

DEPRESSION RESEARCH AND TREATMENT

BIPOLAR DISORDER

GUEST EDITORS: CRISTINA COLOMBO, ANDREA FOSSATI, AND FRANCESC COLOM





Bipolar Disorder

Depression Research and Treatment

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Guest Editors: Cristina Colombo, Andrea Fossati,
and Francesc Colom



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Contents

Bipolar Disorder, Cristina Colombo, Andrea Fossati, and Francesc Colom
Volume 2012, Article ID 525837, 2 pages

Diagnostic Disagreements in Bipolar Disorder: The Role of Substance Abuse Comorbidities,
Rowena Shalini Theodore, Monica Ramirez Basco, and John R. Biggan
Volume 2012, Article ID 435486, 6 pages

Seasonality and Sleep: A Clinical Study on Euthymic Mood Disorder Patients, Chiara Brambilla,
Chiara Gavinelli, Dario Delmonte, Mara Cigala Fulgosi, Barbara Barbini, Cristina Colombo,
and Enrico Smeraldi
Volume 2012, Article ID 978962, 6 pages

**Cognitive Reactivity to Success and Failure Relate Uniquely to Manic and Depression Tendencies and
Combine in Bipolar Tendencies**, Filip Raes, Ine Ghesquire, and Dinska Van Gucht
Volume 2012, Article ID 753946, 4 pages

**Do We Really Know How to Treat a Child with Bipolar Disorder or One with Severe Mood
Dysregulation? Is There a Magic Bullet?**, Rajeev Jairam, Mukesh Prabhuswamy, and Pravin Dullur
Volume 2012, Article ID 967302, 9 pages

Functional Outcome in Bipolar Disorder: The Big Picture, Boaz Levy and Emily Manove
Volume 2012, Article ID 949248, 12 pages

**Self-Referential Thinking, Suicide, and Function of the Cortical Midline Structures and Striatum in
Mood Disorders: Possible Implications for Treatment Studies of Mindfulness-Based Interventions for
Bipolar Depression**, William R. Marchand
Volume 2012, Article ID 246725, 15 pages

Editorial

Bipolar Disorder

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According to the World Health Organization, bipolar disorder is the 6th leading cause of disability in the world and it affects about 5% of the population with dangerous repercussions on multiple aspects in a person's life. The depressive phase of bipolar disorder is often very severe, and suicide is a major risk factor. Studies on the causes of the disorder focus on environmental triggers such as unexpected stressors and circadian variations and on genetic contributions.

Moreover, psychobiological factors seem to play an outstanding role not only in the aetiology of the disorder but also in its outcome and, potentially, in the response or lack of response to pharmacological and psychological interventions. Newer staging models suggest elevated levels of several cytokines and BDNF decreased levels for poor responders. Papers in this special issue treat a vast variety of topics regarding bipolar disorder, reflecting the complexity and the multifactorial aetiology of the disorder. Starting from point of view which considers the intricacy of the disorder, the review "Functional outcome in bipolar disorder: the big picture" gives us a thorough overview on the psychosocial implications after the onset of the illness which influence the quality of the patient's life on a global level. It considers options to enhance patient care and to provide an overall improvement in the functional outcome with therapies such as interpersonal and social rhythms therapy which has been shown to be effective in the long-term clinical management of the disorder.

When we consider the predisposition of the general population toward mood disorders it is important to take into account the detection of depressive and manic cognitive

vulnerability in healthy subjects. F. Raes et al. used self-administered rating scales which address the tendency to react negatively or positively to events based on the person's "bipolar tendency". Interestingly, they find that in subjects with a subclinical bipolar tendency, their tendency correlated significantly with a self-perception of failure in negative events and a self perception of success in positive events suggesting that these mirrored cognitive features both form part of vulnerability to bipolar disorder. Another interesting aspect is the early detection of bipolar disorder, in fact R. Jairam's review examines the controversies tied to the onset and diagnosis of bipolar disorder in children and adolescents. Authors illustrate the difficulty in distinguishing severe mood dysregulation from bipolar disorder highlighting the lack of an effective treatment for this spectrum of childhood disorders.

Another issue involved in the difficulty of an unambiguous diagnosis of bipolar disorder is substance abuse: in fact it is difficult to determine whether substance abuse occurs during an episode itself, or if an abuse leads to the onset of an illness episode. S. Theodore's paper clearly discusses the role of substance abuse in bipolar disorder and the difficulties of avoiding misdiagnosis and of determining the presence of comorbidities. They find that discrepancies in clinicians are common as symptoms can often overlap and suggest the use of symptom time lines to better distinguish and document their origin. In recent years, numerous researches have not focused only on concerns regarding the disorder's symptomatology and comorbidity, but there has been a growing interest in studying the

link between chronobiology and the pathogenesis of mood disturbance. The paper “Seasonality and sleep: a clinical study on euthymic mood disorder patients” discusses the impact of “rhythmical” factors such as seasonality, sleep, and chronotype (chronobiological factors that can strongly influence the course of mood disorders) with the aim of improving our knowledge of somatic treatment strategies.

Lastly, new implications in the psychological treatment of bipolar disorder are discussed in W. Marchand work. This paper highlights critical features of bipolar disorder including anxiety and on a level of more severe aspects, an elevated suicidal risk. Various studies argue that cortical midline structures are involved in the emotional dysregulation in mood disorders. Authors propose that mindfulness-based interventions, which according to neuroimaging studies modulate cortical midline structures, may improve cognitive and emotional dysfunctions typically observed in patients with affective disorders.

In this special issue, we have brought together multiple disciplines and multiple nationalities, treating various aspects of this intricate illness hoping that these new hypotheses, ideas, and findings will stimulate future research to elucidate aspects of the disorder aetiology, treatment and improve patients’ quality of life.

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Research Article

Diagnostic Disagreements in Bipolar Disorder: The Role of Substance Abuse Comorbidities

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Substance abuse can produce symptoms similar to other psychiatric disorders, thus confusing the diagnostic picture. This paper attempts to elucidate how misdiagnosis in bipolar disorder might be explained by the presence of substance abuse comorbidities. The overlap of symptoms, limited information about symptom onset, and inexperienced clinicians can result in the misinterpretation of symptoms of substance abuse disorders for bipolar disorder. The present study found that the presence of a substance abuse comorbidity, the polarity of last episode (depressed, manic, mixed, not otherwise specified), and the total number of comorbidities affected the reliability of a bipolar disorder diagnosis.

1. Introduction

Clinically, the symptoms of Bipolar Disorder (BPD) during manic episodes are quite distinct and relatively easy to identify including elevated mood, rapid speech, agitation, and participation in high-risk behaviors [1]. However, during depressive, mixed, or hypomanic episodes, or when accompanied by psychotic features, BPD shares symptoms with major depressive disorder, schizophrenia, substance abuse disorders, and several personality disorders and can therefore be difficult to distinguish.

It is this overlap in symptoms that makes the diagnostic process challenging [2–4]. In fact, misdiagnosis is common in BPD [5, 6]. For example, Zimmerman and colleagues [6] examined 700 psychiatric patients who reported that they had been previously diagnosed with BPD. Each person was reevaluated using the Structured Clinical Interview for DSM Disorders (SCID for DSM-IV) [7]. They found that only 43.4% of patients who claimed they had been previously diagnosed with BPD met criteria based on the SCID. This is consistent with other studies [5, 8].

The consequences of an incorrect diagnosis are apparent. Treatment decisions are based on diagnosis and, therefore, inadequate and/or incorrect pharmacological treatments might be applied which lead to unpleasant side effects

without the benefit of symptom reduction [9]. These consequences are costly with regard to human suffering and health care service utilization [3].

In addition to overlapping symptoms, comorbidities such as substance abuse, which occurs in 65% of those diagnosed with BPD [10], can produce symptoms that muddle the diagnostic picture [11]. Goldberg and colleagues [5] interviewed patients with substance abuse problems using structured diagnostic interviews during substance-free time periods. They found that only 32.9% of participants previously diagnosed with BPD met full DSM-IV criteria for bipolar I or II disorders. This suggests that prior substance use had contributed to the misdiagnosis. Likewise, Stewart and El-Mallakh [12] studied patients in a substance-abuse treatment program who had been previously diagnosed with BPD. They found that only 42.9% of participants met criteria for BPD.

Substance abuse disorders are prevalent comorbidities among people with BPD [13]. These disorders may begin as primary disorders or may result from self-medication to reduce or alleviate symptoms of BPD [14]. Commonly abused substances include alcohol, cannabis, cocaine, and stimulants. Not all clinicians are familiar with the signs and symptoms of substance abuse and dependence and could easily mistake them as evidence of a mood disorder [15]

because of their effect on mood and behavior. Substance intoxication or withdrawal symptoms may present as symptoms of mania or depression, respectively, thereby misleading clinicians [16]. Errors can easily occur if clinicians rely too much on global heuristics to diagnose patients rather than thoroughly evaluating all symptoms of a disorder [17, 18].

Studies have shown that utilizing structured diagnostic assessments can improve diagnostic accuracy across psychiatric disorders (e.g., [8, 19]), but less specific guidance has been provided regarding the mistakes made by diagnosticians and how they might be avoided. A better understanding of common sources of error in diagnosis might provide clinicians who do not have access to structured diagnostic methods, such as the SCID, with information that improves the accuracy of their diagnoses. For example, if prior or concurrent substance abuse or dependence is common among patients about whom clinicians disagree on a diagnosis of BPD, then comorbid mood symptoms and substance use might cue the need to invest more time and effort in gathering diagnostic information. Similarly, since structured diagnostic assessments are time intensive and costly, they cannot be provided for all patients. If it was determined that diagnostic error was more likely to occur for those suspected of having BPD along with several comorbidities, then using structured methods might be justified in these cases.

The present study reexamined diagnostic accuracy data from Basco et al., [8] to determine if cases in which clinicians disagreed on a diagnosis of BPD could be explained by the presence of substance abuse or dependence, number of comorbidities, or polarity of last episode. Disagreements were cases in which a primary diagnosis of BPD was given by either a treating psychiatrist using routine clinical methods, a nurse using the SCID, or an expert diagnostician using all available data, but was not confirmed by the other sources. It was hypothesized that the presence of substance use disorders would lead to greater diagnostic disagreement because these disorders would present with mood symptoms that could be misinterpreted as a mood disorder. Additionally, the total number of comorbidities identified by the expert or gold standard diagnostician was compared for cases in which diagnostic agreement was achieved between clinicians as compared to those in which there was disagreement. It was hypothesized that a greater number of comorbidities occurring concurrently with BPD would be consistent with more diagnostic discrepancies. Finally, the polarity of the most recent episode was evaluated to determine if discrepancies were more likely to occur when the patient was in a manic, depressed, or mixed state. It was hypothesized that there would be fewer diagnostic discrepancies when patients presented with manic symptoms than with mixed or depressive symptoms as manic symptoms tended to be more striking and stereotypic of the disorder.

2. Method

2.1. Sample. Participants were recruited through clinician referrals and advertisements offering free diagnostic evaluation in a community mental health center. Only participants from the Basco et al. [8] sample who had been diagnosed

TABLE 1: Participant demographic characteristics.

Characteristic	<i>n</i>
Gender	
Female	78
Male	43
Ethnicity	
White	92
Hispanic	10
African American	18
Native American	1
Marital Status	
Single, never married	27
Married	26
Divorced	41
Other	27
Education	
Post-high school	43
High-school	78

with BPD by the clinic psychiatrist, study nurse (with or without medical records), or by the expert gold standard diagnosticians, were included in sample. This resulted in a subsample of 120 patients aged 19 to 65 who were primarily female and Caucasian (see Table 1). All were economically disadvantaged and treated in a clinic for the care of persons with severe mental illnesses. The Institutional Review Board at the University of Texas Southwestern Medical Center at Dallas approved the study, and all participants signed an informed consent to participate. Participants were compensated \$20.00 for completion of diagnostic and follow-up interviews. Gold standard diagnoses were explained to patients by the expert diagnostician, and they were provided with the opportunity to relay the diagnostic information to their treating physician by signing a release of records form.

