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ORIGINAL ARTICLE

Clinical characteristics and influence of childhood trauma on the prodrome of bipolar disorder

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Objectives: To describe the onset pattern, frequency, and severity of the signs and symptoms of the prodrome of the first hypomanic/manic episode and first depressive episode of bipolar disorder (BD) and to investigate the influence of a history of childhood maltreatment on the expression of prodromal symptoms.
Methods: Using a semi-structured interview, the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R), information regarding prodromal symptoms was assessed from patients with a DSM-IV diagnosis of BD. History of childhood maltreatment was evaluated using the Childhood Trauma Questionnaire (CTQ).
Results: Forty-three individuals with stable BD were included. On average, the prodrome of mania lasted 35.8±68.7 months and was predominantly subacute or insidious, with rare acute presentations. The prodrome of depression lasted 16.6±23.3 months and was also predominantly subacute or insidious, with few acute presentations. The prodromal symptoms most frequently reported prior to the first hypomanic or manic episode were mood lability, depressive mood, and impatience. A history of childhood abuse and neglect was reported by 81.4% of participants. Presence of childhood maltreatment was positively associated with prodromal symptoms, including social withdrawal, decreased functioning, and anhedonia.
Conclusions: This study provides evidence of a long-lasting, symptomatic prodrome prior to first hypomanic/manic and depressive episode in BD and suggests that a history of childhood maltreatment influences the manifestations of this prodrome.

Keywords: Bipolar disorder; mania; prodrome; childhood maltreatment; depression; early stages

Introduction

Bipolar disorder (BD) is a chronic and often severe mood disorder.[1] In a large subgroup of patients, BD follows a progressive course, which can lead to structural brain damage and functional impairment.[2] In recent years, staging models for BD have been proposed.[3,4] (A detailed review is available elsewhere.[5]) According to these models, the disorder starts in the "at-risk period" and progresses from the first episode to chronic and, possibly, refractory stages, putatively caused by neurobiological alterations such as an increase in neurotoxic states and reduction of neurotrophic and neuroprotective factors.[6,7] The progression of BD results in deterioration of clinical symptoms, cognition, and functioning, and leads to structural damage. From this perspective, prevention of BD and its early diagnosis and treatment are paramount to reducing the major economic, psychosocial, and functional impact of this disorder by delaying its onset or, perhaps, even preventing its full-blown development.[8,9]

Clinical experience and retrospective studies have reported that the majority of individuals with BD experience mild but identifiable symptoms during childhood and adolescence.[10-12] The symptomatic period preceding the first manic or hypomanic episode, also called the prodrome, lasts from several weeks up to many years before full BD onset,[3,13] and often includes sub-threshold manic symptoms, depressive symptoms, cyclothymic features, anxiety, sleep disturbances, psychotic symptoms, ADHD-like symptoms, and obsessive-compulsive symptoms.[13,14] A systematic review reported that irritability, aggression, sleep disorders, hyperactivity, anxiety,

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and mood swings are common symptoms in the early phase of the BD prodrome (also called the "distal" prodrome).[15,16] Over time, psychopathology progresses and symptoms usually became more specific and similar to those of full BD; this is called the "proximal" prodrome.[15] A 4-year, prospective study found that 38% of children and adolescents initially diagnosed with subsyndromal BD symptoms, and 25% of those diagnosed with BD-II, transitioned to BD-I during follow-up.[17] Nevertheless, few studies have investigated clinical expression of the bipolar prodrome, and the vast majority of these used either unstructured questionnaires or chart-review designs. Most failed to assess the onset pattern of the disorder and symptom severity in the prodromal period.

The majority of published studies that investigated the prodromal features of BD focused on patients with BD-I.[15] Although some included patients with BD-II, there is a lack of investigations focusing on prodromal symptoms in this population. One study that evaluated the prodromal period in individuals with BD-II found that they experienced clinically significant symptoms (predominantly depressive symptoms and anxiety) at an average of more than a decade before their first major mood episode.[18] Most studies combined data from the two subtypes of BD,[19] thus precluding any assessment of potential differences between them. However, identifying differences in the characteristics of the prodromal period of the two BD subtypes may be useful from a prognostic perspective and to better understand the neurobiology of BD.

Environmental factors, such as childhood trauma, may influence the expression of symptoms in BD,[20] as well as the prodromal features of the disorder. Patients with BD exhibit higher vulnerability to traumatic events during childhood.[21] In addition, BD seems to be a stress-sensitive disorder, with the first mood episode often being triggered by psychosocial stressors.[21,22] Childhood trauma also appears to impact the course of the illness, being associated with earlier illness onset, an increased number of comorbidities, and suicidal behavior.[20,23] Although childhood trauma is assumed to have an important role in the early expression of symptoms in BD, to the best of our knowledge, no studies that investigated the prodromal period of this disorder have systematically evaluated the presence of childhood trauma or its influence on the prodromal manifestations of BD.

