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THE PHENOMENOLOGY OF BIPOLAR DISORDER: WHAT DRIVES THE HIGH RATE OF MEDICAL BURDEN AND DETERMINES LONG-TERM PROGNOSIS?

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Abstract

Bipolar disorder (BD) has been classically described as one of episodic mood disturbances. New evidence suggests that a chronic course and multisystem involvement is the rule, rather than the exception, and that together with disturbances of circadian rhythms, mood instability, cognitive impairment, a high rate of medical burden is often observed. The current diagnostic approach for BD neither describes the multisystem involvement that the recent literature has highlighted nor points toward potential predictors of long- term outcome. In light of the new evidence that the long-term course of BD is associated with a high prevalence of psychiatric comorbidity and an increased mortality from medical disease, we propose a multidimensional approach that includes several symptom domains, namely affective instability, circadian rhythm dysregulation, and cognitive and executive dysfunction, presenting in various combinations that give shape to each individual presentation, and offers potential indicators of overall long-term prognosis.

Keywords

bipolar disorder; comorbidity; depression; cardiovascular diseases; anxiety; cognitive symptoms

INTRODUCTION

The Diagnostic and Statistical Manual (DSM-IV) defines bipolar disorder (BD) with a set of clinical criteria that are mostly related to the alternate presence of mania/hypomania or depression. This approach has allowed the diagnosis to become more specific, but at the cost of reduced sensitivity. The categorical structure of the current psychiatric nosology, in fact, fails to capture the multisystem involvement of BD, creating a high prevalence of what may be artificial “comorbidity.” This approach has also greatly influenced the way we treat the disorder, often leading clinicians to target the mood symptoms first (considered the “main” or “core” symptoms of the disorder) and considering the so-called “comorbid” conditions (namely anxiety, eating, substance use/abuse, medical disorders) as separate entities to be addressed (or often ignored) on their own. The approaches to each of these individual problems may conflict with one another and the treatments that we currently have to target the goal of long-term remission are often ineffective.[1] In addition, the current operational diagnostic criteria do not include potential indicators or predictors of long-term outcome. Although we currently do not have an etiologically based approach to diagnosis and

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treatment, a multidimensional model of BD might lead the way to developing better diagnostic tools and comprehensive, interdisciplinary interventions. Furthermore, a more comprehensive description of clinically relevant phenotypes could better guide etiology-focused research. Finally, the emerging evidence of medical burden and increased mortality for medical reasons in individuals with BD has not yet found a proper place in the diagnostic and treatment process. Rather, it is still typically considered an inevitable "side effect" of long-term psychopharmacologic treatment or a consequence of an unpredictable disorder associated with an often extremely erratic lifestyle. Although these factors may certainly play an important role in contributing to the medical burden observed in BD, it is also possible that the physiopathology of the disorder itself may facilitate the development of certain specific medical conditions that would, thus, assume the role of a complication, if not a core feature, of the mental disorder, rather than an incidental event or side effect of treatment. We propose a conceptualization of BD as a multidimensional disorder, the core symptom domains of which include circadian disruption, mood instability, and cognitive dysfunction. These domains may present in various combinations, and one may predominate over the others in any individual patient, leading to the multifaceted individual presentations observed in clinical practice. The medical burden could be an additional cross-sectional dimension, associated with a particular clustering of the three core features. Each of these dimensions presents potential inborn vulnerabilities that may promote the cascade of medical burden and affect the long term course of the illness. Our clinical experience and results of the research conducted by our group are starting to suggest that considering BD in a multidimensional fashion, as opposed to an alternation of depression and mania, may have important treatment and research implications. In this report we will describe the symptom clustering that constitutes our proposed conceptual framework, along with the preliminary evidence that supports its relevance in terms of need for interdisciplinary treatment of BD and new research approaches on its etiology, course, and treatment.