2.2. Procedure. At the time of his or her initial intake evaluation at the clinic, each patient was interviewed by a clinic psychiatrist without the use of structured diagnostic instruments per routine clinic procedures (routine diagnosis). At study entry, participants underwent a Structured Clinical Interview for DSM-IIIIR (SCID) administered by a trained psychiatric nurse. During the diagnostic interview, the general medical history of each patient was recorded, as well as his or her family history of mental disorders. Life charts [20] representing a timeline of the patients' symptoms, including substance use behaviors, were also constructed. Following the SCID, the study nurse documented the diagnosis derived from the SCID interview (SCID diagnosis).

The nurse reviewed each patient's medical records and the SCID diagnosis was updated (SCID + medical records diagnosis) if the additional information suggested a different diagnosis. Finally, an expert doctoral level diagnostician reviewed the SCID, medical history, family mental health

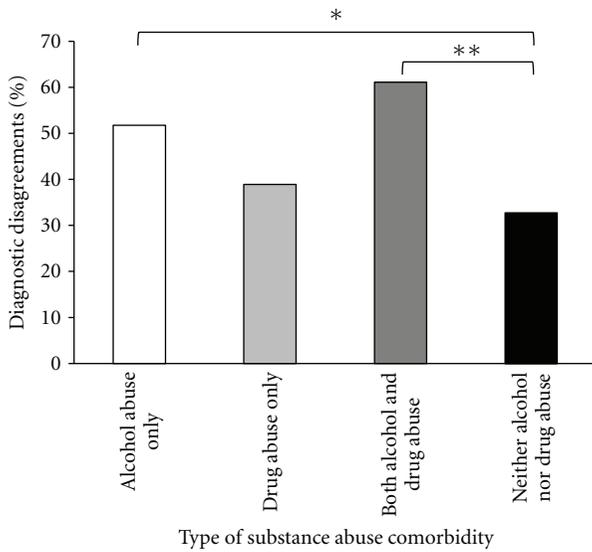


FIGURE 1: Percentage of diagnostic disagreements between the “pregold standard” diagnosis and the “gold standard” diagnosis by the type of substance abuse that was present. * $P < 0.10$, ** $P < 0.05$.

history, and life charts and conducted a follow-up interview with each patient to explore differential diagnoses and to rule out or confirm the SCID + medical records diagnoses (gold standard diagnosis). For the present study, the routine, SCID, and SCID + medical records diagnoses were combined as a “pregold standard” diagnosis.

Because the gold standard diagnoses were assumed to be most accurate, they were used to group patients as having either “alcohol abuse or dependence,” “drug abuse or dependence,” “alcohol and drug abuse or dependence,” or “neither alcohol nor drug abuse or dependence.” In addition, the total number of diagnoses rendered by the “gold standard” for each patient was recorded. In this sample, comorbidities included substance or alcohol use disorders, panic disorder (with and without agoraphobia), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD).

3. Results

Diagnostic agreement and disagreement between the “pregold standard” and the “gold standard” evaluation was analyzed. Chi-square tests of independence were used for all tests below. The expected values for the chi-square tests were obtained by averaging the proportion of agreements and disagreements between the groups and multiplying this average by each of the total number of observations for each group. This was done to reduce the influence of disproportionate cell sizes.

3.1. Substance Use Disorders. The effect of the presence or absence of a substance use disorder on diagnostic agreement and disagreement was assessed using a chi-square test with four categories: alcohol only, drugs only, both alcohol and drugs, and no substance use disorder (Figure 1). The

TABLE 2: Frequencies of substance abuse disorders.

Categories	<i>n</i> (120)	Disagreements
Alcohol abuse	29	15 (51.7%)
Alcohol abuse	4	
Alcohol dependence	25	
Drug abuse only	18	7 (38.9%)
Amphetamine dependence	2	
Cannabis abuse or intoxication	3	
Cannabis dependence	2	
Cocaine abuse or intoxication	1	
Cocaine dependence	1	
>1 type of drug abuse	10	
Both alcohol and drug abuse	18	11 (61.1%)
Neither alcohol nor drug abuse	55	18 (32.7%)

omnibus test found marginally significant differences in the amount of diagnostic agreement and disagreement between the four groups, $\chi^2 (3, N = 120) = 6.34, P = 0.096$ (see Table 2).

A post hoc analysis revealed that there were marginally more diagnostic disagreements among patients in the alcohol only group (51.7%) relative to the no substance use disorder group (32.7%), $\chi^2 (1, N = 84) = 3.11, P = 0.078$. There were also more diagnostic disagreements among the both alcohol and drug group (61.1%) than the no substance use group (32.7%), $\chi^2 (1, N = 73) = 5.90, P < 0.05$. A comparison of diagnostic disagreements between the both alcohol and drug group (61.1%) and the drug only group (38.9%) showed no statistical differences.

3.2. Number of Comorbidities. To test the hypothesis that an increase in number of comorbidities would be related to diagnostic disagreements, the numbers of comorbidities were treated as groups and evaluated using a chi-square test. Cochran [21] stated that chi-square tests become unreliable when 20% of cells contain values that are less than five. Therefore, participants with more than three comorbidities were removed as the cell sizes were small and the expected values for each of these groups (four = 4.05, five = 0.45, and six = 0.45) were less than five. Therefore, the number of diagnostic disagreements was compared for patients with one, two, and three comorbidities (Figure 2). The number of diagnostic disagreements showed marginally significant differences between the groups, $\chi^2 (2, N = 109) = 4.89, P = 0.087$ (see Table 4).

Post hoc comparisons determined that there were marginally more diagnostic disagreements for patients with either two (52.8%), $\chi^2 (1, N = 73) = 3.05, P = 0.051$, or three (52.1%) comorbidities, $\chi^2 (1, N = 73) = 3.05, P = 0.081$ than only one (32%) comorbidity. There was no significant difference in the number of diagnostic disagreements for patients with two (52.8%) compared with three (52.1%) comorbidities.

3.3. Polarity of Most Recent Episode. For the comparison of agreements and disagreements by the type of the last episode,

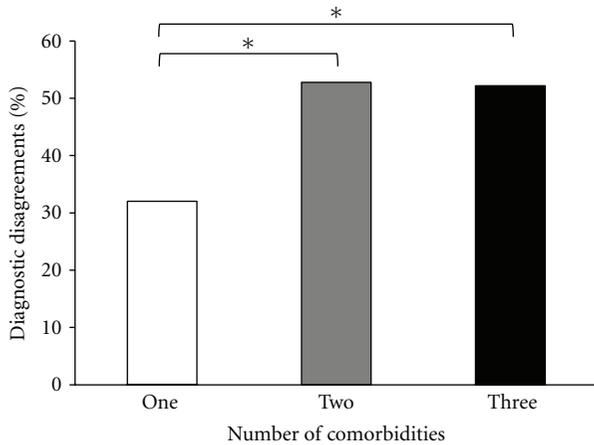


FIGURE 2: Percentage of diagnostic disagreements between the “pre-gold standard” diagnosis and the “gold standard” diagnosis by the total number of comorbidities. $*P < 0.10$.

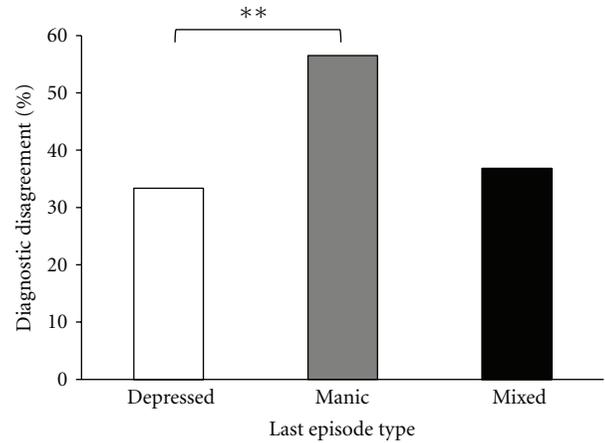


FIGURE 3: Percentage of diagnostic disagreements between the “pre-gold standard” diagnosis and the “gold standard” diagnosis by the type of the last episode experienced. $**P < 0.05$.

TABLE 3: Frequencies of last episode type.

Categories	n (120)	Disagreements
Depressed	54	18 (33.3%)
Manic	23	13 (56.5%)
Mixed	19	7 (36.8%)
NOS	24	13 (54.2%)

TABLE 4: Frequencies of number of comorbid diagnoses.

Categories	n (120)	Disagreements
One	50	16 (32.0%)
Two	36	19 (52.8%)
Three	23	12 (52.2%)
Four	9	3 (33.3%)
Five	1	1 (100%)
Six	1	0 (0.00%)

patients whose last episode was Not Otherwise Specified (NOS) were removed. An omnibus test of the influence of the type of the most recent episode (Depressed, Manic, or Mixed) on diagnostic disagreement revealed no significant differences between the groups (see Table 3). However, a planned post hoc comparison of the number of diagnostic disagreements for those patients whose most recent episode was Depressed (33%) with patients whose most recent episode was Manic (57%) found that significantly more diagnostic disagreements occurred for patients whose most recent episode was Manic, $\chi^2(1, N = 77) = 4.18, P < 0.05$ (see Figure 3). None of the other comparisons showed statistically significant differences.

4. Discussion

The process of assessing psychiatric diagnoses, which relies on patient self-report of symptoms, clinical judgment, experience, and intuition to some extent, is quite complicated.

Most studies of the accuracy of diagnosis [3, 6] attest to this. Structured methods have improved the process [8, 19], but because of the sole reliance on clinical observation and decision-making in the absence of available precise laboratory measures, even these methods are subject to error. The purpose of this research was to attempt to identify clinical features that might explain discrepancies in diagnoses among clinicians, thus providing indicators for heightened sensitivity to diagnostic complexity and the potential for error. Specifically, given the high prevalence of substance use disorders among those with BPD, the association between diagnostic disagreements and the presence of substance use disorders was evaluated. Consistent with previous studies [5, 12], we found that there were, in fact, more diagnostic disagreements for patients diagnosed with BPD who met criteria for comorbid alcohol or substance abuse or dependence (alcohol only or both alcohol and drugs) than for those who did not have substance use disorders. These discrepancies may be due, in part, to the fact that substance intoxication can affect mood (i.e., induce euphoria), disrupt cognitive functioning, and lead to risk taking behaviors, all of which are common in BPD. Withdrawal can be mistaken for symptoms of depression such as dysphoric mood, lethargy, and sleep disturbance. Intoxication and withdrawal can also produce psychotic symptoms such as hallucinations [2], which are not uncommon in the depressive and manic phases of BPD.

It appears that the presence of one co-morbid psychiatric disorder did not cloud the diagnostic picture, as it was not associated with diagnostic disagreement. Clinicians could differentiate one additional disorder from the primary mood disorder. However, the presence of more than one comorbid disorder appeared to contribute to diagnostic confusion, most likely due to the overlap in symptoms among disorders. Similarly, Zimmerman and colleagues [11] found that the errors in the diagnosis of BPD occurred more frequently in patients with three or more comorbid disorders.

The patients in this sample had comorbidities other than substance use disorders, with anxiety disorders being the second most common. It is not unusual for people with

BPD to also experience considerable anxiety that presents in various forms [10]. Likewise, anxiety symptoms such as irritability and psychomotor agitation can be present in both the depressive and manic phases of BPD. While we did not examine the relationship between specific anxiety disorders and BPD diagnostic agreement, our findings on number of comorbidities may suggest that additional caution be exercised during the diagnostic process when anxiety and BPD symptoms are present.

Past research [22, 23] has shown that substance abuse is associated with an increased likelihood of transition in episode polarity, a transition during which a mix of depressive and manic symptoms can confuse the diagnostic picture. In addition, patients who have more than one comorbid substance abuse disorder may have a greater variety of mood fluctuations, thus creating a complex picture that is difficult to disentangle without the opportunity to observe the patients during periods of abstinence.