Therefore, the aim of this study was to describe the onset pattern, frequency, and severity of the signs and symptoms of the prodrome to the first depressive and the first hypomanic or manic episode of BD, using a semi-structured interview (the Bipolar Prodrome Symptom Scale-Retrospective, BPSS-R), and to compare the prodromal features of BD-I with those of BD-II. Furthermore, we sought to explore the influence of demographic and clinical variables, including history of childhood maltreatment, on the expression of prodromal symptoms. We hypothesized that: a) the prodrome to the first depressive episode would be longer than the prodrome to the first manic episode; b) there would be no significant differences between BD-I and BD-II regarding the depressive prodrome, but the hypomanic/manic prodrome would be shorter and more symptomatic in patients with BD-I; and c) a history of childhood trauma would be associated with a greater frequency of certain prodromal symptoms, as well as with a longer prodrome duration.

Methods

This study protocol was approved by the Ethics Committee of Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil, and all individuals provided written informed consent before inclusion.

Population

Forty-three stable outpatients with BD-I or BD-II of no longer than 9 years' duration were included. The diagnosis was established in accordance with the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Clinical stability was defined as a 17-item Hamilton Depression Rating Scale (HDRS) score < 14 and a Young Mania Rating Scale (YMRS) score < 8. The exclusion criteria were presence of neurological/organic disease, inferred mental retardation, illiteracy, dementia, and current moderate or severe mood symptoms (see above).

Outcomes

The primary outcome measures were the duration of the prodrome before the first manic episode, the duration of the prodrome before the first depressive episode, and the frequency of specific prodromal symptoms. The secondary outcomes were the frequency of childhood trauma and its relationship to prodromal patterns, as well as the influence of BD subtype (BD-I vs. BD-II) on prodromal patterns.

Assessment instruments

Prodromal symptoms were evaluated by a trained psychiatrist using the Brazilian Portuguese version of the BPSS-R,[11,24] a semi-structured interview that assesses 36 signs and symptoms that emerge or worsen prior to the first depressive or manic episode. It investigates all DSM-IV symptoms of mania and depression, psychotic symptoms, and general psychopathology, and assesses not only the presence of symptoms, but also their onset pattern, duration, severity, frequency, and possible association with substance abuse. Prodromal symptom severity is rated as 1 = mild, 2 = moderate, or 3 = severe. Symptom frequency is rated as 1 = infrequent, 2 = recurrent, 3 = very frequent, or 4 = static lifetime or character trait. Consistent with conventions used for the psychotic prodrome,[25] symptoms were included in the analysis if they were of at least moderate severity and were not considered a character trait, unless the severity had increased by at least one point before the onset of the disorder. Regarding onset pattern, the prodrome was classified as acute (< 1 month in duration), subacute (1-12 months in duration), or

insidious ($>$ 1 year in duration).[11] Prodromal symptoms that emerged prior to the first depressive or manic/hypomanic episode were systematically investigated through retrospective patient reports.

Childhood maltreatment was assessed using a translated and validated version of the Childhood Trauma Questionnaire (CTQ).[26,27] This is a self-report instrument used to document history of childhood maltreatment in five domains: sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The instrument consists of 28 questions and the severity of trauma is graded on a five-point Likert-type scale, from absent to severe. Childhood trauma is classified as none, low, moderate, or severe. For purposes of analysis, a history of trauma was classified dichotomously as absent (patients who experienced no or minimal trauma) or present (patients who experienced low, moderate, or severe trauma during childhood and adolescence).

Depressive and manic symptom severity was assessed using the HDRS and YMRS[28] respectively. Illness severity was assessed using the Clinical Global Impressions-Severity (CGI-S) scale, and global functioning, using the Global Assessment of Functioning (GAF) scale.

Statistical analysis

Data were tabulated and analyzed in SPSS version 20.0 for Mac. Descriptive statistics included mean and standard deviation or median and percentiles and percentage, as appropriate. Between-group differences (i.e., prodrome to first depressive vs. first hypomanic/manic episode; BD-I vs. BD-II; patients with vs. without childhood trauma) were analyzed using the chi-square and Student's *t* test. All tests were two-tailed and statistical significance was set at $\leqslant 0.05$. Due to the exploratory nature of the analyses, no adjustment for multiple testing was made.

Results

Clinical and demographic characteristics

The clinical and demographic characteristics of the sample are described in Table 1. Altogether, 43 stable