DISRUPTION OF CIRCADIAN AND OTHER ENDOGENOUS RHYTHMS

The specific symptoms of mania and depression (disturbances in sleep, appetite, energy, concentration) are suggestive of a disruption of circadian rhythms as core pathology. The cyclical course of BD points to a disruption in other endogenous biological rhythms. Social Zeitgebers (SZ), literally "time givers," are social and environmental cues that entrain biological rhythms. According to the model proposed by Ehlers et al.[2] certain kinds of life events could trigger mood episodes through loss of SZ and disruption of social rhythms, leading to disruption of endogenous circadian rhythms. In this particular context the focus is on life events not as psychological stressors but provoking agents of changes in daily routines that are apparently neutral or benign from a psychological standpoint, but can nonetheless place considerable stress on the body's attempt to maintain synchronized sleep–wake, appetite, energy, and alertness rhythms. Every organism has internal biological oscillators that are, in turn, synchronized with external environmental cues, of which the light–dark cycle is probably the most important and powerful synchronizer. Nevertheless, particularly in urban industrialized society, human beings are artificially exposed to multiple competing inputs for phase advance and phase delay of the circadian timing system. Under these conditions, social factors such as the timing of work, meals, and social contacts may assume increased importance for maintaining stable circadian timing. In addition to acting as zeitgebers themselves, social routines might act as determinants of how photic zeitgebers are experienced by the individual and might, thus, further influence the circadian system. We argued that, in vulnerable individuals, changes in social time cues could lead to disruptions in circadian rhythms and ultimately to affective episodes and subsequently demonstrated that life events that were characterized by a high degree of social rhythm disruption were significantly associated with the onset of new episodes of bipolar illness, particularly episodes of mania.[3,4] Rhythm irregularity might be a marker of vulnerability to mood

disorders; social rhythm irregularity may reflect or disrupt biological rhythms, leading to somatic and, ultimately, affective symptoms. Targeting rhythm irregularity with interpersonal and social rhythm therapy (IPSRT) has been shown to speed time to remission of bipolar depression,[5] prolong time to recurrence of an affective episode,[6] reduce suicide attempts,[7] and improve occupational functioning.[8] Variability in circadian activity pattern is greater in patients with BD than in controls[9,10] and it appears to be a trait, rather than a state marker. There is preliminary evidence that allelic variability at different loci of the CLOCK genes is related to treatment response, rate of recurrence, and presence of insomnia during the symptomatic phase of BD.[9, 11–13]

The most evident “symptom” of circadian rhythm disruption in mood disorder is the alteration of the sleep architecture and the sleep/wake cycle,[14,15] sleep duration, and quality. In addition, there is evidence for an association among “evening” chronotype, worse sleep quality, and lower lifestyle regularity.[16,17] Individuals with BD tend to be more evening type than healthy controls, and the “eveningness” correlates with mood severity ratings and mood instability.[18] Alterations in the sleep–wake cycle have harmful effects on general health. Insomnia is associated with increased risk of developing hypertension[19] and individuals that report a disturbed sleep pattern have an increased risk of myocardial infarction.[20] Short sleep duration has also been associated with impaired glucose tolerance, in experimental settings[21] and also in community-dwelling samples.[22,23] Sleep deprivation may indeed cause an increased sympathetic activity[21] and may alter cortisol secretion and clearance.[24] Delayed sleep onset is associated with a pre-sleep surge of growth hormone.[25] Self-reported poor sleep quality has been associated to an increased risk of metabolic syndrome and particularly to higher waist circumference, body mass index (BMI), percentage of body fat, and measures of insulin resistance.[26–28]

BD could, thus, confer increased susceptibility to medical diseases through the altered circadian rhythms and neuroendocrine activity. This could also provide a link with abdominal fat distribution frequently observed in bipolar illness and with the less favorable course of illness observed in obese individuals suffering from bipolar disorder.[29,30]

MOOD AND AFFECTIVE INSTABILITY

The mood dimension has been traditionally considered the “core” dimension of BD with great emphasis on the bipolarity of melancholia–euphoria. In the last decades, however, an increasing number of phenomenological studies have shown that both mania and depression tend to be multifaceted and multidimensional.[31,32]

The DSM-IV and IV-TR focus on circumscribed mood disturbances and include instability as a criterion for particular rapid or ultrarapid-cycling subtypes. Studies on large sample of individuals at risk for developing BD and with of those diagnosed with BD show that mood instability and variability are core phenomena that may link comorbidity, suicide, early onset, and a more complex course of illness.[33,34]

Instability-activation, rather than euphoria-elation, has been reported to be the main feature of mania.[32,35] According to Akiskal and colleagues[32] the emotional dysregulation in mania involves more than the two classic euphoric–dysphoric components and distinct depressive aspects can be isolated. The high prevalence of cluster B personality disorders[36] may also act as a pathoplastic factor, contributing to the clinical picture of affective instability and impulsivity.[37]

