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REVIEW ARTICLE

Early stages of bipolar disorder: characterization and strategies for early intervention

Adiel C. Rios,[1,2] Mariane N. Noto,[1,2] Lucas B. Rizzo,[2,3] Rodrigo Mansur,[1,2,3] Flávio E. Martins Jr.,[1] Rodrigo Grassi-Oliveira,[4] Christoph U. Correll,[5,6,7,8] Elisa Brietzke[1,2]

[1]*Program for Recognition and Intervention in Individuals in At-Risk Mental States (PRISMA), Department of Psychiatry, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.* [2]*Interdisciplinary Laboratory of Clinical Neurosciences (LINC), Department of Psychiatry, UNIFESP, São Paulo, SP, Brazil.* [3]*Mood Disorders Neuropsychopharmacology Unit (MDPU), University Health Network, University of Toronto, Toronto, Canada.* [4]*Developmental Cognitive Neuroscience Research Group (GNCD), Centre of Studies and Research in Traumatic Stress (NEPTE), Biomedical Research Institute (IPB), Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil.* [5]*The Zucker Hillside Hospital, Psychiatry Research, North Shore, Long Island Jewish Health System, Glen Oaks, New York, NY, USA.* [6]*Albert Einstein College of Medicine, Bronx, New York, NY, USA.* [7]*The Feinstein Institute for Medical Research, Manhasset, New York, NY, USA.* [8]*Hofstra North Shore, Long Island Jewish School of Medicine, Hempstead - NY, USA.*

Objective: To characterize the early stages of bipolar disorder (BD), defined as the clinical prodrome/subsyndromal stage and first-episode phase, and strategies for their respective treatment.
Methods: A selective literature search of the PubMed, Embase, PsycINFO, and ISI databases from inception until March 2014 was performed. Included in this review were articles that a) characterized prodromal and first-episode stages of BD or b) detailed efficacy and safety/tolerability of interventions in patients considered prodromal for BD or those with only one episode of mania/hypomania.
Results: As research has only recently focused on characterization of the early phase of BD, there is little evidence for the effectiveness of any treatment option in the early phase of BD. Case management; individual, group, and family therapy; supportive therapy; and group psychoeducation programs have been proposed. Most evidence-based treatment guidelines for BD do not address treatment specifically in the context of the early stages of illness. Evidence for pharmacotherapy is usually presented in relation to illness polarity (i.e., manic/mixed or depressed) or treatment phase.
Conclusions: Although early recognition and treatment are critical to preventing unfavorable outcomes, there is currently little evidence for interventions in these stages of BD.

Keywords: Bipolar disorder; first episode of mania; depression; manic-depressive illness; early intervention; staging

Introduction

Bipolar disorder (BD) is a chronic and potentially severe mood disorder. Traditionally, BD has been described as an episodic illness, with the succession of manic/hypomanic and depressive episodes, followed by periods of euthymia, which, putatively, represents a return to a "normal" state.[1] Recently, however, this view has been challenged by findings that, at least for a large group of individuals, the disease follows a chronic, unremitting, and deteriorating course.[2,3] Clinical and preclinical data show that treatment delay and/or exposure to a high number of mood episodes are associated with a worse clinical course.[4,5] This effect can be observed on a number of outcomes, including shortening of inter-episodic interval, persistence of subsyndromal symptoms, cognitive deficits, higher number of hospitalizations, emergence of medical and psychiatric comorbidities, increased suicide risk, worse social adjustment, and poor quality of life.[6-10] Moreover, treatment response also appears to change as a function of episode frequency, as both pharmacological agents (e.g., lithium, olanzapine) and psychosocial interventions (e.g., psychoeducation, cognitive-behavioral therapy) seem less effective in multiepisodic BD.[11,12]