Table 1 Sociodemographic and clinical characteristics of the sample

Variable	Total (n=43)	BD-I (n=32)	BD-II (n=11)	p-value
Age (years), mean (SD)	33.7 (8.0)	34.1 (8.9)	32.7 (9.0)	0.664
Sex (female), n (%)	32 (74.4)	26 (81.3)	6 (54.5)	0.080
Years of education, mean (SD)	11.1 (2.6)	10.6 (2.4)	12.7 (2.6)	0.028
Age (years) at first mood episode, mean (SD)	25.3 (8.1)	26.7 (8.3)	21.2 (5.6)	0.046
Polarity of first mood episode, n (%)				
Depressive	22 (51.1)	14 (43.8)	8 (72.7)	0.097
Manic	14 (32.5)	14 (43.8)	0 (0.0)	0.037
Mixed	5 (11.6)	4 (12.5)	1 (9.1)	0.761
Hypomanic	2 (4.6)	0 (0.0)	2 (18.2)	0.084
Duration of illness (years), mean (SD)	8.5 (7.3)	7.7 (6.2)	10.6 (9.8)	0.267
Years since BD diagnosis, mean (SD)	10.5 (7.5)	10.7 (5.6)	10.0 (9.9)	0.842
Number of mood episodes until an episode of the opposite polarity, mean (SD)	1.7 (2.3)	0.9 (0.8)	3.7 (3.7)	0.038
Number of mood episodes, median (IQR)	4.0 (2.0-9.0)	4.0 (2.0-5.0)	10 (5.0-10.0)	0.035
Number of hypomanic/manic episodes, median (IQR)	3.0 (2.5)	2.7 (2.5)	3.6 (2.7)	0.339
Number of depressive episodes, median (IQR)	2.9 (3.1)	2.2 (2.9)	4.7 (3.1)	0.024
Comorbidity with substance use disorders, n (%)				
Alcohol abuse	2 (4.7)	0 (0.0)	2 (18.2)	0.014
Alcohol dependence	1 (2.3)	0 (0.0)	1 (9.1)	0.084
Illicit drug abuse/dependence	3 (6.9)	1 (3.1)	2 (18.2)	0.091
History of suicide attempt, n (%)	10 (23.3)	8 (25.0)	2 (18.2)	0.189
History of hospitalization, n (%)	18 (41.9)	15 (46.9)	3 (27.3)	0.256
Lifetime history of psychotic symptoms, n (%)	26 (60.5)	24 (75.0)	2 (18.2)	0.001
First-degree relative with BD, n (%)	7 (16.3)	2 (6.3)	5 (45.5)	0.008
HDRS score, mean (SD)	3.4 (4.1)	3.1 (3.8)	4.3 (5.0)	0.401
YMRS score, mean (SD)	0.8 (1.5)	0.6 (1.2)	1.2 (2.0)	0.344
GAF score, mean (SD)	78.5 (13.2)	78.4 (13.4)	78.7 (13.3)	0.951
CGI score, mean (SD)	1.6 (0.8)	1.7 (0.8)	1.8 (1.1)	0.589
History of childhood maltreatment, n (%)				
Emotional abuse	25 (58.1)	22 (68.8)	3 (27.3)	0.016
Physical abuse	13 (30.2)	10 (31.3)	3 (27.3)	0.804
Sexual abuse	12 (27.9)	11 (34.4)	1 (9.1)	0.107
Physical neglect	21 (48.8)	19 (59.4)	2 (18.2)	0.018
Emotional neglect	21 (48.8)	16 (50.0)	5 (45.5)	0.795
At least one modality	35 (81.4)	29 (90.6)	6 (54.5)	0.008

BD = bipolar disorder; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; IQR = interquartile range; YMRS = Young Mania Rating Scale.

individuals (CGI-S = 1.6±0.8; GAF = 78.5±13.2) with BD were included. The mean age was 33.7±6.8 years, 74.4% were females, 74.4% had BD-I, and 25.6% had BD-II, and the mean duration of illness was 3.7±2.3 years. When a depressive episode was the first mood episode, the average time between first depressive episode and first manic/hypomanic episode was 10.4±7.5 years. The mean time since diagnosis of BD, i.e., the period between the first manic or hypomanic episode and the date of the interview, was 3.7±2.3 years. Altogether, 60.5% of participants had experienced psychotic symptoms during at least one mood episode. The median total number of mood episodes was 4.0 (interquartile range [IQR]: 2.0-9.0). The mean number of depressive episodes was 2.9±3.1, and the mean number of manic episodes was 3.0±2.5.

Patients experienced a mean of 1.67±2.3 mood episodes between an episode of one polarity until an episode of the opposite polarity.

The clinical and demographic characteristics of participants with BD type I and type II are shown in Table 1. Compared to participants with BD-II, those with BD-I were older at onset of first mood episode (p = 0.046), had higher lifetime rates of psychotic symptoms (p = 0.001), and were more likely to report childhood trauma (p = 0.008), including specific modalities of trauma such as emotional abuse (0.016) and physical neglect (p = 0.018).

On the other hand, BD-II patients had a higher level of educational attainment (p = 0.028), more mood episodes (p = 0.035), more depressive episodes (p = 0.024), more mood episodes until switch to the opposite polarity (p = 0.038), a higher frequency of comorbid alcohol abuse (p = 0.014), and a higher frequency of positive family history of BD (p = 0.008) compared with BD-I patients.

Duration, onset pattern, and prevalence of prodromal features prior to first hypomanic/manic vs. first depressive episode

All participants reported prodromal symptoms. On average, the mania prodrome lasted 35.8±68.7 months and was predominantly subacute (60.5%) or insidious (32.6%); an acute pattern (< 1 month) occurred in only 7.0% of participants. The depression prodrome lasted 16.6±23.3 months on average, and was also predominantly subacute (66.6%) or insidious (29.6%); acute presentations were even more rare (3.8%).

The most prevalent specific prodromal signs and symptoms are described in Table 2. The prodromal symptoms most frequently reported prior to the first hypomanic or manic episode were mood lability (51.2%), depressive mood (48.8%), and impatience (48.8%). Those most frequently reported prior to the first depressive episode were irritability (51.8%), tiredness or lack of energy (51.8%), and depressed mood (48.1%).

Participants experienced significant differences in the frequency of specific prodromal symptoms prior to the first hypomanic/manic and depressive episode, as shown in Table 2. Compared to the prodrome of the first depressive episode, the following symptoms were more common during the hypomania/mania prodrome: mood lability (p = 0.016), feeling overly talkative (p < 0.01), physical agitation (p = 0.02), racing thoughts (p < 0.01), increased energy (p < 0.01), mood elevation (p < 0.01), being overly cheerful (p < 0.01), and overly self-confident (p < 0.01). Conversely, feeling physically slowed down (p = 0.02) was more common during the depressive prodrome. The duration of specific prodromal symptoms was similar during the depressive and the hypomanic/manic prodrome.