With limited time and without extensive diagnostic and historical information, clinicians are often forced to rely on decision-making heuristics [17, 18] as they attempt to produce the most accurate diagnosis. Unfortunately, the use of heuristics to form a diagnosis can lead to significant misjudgments as it relies heavily on personal preconceptions and past experiences, which are influenced by selective memory and clinical experience that varies greatly across clinicians and over time [3]. For example, perhaps a depression heuristic is activated when clinicians observe symptoms of major depression that are somewhat different from the typical presentation of patients with a unipolar mood disorder. In our sample, patients with a most recent episode of major depression were more likely to be accurately diagnosed with BPD compared to those with a most recent episode of mania. However, overreliance on this heuristic could also lead to inaccuracies as suggested by the finding that patients who were abusing a depressant (i.e., alcohol) were more likely to be incorrectly diagnosed with BPD.

4.1. Limitations. A major limitation of this research was its sample size given that it was derived from a previous study [8]. This limitation precluded investigation of other factors, such as demographics, that might have been associated with greater diagnostic disagreement. The thrust of the Basco et al. [8] study, from which these data were derived, was that the greater the amount of information available, the more accurate clinicians tended to be in their evaluations. Age, for example, can be a proxy for length of illness, with older patients potentially having had more episodes and therefore providing more diagnostic data for their life charts to help distinguish substance-induced mood episodes from comorbid BPD and substance use disorders. In our sample, there was significantly greater diagnostic disagreement (66.7%) for patients under the age of 30 than for older patients (37.9%), $\chi^2(1, N = 77) = 10.06, P < 0.01$. This may be an artifact of providing more information from which to derive a diagnosis.

This study was also based on patients in a single mental health center which may limit the generalizability of the findings. Furthermore, due to the small sample size, this

study focused on diagnostic disagreements among clinicians, not on the accuracy of the initial diagnosis (i.e., also comparing patients who were not diagnosed with BPD who, in fact, had BPD). Thus, we are unable to conclude that the presence of substance abuse comorbidities increased the likelihood of a patient with BPD not being diagnosed with BPD. Replication of this study in different clinical settings with a larger sample size would help address these issues.

Additionally, the diagnoses in this study were made using the DSM-III-R. This may raise a concern that these findings would be different if criteria from the DSM-IV-TR were used instead. However, a comparison of the diagnostic criteria for BPD in the DSM-III-R and the DSM-IV-TR found no significant differences. It is, therefore, believed that the results of this study are applicable to the diagnostic procedures of the DSM-IV-TR.

For future research and elaborations on this study, it would be of interest to study the effects of individual substances on the diagnostic accuracy of BPD. Due to sample size restrictions, comparisons were limited to a combined level. However, if research is able to determine that the consumption of a specific drug affects the diagnostic reliability of a BPD diagnosis, this will enable clinicians to identify the exact category of drug that causes symptom confusion, which will help to simplify diagnostic procedures.

5. Conclusions

This study attempted to explain some of the factors that might interfere with diagnostic accuracy in a community mental health sample of patients with significant mood symptoms. It was found that the presence of substance abuse or dependence, symptoms of mania, and increased number of comorbidities were related to diagnostic disagreements for bipolar disorder. These findings are not surprising. Experienced diagnosticians can attest to the fact that the more complicated the symptom presentation, the more difficult it is to accurately disentangle symptoms, particularly when the same symptoms are common across several disorders.

The draw of substance use is often the alteration in mood. It is this effect that contributes to the confusion in psychiatric evaluations. While structured methods can help organize diagnostic information, clinicians must still make judgments as to the origin of symptoms (i.e., substance related or not). What our findings suggest is that when manic symptoms are present and a substance use history is endorsed, extra caution should be taken in compiling a detailed history of the onset and offset of each. If substance use predates symptom onset that is close in time, a substance-related mood disorder diagnosis is likely. If self-medication with substances of abuse occurs after the onset of mood symptoms, then a mood disorder may be more likely. Comorbidities are best sorted out by use of a life chart [20] or time line where the onset and offset of BPD symptoms and substance abuse symptoms can be documented. This method was used in the original study to help differential diagnoses. However, when mood and substance use symptoms occur simultaneously, it may not be possible to differentiate the two until the patient

discontinues his or her use of substances long enough for its effect on symptoms to dissipate.

As an additional note, as the mental health community prepares for the introduction of the DSM-V (expected in 2013), this is an opportunity to make adjustments to highlight the importance of ruling out substance abuse disorders when diagnosing a patient with BPD, as well as to clarify the differences between both disorders.

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Clinical Study

Seasonality and Sleep: A Clinical Study on Euthymic Mood Disorder Patients

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Background. Research on mood disorders has progressively focused on the study of seasons and on the mood in association with them during depressive or manic episodes yet few studies have focused on the seasonal fluctuation that characterizes the patient's clinical course both during an illness episode and during euthymic periods. *Methods.* 113 euthymic outpatients 46 affected by major recurrent depression and 67 affected by bipolar disorder were recruited. We evaluated the impact of clinical "rhythmical" factors: seasonality, sleep disturbance, and chronotype. Patients completed the SPAQ+ questionnaire, the MEQ questionnaire, and the medical outcomes study (MOS) sleep scale. We used *t*-test analyses to compare differences of clinical "rhythmical" and sociodemographic variables and of differences in the assessment scales among the diagnostic groups. *Results.* Patients reporting a family history for mood disorders have higher fluctuations throughout seasons. Sleep disturbance is more problematic in unipolars when compared to bipolars. *Conclusions.* Sleep, light, and seasonality seem to be three interconnected features that lie at the basis of chronobiology that, when altered, have an important effect both on the psychopathology and on the treatment of mood disorders.

1. Introduction

The degree to which seasonal changes affect mood is known as seasonality. The periodical pattern of recurrence is a biological feature of mood disorders, and the recovery from the first episode of illness is followed by a subsequent recurrence in about 90% of affected patients during their lifetime [1]. In addition, the occurrence of diurnal variations in mood and of distressful and pervasive disruption in sleep suggests a primary disturbance of biological rhythms for mood disorders [2].

The typical pattern of recurrence of mood disorder follows interindividual rules, since each patient presents their own specific pattern with a few episodes during their life, or more than four episodes each year (rapid cyler). Some authors have stressed the concept of seasonality, as many patients show critical months of the year when they tend to have a new recurrence independent of polarity [3]. The recurrence pattern is also affected by external factors, such as

exposition to light which appears to have an antidepressant effect both on its own and when associated to acute pharmacological treatments, which shorten the subsequent cycle of illness [4] and maintenance treatments, which are expected to decrease the episode rates. Mood stabilizers, the first choice of treatment for bipolar disorder, can successfully sustain the effect of chronotherapeutics and can help to manage the low risk of manic switches [5]. Chronotherapeutic treatments such as sleep deprivation have been successfully associated with antidepressant drugs with a serotonergic [6–8] noradrenergic [9], mixed serotonergic-noradrenergic [10–12], and dopaminergic [13] mechanism of action. In a similar way, light therapy has been shown to hasten response to serotonergic antidepressants in nonseasonal depression [8, 14]. Therefore, an environmental regulator of fundamental importance on biorhythms in living organisms is represented by the photoperiod, which is the variability of hours of light throughout seasons. The disruption of circadian rhythms, including an abnormal response to sunlight, have a role

in the pathophysiology of mood disorders; consequently, both climate and latitude may influence seasonality [15]. On the extreme end of the spectrum, such as with seasonal affective disorder (SAD), the change of symptoms with the seasons is associated with significant dysfunction. Yet, even patients with mood disorders not formally diagnosed as SAD can show seasonal worsening of their symptoms [16] meaning that seasonality can be considered as a continuum.

What is the nature of sleep disorders in major depression? It has been hypothesized that the circadian type, in other words, a person's chronotype, may have a role in seasonal susceptibility in morningness and eveningness types [17]; morningness types maintain a more regular sleep-wake cycle and prefer to carry out its activities during the day time, while eveningness types have a more flexible sleep-wake cycle and are more active in the evening hours. Natale et al. (2005) found that evening types seem to feel better in summer (long photoperiod) than in other seasons, while morning types seem to feel better in winter (short photoperiod) [18]. It can be hypothesized therefore that the duration of the photoperiod and its variations throughout the seasons may influence the relapse or the reoccurrence of an illness episode on the basis of the subject's chronotype. Furthermore, Perlman and colleagues (2006) found that a persistent sleep deficit after recovery (at least partially) from a mood episode in Bipolar patients predicted depressive symptoms during a six month follow-up period [19].

1.1. Genetic Factors. Various twin studies suggest that there is a genetic component behind susceptibility to seasonal changes. A large study involving 4,638 adult twin pairs from Australia found that genetic factors accounted for 29% of the variance in seasonality. They also found that in each behavioral domain, (i.e., mood, energy, social activity, sleep, appetite, and weight), there is a significant genetic influence on the reporting of seasonal changes [20]. Another twin study involving 339 twin pairs [21] found that genetic factors accounted 45.5% in males and 30.5% in females of the variance for seasonality.

2. AIM

The purpose of this clinical study was to evaluate the effect of clinical "rhythmical" factors such as seasonality, sleep disturbance, and chronotype, which can have an influence on the course of the patient's illness during a period of euthymia. We obtained information on their seasonal and sleep disturbances during a period of euthymia and compared these variables between unipolars versus bipolars. We compared patients with or without family history of mood disorders for the variable "seasonality", we compared morningness and eveningness chronotypes to assess differences in sleep quality and at last, we evaluated the effect of a lithium maintenance therapy on chronobiological parameters comparing the patients with or without lithium salts.

3. Methods

3.1. Participants. The sample in this cross-sectional longitudinal study included 113 outpatients (80 females and 33 males): 46 affected by major depressive disorder (unipolars) and 67 affected by bipolar disorder. The sample was recruited during the patients checkups at the outpatient Mood Disorder Unit of the San Raffaele Hospital in Milan, from January, 2009 to March, 2010. Inclusion criteria were (1) bipolar or unipolar disorder diagnosis according to DSM-IV-TR criteria, (2) euthymic patients which had a normal ranged mood, without a depressed or elated mood for a period of at least 24 months as measured by the hamilton depression rating scale (HDRS) <8 or the young mania rating scale score = 0, and (3) lithium or antidepressant (SSRIs) maintenance therapy, according to the polarity of the forms and clinical judgment. The lithium dosage was given on the basis of the tested plasma level between 0.5 and 0.7 mmol/L. Table 1 summarizes the clinical and demographic characteristics of the sample. This study has been approved by the local sanctioning board (ASL, Città di Milano), and it meets ethical standards.

3.2. Measures. The protocol for data collection consisted of an anamnestic sheet filled out by the psychiatrist during the patient's checkup, and in a series of self-administered questionnaires: *seasonal pattern assessment questionnaire (SPAQ)*, *morningness eveningness questionnaire (MEQ)*, and *medical outcomes study (MOS) sleep scale*.

In the anamnestic sheet, the following data was collected: age, sex, the polarity of the mood disorder, other Axis II and III diagnoses (according to the DSM IV-TR), the age of onset, total of number episodes, the recurrence index (number of previous episodes/duration of illness), years of education, family history of mood disorders, the current therapy, and the duration of euthymia duration of maintenance therapy. Most bipolar patients were on a monotherapy long-term treatment with lithium salts.

3.2.1. Seasonal Pattern Assessment Questionnaire (SPAQ+). The SPAQ+ (Italian version, [22]) is a self-administered questionnaire which quantifies (regardless of the presence or absence of a psychiatric disorder), the individual's tendency to seasonal mood and behavioral changes, and this is defined as "seasonality." The SPAQ [23] investigates several areas including demographic data, seasonal changes in sleep length, social activity, mood, weight, appetite, and energy level (Likert scales scored 0–4, used to calculate the global seasonality score or GSS, with a total score ranging from 0–24).

3.2.2. Morningness-Eveningness Questionnaire (MEQ) Morningness types are those people who consistently prefer diurnal activity, while eveningness types are those who prefer nocturnal activities. The morningness/eveningness dimension is regulated by a complex interaction among social, geographic, and genetic factors. The morningness/eveningness questionnaire [24] is the most commonly used self-report

TABLE 1: Demographic and clinical characteristics of the sample.