The clinical progression described above is hypothesized to be subserved by neurobiological changes, the so-called neuroprogression.[13-15] This hypothesis is based on observations that brain morphology alterations, such as reductions in volume and gray matter and enlargement of ventricles, are more pronounced in chronic patients than in individuals with fewer episodes. Similarly, evidence indicates a different profile in peripheral biomarkers linked to BD pathophysiology and a wider range of abnormalities in such biomarkers in these patients,[16] including differences in levels of neurotrophins, specifically the brain-derived neurotrophic factor, and inflammatory and oxidative stress markers.[2]

A consequence of understanding BD as a progressive disorder is the development of a staging model: a framework devised to better describe the evolution of patients from early to late stages, as in staging models developed and incorporated into clinical care of individuals with cancer

Correspondence: Elisa Brietzke,Rua Pedro de Toledo, 669, 3° andar, Vila Clementino, CEP 04039-032, São Paulo, SP, Brazil.
E-mail: elisabrietzke@hotmail.com
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or heart failure.[17,18] Different criteria for a specific staging classification have been proposed, although the principles are the same. A summary of a staging classification for BD can be found in Table 1. A classification based on clinical stages would add an evolutionary dimension to diagnosis and, potentially, subserve the development, testing, and application of specific, stage-oriented interventions.[19]

Nevertheless, despite strong evidence for clinical and neurobiological progression in BD and considerable effort to advance definitions of clinical staging in BD, treatment of BD is not stage-oriented.[21] In contrast, in the psychosis field, the importance of early intervention is already well established.[22-24] The paradigm of early intervention in this disorder has led to the spread of mental health services focused on early psychosis, an initiative shown to lead to more favorable long-term outcomes and that is cost-effective.[25,26]

The objective of this study was to review the literature related to the characterization of the early stages of BD, defined as the clinical prodrome/subsyndromal stage and first-episode phase, and to their respective treatment.

Methods

A selective, non-systematic literature search of the PubMed, Embase, PsycINFO, and ISI databases from inception until March 2014 was performed, using the following keywords: "bipolar disorder," "manic disorder," "depression, bipolar," "manic depressive psychosis" AND "staging," "prodromal," "first manic episode." We included articles published in English, Spanish, or Portuguese that a) characterized clinically prodromal and first-episode stages of BD or b) detailed the efficacy and safety/tolerability of interventions in patients considered prodromal for BD or those with only one episode of mania/hypomania. The reference lists of all included articles were checked for relevant additional sources of information. We excluded review articles, studies with repeated data, and studies that included individuals in different stages of BD without specifying these stages. Overall, 166 entries were selected for abstract reading, which was performed by the authors AR, RBM, and FEMJ.

Results

Prodromal period of first manic episode (stage I)

The prodromal period of BD is the symptomatic period preceding the first manic/hypomanic episode. It can last several weeks up to many years before full development of the disorder.[18,27,28] Mood symptoms commonly exhibited by children, adolescents, and young adults in the prodromal period include syndromal and subsyndromal major depressive disorder (MDD), anxiety and episodic subsyndromal manic symptoms, such as sleep disturbances, anger or irritability, increased energy, and rapid mood fluctuations[22] (also termed cyclotaxia).[29,30] Over time, there is a propensity to progression of psychopathology, and symptoms usually become more specific and more similar to those of full BD.[30,31] Accordingly, a 4-year follow-up prospective study found that 38% of children and adolescents initially diagnosed with BD not otherwise specified and 25% of those diagnosed with BD type II transitioned to BD type I.[23] At least one depressive episode frequently precedes the onset of mania and is commonly treated with antidepressant medications, regardless of the risk for developing BD.[24] However, an emerging body of evidence suggests that treatment with antidepressants may precipitate or exacerbate suicidality and manic symptoms and possibly reduce the age at onset of mania. Cognitive symptoms, particularly deficits in concentration and attention, also commonly precede initial onset of BD, which can lead to exposure to psychostimulant medications. Although the role of early treatment with psychostimulants in the pathophysiology of mania is poorly understood, acute treatment with psychostimulants may produce clinical features that are similar to mania.[24] Adolescents with BD and a history of stimulant exposure have an earlier age at onset of mania than those without prior stimulant exposure, independently of co-occurring attention-deficit/hyperactivity disorder.[24]