Duration and prevalence of prodromal features prior to first hypomanic/manic episode and first depressive episode in patients with BD type I vs. BD type II

The frequency and duration of prodromal symptoms to the first depressive and the first hypomanic/manic episode in patients with BD-I (n=32) and BD-II (n=11) are shown in Tables 3 and 4, respectively.

The duration of the depressive (p = 0.080) and hypomanic/manic (p = 0.674) prodromes was similar in patients with BD-I and BD-II. In patients with BD type I, the depressive prodrome lasted 9.88±17.04 months and the hypomanic/manic prodrome lasted 33.26±63.06 months, on average; in those with BD type II, the depressive prodrome lasted 31.87±29.43 months, and the hypomanic/manic prodrome lasted 43.54±86.35 months. Among specific prodromal symptoms, only suspiciousness differed significantly in terms of duration between the two groups, lasting longer in the depressive prodrome of BD-II compared to BD-I patients (p = 0.001).

In BD type I patients, the prodromal symptoms most frequently reported prior to the first hypomanic/manic episode were mood lability (56.3%), impatience (51.3%), and insomnia (51.3%). The prodromal symptoms most frequently reported prior to the first depressive episode were depressed mood (28.1%), irritability (28.1%), and tiredness or lack of energy (28.1%).

In BD type II patients, the prodromal symptoms most frequently reported prior to the first hypomanic/manic episode were depressed mood (54.5%) and anxiety (45.4%), whereas the prodromal symptoms most frequently reported prior to the first depressive episode were irritability (45.5%) and tiredness or lack of energy (45.5%).

The only symptom that differed between the two groups was feeling guilty or worthless, which was more frequent in the depressive prodrome of BD-II compared to BD-I (p = 0.033).

Duration and prevalence of prodromal features in BD patients with and without a relevant history of childhood maltreatment

In patients who experienced trauma during childhood, the mean durations of the depression prodrome and of the hypomania/mania prodrome were 15.6±25.19 months and 41.47±74.89 months respectively. In those who did not experience trauma during childhood, the durations of these prodromal periods were 20.16±17.74 months and 11.5±17.71 months respectively. The duration of the prodrome to first depressive episode was similar in these

Table 2 Frequency and duration of symptoms occurring during the prodrome to first depressive vs. first hypomanic or manic episode

	Frequency, n (%)			Duration in months, mean (SD)		
Prodromal symptoms	(Hypo)mania prodrome (n=43)	Depression prodrome (n=27)	p-value	(Hypo)mania prodrome (n=43)	Depression prodrome (n=27)	p-value
Mood lability	22 (51.2)	6 (22.2)	0.016	9.3 (18.9)	22.3 (31.8)	0.214
Depressed mood	21 (48.8)	13 (48.1)	0.955	13.9 (22.1)	11.6 (13.5)	0.739
Impatience	21 (48.8)	7 (25.9)	0.056	12.2 (22.2)	10.6 (11.5)	0.855
Overly talkative	20 (46.5)	1 (3.7)	< 0.001	7.6 (18.1)	6.0 (0.0)	0.930
Anxiety	19 (44.2)	11 (40.7)	0.776	8.5 (12.6)	5.4 (4.6)	0.434
Anhedonia	19 (44.2)	6 (22.2)	0.061	13.0 (19.6)	15.8 (27.5)	0.799
Physically agitated	19 (44.2)	5 (18.5)	0.027	8.0 (18.7)	6.5 (10.0)	0.866
Racing thoughts	19 (44.2)	2 (7.4)	< 0.001	7.9 (16.6)	3.5 (3.5)	0.747
Irritability	18 (41.9)	14 (51.8)	0.413	8.7 (13.9)	9.7 (14.1)	0.841
Increased energy or goal-directed activity	17 (39.5)	0.0 (0.0)	< 0.001	6.0 (11.1)	-	-
Decreased concentration	16 (37.2)	8 (29.6)	0.515	17.7 (38.0)	18.6 (30.8)	0.948
Tiredness or lack of energy	15 (34.9)	14 (51.8)	0.160	17.7 (24.4)	5.1 (4.8)	0.082
Weight gain or increase in appetite	15 (34.9)	6 (22.7)	0.260	22.2 (41.1)	9.0 (8.6)	0.569
Mood elevation	14 (32.6)	1 (3.7)	< 0.001	9.1 (13.4)	30.0 (0.0)	0.159
Overly cheerful	13 (30.2)	2 (7.4)	0.020	15.6 (24.6)	18.0 (16.9)	0.902
Social isolation	11 (25.3)	12 (44.4)	0.101	14.5 (20.0)	5.0 (6.3)	0.158
Decreased school or work functioning	10 (23.3)	7 (25.9)	0.799	12.4 (25.2)	14.2 (25.5)	0.882
Difficulty making decisions	10 (23.3)	5 (18.5)	0.638	25.5 (60.2)	31.4 (38.0)	0.847
Feeling worthless or guilty	9 (20.9)	6 (22.2)	0.898	11.2 (18.5)	16.0 (21.6)	0.659
Suspiciousness	9 (20.9)	4 (14.8)	0.378	8.0 (15.4)	24.7 (39.5)	0.468
Weight loss or decrease in appetite	9 (20.9)	2 (7.4)	0.118	15.1 (30.4)	3.5 (3.5)	0.620
Overly self confident	9 (20.9)	1 (3.7)	0.043	11.1 (16.5)	36.0 (0.0)	0.311
Difficulty thinking or communicating clearly	7 (16.3)	5 (18.5)	0.808	3.0 (2.3)	19.6 (36.0)	0.362
Overly creative	7 (16.3)	1 (3.7)	0.107	13.5 (18.2)	30.0 (0.0)	0.433
Defiant behavior	6 (14.0)	2 (7.4)	0.334	36.8 (60.9)	27.0 (29.6)	0.840
Inversion of the sleep/wakefulness pattern	6 (14.0)	2 (7.4)	0.334	16.0 (33.3)	13.5 (14.8)	0.922
Physically slowed down	5 (11.6)	9 (33.3)	0.027	14.4 (25.5)	5.5 (7.2)	0.488
Insomnia	5 (11.6)	6 (22.7)	0.235	16.6 (39.7)	7.3 (9.2)	0.577
Thinking about suicide	(5 (11.6)	4 (14.8)	0.483	49.2 (106.6)	24.8 (13.1)	0.677
Obsessions or compulsions	5 (11.6)	0 (0.0)	0.079	69.2 (74.9)	-	-
Increased sexual energy	5 (11.6)	0 (0.0)	0.079	43.4 (65.7)	-	-
Hypersomnia	3 (7.0)	6 (22.7)	0.070	3.6 (2.0)	7.8 (8.1)	0.424
Reckless or dangerous behavior	3 (7.0)	1 (3.7)	0.498	105.3 (148.6)	1.0 (0.0)	0.725
Others	2 (4.7)	1 (3.7)	0.670	9.0 (4.2)	6.0 (0.0)	0.667
Hallucinatory experiences	2 (4.7)	0 (0.0)	0.373	7.0 (7.0)	-	-
Self-harming behavior	1 (2.3)	0 (0.0)	0.614	0.3 (0.0)	-	-
Risky sexual behavior	1 (2.3)	0 (0.0)	0.614	0.3 (0.0)	-	-
Strange or unusual ideas	1 (2.3)	0 (0.0)	0.614	2.0 (0.0)	-	-
Attempting suicide	0 (0.0)	0 (0.0)	-	-	-	-