Tot. $n = 113$	Unipolar	Bipolar
	$N = 46$	$N = 67$
	mean \pm SD	mean \pm SD
Age	54.98 \pm 11.88	51.32 \pm 13.20
Education years	11.83 \pm 4.24	12.05 \pm 4.31
Age of onset	34.00 \pm 14.44	31.72 \pm 13.47
Duration of Illness (years)	20.98 \pm 12.88	18.98 \pm 12.15
Total no. of episodes	5.39 \pm 4.86	8.36 \pm 7.91
Depressive episodes	5.21 \pm 4.35	5.20 \pm 5.32
Manic episodes	/	4.63 \pm 12.45
Duration of euthymia (months)	29.93 \pm 37.19	30.57 \pm 35.60
Duration of maintenance Therapy (months)	40.36 \pm 50.91	54.51 \pm 48.84

questionnaire for the assessment of preferred timing of complex behaviors regarding sleep-wake habits and rhythms. The questionnaire is normally distributed [25], and this allows us to consider the circadian types as a continuum [26]. The Italian version of the MEQ [27] includes 19 items, and the sum yields a global score, ranging from 16 to 86 with lower scores indicating greater evening tendencies and higher scores indicating greater morningness tendencies.

3.2.3. Medical Outcomes Study (MOS) Sleep Scale. The MOS [28] is a self-administered instrument which consists of 12 items which measure six important dimensions of sleep, including initiation (time to fall asleep), sleep disturbance (have trouble falling asleep, how long to fall asleep, sleep was not quiet, awakenings during sleep and having trouble falling back to sleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived sleep adequacy (get enough sleep to feel rested upon in the morning, getting the needed amount of sleep), and day-time somnolence (drowsiness during the day, nap taking). Answers were based on a retrospective assessment over the past 4 weeks.

3.3. Statistical Analysis. A descriptive statistics of the sample was carried out using SOFTSTA 6.0. In accordance with diagnosis, gender, chronotype, family history, maintenance therapy non paired Student's t -tests were carried out for the sociodemographic, clinical variables, and rating scale scores (Table 1).

4. Results

We then performed a t -test analysis to compare the two different disorders, unipolar and bipolar patients, and found a significant difference for greater sleep disturbance in unipolar patients ($t = -2.27$; $P = 0.003$). There is a significant difference also in the recurrence index, with a higher recurrence in bipolar patients ($t = -0.55$; $P > 0.000$) (Table 2).

We performed a t -test analysis between patients that reported a family history for mood disorders, and we found significant difference in the following variables: age of onset ($t = 3.74$; $P < 0.000$) which is lower in individuals with a family history, duration of illness ($t = -3.25$; $P < 0.001$) which is longer for patients with a family history, number of depressive episodes ($t = -2.66$; $P = 0.009$) and total number of episodes ($t = -2.58$; $P = 0.011$), which are higher for patients with a positive family history and GSS ($t = -2.13$; $P = 0.035$) which is higher for patients with a positive family history (Table 3).

We decided to analyze if lithium salts (the maintenance therapy considered a gold standard in the treatment of bipolar disorders) when compared to other therapies, has an effect on the variables analyzed earlier as its effects on sleep quality have not previously been taken into consideration in literature. In our sample of unipolar and bipolar patients, we performed a t -test analysis between patients that take lithium in their maintenance therapy for at least 6 months versus patients that do not. There were significant differences for sleep disturbance ($t = 3.03$; $P = 0.003$), shortness of breath ($t = 3.83$; $P < 0.000$), sleep adequacy ($t = 3.63$; $P < 0.000$), and a notable even if not significant difference in sleep somnolence ($t = 1.79$; $P = 0.060$) indicating that these sleep quality parameters better in those patients that use lithium salts as a maintenance therapy (Table 4).

We also divided subjects according to their chronotype to verify if being a morningness versus eveningness type would influence our variables. The chronotype division was performed using the subjects' MEQ scores. We performed a t -test analysis dividing MEQ according to categories of chronotype into greater "morningness" (>59) and greater "eveningness" (<41) and intermediate (>41 and <59) [26]. Patients highlighted a significant difference in sleep disturbance ($t = 2.52$; $P = 0.010$) with morningness types reporting a lower sleep disturbance and a better sleep adequacy ($t = 2.53$; $P = 0.013$) (Table 5).

5. Discussion

Seasonality seems to have a tie with a family history for mood disorders: patients (both unipolar and bipolar) reporting a positive family history for their disorder have a significantly higher seasonality, indicating that there might be a genetic component that influences the amount of mood, energy, appetite and sleep fluctuation throughout seasons. This data is consistent with the findings of Jang et al. [21] who found that a genetic factors accounted for 45.5% (males) and 30.5% (females) of the variance. Future genetic studies on the heritability of seasonality could support further confirmations of these findings.

Patients that take lithium salts as a maintenance therapy have a lower sleep disturbance, a lower shortness of breath, a better sleep adequacy and an overall improved sleep quality. This may suggest that lithium salts aid in stabilizing not only mood fluctuations themselves, but also help to regulate all the rhythmical parameters such as sleep rhythms, which are directly involved with the pathophysiology of mood

TABLE 2: *t*-test analysis between unipolar and bipolar patients.

	Unipolars (<i>N</i> = 46)	Bipolars (<i>N</i> = 67)	<i>t</i> value	<i>P</i>
	Mean ± SD	Mean ± SD		
Total Number of episodes	5.39 ± 4.86	8.36 ± 7.91	-2.27	0.025
Duration of maintenance therapy (months)	40.36 ± 50.91	54.51 ± 48.83	-1.25	0.214
Episodes during maintenance therapy	0.26 ± 0.77	0.68 ± 1.50	-1.67	0.097
GSS	8.39 ± 4.88	8.22 ± 4.65	0.18	0.854
Sleep disturbance	37.39 ± 25.04	24.32 ± 20.40	3.01	0.003
Snoring	38.67 ± 29.05	48.91 ± 39.96	-1.47	0.145
Short of breath	19.57 ± 24.03	14.38 ± 23.49	1.13	0.260
Sleep adequacy	36.00 ± 26.26	27.34 ± 27.62	1.65	0.101
Sleep somnolence	31.39 ± 20.54	38.59 ± 27.80	-1.49	0.139
Sleep hours	7.26 ± 1.73	7.41 ± 1.36	-0.52	0.604
Recurrence index	2.87 ± 2.95	4.36 ± 2.99	-0.55	0.010

TABLE 3: *t*-test analysis between unipolar and bipolar patients that have a family history for mood disorders versus those that do not.

	No family history (<i>N</i> = 34)	Family history (<i>N</i> = 78)	<i>t</i> value	<i>P</i>
	Mean ± SD	Mean ± SD		
Age	53.18 ± 14.39	52.46 ± 12.03	0.27	0.786
Education	11.21 ± 4.40	12.37 ± 4.14	-1.34	0.181
Age of onset	39.79 ± 14.82	30.18 ± 11.36	3.74	0.000
Duration of illness (years)	14.15 ± 8.26	22.14 ± 13.23	-3.25	0.002
Number of depressive episodes	3.35 ± 2.21	6.00 ± 5.48	-0.34	0.009
Number of manic episodes	1.29 ± 1.49	3.33 ± 11.75	-2.66	0.319
Total number of episodes	4.59 ± 3.13	8.19 ± 7.83	-1.00	0.011
Duration of maintenance therapy (months)	53.73 ± 52.33	48.23 ± 49.06	-2.58	0.636
GSS	6.85 ± 4.16	8.90 ± 4.87	-2.13	0.035

disorders. This could be a possible explanation to the fact that unipolar patients reported more sleep problems, as the majority of them do not take lithium Salts (38 do not take it out of 46) as opposed to most bipolar patients who do (50 take it out of 57) In a previous study, our group [13], discussed the benefits of lithium salts on sleep. A possible explanation is that lithium is known to delay circadian rhythms in animals [29] and lengthen the period of the sleep-wake cycle in humans [30], leading to a phase delay of circadian rhythms both in normal subjects and in bipolar patients [31]. Given the effects of lithium on the rhythmicity of brain neurotransmitter function [32] and recent findings about the regulation of circadian rhythmicity in mammals [33, 34], the chronobiological effect of lithium has been proposed to at least partially explain its clinical effect [35, 36].

When we subdivided our patients according to chronotype, we found morningness patients to have a sleep rhythm which is less disturbed and a more adequate sleep quality. Hätönen et al. [37] and Mansour et al. [38] have found that circadian-type preference for evening activities has been shown in bipolar patients: eveningness seems to be related to morbidity and especially to sleep and mood disorders [39]. It has been hypothesized that mood disorders may

be more prevalent in individuals with a shifted clock. One hypothesis is that clock genes have been shown to regulate circadian behaviour and preference [40], so sleep and rhythm performance may be a part of the phenotype corresponding to these circadian clock shifts [41]. Another possible explanation is that since exposure to outdoor light affects the phase of entrainment and our society has schedules for the most part synchronised according to morningness types, eveningness types pay the consequences in terms of sleep loss and reduced sleep quality [42]. It has been shown that repeated sleep restriction causes a cumulative increase in daytime sleepiness and waking neurobehavioral deficits [43]. This is a relevant issue especially for mood disordered patients, because altered sleep quality can be one of the triggers for an illness episode. As it is widely known, sleep loss is often a precursor and/or a precipitant of hypomania or mania in bipolar patients. Knowing a patient's chronotype can be useful in helping the patient to maintain a regular sleep hygiene to prevent sleep loss and consequently a circadian rhythm deregulation.

We found, on the contrary to studies carried out by Shin et al. (2005) who found that individuals with bipolar disorder experience a higher seasonality variation, no differences among diagnosis in seasonality scores [44]. This could be

TABLE 4: *t*-test analysis between unipolar and bipolar patients that are in maintenance therapy with lithium salts versus patients that are not.

	No lithium (<i>N</i> = 38 unipolars, 17 bipolars) (<i>N</i> = 55)	Lithium (<i>N</i> = 5 unipolars, 50 bipolars) (<i>N</i> = 55)	<i>t</i> value	<i>P</i>
	Mean ± SD	Mean ± SD		
Sleep disturbance	36.28 ± 24.11	23.30 ± 20.64	3.03	0.003
Short of breath	24.72 ± 28.54	8.361 ± 13.71	3.83	0.000
Sleep adequacy	39.93 ± 27.81	22.00 ± 23.76	3.63	0.000
Sleep somnolence	39.83 ± 23.83	31.33 ± 25.98	1.79	0.060

TABLE 5: *t*-test analysis between morningness and eveningness patients.

	Eveningness types (<i>N</i> = 16)	Morningness types (<i>N</i> = 67)	<i>t</i> value	<i>P</i>
	Mean ± SD	Mean ± SD		
Sleep disturbance	40.17 ± 28.07	25.61 ± 18.71	2.52	0.010
Short of breath	18.75 ± 17.08	17.42 ± 27.22	0.19	0.853
Sleep adequacy	47.50 ± 33.37	28.09 ± 26.24	2.53	0.013
Sleep somnolence	48.58 ± 28.873	35.33 ± 25.46	1.83	0.071

due to the fact a large portion of our sample has a history of maintenance therapy; unipolar subjects with a high rate of depressive recurrences are treated with maintenance therapy (mainly with SSRI), while bipolars are for the most part on long-term lithium treatment, which, as mentioned previously, may alter and reduce seasonal fluctuations.

Limitations of our study include that the use of retrospective questionnaires (such as the SPAQ+) always raise the possibility of recall bias. Furthermore, we have a lack of information about the lighting conditions to which subjects were exposed in their usual environment and the study period was relatively short in length and multiple years of data may be required to detect statistically significant seasonal effects. Another major limitation of our study is that we did not collect a control sample. Finally, as we have seen, sleep, light, and seasonality seem to be three interconnected features that lie at the basis of chronobiology that, when altered, have an important effect both on the psychopathology and on the treatment depression. These findings, paired with future acquisitions, will be useful in the clinical practice, both for prevention and for the manipulation of these features for a therapeutic aim.

