromal phase, they may have been influenced by recall bias.

Fortunately, prospective studies have been conducted that avoid recall bias. Two general approaches have been adopted: focusing on clinical groups that are likely to be at high risk of BD or on 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 [23, 31–34]. However, individuals in these samples have already been introduced to clinical services. Therefore, they may 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 and Meyer [36] applied measures of hypomanic personality, impulsive non-conformity, and rigidity to a sample of 114 individuals who were followed up for 2 years after an initial screening. None of the measures were 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 2 years. Therefore, results of this study do not allow us to formulate conclusions on the specificity of hypomanic personality to the prodrome of BD.

The studies by Angst et al. [35] and Tjissen et al. [37•] provide clearer evidence of the clinical features preceding the onset of BD. In addition to participants from the general

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

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. Of these common symptoms, mood lability looks likely to be the strongest risk factor for the subsequent diagnosis of a bipolar spectrum disorder (OR, 14) [35]. A positive family history of mania was found to be an additional risk factor, though it was 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 also have been identified prior to the onset of BD [16, 32, 34, 35, 39]. However, as these features 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, several 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 previously, several different symptoms are evident prior to the development of BD, and no single pathognomic symptom or clinical feature exists. Thus, different “state” features may be evident in different individuals.

Furthermore, trait factors, including family history of BD and cyclothymic personality traits, also have 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] recently developed clinical criteria for identifying individuals who are at incipient risk of developing first-episode mania, and thus are likely to be in the prodrome to BD. These use the same “close-in” approach that was previously used for psychotic disorders—that is, focusing on symptomatic individuals who are distressed by their symptoms and seeking help. 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]. Ultra high-risk 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 past 12 months: 1) subthreshold mania, 2) depression plus cyclothymic features, and 3) depression plus genetic risk. After a mean follow-up 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 ultra high-risk criteria, compared with 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 six patients developed BD in total). Nevertheless, the findings indicate that this combination of state and trait factors can be used to identify the prodromal phase to BD, although the proposed criteria need to be evaluated further in prospective clinical studies.

Bipolar I Disorder Versus Bipolar II Disorder

Differentiating the prodrome to bipolar I disorder (BD-I) from that to bipolar II disorder (BD-II) may be useful 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 with 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 one study specifically investigated the initial prodromal phase of BD-II [29]. This study used in-depth interviews with 15 patients and at least 1 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 thus may 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 to be evaluated before it can be useful clinically.

Time Course of the Prodrome

Evidence suggests that some temperamental traits associated with the subsequent development of BD may be present from very early in childhood (eg, high irritability and dyscontrol have been reported in infants who went on to develop a bipolar spectrum disorder years later) [30•]. Current data on the mean duration of the prodrome vary 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 suggest 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 may be explained by differences in defining the onset (eg, the first reported affective symptoms or unusual behavior) and the end of the prodromal phase (eg, first admission to hospital) (ie, the transition to BD), as well as differences in the samples being studied.

Model of the Development of Bipolar Disorder

Howes et al. [30•] 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 area vulnerability markers and may be present many years before the development of the frank illness (ie, they form the pre-prodromal phase) [37••, 47]. 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 may 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 (eg, mood stabilizers) 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, whereas interventions with a

lower risk of side effects (eg, psychoeducation or psychotherapy) would be used in the pre-prodromal phase. Evidence from a study of family therapy indicates that psychotherapy can be effective in individuals at risk of BD [48]. The study found that family therapy was acceptable and associated with a reduction in symptoms and an improvement in functioning at 1 year. Although this is encouraging, the study was small ($N=13$) and lacked a comparator group. As such, these results should be considered 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 play a role in the evolution of the prodromal phase and the triggering of 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 for factoring in the assessment of individuals who may be at risk of BD, and for developing interventions. A recent study provided some preliminary evidence in this area [28]. 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 (associated with attention-deficit/hyperactivity disorder [$n=3$] or specific learning difficulties [$n=2$]) was associated with earlier age at 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 may constitute a vulnerability marker of earlier transition, whereas the factors associated with the high-functioning group may be protective. Although this study does have limitations—that the neurocognitive impairment group confounds comorbidity with neurocognitive difficulties, its relatively sample size, and its retrospective design—it does suggest that these factors should be evaluated further. 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. Because there is no pathognomic feature

for the prodrome to BD, there will be a risk of false-positive cases who are not at risk of developing BD. Thus, there is 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 individuals at risk of BD is as accurate as possible, and that individuals fully understand the nature of their risk for BD and 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 (eg, the potential of making it harder to obtain work or health insurance). These issues would be of particular concern if community screening programs were developed but are likely to be less of an issue for most clinical settings, in which individuals self-present because they are distressed and seeking help and advice.

Conclusions

Many patients report distressing symptoms that predate the onset of BD by years in some instances. Furthermore, this period is associated with significant levels of suicidal behavior and help seeking, which suggests a need and desire for medical attention, at least for 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 most 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 [30]. The high sensitivity is promising for the development of early intervention in BD, as it suggests that intervention can be targeted to individuals likely to be in the prodrome to the illness. However, there are several challenges to targeting the prodrome to BD. 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. While 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 individuals, suggesting that

the bipolar prodrome may be best considered in terms of a cluster of symptoms [42]. Other risk factors, such as genetic risk or personality characteristics (ie, cyclothymia), may further increase the overall risk of developing the disorder. Preliminary evidence suggests that the combination of symptoms with high predictive accuracy for a later diagnosis of BD with other risk factors improves the identification of individuals at highest risk of imminently developing BD. The pattern of prodromal features that has been identified thus far also includes symptoms seen in other conditions. Therefore, studies using adequate psychiatric control groups are needed to further clarify which prodromal features are most specific for BD. Furthermore, thus far, the impact of incipient prodromal symptoms on the life and behavior 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 are unknown. Large-scale studies of prodromal symptoms in the general population are needed to address these issues.

Although 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 individuals who are in the prodromal phase of BD is the first step, and good progress has been made toward this. The next step will be to evaluate whether interventions targeted to individuals with prodromal signs of BD can reduce symptoms and the risk of developing BD.

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- Of major importance

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