BD = bipolar disorder; SD = standard deviation.

two groups (p = 0.68), while the prodrome to first hypomanic/manic episode was significantly longer (p = 0.04) in individuals with a history of childhood trauma.

Participants with a history of childhood maltreatment had higher rates of specific prodromal symptoms preceding the first depressive episode compared with the group who did not report these experiences (Table 5). These symptoms included social isolation (p = 0.002), decrease in functioning (p = 0.03), and anhedonia (p = 0.05). On the other hand, individuals who did not experience trauma during childhood were more likely to report symptoms such as excessive cheerfulness or happiness (p = 0.04), feeling excessive self-confidence (p = 0.04), and increased creativity (p = 0.04) preceding the first depressive episode.

Experiencing emotional neglect during childhood was associated with increased frequencies of anhedonia (p = 0.006) and difficulty making decisions (p = 0.01) during the prodrome to the first depressive episode. Conversely, not experiencing emotional neglect was related to more frequent insomnia (p = 0.03) in the prodrome to the first depressive episode. Regarding the first hypomanic/manic episode, strange or unusual ideas were more common as a prodromal feature in participants who had not experienced trauma during childhood (p = 0.034).

Individuals who reported having experienced emotional abuse in childhood reported higher rates of oppositional behavior (p = 0.02) as a part of the prodrome to the first hypomanic/manic episode than did individuals with no such history. Experiencing sexual abuse during childhood was associated with an increased frequency of several specific prodromal symptoms prior to the first hypomanic/manic episode, including feeling guilty or worthless (p = 0.004), dangerous or reckless behavior (p = 0.004), suspiciousness (p = 0.032), and hallucinatory experiences (p = 0.02). Individuals who experienced physical abuse during childhood reported feeling worthless or guilty (p = 0.007) more often in the prodrome of the first hypomanic/

Table 3 Frequency and duration of symptoms occurring during the prodrome to first hypomanic/manic episode in patients with BD-I and BD-II