On the other hand, depression in the course of BD is characterized by mixed features. Hantouche and Akiskal[38] describe bipolar depression as more often characterized by suicidal ideation, guilt, hypersomnia, and weight gain, but yet psychomotor agitation, when

compared to unipolar depression. Anxiety is another prominent feature in bipolar depression and reported rates of lifetime comorbid anxiety disorders in bipolar patients are as high as 52.8%[39]. The presence of anxiety is predictive of suicidal ideation and suicide attempts[39,40] and seems to mediate some aspects of the severity of BD. Anxiety may be a core feature of bipolar depression, or at least of certain subtypes of bipolar depression, instead of a comorbid condition.[41] Subsyndromal and atypical anxiety symptoms are also relevant and are associated with a more severe course of BD.[42,43] In particular, recent results from Fagiolini and colleagues[42] indicate that a high burden of anxiety symptoms is a specific subtype of BD, with unique demographic and clinical course characteristics. Preliminary data also indicate that individuals with the "comorbid" type of BD are also more likely to develop medical comorbidities (Soreca et al., unpublished data): in 225 patients with bipolar I and II disorders enrolled in the Bipolar Center for Pennsylvanians study, we observed that baseline scores of medical burden and number of organ systems involved, assessed with the Cumulative Illness Rating Scale (CIRS), were positively correlated (r = .21, P = .0015 for CIRS total score and r = .16, P = .015 for CIRS number of organ/systems involved) with lifetime Panic–Agoraphobic Spectrum[44] scores.

In addition to the cross-sectional characteristics of individual episodes, longitudinal aspects of the illness course need to be considered. Kraepelin[45] first observed the high instability and unpredictability both within and across episodes. He described manic–depressive illness as the "good prognosis" major mental illness, in contrast to schizophrenia, for which deterioration and disability were the most common outcomes. A more modern description of BD, however, points to the substantial chronicity of the illness, with patients being symptomatic almost 50% of the time, despite being in treatment,[46] and presenting residual symptoms during a considerable percentage of time in "remission."[46,47] Subsyndromal depressive symptoms during the remitted phases have been associated with the low occupational and psychosocial functioning and the high level of disability suffered by these patients.[48–51]

Two main course "typologies" have been described: the manic type and the depressive type. Evidence suggests that ongoing depression may be a prominent feature for the majority of patients[46,52] and that polarity of the first episode might be a good indicator of the subsequent course.[53] have shown that those patients who "start" with depression tend to have an earlier onset of illness, a higher number of depressive, rather than manic, episodes, and higher prevalence of comorbid psychiatric disorders (especially anxiety and alcohol/substance abuse); women are over-represented among those who show this course pattern.

There is also evidence that the association between obesity and mood disorders may be mainly mediated by depression. The presence of depression in adolescence is a predictor of higher BMI in adult life[53,54] obesity and, specifically, abdominal obesity are associated with higher number of lifetime depressive, but not manic, episodes in adult patients with BD.[30]

Patients with BD are afflicted by a high rate of morbidity and mortality from medical disorders, especially those that are obesity-driven, such as various forms of cardiovascular diseases.[29,55] Taken together, this evidence argues for a key role of depression associated with the medical burden in BD.

Nevertheless, rates of mortality and morbidity from cardiovascular diseases are lower in unipolar depression than in BD,[55,56] making it arguable that there might be some specific features in bipolar depression that drive the medical burden or that manic episodes somehow further increase risk of cardiovascular disease above what is attributable to depression alone.

One hypothesis is that the affective instability, the presence of anxiety, the dysrgulation of affect and reward systems, and altered eating patterns, could lead to increased medical burden, through a number of mechanisms, including shared biological vulnerability, unhealthy lifestyle, high rate of alcohol and substance abuse,[57] exposure to a wider range of medications (possibly, higher medication nonadherence), poorer treatment response, and lower rates of remission.

COGNITIVE AND EXECUTIVE DYSFUNCTION

A number of neurocognitive deficits have been reported in patients with BD across different clinical states as well as during euthymic phases.[58,59] The most consistent findings involve deficits in attention,[60] memory,[61] and executive functions such as planning, cognitive flexibility, cognitive control, and verbal fluency.[62,63] A pattern of neurocognitive deficits that is specific to BD, however, has not been described and the reported dysfunctions in memory, executive functions, and attention partly overlap with those described in unipolar depression[64] and those described in schizophrenia[65] even though the profile of impairments may be different across the diagnostic categories,[65,66] with bipolar patients showing less severe impairment than schizophrenia patients with respect to measures of learning, verbal knowledge, and verbal fluency. The importance of the cognitive functioning domain resides in its correlation with functional outcome, even in absence of residual symptoms.[67]