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Research Article

Cognitive Reactivity to Success and Failure Relate Uniquely to Manic and Depression Tendencies and Combine in Bipolar Tendencies

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The present study examined simultaneously the relations between cognitive reactivity to success and failure, on the one hand, and depression, manic, and bipolar tendencies, on the other hand. Participants (161 students) completed measures of success and failure reactivity, current manic and depressive symptoms, and tendencies towards depression, mania, and bipolarity. Results showed that respondents with a greater tendency towards depression evidenced greater (negative) reactivity to failure, whereas those with a greater tendency toward mania evidenced greater (positive) reactivity to success. Depression vulnerability was unrelated to success reactivity, and manic vulnerability was unrelated to failure reactivity. Tendencies toward bipolarity correlated significantly with *both* failure and success reactivity in a negative and positive manner, respectively. These findings add to the growing body of literature, suggesting that different features or cognitive tendencies are related to depression vulnerability versus manic vulnerability and imply that these “mirrored” cognitive features both form part of vulnerability to bipolar disorder.

1. Introduction

A key feature of depression vulnerability is increased cognitive reactivity to negative events or negative mood [1, 2]. It refers to the degree to which a mild dysphoric state reactivates negative cognitions. It is believed that such increased cognitive reactivity exacerbates negative emotion and, that way, precipitates depressive episodes [3, 4]. Parallel to such a pattern of increased *negative* reactivity to negative events, more recent findings from a largely separate literature suggest that patients with bipolar disorder experience greater reactivity to *positive* events (see [5] for a review), which, in turn, might boost positive emotion and, that way, increase manic symptoms over time [6].

Whereas the association between negative reactivity and depression (vulnerability) has been extensively studied and is well established, research on the relationship between positive reactivity and mania/bipolarity is clearly lagging behind. Also, negative and positive reactivity have been studied in largely separate literatures, focusing either on (unipolar)

depression or on bipolar depression and mania, thereby limiting potential integration and crucial linking of important patterns of findings. Given that these two “mirrored” forms of cognitive reactivity have been put forward as potentially relevant in explaining vulnerability to depression and mania, much more insight could be gained from research that simultaneously focuses on positive and negative reactivity in relation to both depression and mania. Although sorely needed, such studies are rare. Eisner et al. [7] have recently started to examine positive and negative reactivity (focusing on success and failure reactivity) in relation to both mania and depression. They showed that increased reactivity to failure was associated to depression vulnerability, whereas increased reactivity to success was uniquely related to mania vulnerability. Whereas Eisner et al. [7] still investigated success and failure reactivity in relation to mania and depression separately (one study focusing on failure reactivity and the other on success reactivity), Carver and Johnson [8] recently studied the associations in one and the same sample in a single study, replicating the findings of Eisner et al. [7].

Eisner et al. [7] rightly cautioned that their findings should be considered preliminary and, thus, that replication is needed by independent researchers preferentially using different measures for manic/depression tendencies and success/failure reactivity. This is precisely what the present study set out to do. In a sample of Belgian high school students, we administered a new measure that we constructed to assess failure and success reactivity (SFRS, see below) and a measure to assess depression and manic tendencies which was different to the ones used previously [7, 8]. Consistent with Eisner et al. [7], we hypothesized that failure, but not success reactivity, would be related to depression tendencies, whereas manic tendencies would be related to success but not to failure reactivity.

Besides extending the previous findings using different measures, the current study attempted to take the previous work a step further in yet another important way. The mania/depression measure used in the present study includes, besides items assessing propensity to either mania or depression symptoms, also the so-called biphasic items that assess fluctuation between depressive and hypomanic states (i.e., propensity towards bipolarity). The latter allowed us to test, for the first time, whether failure and success reactivity, which are supposed to *uniquely* relate to depression, and manic tendencies, respectively, are *both* associated to tendencies to bipolarity. Given that depression (vulnerability) is characterized by negative reactivity and mania (vulnerability) by positive reactivity, those who are characterized by both tendencies toward depression and mania (and thus bipolarity) are expected to exhibit positive as well as negative reactivity. Thus, besides our hypotheses that failure, but not success reactivity, would be related to depression tendencies and that manic tendencies would be related to success, but not to failure reactivity, we additionally hypothesized that tendencies toward bipolarity would be related to *both* forms of reactivity. Finally, we hypothesized that these associations would remain even after controlling for current symptoms of depression and mania.

2. Method

2.1. Participants and Procedure. Participants were 161 Belgian Dutch-speaking students from the last two years of secondary school (105 women, 56 men). The average age was 16.68 years (SD = 0.67; range: 16–19). All respondents participated without compensation. Following informed consent, participants completed all measures (see below) at home.

2.2. Measures

2.2.1. General Behavior Inventory (GBI). The GBI [9] assesses unipolar and bipolar affective conditions on trait or lifetime basis. It contains 73 items, which comprise three subscales. A first subscale of 45 items measures symptomatic behaviours associated with depression (e.g., “Have there been times of several days or more when you really got down on yourself?”). A second subscale of 21 items measures symptomatic behaviours associated with (hypo)mania (e.g.,

“Have there been periods of several days or more when your friends or family told you that you seemed unusually happy or high-clearly different from your usual self or from a typical good mood?”). A third subscale of 7 biphasic items measures fluctuation between both depressive and hypomanic behaviours (e.g., “Have you had periods lasting several days or more when you felt depressed or irritable, and then other periods of several days or more when you felt extremely high, elated, and overflowing with energy?”). Items are rated on a 4-point scale, *never or hardly ever* (1), *sometimes* (2), *often* (3), and *very often* (4). The four alternatives are scored 0, 0, 1, and 1 [9]. Adequate psychometrics are reported for the original English GBI [9] as well as for the Dutch version [10]. Cronbach’s alphas in the present study were .92, .82, and .72 for the depression, (hypo)mania, and bipolar/biphasic scale, respectively.¹ As the GBI includes items focused on a lifetime history of depression, (hypo)manic, and biphasic/bipolar symptoms, scores on each of these scales were, following Carver and Johnson [8], conceptualized as tendencies towards these affective conditions, or risks or vulnerabilities for these conditions.

2.2.2. Depression Anxiety Stress Scale (DASS). The DASS is a 21-item self-report instrument to assess current (past week) depression, anxiety, and stress symptomatology [11]. Each of the three subscales consists of seven items, all scored on 0–3 scale. Good psychometric properties are reported [11]. Only the Depression subscale (DASS-D) of the Dutch version by de Beurs et al. [12] was used. Cronbach’s alpha in the present sample was .82.

2.2.3. Altman Self-Rating Mania Scale (ASRM). The ASRM [13] assesses current (past week) manic symptoms using five items (increased cheerfulness, inflated self-confidence, talkativeness, reduced need for sleep, and excessive behavioral activity). Each item consists of a group of five statements with increasingly severe descriptions (0–5 scale). The ASRM has good psychometric properties and correlates strongly with clinician-administered ratings [13]. The English ASRM was translated into Dutch by F. Raes and D. V. Gucht (FR and DVG). Next, the Dutch ASRM was translated back into English by Professor Dr. Kristin Blanpain, a native Dutch speaker with a Ph.D. degree in English Literature and extensive expertise in translating and revising academic documents (including backtranslation of questionnaires). Finally, the backtranslation was evaluated and approved by Dr. Altman, the main author of the original English version. Cronbach’s alpha in the present sample was .76, comparable to internal consistency values reported in the literature for the English version (e.g., .70; [14]).

2.2.4. Success and Failure Reactivity Scales (SFRS). Respondents are asked to imagine that they feel neither particularly sad nor particularly cheerful and that they *fail* at something which is important to them. Then, they are instructed to keep this situation in mind when indicating how they would typically feel/think about themselves after such a *failure experience* on two –10 to +10 rating scales: *I feel much less*

self assured than before (-10) over I feel as self assured as before (0) to I feel much more self assured than before (+10) and I think I'm not good at anything at all (-10), over I still think the same about myself (0), to I think I can achieve everything (+10). Success reactivity is assessed using the same two items. Now, respondents are asked to imagine that they feel neither particularly sad nor particularly cheerful and that they *succeed* at something which is important to them. They are then instructed to keep this situation in mind when indicating how they would typically feel/think about themselves after such a *success experience* using the same two -10 to +10 rating scales with identical anchor points. A total failure reactivity score is derived averaging both failure item scores (Cronbach's alpha = .76; $r = .61$). Likewise, a total success reactivity score is obtained averaging both success item scores (Cronbach's alpha = .84; $r = .73$).

3. Results

Mean scores, standard deviations and ranges for all variables included were as follows: GBI depression ($n = 151$; $M = 6.22$; $SD = 6.92$; range = 0–32); GBI (hypo)mania ($n = 151$; $M = 3.30$; $SD = 3.45$; range = 0–17); GBI biphasic ($n = 156$; $M = 1.50$; $SD = 1.73$; range = 0–7); DASS-D ($n = 161$; $M = 3.60$; $SD = 3.61$; range = 0–18); ASRM ($n = 161$; $M = 4.50$; $SD = 3.46$; range = 0–19); failure reactivity ($n = 161$; $M = -3.55$; $SD = 2.66$; range = -10–5); success reactivity ($n = 161$; $M = 4.48$; $SD = 2.43$; range = -2–10).

As predicted, tendencies toward depression (GBI depression scores) correlated significantly negatively with failure reactivity scores but were unrelated to success reactivity scores (see Table 1). Second, tendencies toward mania (GBI (hypo)mania), on the other hand, were unrelated to failure reactivity, but correlated significantly positively with success reactivity. Third, tendencies toward bipolarity (GBI biphasic scores) correlated significantly with both failure and success reactivity in a negative and positive manner, respectively. Finally, these associations remained after controlling for current symptoms of depression (DASS-D scores) and mania (ASRM scores) (also see Table 1), indicating that the observed associations are not attributable to current mood symptoms.

4. Discussion

The present study examined simultaneously the relations between success and failure reactivity, on the one hand, and depression, manic, and bipolar tendencies, on the other hand. People with a greater tendency toward depression evidenced greater (negative) reactivity to failure, whereas people with a greater tendency toward mania evidenced greater (positive) reactivity to success. Depression vulnerability was unrelated to success reactivity, and manic vulnerability was unrelated to failure reactivity. Thus, success and failure reactivity relate uniquely to manic versus depression tendencies, which is consistent with earlier findings by Eisner et al. [7] and Carver and Johnson [8]. The present results further extend these prior findings to a different sample using

TABLE 1: Correlations and partial correlations (current manic and depression symptoms partialled) between depression ($n = 151$), (hypo)mania ($n = 151$), and biphasic ($n = 156$) GBI-scores and failure and success reactivity.

	Failure reactivity ^a	Success reactivity ^a
GBI depression	-.24** (-.20*)	.09
GBI (hypo)mania	-.06	.33*** (.32***)
GBI biphasic	-.26** (-.23**)	.16* (.26**)

GBI: general behavior inventory; values between brackets are partial correlations between variables controlled for current manic (ASRM) and depression (DASS-D) symptoms; n varies because of missing data.

^aHigher scores on the reactivity scales reflect higher levels of self-assurance/self-confidence; lower scores reflect lower levels of self-assurance/self-confidence;

* $P < .05$. ** $P < .01$. *** $P < .001$.

different measures to assess depression and manic tendencies and success and failure reactivity. Furthermore, unlike Eisner et al. [7], we established these unique relationships for success and failure reactivity in one and the same sample [8]. Together with the study of Carver and Johnson [8], the present study represents one of the rare comprehensive studies in which positive and negative cognitive tendencies are jointly studied in relation to both mania and depression, which adds to its importance. Of most importance, the present study was the first to examine and establish the *combined* existence of failure and success reactivity in bipolar tendencies, separate from depression and manic tendencies: tendencies toward bipolarity correlated significantly with *both* failure and success reactivity in a negative and positive manner, respectively.

These findings suggest that patients with bipolar disorder, or with a propensity towards this diagnosis, may have an increased reactivity to both success and failure reactivity, of which only the latter is shared by patients suffering from unipolar depression or people with a propensity towards unipolar depression. Just as that increased reactivity to failure (and to other negatively valenced events in general) can precipitate and exacerbate depressive symptoms, increased reactivity to success (and other positive events more generally) may precipitate (hypo)manic episodes. Thus, people who score high on bipolar tendency are characterized by both increased negative and positive reactivity to failure and success, respectively, which may underlie their experiencing of both depressed and (hypo)manic episodes.