	Frequency, n (%)			Duration in months, mean (SD)		
Prodromal symptoms	BD-I (n=32)	BD-II (n=11)	p-value	BD-I (n=32)	BD-II (n=11)	p-value
Mood lability	18 (56.3)	4 (36.4)	0.255	9.6 (20.2)	8.3 (14.4)	0.910
Impatience	17 (53.1)	4 (36.4)	0.337	9.6 (20.9)	23.5 (27.6)	0.273
Insomnia	17 (53.1)	4 (36.4)	0.337	16.7 (42.6)	16.2 (29.2)	0.982
Overly talkative	17 (53.1)	3 (27.3)	0.138	8.8 (19.5)	0.9 (0.1)	0.501
Physically agitated	16 (50.0)	3 (27.3)	0.190	9.1 (20.3)	2.0 (1.0)	0.560
Depressed mood	15 (46.9)	6 (54.5)	0.661	13.6 (22.7)	14.8 (23.0)	0.914
Racing thoughts	15 (46.9)	4 (36.4)	0.545	9.8 (20.7)	0.7 (0.4)	0.403
Increased energy or goal-directed activity	15 (46.9)	2 (18.2)	0.093	6.8 (11.7)	0.5 (0.6)	0.472
Anxiety	14 (43.8)	5 (45.5)	0.922	9.5 (14.2)	5.8 (7.1)	0.583
Irritability	14 (43.8)	4 (36.4)	0.668	8.7 (14.4)	8.7 (14.1)	0.998
Decreased concentration	12 (37.5)	4 (36.4)	0.946	17.9 (41.8)	17.0 (28.7)	0.966
Tiredness or lack of energy	12 (37.5)	3 (27.3)	0.539	14.4 (24.0)	28.0 (28.3)	0.412
Mood elevation	12 (37.5)	2 (18.2)	0.238	8.1 (12.9)	15.5 (20.5)	0.495
Overly cheerful	12 (37.5)	1 (9.1)	0.077	14.5 (25.3)	30.0 (20.5)	0.568
Anhedonia	10 (31.3)	4 (36.4)	0.755	11.3 (16.5)	17.2 (28.5)	0.631
Social isolation	9 (28.1)	2 (18.2)	0.514	10.5 (14.6)	33.0 (38.1)	0.556
Decreased school or work functioning	8 (25.0)	2 (18.2)	0.644	14.1 (28.3)	5.5 (0.7)	0.691
Decreased need for sleep	8 (25.0)	3 (27.3)	0.536	8.5 (16.0)	1.3 (0.5)	0.475
Overly self confident	7 (21.9)	2 (18.2)	0.795	9.8 (16.9)	15.5 (20.5)	0.700
Feeling worthless or guilty	7 (21.9)	2 (18.2)	0.795	5.0 (3.8)	33.0 (38.1)	0.489
Suspiciousness	7 (21.9)	2 (18.2)	0.795	10.1 (17.1)	0.8 (0.3)	0.483
Weight loss or decrease in appetite	6 (18.8)	1 (9.1)	0.454	16.7 (33.0)	6.0 (0.0)	0.775
Difficulty making decisions	6 (18.8)	4 (36.4)	0.233	9.2 (19.0)	50.0 (94.9)	0.455
Difficulty thinking or communicating clearly	6 (18.8)	1 (9.1)	0.454	3.3 (2.3)	1.0 (0.0)	0.398
Inversion of the sleep/wakefulness pattern	6 (18.8)	0 (0.0)	0.122	16.0 (33.3)	-	-
Overly creative	5 (15.6)	2 (18.2)	0.843	12.6 (19.9)	16.0 (19.7)	0.847
Defiant behavior	5 (15.6)	1 (9.1)	0.590	13.0 (19.7)	156.0 (0.0)	0.003
Thinking about suicide	4 (12.5)	1 (9.1)	0.761	1.5 (0.5)	240.0 (0.0)	< 0.001
Obsessions or compulsions	4 (12.5)	1 (9.1)	0.761	41.5 (48.7)	180.0 (0.0)	0.085
Increased sexual energy	4 (12.5)	1 (9.1)	0.761	54.0 (70.8)	1.0 (0.0)	0.551
Weight gain or increase in appetite	3 (9.4)	1 (9.1)	0.978	29.3 (47.3)	1.0 (0.0)	0.656
Physically slowed down	3 (9.4)	2 (18.2)	0.432	2.0 (1.0)	33.0 (38.1)	0.456
Reckless or dangerous behavior	3 (9.4)	0 (0.0)	0.292	105.3 (148.6)	-	-
Hypersomnia	2 (6.3)	1 (9.1)	0.750	2.5 (0.7)	6.0 (0.0)	0.154
Hallucinatory experiences	2 (6.3)	0 (0.0)	0.396	7.0 (7.0)	-	-
Others	1 (3.1)	1 (9.1)	0.418	12.0 (0.0)	6.0 (0.0)	-
Self-harming behavior	1 (3.1)	0 (0.0)	0.553	0.2 (0.0)	-	-
Risky sexual behavior	1 (3.1)	0 (0.0)	0.553	0.3 (0.0)	-	-
Strange or unusual ideas	0 (0.0)	1 (9.1)	0.084	-	2.0 (0.0)	-
Attempting suicide	0 (0.0)	0 (0.0)	-	-	-	-

BD = bipolar disorder; SD = standard deviation.

manic episode, as did those who reported experiences of emotional neglect during childhood ($p = 0.03$).

Discussion

The results of this study suggest that the experience of a symptomatic prodromal period before both the first manic and the first depressive episode is very frequent among individuals with BD. Generally, the prodrome was subacute or insidious, corroborating the findings of a previous study that systematically investigated the prodromal period of individuals with early-onset BD.[11]

This relatively long period of mild symptoms before the first mood episode and, specifically, before the first episode of mania is relevant, because it suggests a possibility of recognizing and trialing possible interventions to prevent or delay the first manic episode. Interpreted more conservatively, this finding suggests that individuals in putatively prodromal stages might at least be protected from exposure to potentially deleterious interventions, such as administration of antidepressants or psychostimulants without mood-stabilizing agents. Sub-threshold manic symptoms and mood lability were reported significantly more frequently before the onset of the first manic episode than before the first depressive episode. This is in line with the preliminary definition of bipolar at risk (BAR) criteria proposed by Bechdolf et al.,[29] which include cyclothymic features and depression, subsyndromal manic symptoms or depression, and genetic risk.