Although most of the adverse consequences of having a BD (namely global dysfunction, suicide attempts, weight gain, and medical comorbidities) are thought to be related to depression, some specific deficits in verbal learning and memory appear to be related to the number of manic episodes.[61] It has been shown that better performance on tasks exploring frontal executive function is positively correlated with occupational status, whereas patients with longer illness duration, a higher number of hospitalizations and suicide attempts, and greater number of previous manic episodes tend to perform more poorly on tasks exploring executive functions and memory.[61] A negative correlation between executive task performance and number of hospitalizations for mania has also been shown in bipolar patients with a history of psychotic symptoms.[68] Frangou and colleagues[69] report that longer illness duration is associated with worse performance on the Hayling Sentence Completing Task, which engages the ventrolateral prefrontal cortex inhibitory processes, thus hypothesizing a loss of inhibitory control and response planning over time, as a form of deterioration. Newer evidence, however, shows that performance on tasks requiring executive control and inhibition are impaired very early in the course of the disorder.[70,71] It is not clear, therefore, whether neurocognitive deficits are an adverse consequence of the long illness course or an early marker or a risk factor for the disease. In addition, the role of iatrogenic factors such as long-term pharmacotherapy exposure and/or polypharmacy on neurocognitive dysfunction has not been clarified. Most of the current data come from cross-sectional studies that retrospectively assess the clinical course of illness and this greatly limits the possible inferences that can be drawn on cause and effect.

Recently, Clark and colleagues reported attentional deficits in first-degree relatives of patient with BD, patients with recurrent depression, but not healthy controls[72] and Antila and co-workers[73] reported impaired executive function and psychomotor processing speed in unaffected first-degree relatives of patients with BD compared to healthy controls. Family members of individuals with BD represent a high-risk group for the disorder; therefore, the presence of neurocognitive impairment in this population would point toward a trait characteristic or a risk factor. Increasing importance, however, has been placed on developmental factors in shaping the phenomenology of BD: in this perspective, the

distinction between state markers and trait (vulnerability) markers would need to be re-conceptualized, emphasizing the role of time and aging in the pathoplastic process.[74]

Cognitive deficits have been reported in elderly patients with BD as well,[75] although it is not clear what would be the relationship of these findings to results from the adult population, given that most of the information comes from cross-sectional studies. Gildengers and colleagues[76] have shown that elderly patients with BD display an array of deficits in sustaining attention and working memory, which are consistent with what is found in adult and young patients; in addition, these deficits were more pronounced in the bipolar group, compared to age, gender, and education-matched healthy controls. On the other hand, studies conducted on the elderly population show that a lifetime diagnosis of a major psychiatric illness, and more specifically BD and major depression, confers an increased risk for dementia in late life.[77,78] This increased risk does not appear to be related to atherosclerosis and cardiovascular diseases.[78] This preliminary evidence is suggestive of the existence of a subtype of BD with relatively better long-term prognosis and survival, possibly associated with the development of cognitive deficits and risk for dementia. The pathogenesis of cognitive impairment and dementia in elderly individuals with BD might be unrelated to the cardiovascular risk factors/disease,[78] which would, in turn, cause an increased mortality at a younger age.[55,56]

THE MEDICAL BURDEN

BD ranks as the sixth leading cause of disability in the world, with an economic burden that in the US alone has been estimated at $7 billion in direct medical costs and $38 billion (1991 values) in indirect costs.[79] More recent studies have indicated that patients with BD sustain health-care utilization costs that are as much as four times greater than costs for nonbipolar patients[80] and a considerable part of these costs is driven by medical illness.[81]

It has always been assumed that the functional impairment associated with BD results from the psychiatric (and, more recently) cognitive symptoms associated with the illness, but it now seems reasonable to ask whether a large part of this disability might not be linked to poor physical health rather than psychiatric symptoms? The medical problems that have most commonly been described in this population are cardiovascular diseases, diabetes, obesity, and thyroid disease.[30,55,82–84] The most common causes of death for individuals with BD, not including suicide, are cardiovascular and cerebrovascular diseases,[55] which occur at twice the rate of the general population.[56] Given that obesity is very prevalent in patients with BD and that all the medical conditions described in this population are either triggered or worsened by weight gain, weight gain seems to be a major factor of medical burden. Body fat distribution is also important in determining the harmful consequences of weight gain. In fact, abdominal obesity, measured by waist circumference, is a criterion for the diagnosis of metabolic syndrome.