The current study has two potential limitations that are noteworthy. The first is that we only relied on self-report measures to assess mania/depression and success/failure reactivity. Secondly, the present results were obtained in a student population, limiting the generalizability to, for example, more clinical populations. As such, future research should test the replicability of these findings using clinician-administered instruments (mania/depression) and behavioral laboratory paradigms (e.g., experimental induction of failure and success experiences; [15, 16]) in both clinical and control/community samples.

In summary, the current study examined and established, for the first time to our knowledge, the *combined* existence

of failure and success reactivity in bipolar tendencies, two contrasting forms of reactivity that each uniquely relates to depression and manic tendencies, respectively. The present findings, then, add to the growing body of literature suggesting that different features or cognitive tendencies are related to depression vulnerability versus manic vulnerability [7, 8] and suggest that these “mirrored” cognitive features both form part of vulnerability to bipolar disorder.

Endnotes

1. We also developed a shortened 28-item version of the 73-item GBI which could be of use in time and cost intensive survey research. Similar to the full GBI, the GBI short form (GBI-SF) contains three sets of items: 14 depression items (items 3, 14, 16, 23, 32, 34, 36, 55, 56, 62, 63, 68, 71, and 73), 7 hypomanic items (items 4, 8, 11, 30, 38, 54, and 61), and 7 biphasic items (same items as in the original GBI: 2, 19, 24, 35, 40, 48, and 53). Cronbach's alphas for the shortened depression and hypomania scales are .90 and .72, respectively. Correlations between the depression and hypomania subscales for the long and short form were .94 and .92, respectively. Also, the pattern of correlations with, for example, current depression and mania symptoms did not significantly change when using the shortened subscales.

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Review Article

Do We Really Know How to Treat a Child with Bipolar Disorder or One with Severe Mood Dysregulation? Is There a Magic Bullet?

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Background. Despite controversy, bipolar disorder (BD) is being increasingly diagnosed in under 18s. There is scant information regarding its treatment and uncertainty regarding the status of “severe mood dysregulation (SMD)” and how it overlaps with BD. This article collates available research on treatment of BD in under 18s and explores the status of SMD. *Methods.* Literature on treatment of BD in under 18s and on SMD were identified using major search engines; these were then collated and reviewed. *Results.* Some markers have been proposed to differentiate BD from disruptive behaviour disorders (DBD) in children. Pharmacotherapy restricted to short-term trials of mood-stabilizers and atypical-antipsychotics show mixed results. Data on maintenance treatment and non-pharmacological interventions are scant. It is unclear whether SMD is an independent disorder or an early manifestation of another disorder. *Conclusions.* Valproate, lithium, risperidone, olanzapine, aripiprazole and quetiapine remain first line treatments for acute episodes in the under 18s with BD. Their efficacy in maintenance treatment remains unclear. There is no validated treatment for SMD. It is likely that some children who are currently diagnosed with BD and DBD and possibly most children currently diagnosed with SMD will be subsumed under the proposed category in the DSM V of disruptive mood dysregulation disorder with dysphoria.

1. Introduction

A popular myth in psychiatry was that bipolar disorder is easily recognisable with clear episodes of mania and depression interspersed with lengthy periods of normal functioning. And that even when it onsets in children and adolescents it is straightforward to diagnose and can be treated with the same concoction of mood stabilizers and antipsychotics that “cures or controls” adults with bipolar disorder (BD). This myth has been decimated by the mountain of literature that has accumulated on paediatric bipolar disorder (PBD) over the last two decades. Much has been written about the difficulties and controversies surrounding its presentation and diagnosis, including whether DSM IV criteria can be reliably applied to diagnose children with bipolar disorder, whether irritability rather than euphoria is the predominant mood

state and whether these outbursts of pathological mood states fulfil the required duration criteria. The reported high rates of comorbidity of attention-deficit hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs) with PBD are another contentious area [1–4]. Evidence is beginning to emerge on the longitudinal course of PBD when it onsets in childhood or adolescence. Recent methodologically sound studies endorse childhood onset bipolar disorder as a relapsing disorder enduring into adulthood [5–7]: little, however, is known with regards to management of these children. Most treatment trials assume that all children with PBD present with an acute manic episode and should be treated as such. Consequently the majority of evidence is for time-limited pharmacotherapy in adolescents [8]. There are gaps in our knowledge in how to treat younger children with BD and in effective psychological and social forms of

treatment. A thorough examination of this question is not complete without devoting some attention to children with “severe mood dysregulation” (SMD) who at face value seem to share a lot of characteristics with BD not otherwise specified (BD NOS), and to see what works for them. Different research groups have had different definitions for BD NOS, and consequently these have different conversion rates to BD [4]. Recent research also suggests a lower conversion rate of SMD to the classic bipolar phenotype when compared to the narrow phenotype bipolar disorder in the longitudinal course [9]. Perhaps the solution to the PBD puzzle lies in the amalgamation of psychosocial and pharmacological strategies that can effectively “control” this disorder so that its impact on normal development can be limited and positive health promoted. This paper will first briefly examine diagnostic issues and information on the course and outcome of PBD, followed by a synopsis on the current status of “severe mood dysregulation” as an entity. We will then examine the current evidence with regards to both pharmacotherapy and psychosocial management of both PBD and SMD.

2. Methods

A search was conducted using PubMed, Embase, and Psychlit from 1990 through 2011 using the search terms *pediatric bipolar disorder*, *mania*, *children*, *treatment*, *antipsychotics*, *mood stabilizers*, and *severe mood dysregulation*. The search was limited to clinical trials published in the English language. Weight-age was given to articles based on its type (review, original research, meta-analysis), its source of funding and kind of study (open trial, double blind trial, whether randomized control or not), and recency. The references of all recent review articles on pediatric bipolar disorder were reviewed manually to limit studies being missed. Some non-published studies which were presented in conferences were quoted in view of their importance. Older studies of lithium in PBD were included owing to limited recent data. The identified articles were reviewed by the three authors of the study and the results collated.

3. Diagnosis of Paediatric Bipolar Disorder

Breaking free of existential issues, the presence of BD in children and adolescents is now accepted [10–12]. Several aspects of it however remain controversial; for example, “How common is it?” Few prevalence studies of BD in adolescents exist and the most commonly quoted prevalence figure is 1% [10, 13]. There are no known prevalence studies of BD in prepubertal children. Diagnosis of bipolar disorder in adolescents is subject to little controversy. However the same issue in prepubertal children seems a different kettle of fish altogether. Those children and adolescents that demonstrate traditional DSM IV or ICD 10 criteria for BD are relatively straightforward to diagnose [14, 15]. These are the ones with BD type I and those with BD type II who present with clear hypomanic episodes. It is usually the other group of children who generate diagnostic controversy. They usually have very poor emotional regulation with significant outbursts, poor frustration tolerance, insecure attachments, and a learned

pattern that temper tantrums and threats succeed in getting them what they want. Although there is a high comorbidity with disruptive behavior disorders (DBDs), that disorder alone does not explain all of their symptoms. These are a difficult group of children that clinicians often struggle with and it is tempting to dismiss this group as not being representative of bipolar disorder. After all, they lack the characteristics that have long been traditionally thought to correlate with BD including a week of mania (or four days of hypomania), clear-cut episodicity with the episodes lasting weeks or months, and good interepisode functioning. It is crucial to differentiate manic/mixed symptoms from disruptive behavior disorders, difficult temperament, developmentally appropriate excitement, and fantasy and those that are accentuated owing to the presence of a chaotic psychosocial environment [16, 17].

Some features whose presence would prompt a clinician to suspect BD not otherwise specified are as follows. (i) Onset: BD is not a developmental disorder, it is usually possible on thorough assessment involving the child and caregivers to establish premorbid functioning and an onset of current mood symptoms, (ii) Lack of clear precipitants: the occurrence of severe mood episodes appears to be internally driven rather than as a response to psychosocial precipitants, (iii) Unpredictable and unstable mood: which is a hallmark of a severe affective disorder like BD, (iv) Cycles of irritability, depression, elation and grandiosity lasting at least 4 hours—longer than could be explained by regular temper tantrums. In addition, these children have a chronic course with the mood disturbance sometimes lasting years, their mood cycles several times a day, and this type of BD has a younger average age of onset than the more traditional form. A positive family history of mood disorder is another common finding in this group of children [7, 12]. A landmark study which has clarified this further is the COBY study in which a four-year followup of 141 children with BD NOS revealed a 40% rate of conversion to BP I or II. They concluded that subsyndromal DSM-IV criteria may be valid to define BD NOS which is a strong predictor of BP I or II [7].

4. Outcome of Paediatric Bipolar Disorder

Available outcome studies of this group of children paint a bleak picture [5–7]. Studies on the course of BD which onsets in childhood and adolescence have yielded differing results. One set of studies show it to have a classical episodic course, with episodes lasting few months [18, 19] whereas others have found it to be more protracted with episodes lasting years [6, 20].

There have been five major retrospective studies over last two decades which compared adolescent onset with adult onset BD and found that those with adolescent onset had longer episodes, more number of episodes, greater comorbidity, longer time of illness before treatment, more rapid cycling, more suicidality, and poorer overall outcome [21–25]. Key prospective studies of children and adolescents with BD to date include two Indian and five American studies which have had sample sizes ranging from 25 to over 400 children with a one-to-eight year duration of followup

[6, 7, 19, 26–28]. Overall these studies found that, with treatment, the mean index manic/mixed episode length was 10–14 weeks, 81–100% have episodic recovery, 50–80% experience one or more recurrences over a 5-year period, and the majority of recurrences occur in the first two years of the index episode. In addition over the duration of the study period, there was a switch from BP-NOS to BP I or II disorder and from BP II to BP I and the trend was child-adolescent-adult = BP NOS to BP I. In addition the studied young people had high rates of hospitalisation and health service utilization, high unemployment, legal problems, and poor academic and psychosocial functioning. Predictors of poor outcome included early onset, low socio-economic status, subsyndromal mood symptoms, longer duration of illness, BP NOS (rather than types I or II), other psychiatric comorbidities, and presence of significant family psychopathology. These findings however should not be overinterpreted as there have been few studies with small sample sizes with relatively short duration of followup as compared to adults with BD who have been followed up over a few decades, the studies used different methodologies and definitions of BD, and most studies recruited mainly BP I population. Further, the subjects entered various studies at different stages of illness, and there were different cultural and ethnic groups [5].

5. Pharmacological Treatment of Paediatric Bipolar Disorder

In stark contrast to adult research, there is limited data on the treatment of bipolar disorder in children and adolescents. Evidence is predominantly from open-label trials and few randomized control trials (RCTs). The American Academy of Child and Adolescent Psychiatrists came up with practice parameters in 2007 [29]. There is some evidence for the use of mood stabilisers including lithium and anticonvulsants, and antipsychotics (APs)—both typical and atypical in PBD and limited data available on other treatments. The only FDA-approved mood stabiliser for PBD is lithium (age 12 and older). FDA-approved antipsychotics are aripiprazole, risperidone, and quetiapine to treat acute manic and mixed episodes in BD aged 10–17 years. Olanzapine has been approved for BD aged 13–17 years. Aripiprazole was also approved for maintenance treatment in PBD aged 10–17 years. In Australia, no psychotropic medication is approved for use in persons under age of 18 years.

5.1. Synopsis of Key Studies on the Treatment of PBD. Kafantaris et al. used lithium and AP (haloperidol/risperidone) for treating acute bipolar mania in adolescents and noted lower relapses if the AP was maintained for at least 4 weeks [30]. Another study attempted lithium discontinuation after patients were acutely stabilised on lithium by randomising to lithium or placebo. As relapse rates in both the groups were high, a question of whether lithium is efficacious over a period of time was raised [31]. Yet another open-label study by this group demonstrated good efficacy in patients treated with lithium but noted that many patients were also on antipsychotics. The study did not clarify to what degree

the response could be attributed to lithium [32]. Other trials have looked at the efficacy of lithium compared to valproate/placebo or lithium versus valproate/carbamazepine [33, 34]. Both these trials which were RCTs demonstrated better results with valproate than lithium or carbamazepine. However, a subsequent trial did not demonstrate any superiority for valproate over placebo [35]. Given the good efficacy in adults and the lack of strong methodologically rigorous studies on lithium, definitive studies pertaining to the efficacy in acute and long-term treatment of PBD (the Collaborative Lithium Trials (CoLT)) are currently in progress [36]. Furthermore, two trials of oxcarbamazepine did not support any significant benefit [37, 38]. Biederman et al. noted a significant improvement in the treatment of acute mania with Lamotrigine in a 12-week open-label trial of 39 adolescents [39]. However, this study had a higher dropout rate due to side effects especially skin rash.