This was the first study to conduct a systematic evaluation and comparison of the prodromal period in patients with BD type I and those with BD type II. The characteristics, duration, and onset pattern of prodromal symptoms were similar in the two subtypes of BD. Our observations of the signs and symptoms of patients with BD-II were similar to those reported in a previous preliminary study that evaluated 15 patients with this disorder.[18] While our findings could be interpreted to

Table 4 Frequency and duration of symptoms occurring during the prodrome to first depressive episode in patients with BD-I and BD-II

	Frequency, n (%)			Duration in months, mean (SD)		
Prodromal symptoms	BD-I (n=32)	BD- II (n=11)	p-value	BD-I (n=32)	BD-II (n=11)	p-value
Irritability	9 (28.1)	5 (45.5)	0.305	5.5 (7.3)	17.4 (20.8)	0.276
Tiredness or lack of energy	9 (28.1)	5 (45.5)	0.305	3.6 (2.3)	7.8 (7.1)	0.271
Depressed mood	9 (28.1)	4 (36.4)	0.305	8.1 (9.2)	19.5 (19.8)	0.175
Social isolation	8 (25.0)	4 (36.4)	0.318	6.2 (7.4)	2.7 (2.3)	0.392
Anxiety	8 (25.0)	3 (27.3)	0.266	4.0 (2.2)	9.0 (7.9)	0.394
Physically slowed down	6 (18.8)	3 (27.3)	0.318	7.0 (8.5)	2.6 (2.8)	0.436
Impatience	6 (18.8)	1 (9.1)	0.055	7.4 (8.4)	30.0 (0.0)	0.057
Decreased school or work functioning	6 (18.8)	1 (9.1)	0.129	15.6 (27.6)	6.0 (0.0)	0.759
Insomnia	5 (15.6)	1 (9.1)	0.181	8.6 (9.7)	1.0 (0.0)	0.514
Physically agitated	5 (15.6)	0 (0.0)	0.053	6.5 (10.0)	-	-
Decreased concentration	4 (12.5)	4 (36.4)	0.139	2.6 (2.4)	34.7 (39.0)	0.198
Hypersomnia	4 (12.5)	2 (18.2)	0.318	9.7 (9.6)	4.0 (2.8)	0.475
Difficulty thinking or communicating clearly	4 (12.5)	1 (9.1)	0.239	3.5 (2.8)	84.0 (0.0)	0.000
Thinking about suicide	4 (12.5)	0 (0.0)	0.081	24.8 (33.1)	-	-
Mood liability	3 (9.4)	3 (27.3)	0.181	6.0 (0.0)	38.6 (41.6)	0.246
Anhedonia	3 (9.4)	3 (27.3)	0.181	5.0 (1.7)	26.6 (39.3)	0.394
Weight gain or increase in appetite	3 (9.4)	2 (18.2)	0.296	12.0 (10.3)	4.5 (3.5)	0.416
Suspiciousness	3 (9.4)	1 (9.1)	0.292	5.0 (1.7)	84.0 (0.0)	0.001
Feeling worthless or guilty	2 (6.3)	4 (36.4)	0.033	6.0 (0.0)	21.0 (26.1)	0.487
Difficulty making decisions	2 (6.3)	3 (27.3)	0.101	3.5 (3.5)	50.0 (39.9)	0.217
Racing thoughts	2 (6.3)	0 (0.0)	0.169	3.5 (3.5)	-	-
Inversion of the sleep/wakefulness pattern	2 (6.3)	0 (0.0)	0.169	13.5 (14.8)	-	-
Hallucinatory experiences	2 (6.3)	0 (0.0)	0.130	-	-	-
Reckless or dangerous behavior	1 (3.1)	0 (0.0)	0.235	36.0 (0.0)	-	-
Defiant behavior	1 (3.1)	1 (9.1)	0.272	6.0 (0.0)	48.0 (0.0)	-
Weight loss or decrease in appetite	1 (3.1)	1 (9.1)	0.272	1.0 (0.0)	6.0 (0.0)	-
Decreased need for sleep	1 (3.1)	1 (9.1)	0.272	1.0 (0.0)	1.0 (0.0)	-
Overly cheerful	1 (3.1)	1 (9.1)	0.272	6.0 (0.0)	30.0 (0.0)	-
Overly talkative	1 (3.1)	0 (0.0)	0.235	6.0 (0.0)	-	-
Mood elevation	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Overly self confident	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Overly creative	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Others	0 (0.0)	1 (9.1)	0.095	-	6.0 (0.0)	-
Self-harming behavior	0 (0.0)	0 (0.0)	0.130	-	-	-
Risky sexual behavior	0 (0.0)	0 (0.0)	0.130	-	-	-
Strange or unusual ideas	0 (0.0)	0 (0.0)	0.130	-	-	-
Attempting suicide	0 (0.0)	0 (0.0)	0.130	-	-	-
Obsessions or compulsions	0 (0.0)	0 (0.0)	0.130	-	-	-
Increased sexual energy	0 (0.0)	0 (0.0)	0.130	-	-	-
Increased energy or goal-directed activity	0 (0.0)	0 (0.0)	0.130	-	-	-

BD = bipolar disorder; SD = standard deviation.

suggest that prodromal symptoms are not specific and showed no differences from a prognostic perspective of development of different subtypes of BD, these results are very preliminary, as the subgroups were very small and the study may have been underpowered to detect significance in numerically large differences.

