Arch Psychiatry. 2024;2(1):49-53.

The Archives of Psychiatry | Short Communication

What are the Elements to Target the Anticipatory Signs of Bipolar Disorder Before Diagnosis?

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Received date: May 23, 2024, **Accepted date:** August 07, 2024

Citation: Bourin M. What are the Elements to Target the Anticipatory Signs of Bipolar Disorder Before Diagnosis?. Arch Psychiatry. 2024;2(1):49-53.

Abstract

Being able to anticipate the discovery of a disease in a given individual remains a clinical challenge. In the case of bipolar disorder (BD), the prodromal phase can be relatively long. Mood lability and the manifestation of depression are the most consistent warning signs. Anxiety, particularly panic attacks, is often a precursor. Early detection of prodromal symptoms may contribute to improving the prognosis of patients with BD. The main objective of this paper is to present the different procedures for the identification of initial and relapse prodromes in these patients.

Keywords: Bipolar disorder, Prodromal symptoms, Mood lability, Depression, Anxiety.

Introduction

A prodrome constitutes a period of disturbance characterized by symptoms leading to the development of the full-blown disorder. Although the prodrome is often determined retrospectively, it can nevertheless be useful to characterize subjects risking to develop a disease or disease recurrence prospectively, provided that the prodrome is of satisfactory specificity and sensitivity [1,2]. Recent evidence hypothesized BD as a progressive disease, whose trajectory starts from a specific non-mood symptoms, such as those of childhood anxiety disorders, and continues with depression or subthreshold hypomanic episodes in adolescence and early adulthood, up to the onset of first full mood episode [3]. A challenge regarding the identification of the prodrome, in order to be able to discriminate patients who really have a prodrome from those who do not; so that support can be properly established for those who can benefit from it. This can be complicated by comorbidity: alcohol abuse, drug abuse, or attention disorders, for example [4,5].

When the specificity of the characteristics used to identify individuals potentially presenting with a prodrome is weak, there will be a high rate of false positives and, therefore, if a therapeutic intervention is offered, a large number of patients will receive treatment unnecessarily [6,7]. The benefit/risk analysis in the event of a prodrome is crucial and depends on the therapeutic intervention to be proposed. It may be acceptable to offer treatments with moderate side effects even if the probability and expected benefit may be low [7,8].

Another challenge is that BD presents with changing symptomatic manifestations and prodromal symptoms of BD also appear to fluctuate over time. This leads clinicians to neglect fluctuating prodromal manifestations [9]. This poses a risk for adherence to treatment. Intervention proposals should be flexible, maintaining contact when possible and allowing individuals to return for consultation again after dropping out [10]. Additionally, while the diagnosis of BD is often not made until the first hypomanic/manic episode, many individuals will have already experienced one or more depressive episodes. The role of prior depressive episodes as a risk factor requires further evaluation. This also poses diagnostic problems because there is often no contemporaneous diagnosis for each of the depressive episodes [11]. However, a retrospective diagnosis can then be made, but the reliability of these retrospective diagnoses is not known and often doubtful. Indeed, certain symptoms preceding the onset of BD can

be part of a continuum with normal or anxious personality characteristics. This is a source of disagreement between psychiatrists despite international classifications which do not consider the prodromal aspect of the disease.

Current Evidence for Prodromal Characteristics

A number of retrospective studies have found that the majority of patients with BD, experience symptoms before the onset of the first episode, such as episodic mood changes, irritability, or impulsivity [12]. Although these results support the existence of a prodromal phase, these kinds of studies induce through the questioning, what is called a recall bias.

Two general approaches have been taken, focusing either on clinical groups likely to be at high risk of BD or on large samples of the general population. Clinical groups were created on the basis of symptoms such as depression, brief psychotic episodes, anxiety, mood swings or sleep disturbances. However, the individuals in these samples had already attended clinical services [13,14]. Therefore, they may not be a way to find individuals at risk in the general population. Prospective studies using general population samples are far better to find people having a high risk to developpe a bipolar disease [15].

Overall, retrospective and prospective studies reveal a pattern of presumed prodromal symptoms, among which mood lability/mood swings and depressed mood are the most commonly reported. Among these common symptoms, mood lability appears to be the most important risk factor for later diagnosis of bipolar spectrum disorder. A history of mania among family members could be an additional risk factor. On the other hand, the putative bipolar prodrome is also characterized by more general symptoms such as anxiety, racing thoughts, irritability and physical agitation, in addition to depression and mood lability [16].

Symptoms related to aspects of personality such as cyclothymia have also been identified before the onset of BD. However, as these features have also been found in healthy relatives of BD patients, they may constitute an endo phenotype of BD [17].

Combination of Factors

A number of different symptoms are evident before BD diagnosis and there is no pathognomonic (i.e. absolutely sure) symptom or single clinical feature. Thus, different "state" characteristics may be evident in different individuals [18]. Additionally, family history of bipolarity, and cyclothymic personality traits, have also been associated with a higher risk of developing BD. A combination of state characteristics and risk factors may be useful in identifying individuals at high risk of being bipolar. Clinical criteria have thus been developed to identify people who are at probable risk of developing a first episode of mania, and who are therefore likely to be bipolar [19].

Bipolar I Versus Bipolar II Prodrome

Pointing out the prodrome of bipolar I disorder (BD-I) from that of bipolar II disorder (BP-II) may be useful both prognostically and to inform understanding of developmental neurobiology of bipolarity. However, it is possible to find studies comparing the prodromal phase of BD-I to that of BD-II [20]. Prior to the first depressive episode, the prevalence of mania index total differed between patients with BD-I and BD-II. Although each item in the mania symptom index showed no statistical difference between the two BD groups, some items deserve attention. The item of "irritability or anger" and "overly talkative" tended to occur more in BD-II group [21].