Increasing evidence from retrospective and prospective studies is beginning to elucidate some criteria to identify individuals that are at high risk of developing mania. In general, high-risk criteria involve having a first-degree relative with BD or schizophrenia, a history of subthreshold mood or psychotic symptoms, and being in the age range most frequently associated with onset of BP or schizophrenia (i.e., adolescence).[25] Recently, a research group proposed a preliminary definition of bipolar at-risk (BAR) criteria for use in prospective studies. The authors proposed to consider that initial phases of BD may feature symptoms that are insufficient in frequency, severity, or duration to characterize the full-blown disease, but that can represent a high risk of transition to BD in a short period of time.[22] The BAR criteria include individuals under the age of 25 years with: 1) subthreshold mania; 2) depression plus cyclothymic features; or 3) depression plus genetic risk. In a retrospective chart review study, approximately 23% of individuals in the BAR group developed BD over 8 months.[22]

Although these preliminary criteria have recently been validated prospectively by the same group,[26] more research is needed to validate and refine the diagnostic BAR criteria.[24] Although research for this purpose is underway, there is also increasing experimental interest in developing and evaluating interventions that can be delivered before the initial onset of manic or psychotic symptoms to slow or prevent illness progression in high-risk populations.[24]

Table 1 Clinical stages of bipolar disorder (adapted from Scott J et al.[20])

I	The asymptomatic stage may or may not be followed by subthreshold clinical phenomena that incorporate some aspects of current diagnostic concepts (e.g., brief or recurrent hypomania, disrupted sleep-wake cycle, increased or decreased energy).
II	First manic episode.
III	Incomplete remission of first episode. Recurrence or relapse of manic and depressive episodes, cognitive and functional decline.
IV	Severe, persistent and unremitting symptoms. Unable to live independently.

In clinical practice, the prodromal stages usually progress gradually to full-blown BD. Patients, caregivers, and medical staff report significant difficulty in identifying the exact moment at which the transition occurs.[22] Therefore, separation between stages I and II, despite its potential clinical utility, should be interpreted as not always clear. Current limitations of this classification include fluctuation in severity of manic symptoms, variability in degree of suffering and functional impairment, and presence of comorbidities that made the diagnosis process more complex.

First episode of mania (stage II)

A recent review identified seven independent programs clinically evaluating first-episode BD.[27] Tohen et al.[28] analyzed outcomes of a first manic episode, including recovery and relapse. The study involved 24 individuals in a naturalistic 4-year follow-up. Symptom relapse occurred in 54% of the individuals (Table 2), with psychotic symptoms during the first manic episode and history of alcohol abuse being predictors of relapse (Table 3). Patients' functionality was very high; more than 80% were working and 92% were able to live independently during the follow-up period. These data seem to contrast with recent studies that found poor functional outcomes with progression of the disorder,[29] yet the early 4-year course may be different from the more chronic course that is characterized by more frequent relapses.