In addition, we found that childhood trauma was associated with specific prodromal features prior to the first major mood episode. Previous studies that assessed the influence of this experience in BD reported that childhood trauma and maltreatment were highly prevalent and associated with triggering of bipolar manic and depressive episodes, as well as with a worse clinical course.[23,30,31] Our data suggest that childhood maltreatment might be associated with different clinical characteristics even prior to the first major mood episode, i.e., in the prodromal phase. These differences may be explained by the influence of early stressors on the development of affective lability,[22] suggesting that, in patients with a greater burden of adverse environmental factors, the disease might be different from a more ''endogenous'' type. Alternatively, one may postulate that those symptoms are part of a trauma-related psychopathology and might be found in similar rates in individuals with a history of childhood maltreatment without BD. In fact, previous studies found that experiencing trauma during childhood is related to specific psychiatric symptoms.[32] Therefore, the expression of psychopathology, including before the first mood episode, may be influenced by adverse childhood experiences.

Certain limitations need to be taken into account when interpreting the results of this study. Due to its retrospective design, patients had to remember symptoms that were at least moderate and that might have occurred years before the interview, and a recall bias has to be taken into account. In addition, the occurrence of depressive symptoms before the first manic/hypomanic episode could be considered both as a marker of syndromal progression and as a prodromal manifestation of BD, depending on severity. Moreover, the small sample

Table 5 Prodromal symptoms with significantly different frequencies in patients with vs. those without a history of childhood maltreatment

A. Depression prodrome			
	Any CM (n=20)	No CM (n=7)	p-value
Social isolation	12 (60.0)	0 (0.0)	0.002
Decreased school or work functioning	7 (35.0)	0 (0.0)	0.034
Overly cheerful	0 (0.0)	1 (14.2)	0.040
Overly self-confident	0 (0.0)	1 (14.2)	0.040
Overly creative	0 (0.0)	1 (14.2)	0.040
Anhedonia	6 (30.0)	0 (0.0)	0.050
	Emotional neglect (n=12)	No emotional neglect (n=15)	p-value
Anhedonia	6 (50.0)	0 (0.0)	0.006
Insomnia	0 (0.0)	6 (40.0)	0.030
B. Hypomania/mania prodrome			
	Any CM (n=35)	No CM (n=8)	p-value
Strange or unusual ideas	0 (0.0)	1 (12.5)	0.034
	Emotional abuse (n=25)	No emotional abuse (n=18)	p-value
Defiant behavior	6 (24.0)	0 (0.0)	0.025
	Physical abuse (n=13)	No physical abuse (n=30)	p-value
Feeling guilty or worthless	6 (46.1)	3 (10.0)	0.007
	Sexual abuse (n=12)	No sexual abuse (n=31)	p-value
Feeling guilty or worthless	6 (50.0)	3 (9.6)	0.004
Reckless or dangerous behavior	3 (25.0)	0 (0.0)	0.004
Suspiciousness	5 (41.6)	4 (12.9)	0.032
Hallucinatory experiences	2 (16.6)	0 (0.0)	0.020
	Emotional neglect (n=25)	No emotional neglect (n=18)	p-value
Feeling worthless or guilty	8 (32.0)	1 (5.5)	0.035

Data presented as n (%).
CM = childhood maltreatment.
The following types of childhood maltreatment did not show significant differences between groups: A) in depression prodrome: emotional abuse, physical abuse, sexual abuse, and physical neglect; B) in hypomania/mania prodrome: physical neglect.

size may limit the generalization of findings, and certainly reduced statistical power for our comparison between subgroups. As this is an exploratory analysis, we chose not to correct for multiple comparisons, as done by Zeschel et al.[33] To minimize the limitation posed by recall bias, we included only individuals who were clinically stable at the time of the study and limited the duration of illness to $\leqslant$ 9 years. In addition, we assessed prodromal symptoms using a highly detailed instrument, which made it possible to differentiate traits and personality from emerging symptoms and to evaluate the severity and interference with functioning of each of the reported prodromal symptoms. Nevertheless, this was the first study to compared the prodromes of BD type I and BD type II. The similarities between their manifestations suggest an overlap of symptomatology in the early stages of both BD subtypes, with definitive differentiation only after the first manic episode. In addition, we utilized a highly reliable instrument to evaluate the history of childhood maltreatment. Although the CTQ does not assess all types of traumatic experiences that may occur during childhood and adolescence (e.g., it does not cover exposure to violence or natural disasters), it is a valid instrument to detect different modalities of abuse and neglect which are robust markers of environmental toxicity.

In summary, this study investigated the BD prodrome using a semi-structured interview, and, to our knowledge, was the first to analyze childhood trauma and its influence on the presentation of prodromal symptoms. Our results provide evidence of a long-lasting, symptomatic prodrome in BD and suggest an influence of clinical and environmental variables on the expression of symptoms. This should prompt increased efforts into early recognition of BD and development of low-risk preventive interventions.

Disclosure

The authors report no conflicts of interest.

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