Two main categories of presumed prodromal symptoms before BD-II were identified:

- affective symptoms (mood swings, depression-like symptoms, mania-like symptoms)
- general symptoms: anxiety, irritability/aggression, sleep disorders, other symptoms [22]

Among these, symptoms such as anxiety and depression were the most common. Only a minority of patients experienced mood swings or manic-like symptoms, mainly in the final stages before the first major affective episode had appeared. Mood swings could therefore be useful in differentiating the prodrome of BD-I from that of BD-II [23].

Temporal Evolution of the Prodrome

There is evidence that some character traits associated with the later development of BD may be present very early in childhood, for example high irritability has been reported in infants who developed bipolar spectrum disorder years later should be followed by a period [24]. Current data on average prodrome duration vary widely. Other results suggest that the first symptoms generally occur years before the onset of symptoms characteristic of bipolarity (with periods of duration ranging from 2 to 7 years). These divergent results could be explained by differences in the definition of the beginning (e.g. first reported affective symptoms or unusual behavior) and end of the prodromal phase (e.g. first hospital admission), i.e. the transition to BD [25].

Developmental Model of Bipolar Disorder

A model was proposed summarizing the characteristics of the possible trajectory to BD, based on existing evidence of probable prodromal symptoms and the temporal course of their onset [26]. According to this model, personality traits such as cyclothymia are a marker of vulnerability and may

be present several years before the development of frank disease, that is, they form the pre-prodromal phase. Over time, these symptoms become more pronounced and other symptoms appear associated with significant difficulties. This exacerbation is in fact the prodrome of BD. This model highlights the existence of several potential identifiable moments for prevention. Primary prevention could be implemented during the pre-prodromal phase, while secondary prevention could begin when life events as well as other triggers could cause the onset of the prodrome [27]. The model suggests that the type of intervention is adapted to the phase taking into account the characteristics, as well as the potential benefits/risks ratio probably evolves according to the phase. Psychotherapy can be effective in patients at risk for BD from a family therapy study. The study found that family therapy led to reduced symptoms and improved functioning for one year. While this is encouraging, the study was small and lacked a comparison group. These results should be considered preliminary and further studies should make it possible to demonstrate the effectiveness and acceptability of early intervention [28].

Precipitating or Protective Factors

Life events appear to play a role in the development of the prodromal phase and the onset of the first frank manic episode; the role of these factors in the development of BD has been little studied. It would be useful to identify the triggering factors as well as those that could be protective against the development of BD, or those that are associated with a more benign outcome. Both to assess individuals likely to be at risk of developing BD and thus to be able to anticipate treatment [29]. Detailed life charts were used to group patients based on whether they had signs of neurocognitive impairment before the development of BD. The presence of neurocognitive deficits (associated with ADHD), or learning difficulties was associated with an earlier age of symptom onset before the onset of BD compared to the group with high cognitive functioning [30]. The high-functioning group was characterized as such on the basis of academic performance, social popularity, pleasant positive attitude, and regular mood. Thus, the presence of neurocognitive disorders could constitute a marker of vulnerability to BD [31]. However, it is more useful to study the role of factors that can be modified, such as psychosocial stress and sleep habits, because they can be addressed relatively early [32].

Potential Ethical Issues

Intervening in the development of BD leads to ethical problems. As there is no pathognomonic feature for bipolar prodromes, there will be a risk of false positives of non-development of BD [33]. We may fear that patients are unnecessarily worried because they may be misdiagnosed as being at risk for BD and, thereby receiving treatment, also receive treatment that is not necessary. This highlights the importance of ensuring that the identification of individuals at risk for BD is as accurate as possible and that individuals fully understand the nature of their BD risk and the potential risks and benefits of any intervention [34]. Another concern with early detection is that even being correctly identified as being at risk for BD can have undesirable consequences for the individual, for example, potentially making it more difficult to obtain work [35].

Conclusion

Many patients report symptoms of anxiety for several years preceding the onset of BD. Longitudinal studies indicate that a full-blown manic episode is often preceded by a variety of prodromal symptoms, particularly subsyndromal manic symptoms, therefore supporting the existence of an at-risk state in BD that could be targeted through early intervention. In addition, this period carries significant risks of suicidal behavior and a need for help, leading to a need and desire for medical care, at least for some people. To date, studies of bipolar prodrome have primarily identified mood-related symptoms, such as depression, mood lability, irritability, and personality characteristics, such as cyclothymia. These results suggest that the majority of symptoms of the putative bipolar prodrome can be conceptualized as attenuated symptoms of BD. High specificity, but low sensitivity is evident in many of these prodromal features because it suggests that therapeutic intervention can be targeted to individuals likely to be in the prodromal phase of the disease. However, targeting the BD prodrome presents a number of challenges. Probably the most important of these remains the lack of data on the sensitivity and specificity of some of the prodromal features known to date, the fluctuating nature of symptoms and often the significant delay between the appearance of prodromes and clearly linked symptoms. in BD. Once these challenges are resolved, it will be possible to develop and evaluate interventions to target the prodrome. Although prevention of the onset of BD is the ultimate goal, it is important to note that people with the presumed prodromal symptoms are distressed by their symptoms and seek help, and relief of symptoms and reduction of suicide risk are also important endpoints. There are also identifiable risk factors that influence the course of bipolar disorder, some of them potentially modifiable. Valid biomarkers or diagnosis tools to help clinicians identify individuals at high risk of conversion to BD are still lacking, although there are some promising early results. Pending more solid evidence on the best treatment strategy in early phases of bipolar disorder, physicians should carefully weigh the risks and benefits of each intervention.

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