The McLean First-Episode Psychosis cohort consists of patients with first-episode psychosis, which also included bipolar patients.[30] The patients were evaluated using DSM-III and, later, DSM-IV criteria. Symptom recovery was defined with rigorous criteria, involving at least 6 weeks with low severity of symptoms. An episode occurring within the first 6 weeks was considered a relapse; if it occurred after that time, it was considered recurrence. Sixty patients with BD were evaluated for 6 months after discharge. During this period, 85% had syndromic recovery, although functional recovery was present in only 68%. In addition, 19% had symptom relapse and nearly 20% had a recurrence (Table 2).[30] In a subsequent study with a larger sample (n=173) and 2-4 years of follow-up, more than 95% reached syndromic recovery after 2 years, but symptom recovery was achieved by 72% and functional recovery was present only in 43%. Nearly 6% had relapsed and 34% had a recurrence (Table 2). Predictors of new episodes were also analyzed. Psychotic features, low premorbid occupational status, and non-mixed initial mania were related to new manic episodes, while higher occupational achievement, initial mixed dysphoric states, and psychiatric or medical comorbidity were associated with new depressive episodes (Table 3).[31] In a cohort of 87 patients with first-episode psychotic mania, Conus et al. found 90% syndromic, 60% symptomatic, and 39% functional recovery at 12-month follow-up.[7] Patients without family history of affective disorders, without substance use, and older age were more likely to achieve functional recovery after 12 months.[7] In a study by Strakowski et al.[32] including 109 patients in first-episode affective psychosis, similarly low functional recovery rates (35%) were observed. Symptom recovery was equally low (35%) (Table 2), and lower than in prior studies. This diminished symptom recovery possibly occurred because the sample enrolled patients with major depression and BD who also had psychosis.[32] A recent study from the Systematic Treatment Optimization Program for Early Mania Project (STOP-EM) recruited a cohort of patients with BD type I without psychosis (n=53).[31] Almost 90% achieved syndromic recovery and 53% had symptom recurrence during 1-year follow-up (Table 2). Functional outcomes were not reported.

Table 2 Outcomes in longitudinal studies involving patients with first-episode bipolar disorder

Study	n	Population	Follow-up duration	Relapse/ recurrence	Syndromic recovery	Symptom recovery	Functional recovery
McLean-Harvard							
Tohen[28]	24	Individuals after recovery from first manic episode	4 years	54%	NR	NR	80% working, 92% living independently
Tohen[30]	60	Subgroup with bipolar disorder from a first psychotic episode population	6 months	19% (recurrence: 20%)	85%	NR	68%
Tohen[31]	173	Individuals after recovery from first manic episode	2-4 years	6% (recurrence: 34%)	95% (2 tears)	72%	43%
University of Cincinnati							
Strakowski[32]	109	First episode of psychotic affective illness	1 year	NR	NR	35%	35%
Early Psychosis Prevention and Intervention Centre							
Conus[7]	67	Individuals after recovery from first episode of psychotic mania	1 year	NR	90%	60%	39%
STOP-EM							
Kauer-Sant'anna[2]	53	Individuals after recovery from first manic episode	1 year	53%	90%	62.3%	37.7%

NR = not reported; STOP-EM = The Systematic Treatment Optimization Program for Early Mania Project.

Table 3 Predictors associated with relevant outcomes in first-episode bipolar disorder

Variable of interest	Predictors	References
Relapse	Psychosis, alcohol abuse.	Tohen[28]
Recurrence of mania	Psychotic features, low prehospitalization occupational status, and non-mixed initial mania.	Tohen[31]
Recurrence of depression	Initial mixed dysphoric states and psychiatric or medical comorbidity.	Tohen[31]
Quality of life	Shorter illness duration, less severity of depressive symptoms at baseline and 6 months, lower number of depressive episodes.	Tohen[31]
Early age at onset	Family history of mood disorders, higher rates of suicide, higher cycling frequency, more episodes of mania and depression, higher measures of lifetime depressive symptoms.	Hamsher[33]
	More comorbid anxiety and substance use, more recurrences, shorter euthymia, more suicide attempts.	Perlis[34]
	Childhood abuse and neglect.	Daruy-Filho[35]
Childhood abuse and neglect	Suicide behaviors, substance abuse disorder, worse clinical course and response to treatment.	Daruy-Filho[35]
	Poorer cognitive performance.	Bücker[36]
Diagnostic shift from non-affective psychosis to bipolar disorder	Female gender, short duration of untreated psychosis, high premorbid functioning, mood lability, mood elation, hyperactivity, delusions of a religious or grandiose nature.	Kim[37]
Diagnostic shift from psychotic depressive disorder to bipolar disorder	Mood lability, hypomanic symptoms.	Tohen[38]