Patients with a BMI in the normal range can still be at an increased risk for metabolic disturbances if the waist-to-hip (W/H) ratio and waist circumference are increased. The combination of a high BMI and a high W/H ratio confers a particularly high risk for metabolic disturbances, including insulin resistance, type 2 diabetes, and metabolic syndrome itself.[85,86] It is not clear, however, whether individuals with BD have an increased risk for abdominal obesity once BMI is controlled for. Elmslie and colleagues,[87] for example, compared anthropometric characteristics of 89 patients with bipolar disorder with those of 445 age-matched individuals randomly chosen from the general population and found that patients had increased prevalence of central obesity, compared to individuals from the general population. Nevertheless, this study failed to control for BMI and the patients showed also an increased prevalence of overweight and obesity, which could

account for the greater endorsement for abdominal obesity. On the other hand, results from a pilot study that was conducted in our clinic showed no difference in body composition and body fat distribution measured with dual energy X-ray absortiometry in 10 patients with bipolar I disorder and healthy controls, carefully matched for gender, age, BMI, and ethnicity (Soreca et al., unpublished data). These results would point toward an obesity-driven visceral adiposity and insulin resistance, rather than being a specific characteristic of BD. It is possible, however, that the conventional risk factors and screening tools may not be sensitive enough to capture early and subtle metabolic differences that may differentiate patients with BD lipoprotein from the general population. We also measured the triglycerides/high density lipoprotein (TG/HDL) ratio in the 10 patients with BD and the matched healthy controls. The TG/HDL ratio of 3.5 mg/dl or greater has been shown to reliably predict the presence of small low-density lipoprotein particle subfractions[88] and insulin resistance.[89]

Patients had a significantly higher TG/HDL ratio than controls (2.78 versus 1.33, $F = 3.82$, $P = .032$); only three patients and none of the controls had the ratio > 3.5 mg/dl. Of note, the two groups did not significantly differ on other measures such as percentage of body fat and regional distribution of the body fat, which is a known correlate of insulin resistance.[85] In addition, none of the patients were currently taking antipsychotic medications. This might indicate that alternative measures may be needed to identify those patients who display obesity-related risk factors in this particular population. Regardless of whether visceral obesity may be more prevalent in patients with BD than in the general population, it seems clear that, when present, abdominal obesity is related to worse psychiatric outcome,[29] namely a higher number of depressive episodes and suicide attempts.[29] It is possible that bipolar patients are not at risk for a more “malignant” type of obesity, compared to controls, once they become obese, but obesity is related to a less favorable prognostic type of BD. It is possible, on the other hand, that heterogeneity of risk factors might exist and those specific to the bipolar population are yet to be elucidated.

The association between obesity and mood disorder is well accepted and established,[90] although the causal direction of this association is less clear. During the pre-psychopharmacologic era, Kretschmer[91] described a somatic typology (habitus picnicus) characterized by an abdominal fat pattern, associated with “cycloid temperament,” at risk for developing manic– depressive psychosis. A more recent theoretical model is looking at a common genetic diathesis and neurobiological vulnerability.

Preliminary evidence supports a common vulnerability between emotion dysregulation and disordered eating, as indicated by a high rate of comorbidity between BD and binge eating disorder[92–94] and further confirmed by neuroimaging studies that show a partial overlap between neural circuits involved in affect regulation and neural circuits involved in reward-guided behaviours and processing of food-related stimuli.[95–98] The dysregulation of affect and reward systems, possibly coupled with impulsivity traits,[99,100] may also explain the high rate of nicotine and alcohol consumption[101,102] and substance abuse observed in individuals with BD.[100] Substance and alcohol abuse have been associated with increased likelihood of metabolic syndrome,[103] pancreatitis, and diabetes mellitus.[104] Other putative mechanisms linking BD to obesity and abdominal obesity involve persistent elevated cortisol levels across depressive, manic, and remitted states[105,106] hypercortisolemia is associated with abdominal obesity in the general population[107] and it affects peripheral glucose uptake leading to diabetes.[108] There is preliminary evidence that it could be a link between mood disorders and cardiovascular risk factors.[109,110]

In addition, the lifelong exposure to the medications such as atypical antipsychotics, lithium and other mood stabilizers is postulated as one important determinant of weight gain and

medical burden and there is evidence for an association between long-term use of medications and cardiovascular diseases, obesity, diabetes,[111] thyroid disease,[112] and bone-density loss[113] in individuals with BD. Finally, there is evidence that the association between mood disorder and obesity may involve different peripheral mechanisms, such as resting metabolic rate[114] and rate of fat oxidation (Fleet, Soreca et al, manuscript in preparation).