Based on current evidence of mood stabilizer monotherapy for PBD, valproate has some evidence in controlled trials, while the evidence for lithium seems to come from open studies. Carbamazepine did not fare well.

Two studies evaluated lithium-valproate combinations in the acute treatment of bipolar mania or mixed states. One showed that patients with acute PBD depression or manic type respond to lithium-valproate combination therapy [40] and the other showed that most youth who had been stabilised on a combination therapy, who then relapsed on monotherapy, could be restabilised on combination therapy [41].

The most recent studies have tended to evaluate use of atypical antipsychotics in the treatment of acute bipolar mania. Pavuluri et al. compared risperidone to valproate in 66 patients and noted that risperidone was slightly faster acting and that group tended to have a better retention rate [42]. Another study found that quetiapine was as effective as valproate and faster acting in the acute manic phase of PBD [43]. Wozniak et al. noted that a combination of olanzapine and topiramate was no better than olanzapine monotherapy for acute mania in adolescents [44].

There have been few short-duration trials with other antipsychotics. Haas et al. noted that risperidone (0.5–2.5 mg/day) was efficacious and relatively well tolerated in the acute treatment of manic or mixed episodes in children and adolescents in the ages of 10 to 17 years [45]. In another RCT, 161 adolescents with an acute manic or mixed episode, Olanzapine (2.5–20 mg/d) was superior to placebo after 3 weeks [46]. Delbello et al. concluded that quetiapine, at doses of 400 and 600 mg/d, was more effective than placebo in treating acute manic symptoms in children and adolescents with BD in the ages of 10 to 17 years. Although the study duration was short (3 weeks), the sample size was large (277) [47]. Findling et al. (102) noted that Aripiprazol was effective in PBD (manic or mixed subtype) at doses of 10 mg/day and 30 mg/day [48]. Ziprasidone (dose 80–160 mg/day) was found to be superior compared to placebo in 238 adolescents aged 10 to 17 [49]. However, in April 2010, the FDA cited that the drugmaker had failed to properly ensure monitoring of its study, and as a result, widespread overdosing of patients at multiple study sites was neither detected nor corrected in

a timely manner. So far, Ziprasidone has not been approved for treatment of PBD [50].

Very few studies evaluated maintenance therapy in PBD. Some studies have commented on the efficacy of lithium in preventing relapse [26, 51]. Findling et al. noted that both lithium and valproate were good maintenance agents but noted that, in both trials, symptoms returned subsequently in about 16 weeks [52]. Another study noted that aripiprazole was superior to placebo at 30 weeks [53]. Superiority of AP in maintenance treatment has not been demonstrated, and increased adverse events are observed with long-term treatment. Recommendations for MS (alone or in combination with AP) will be more accurate for maintenance therapy based on some studies; however there is still need for more research in this field.

Bipolar depression is probably the least studied of all the bipolar presentations in children and adolescents. Patel et al. found significant improvement for treatment of bipolar depression with lithium in an open-labelled trial [54]. Chang et al. noted that 63% were responders for lamotrigine in another open-label trial of paediatric depression [55]. Delbello et al. noted no difference in efficacy between quetiapine (300–600 mg/day) and placebo in a similar sample [56]. It is important to note that no difference was noted due to high rates of placebo response. There is a significant lack of studies on treatment of bipolar depression in children and adolescents, and more RCTs are needed to clarify the same.

In view of the vast data on the metabolic complications of atypical AP in paediatric patients, caution would be advocated in the use of APs in PBD [57]. One example was the study by Tohen which found significant weight gain and metabolic abnormalities in subjects on olanzapine [46]. Increased TG and cholesterol were noted especially with olanzapine and quetiapine and increased TG with risperidone and no significant metabolic changes with aripiprazole. It is important to note that the metabolic risk is heterogenous across AP. Maximum weight gain has been reported with olanzapine and least with aripiprazole [58, 59].

As no study has compared treatment efficacy between prepubertal and adolescent patients with PBD, recommendations for prepubertal patients cannot be made independent of adolescent patients. The limited data would suggest that, while acute mania in adolescents responds to either mood stabilisers or antipsychotics, short-term efficacy is probably better for antipsychotics than mood stabilisers [8]. Adult data suggest that the choice of mood stabiliser lithium versus valproate would depend on several factors. Some factors identified in adults with acute mania which favour a better response to lithium are euphoric mania rather than dysphoric, first episode mania, positive family history of bipolar disorder, positive family history of response to lithium, and absence of medical complications or substance abuse [60]. These factors need to be validated in PBD. Current data only supports the use of mood stabilisers for long-term maintenance, and the use of APs for this purpose should be pursued cautiously. The evidence for bipolar depression is even more limited but seems to reflect the adult guidelines which suggest first-line treatment should be lithium or lamotrigine [61].

6. Psychosocial Management of Paediatric Bipolar Disorder

Traditionally psychosocial interventions for PBD have focussed on psychoeducation of the illness, augmenting coping skills, and implementation of strategies to maximise medication compliance. As discussed earlier, the effectiveness of pharmacotherapy in returning a child with BD to premorbid functioning is unclear. In addition there are difficulties with compliance and with side effects of medications which may prevent a desired trial. As a result, there has been a renewed interest in evaluating the effectiveness of various psychosocial strategies in PBD, both as adjuncts and alternatives to pharmacotherapy and also in various stages of illness, right from those at high risk to develop PBD through to those who have had it for several years.

The feasible interventions that have been developed and have been received well by families in PBD include family-focused treatment (FFT), multifamily psychoeducation groups, interpersonal and social rhythm therapy (IPSRT), Cognitive Behavioural Therapy (CBT), and Dialectical Behavioural Therapy (DBT) [62].

Family-focussed therapy and multifamily psycho-education groups have demonstrated efficacy in alleviating mood symptoms, preventing recurrences, and enhancing psychosocial functioning in PBD. In addition, youth at high risk for BD including those with SMD have shown some benefit from targeted psycho-educational therapy or behaviour modification approaches and one study found that multifamily psychoeducation groups could exert a protective effect on conversion to BD among children with depressive spectrum disorders [63–67]. The skill-training modules of FFT attempt to ameliorate the impact of high-EE attitudes and behaviours in families, including aversive communication between parent and offspring, hostility, low family cohesion and adaptability, and difficulties with conflict resolution [68]. A recent study examined one-year treatment outcome trial of an adapted version of FFT for youth (mean age 13.4 yrs) who were at high risk of developing BD-I or BD-II. These youth showed significant reductions in depression and hypomania symptoms and improvements in global functioning over one year [69]. There is consensus that psychosocial interventions need to focus on educating about signs of early relapse, adherence to treatment, coping strategies in interpersonal relations, and stress management. This can be achieved by using a combination of the above treatments. Stress management is a big part of psychosocial intervention since stress and trauma act as both contributing factors and as outcomes of manic/depressive episodes. There is evidence to suggest that young onset mania is triggered more often by stress than adult onset [70]. While there is more evidence in adults for the efficacy of these interventions, similar outcomes are starting to be reported in children and adolescents [71]. To date there is no data to suggest that any one form of psychosocial intervention is better than the other and all of them have been trialled in conjunction with pharmacotherapy. As with pharmacotherapy, the impact of psychosocial interventions on the social and academic functioning and quality of life of children with BD is unclear. Preventing

or minimizing the toxic and impairing effects of BD early before they become chronic or recurrent may help prevent long-term functional disability.

7. Severe Mood Dysregulation (SMD)

7.1. Concept and Controversies. Rages, irritability, or anger outbursts which are out of proportion in both intensity and duration to the trigger can be a feature in several psychiatric and behavioural disorders in children and adolescents. SMD is a label that is often applied to prepubertal children with these rages. Other diagnoses that these children attract include major depression, oppositional defiant disorder (ODD), and attention deficit hyperactivity disorder (ADHD), Anxiety spectrum disorders and BD/PBD. SMD shares symptoms of severe irritability and hyperarousal seen in BD but the irritability is chronic and also the more common features of mania such as elation or grandiosity (as described in DSM-IV) are absent. Children with SMD exhibit developmentally inappropriate reactivity to negative emotional stimuli, such as “outbursts characterized by yelling and/or aggression,” which occur at least 3 times a week, and are impairing in at least 2 settings (home, school, peers). In addition, these children experience symptoms for at least a year without more than 2 symptom-free months. Onset is usually before age 12 with one study claiming an average age of onset of 5.1 years [72]. The DSM-5 task force has proposed the putative category of temper dysregulation disorder with dysphoria (TDDD) which has recently been changed to disruptive mood dysregulation disorder (DMDD) to describe children with severe irritability, and this is likely to replace SMD. DMDD is yet to be systematically studied but in essence is trying to describe the mood symptoms seen in children with SMD which is not described by just a diagnosis of ODD (and ADHD). Also it seems that DMDD diagnosis is not going to include the hyperarousal symptoms described in children with SMD; this would be a very heterogeneous group with chronic irritability and recurrent severe temper outbursts. Owing to the ubiquitous nature of some of the proposed criteria, this diagnosis, if it makes it to DSM V, is likely to attract controversy [73]. The introduction of DMDD may however reduce the possible overdiagnosis of BD.

One of the biggest controversies in child mental health in the recent past has been the phenomenal increase in the prevalence figures for BD especially in the USA where a 500% increase has been reported [74]. Whether this is a fact or an artefact is a big debate in itself. What is relevant is whether rages or nonepisodic irritability is being diagnosed as “bipolar” (since irritability is considered to be more common than typical elation or sadness in early onset mood disorders) or if treatment options such as antipsychotics or mood stabilizers which are commonly prescribed for rages are driving a bipolar diagnosis. Other factors to consider are antecedent “benefits” of a “diagnosis” such as subsidised medication and access to supportive services.

Different research groups profess diverse views on the concept of SMD. Leibenluft et al. suggested these children with rages actually belong to a separate type of BD and compared the various clinical features, treatment, and family

factors of these children with those with classical BD. The label SMD was borne out this effort which suggested that they are a different from the PBD group. Children with SMD also exhibit ADHD- and mania-like symptoms, including 3 of the following: insomnia, intrusiveness, and pressure of speech, flight of ideas/racing thoughts, distractibility, and psychomotor agitation. However, the severity of irritability and the intensity of mood/anxiety symptoms are greater in youths with SMD than those with ODD and ADHD. Biederman et al. suggest that the “SMD group” can be just subsumed under a combination of ADHD and ODD. However the ADHD plus ODD diagnosis fails to capture the mood and anxiety that characterize SMD youth. Carlson et al. suggested that it is important to recognize that a substantial proportion of children with this presentation have a learning disorder or a pervasive developmental disorder [75]. What contributions ODD, ADHD, and developmental disorders including autistic spectrum disorders make to the entity of SMD needs further study. The hope out of all of this is the eventual homogenization of this difficult-to-treat population and the development of treatment guidelines which can prevent the overprescription of mood stabilizers and other medications.

Recent studies have thrown more light on SMD. It is getting clearer now that these children are not as much at risk to develop BD as once thought or as one would intuitively presume. In fact, ADHD and depression have been more common in follow-up studies of this population [76, 77]. Family genetic studies have suggested that kids with SMD have family members with lower psychiatric morbidity rates than those seen in BD, ADHD, and ODD/CD [78]. This also points to SMD possibly being a separate entity and raises more questions about its genetic basis.

As evident from the above discussion there are several issues about SMD that are unknown and/or unclear. With its nosological status becoming clearer and with operationalized criteria in place one would hope to learn more about this group in the near future.