In another study of first lifetime hospitalization in the period between 1989 and 1996, 219 patients with a DSM-IV psychotic affective illness were assessed at intervals over 24 months. At 24 months, syndromic recovery was attained by 97.5% of the subjects. Functional recovery at 24 months (37.6% of patients) was 2.7 times less likely than syndromic recovery (Table 2). Functional recovery was associated with older age at onset and shorter hospitalization.[39] Current evidence suggests that functional recovery is less frequent than syndromic recovery. Because issues of recovery can significantly affect disability, quality of life, and outcome, early intervention for first-episode individuals with BD is clearly an important objective.[6] An assessment of quality of life after recovery from a first manic episode indicated that quality of life is related to length of illness and severity of depressive symptoms at both baseline and 6 months, as well as to the number of depressive episodes (Table 3),[40] indicating a need for aggressive treatment of depressive symptoms in this population.

Another possible strategy to investigate first-episode BD is to approach individuals in their first episode of psychosis. The first psychotic episode (FPE) generally refers to the first time an individual presents with symptoms of delusions or hallucinations or disorganized thinking/behavior.[2] Considering its fluctuating symptomatology and unclear mood symptoms, FPE is more vulnerable to diagnostic changes over time compared to later stages of psychosis, and final diagnosis is possibly more definite only after recurrence.[1]

In an evaluation of the diagnostic stability of a FPE and of predictive factors associated with a diagnostic shift performed in 150 patients who had been admitted to the psychiatric ward of the Samsung Medical Center (Republic of Korea) from 1994 to 2009, both for first episode and for recurrence of psychosis, BD was the first diagnosis for 25.3% of the subjects.[37] The diagnoses were revised upon recurrence in 20.7% of patients. The most common change was to BD, accounting for more than half of all diagnostic changes. Schizophrenia exhibited the highest prospective (91.3%) and retrospective (90.3%) consistencies. BD showed a comparable prospective consistency (86.4%), but had a much lower retrospective consistency (64.7%).[37] Female gender, short duration of untreated psychosis, high level of premorbid functioning, and several symptoms, including mood lability, mood elation, hyperactivity, and delusions of a religious or grandiose nature, were identified as predictive factors for a diagnostic shift from non-affective psychosis to BD[37] (Table 3).

Another study, performed in 500 subjects selected among patients entering the International First Episode Project based at McLean Hospital and the University of Parma from 1983 to 2003, evaluated diagnostic stability with assessments based on the Structured Clinical Interview for DSM Disorders (SCID) at baseline and again at 24 months. Initial DSM-IV diagnoses included a majority (61.6%) of psychotic affective disorders (BD type 1 or MDD). Diagnoses remained stable in 74.0% of the patients. The most stable diagnosis was BD type 1 (96.5%). Most diagnoses changed were to schizoaffective disorder (53.6%) and to BD type 1 (25.9%). Diagnostic change was associated with non-affective psychosis, auditory hallucinations, young age, male sex, and gradual onset (Table 3).[41]

Specific interventions for stages I and II of bipolar disorder

Interventions for stage I of bipolar disorder

Non-pharmacological

Choosing the appropriate interventions for each individual always requires a careful assessment of the risk-benefit balance. The use of psychoeducational and psychotherapeutic interventions is preferable as a first step in ill-defined and low-severity presentations, because early symptoms (i.e., mood swings, impairment in social interactions, and disruption of diurnal rhythm) could be especially responsive to psychotherapy.[42] Psychotherapeutic interventions have an exceptionally favorable benefit/risk ratio and are therefore