HYPOTHESES

The course of illness in BD is multiform and often unpredictable. The current diagnostic approach to BD, as exemplified in the DSM criteria, does not describe the multisystem involvement that the recent literature has highlighted nor does it point to potential indicators for long-term outcome. This categorical conceptualization is also reflected in the current treatment guidelines, primarily focused on targeting mood symptoms in both the acute and long-term prophylactic treatments.

In light of the new evidence that the long-term course of BD is associated with a high prevalence of psychiatric comorbidity and an increased mortality from medical disease, we propose a multidimensional approach that includes different symptom domains (Table 1), presenting in various combinations that give shape to each individual presentation, and offers potential indicators of severity, clinical course, and long-term prognosis. Such an approach has to be considered complementary to the categorical diagnosis, as an attempt to better define severity and prognostic indicators.

Both increased mortality due to cardiovascular disease[55,56] and increased risk for dementia[78] have been reported for patients with BD. Of note, the studies indicating an increased risk for dementia have been conducted on a dementia population, by retrospectively comparing the odds of lifetime psychiatric diagnoses versus other medical diagnoses (including diabetes). This method selects the “survivors” and, by definition, excludes most of those patients at increased risk of mortality from medical diseases. Different combinations of different domains (mood, cognition, circadian rhythms) may give rise to different patterns and different courses of illness that are specific for each individual. Different patterns of symptoms and different courses of illness may, in turn, have different long-term prognoses. It is possible that one extreme of the bipolar spectrum comprises a subset of patients with early onset of the disorder, prominent depressive symptoms, altered circadian rhythms, tendency to chronicity, high rate of comorbidity with eating disorders, anxiety, alcohol and substance abuse, who develop a high rate of medical burden at relatively young age and show increased mortality from cardiovascular disease. A different subset of patients may have lower rates of comorbidity and a relatively more benign course of illness. In these individuals the increased risk for cognitive decline and dementia may become apparent, as a result of longer life expectancy.

CONCLUSIONS

BD has been classically defined by episodic mood disturbances. New evidence points to the fact that multisystem involvement is the rule, rather than the exception. Together with mood instability, we often observe disturbances of circadian rhythms, cognitive impairment, and a high rate of medical burden. Although both researchers and clinicians are starting to be aware of the complexity of BD and the frequent medical involvement, several questions still need to be answered. For example, knowing how medical burden is related not only to aging but also to the duration and to the type of symptoms of the bipolar illness would help to implement preventive and screening strategies on target populations. Furthermore, clarifying the role of medical burden as a possible mediator of treatment response would be a first step

for revisiting the category-guided treatment approach toward an integrated treatment strategy that will comprise prevention, education, lifestyle intervention, as well as tailored pharmacological and psychotherapeutic treatment.

The accumulating new evidence calls for a new diagnostic approach that would better describe the clinical complexity of the disorder. A sharper definition of prognostic and treatment-relevant phenotypes could be a first step toward pathophysiology-directed research and etiologically informed treatment.

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TABLE 1

Symptoms Dimensions in Bipolar Disorder

Dimension	Main symptoms	Assessments
Circadian rhythm instability	Daily rhythm irregularity and variability, insomnia and/or oversleeping, diurnal and seasonal variation of energy levels	Review the social rhythm metric (SRM) at every visit with the clinician
Mood and affect instability	Variability of mood symptoms, presence of mixed symptoms during depression, dysphoric mood, anxiety	MOODS-SR, PAS-SR, ABS-SR at intake and annually
Cognitive and executive functioning	Attentional deficits, deficits in verbal learning and memory	Wechsler Adult Intelligence Scale (WAIS), Wisconsin Card Sorting Test (WCST), or Tower of London (basic battery) at intake and annually
Medical burden	Obesity, cardiovascular diseases, cerebrovascular diseases, diabetes	Physical exam and comprehensive blood tests at intake, and annually, assess weight, waist circumference, and blood pressure at every visit

MOODS-SR, Mood Spectrum Self-Report[115]; PAS-SR, Panic- Agoraphobic Spectrum Self-Report[44]; ABS-ST, Anorexic-Bulimic Spectrum Self-Report.[116]