more acceptable to young patients and their families than pharmacologic treatments. Moreover, preliminary evidence indicates that psychotherapeutic interventions may also have a preventive effect. In an exploratory data analysis from a controlled study of multi-family psychoeducational psychotherapy, 12 (32.4%) of 37 children with depression spectrum disorder and additional transient manic symptoms converted to a BD-spectrum disorder (3 to BD-I, 5 to BD-II, 3 to BD not otherwise specified, and one to substance-induced mood disorder with manic features) in an 18-month follow-up. Of the 11 patients who had converted at 12-month follow-up, only 2 (11.8%) were among the 17 patients who had been randomized to multi-family psychoeducational psychotherapy, compared to 9 (45.0%) from the 20 subjects who had been randomized to the 1-year waiting list group.[43] In clinical practice, interventions such as family based-therapy for families with significant conflicts, cognitive-behavioral therapy, support therapy, and psychoeducation could be conducted in adapted protocols.[24,44]

Pharmacological

A double-blind, placebo-controlled trial of lithium administration was conducted in prepubertal children with predictive factors for BD, such as depression and family history.[45] Lithium was not significantly more efficacious than placebo for prepubertal MDD in individuals with family history predictors of future prepubertal bipolarity. Divalproex has demonstrated efficacy in the treatment of mania in adults, and has been suggested as effective in children and adolescents with BD in open studies.[46] Because of its putative anti-kindling properties and efficacy in the treatment of mania, authors studied the efficacy of divalproex in bipolar offspring with mood or behavioral disorders (but not yet with fully developed BD) and at least mild affective symptoms. Chang et al. studied 24 children aged 6-18 years (mean = 11.3 years; 17 boys, 7 girls) with at least one biological parent with BD. In this study, participants were diagnosed with at least one of the following DSM-IV disorders: MDD, dysthymic disorder, cyclothymic disorder, or attention-deficit/hyperactivity disorder. All subjects had at least moderate affective symptoms (28-item Hamilton Rating Scale for Depression or Young Mania Rating Scale score $>$ 12). Eighteen subjects (78%) were considered good responders by primary outcome criteria (very much improved or much improved on the Clinical Global Impressions-Improvement scale). Divalproex was well tolerated, with no discontinuations due to adverse effects.[47] Although well tolerated, in another study by Findling et al., divalproex sodium did not produce clinically meaningful improvements in the treatment of symptomatic youths with either BD not otherwise specified or cyclothymia who were at genetic risk of developing BD.[48] A 12-week single-blind trial to investigate the effectiveness and tolerability of quetiapine in the treatment of adolescents at high risk of developing bipolar I disorder found that it may be an effective treatment for mood symptoms in adolescents with familial risk factors for BD-I. However, conclusions are limited by the small sample size (n=25).[49] In clinical practice, using the available data, divalproex sodium and quetiapine are supported as symptom-targeted therapeutic options. To date, no study has been designed to prevent transition to a diagnosis of BD type 1 or type 2. The potential of mood stabilizers in primary prevention of BD remains unknown.

Interventions for stage II of bipolar disorder

Non-pharmacological

There is a paucity of studies evaluating psychosocial interventions in the first episode of mania (FEM). Although the need for non-pharmacological interventions for FEM has been increasingly recognized, few studies have assessed their effectiveness. A small study designed an adapted a cognitive-behavioral therapy program for euthymic, newly diagnosed individuals with BD.[44] The cognitive-behavioral therapy sessions were more focused on symptom recognition and relapse prevention. After this open trial, patients displayed a better understanding of early warning signs of mood episodes and used more adaptive coping strategies.[44] Two services developed to provide follow-up after a FEM, the Early Psychosis Prevention and Intervention Centre (EPPIC) and the STOP-EM,[7,50] included psychosocial interventions as well as regular clinical practices. These interventions included case management, individual, group, and family therapy[8]; supportive therapy; and a group psychoeducation program.[40] Reported outcomes of patients enrolled in these services suggest positive effects on symptomatic and functional recovery.[7,50] However, both studies were naturalistic and uncontrolled, and the efficacy of the non-pharmacological treatments was not independently assessed. In clinical practice, the few available data support the use of case management, individual, group, and family therapy, supportive therapy, and group psychoeducation. Although psychosocial approaches are often combined, this practice has not been sufficiently evaluated. A significant limitation for research is the lack of availability of protocols specifically designed for early-stage patients. For this population, issues such as acceptance of diagnosis and stigma are even more problematic, as are age-related problems.

Psychopharmacological

No placebo- or active comparator-controlled trials to date have specifically targeted patients with first-episode BD. Although there is a consensus that the earlier targeted treatment begins the better, much is still unknown about the most appropriate treatments for this population and the timing of their administration. The timing of neurobiological changes suggests that the optimal period for neuroprotective interventions is during the early stages of illness, when structural and functional brain changes are probably still limited.[7] There is substantial evidence that the number of previous affective episodes is a risk factor for episode recurrence, chronicity, and suicide; thus, appropriate early treatment would likely decrease the risk of these negative outcomes.[6]

Most evidence-based BD guidelines do not address treatment specifically in the context of the early stages.

Evidence for pharmacotherapy is usually presented in relation to the polarity of BD (i.e., manic, mixed or, depressive episode) or treatment phase (i.e., acute or maintenance).[8]

The absence of any double-blind, placebo- or active-controlled trial of pharmacotherapy for FEM clearly indicates a research gap and a need for such studies. In the research agenda, development of pharmacological treatments for early stages of BD should address symptom control, promotion of remission, and prevention of progression.

Perspectives

The idea that BD progresses across stages is receiving growing support in the literature. We conducted a non-systematic review that, despite the limitations inherent to this research design, clearly indicates a paucity of data on stage-specific interventions, especially for the stage of illness at which the natural history of the disease might be most susceptible to intervention. The potential and incremental gains of early recognition and intervention require detailed investigation.

However, the study of these strategies in FEM is beset by limitations. The first concern is related to phenotypic heterogeneity. This pertains both to the at-risk stage and to the first episode itself. The non-specificity of symptoms and risk of false positives is highest in stage I. The prodrome to mania can be conceived as more complex and complicated than in non-affective psychotic disorders (schizophrenia), due to fluctuation of symptom severity and variations in recognition of functional impairment. BD is, by definition, an episodic illness; therefore, its trajectory is more complex to chart. In addition, there is a taxonometric overlap with commonly found comorbidities, such as attention-deficit/hyperactivity and disruptive behavioral disorders and cluster B personality disorders.

Even after the FEM, despite the apparent stability of a BD diagnosis, individuals frequently exhibit significant variability in terms of age of onset, previous psychiatric treatment for other diagnoses, history of depressive episodes, comorbidities, and previous pharmacological treatments for BD.[6] The second issue is that, compared with existing models in psychosis, the dominant paradigm of BD treatment is not early intervention. The long delay between symptom onset and their proper recognition and treatment[18] is an obstacle for the conduct of large cohort and randomized studies, which should preferentially involve community-based samples with FEM. In addition, new developments in BD research have not yet been incorporated into FEM research. These include the search for biomarkers and the well-documented deleterious impact of weight gain and metabolic changes, both related with the disease and associated with its treatment, on the neurobiology of BD and its morbidity and mortality. Whether preventing obesity and the metabolic syndrome or choosing the most weight gain-neutral medications early in the course of BD would have a beneficial effect on long-term prognosis is unknown.

In summary, research on the early stages of BD has been neglected when compared to FPE.[18] In the future, we expect a migration of research interest to the early stages of BD, focusing on phenomenological and neurobiological aspects, as well as on the development of stage-specific interventions. Especially during the at-risk stage, the risk of interventions needs to be titrated for the likelihood of conversion to BD, and additional biomarkers are sorely needed to enhance the predictive validity of emerging at-risk criteria. It is hoped that these developments and efforts will help provide data that can guide clinicians toward intervening with greater success in patients with BD and those at risk of BD.

Disclosure

The authors report no conflicts of interest.

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