7.2. Treatment of SMD. What is known about treatment for SMD is mostly from expert views, clinical experience, and limited controlled trials. So far there are no specific validated treatments for SMD. The primary difficulty is in being able to define a relatively “homogenous” population. Almost all the drugs used in bipolar disorders have been trialled in SMD in addition to stimulants along with conjunct psychosocial therapies. Both lithium and divalproex sodium have shown some promise in this population [79] with one randomized placebo-controlled trial with lithium which showed a high placebo response (in the run-in phase) and also no significant difference between lithium and placebo in the randomized patients [80]. This needs to be studied in larger controlled studies. Treatment with antidepressants may need to be considered based on evidence from follow-up studies that major depression is a frequent outcome. We are some distance from being able to formulate treatment guidelines for SMD. With the introduction of operationalized criteria for DMDD and the advent of systematic studies, one would expect more robust literature on treatment of this

challenging group of young people. However with the above discussion it appears that mood stabilizers do not seem to be the answer for children with SMD at this stage. It is important to tailor-make treatment for each child, use appropriate psychosocial interventions with active liaison with the school and all other stakeholders before using medications, treat ADHD appropriately, use medication like low doses of antipsychotics if arousal is the main problem, SSRIs if dysphoria is prominent (with careful monitoring for emerging suicidality or switch to mania), and have ongoing case management, the utility of which cannot be overstated. The potential risk of “creating” bipolar children with treatment especially antidepressants has to be kept in mind before initiating any pharmacotherapy. It is of utmost importance to make informed clinical decisions with the family once all these issues are discussed at length.

8. Summary

Controversy surrounding its morphology has not prevented PBD from being diagnosed in increasing numbers [81]. Attempts at defining a set of “criteria” to differentiate PBD from disorders such as DBD and SMD are being formulated. The precise manifestations of BD in prepubertal children will hopefully become clearer as more data on long-term outcome studies becomes apparent as it is this that will throw light on the early manifestations. The available long-term studies have been able to identify some predictors of outcome, and it does appear that the morphology of BD becomes more classical as the child grows older. Diagnostic controversy aside, treatment evidence for these children is extremely scant. Bulk of the studies have been pharmaceutical industry sponsored short-term trials of atypical antipsychotics and mood stabilizers. The available studies have significant limitations including small numbers, heterogeneity of sample (most studies of acute bipolar treatment include mania, hypomania or mixed) and short durations. Little is known about the benefits/efficacy of maintenance therapy or the acute treatment of bipolar depression. Lithium and atypical antipsychotics such as risperidone, olanzapine, aripiprazole and quetiapine remain first line treatments for acute episodes in PBD. Although their use is advocated in maintenance treatment, their efficacy remains unclear. Although commonly used, evidence supporting the use of sodium valproate in this population is lacking. Further trials with larger samples, longer duration, and homogeneity of diagnosis are clearly warranted. There is also a lack of well-researched psychosocial interventions for this population. Both family-focused therapy and multifamily psycho-education appear to show promise. This area needs particular attention as medication alone is unlikely to be successful as a sole treatment in this developmentally crucial time. Other factors to consider are the presence of other comorbid psychiatric disorders, attachment difficulties, and family dysfunction which make diagnosis and treatment more complex.

SMD either as a symptom or as a disorder has generated recent interest. Although these children share some features of PBD, long-term outcome seems to suggest that these children may go on to develop depression with or without

ADHD. The worry is that all those children who do not meet full PBD criteria are likely to receive the SMD diagnosis which is likely to make it another ragbag category. Effective treatment for SMD is likely to involve a combination of pharmacological and psychosocial treatment with significant involvement of the primary caregivers. However research to demonstrate treatment efficacy is still in its infancy. SMD is likely to be subsumed under the broad rubric of DMDD (DSM V) along with some of those currently diagnosed as PBD or DBD. There are already early signs that DMDD (previously TDDD) is not going to be without controversy either [73, 77].

PBD and SMD represent two diagnoses along the mood disorder spectrum that affects a subgroup of children. Tools to improve diagnoses, studies demonstrating long-term outcome, and longer treatment trials with both pharmacological and psychosocial therapies are the need of the hour.

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Review Article

Functional Outcome in Bipolar Disorder: The Big Picture

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Previous research on functional outcome in bipolar disorder (BD) has uncovered various factors that exacerbate psychosocial disability over the course of illness, including genetics, illness severity, stress, anxiety, and cognitive impairment. This paper presents an integrated view of these findings that accounts for the precipitous decline in psychosocial functioning after illness onset. The proposed model highlights a number of reciprocal pathways among previously studied factors that trap people in a powerful cycle of ailing forces. The paper discusses implications to patient care as well as the larger social changes required for shifting the functional trajectory of people with BD from psychosocial decline to growth.

1. Introduction

Psychosocial functioning in bipolar disorder (BD) runs the full gamut of human potential. Whereas some people with BD accomplish historical landmarks in human achievement [1–3], others experience significant difficulties in managing tasks of daily living [4]. The remarkable functional variability in BD highlights an inherent prognostic complexity [5–7], which is not immediately evident in the diagnosis [8]. Many studies have illuminated various aspects of illness progression in BD [9–11], yet significant improvement to functional outcome may require further theoretical and clinical advancement [12].

The astounding functional differences among people with BD present one of the toughest challenges to this effort, as these emerge across the entire spectrum of human development [7, 13–16]. Early emotional abnormalities and poor premorbid functioning tend to occur in BD [17–19]; however, adequate psychosocial adjustment prior to the first manic episode is also common [20–22]. Furthermore, after illness onset, many people with BD regain psychosocial functioning [13, 23], yet others suffer inordinate functional decline, which progresses from a state of psychosocial adjustment to a state of disability [23, 24]. The latter group is of particular interest to clinical research. Understanding the

nature of the sometimes dysfunctional trajectory of BD may help to diminish it, and thereby reduce suffering and cost.

This paper examines the strongest predictors of functional outcome in BD, which have been separately summarized in multiple previous reviews. In this regard, the paper does not aim to provide a comprehensive review of studies linking each of the factors under discussion to psychosocial functioning in BD. Instead, it offers an integrated view on previously reviewed findings and discusses potential implications for prevention and patient care.

2. Direct Effects of Cognitive Dysfunction

Cognitive impairment is among the strongest predictors of psychosocial disability in BD [6, 25]. Cross-sectional studies, now summarized in several comprehensive reviews and meta-analyses, indicate that cognitive deficits often persist into periods of euthymia [26–28], especially in people who suffer from marked psychosocial impairment during affective remission [29, 30]. The co-occurrence of cognitive and psychosocial impairment in the absence of mood symptoms advanced hypotheses about the ill effects of cognitive dysfunction on psychosocial adjustment in BD [31, 32]. Although practical considerations limit investigative efforts

to nonexperimental evidence, this hypothesis gained considerable support from longitudinal studies that employed cognitive measures to predict long-term functional outcome in BD [13, 25, 33–37]. Longitudinal predictions that account for the confounding effects of mood symptoms suggest that cognitive impairment diminishes psychosocial functioning in BD [13, 25, 34].

In a broad view, the logic behind linking cognitive impairment to psychosocial disability in BD may parallel the reasoning that has created this association in dementia. The resemblance between cognitive symptoms of BD and those of dementia often goes unnoticed, because the degree of functional limitation can differ substantially between these disorders. Whereas the large contribution of cognitive impairment to psychosocial decline is widely recognized in dementia, the effects of cognitive impairment on functional outcome in BD may be more selective and subtle. Relative to that in dementia, the cognitive impairment in BD is milder, and the disruption to psychosocial functioning is less dramatic; however, the basic notion linking cognitive impairment to psychosocial disability is similar in nature. In some respects, people with BD who suffer from significant functional disability during euthymia may experience the illness as an attenuated or subclinical form of dementia. This view is supported by evidence that cognitive impairment in BD tends to be progressive over the course of illness [38–40] and correlates with psychosocial decline [41].

Cognitive impairment is milder in BD than in certain forms of dementia (e.g., Alzheimer's type) partly because it is not characterized by a severe amnesic syndrome [42]. The core dysfunction in BD during euthymia is executive in nature [43, 44]. Some researchers have even suggested that deficits in learning and memory are probably secondary to executive impairment [45]. The absence of a severe amnesic syndrome spares basic learning capacities and psychosocial functions; however, the executive dysfunction in BD may be significant enough to quickly limit the utility of preserved functions, particularly as task complexity increases [7, 32]. In BD [46] and in geriatric populations generally [47–49], disturbances in executive functioning have been tied to difficulties in accomplishing tasks of daily living. Studies also indicate that executive dysfunction in BD predicts poorer academic performance [50], worse vocational outcomes [25, 51], reduced social adjustment [52], and diminished quality of life [53, 54].

Thus, although cognitive impairment in BD is not completely incapacitating, the balance of the data suggests that it generates significant disruption to social and vocational adjustment [6, 13, 55, 56]. In other words, people with BD who suffer significant executive impairment during euthymia may not need custodial care, but they probably struggle to fit into mainstream environments, where functional expectations are typically set for the cognitively intact.

3. Direct Effects of Illness Severity

Illness severity is another strong predictor of psychosocial disability in BD [57]. Younger age of onset [58], longer

duration of mood episodes [6], higher number of psychiatric hospitalizations [51], lingering residual symptoms [59, 60], psychosis [61], and substance use disorders [62, 63] all predict greater psychosocial dysfunction in BD.

The argument for a direct impact of illness severity on psychosocial functioning in BD probably provides the most intuitively appealing explanation for the correlation between these two variables. Younger age of onset disrupts psychosocial development at an earlier stage, altering the trajectory of educational, professional, and interpersonal growth [64, 65]. In addition, the break of psychiatric illness early in life likely carries deleterious effects on identity development [66]. Coupled with the stigma associated with mental illness generally and BD in particular [66–71], these internal effects may hamper efforts to achieve social adjustment [69, 71]. Further challenge to these efforts comes from recurrent mood episodes and frequent hospitalizations over the course of illness, imposing inconsistency to educational and vocational pursuits and repeated disruption to interpersonal engagement [5, 66, 68, 72–74]. Lingering residual symptoms between mood episodes impede efforts to reengage with psychosocial demand [25, 30, 33], and thereby make functional recovery after hospital discharge more challenging [75]. Finally, episodes of psychosis and chronic substance misuse contribute to an erratic course of development [61, 62]. The emotional and behavioral lack of control associated with substance use and psychosis diminishes the likelihood of obtaining psychosocial adjustment later in life [61, 62]. Taken together, all of these factors carry direct effects on psychosocial functioning and development in BD.

4. The Link between Cognitive Dysfunction and Illness Severity

The direct impact of cognitive impairment and illness severity on psychosocial functioning in BD may be compounded by the potential synergy between these factors. An increasing volume of studies indicate a robust association between illness severity and cognitive functioning in BD [40, 76, 77]. In particular, the number of mood episodes negatively correlates with cognitive functioning in a number of domains, including executive functioning and verbal memory [78]. In addition, cognitive dysfunction in BD is associated with the number of hospitalizations and the duration of mood episodes [77, 79]. These studies advanced the hypothesis that a more severe course of illness leads to progressive cognitive decline in BD in a process that may involve neurodegeneration [76, 80].

The neurodegenerative hypothesis holds that chronic mood instability generates physiological stress with neurotoxic effects, leading to neurological damage and cognitive decline over the course of illness [76, 80]. Within this model, Kapczinski et al. [80] applied the notion of “allostatic load” (AL) to BD. AL generally refers to the “wear and tear” of biological systems that occurs during physiological adjustment to stress, whereby this process becomes distorted and no longer efficient. In biomedicine, the concept of AL

captures the biological toll of adaptation to excessive stress [81]. The higher rates of morbidity and mortality found in people with BD due to medical conditions not directly related to their psychiatric disorder, such as cardiovascular disease, obesity, diabetes mellitus, and metabolic syndrome [82–84], evince the deleterious physiological effects of stress in BD [85, 86]. Evidence for possible effects of stress on the brain comes from neuroimaging studies that found morphological abnormalities in BD [87]. In a recent review, Arnone et al. [87] concluded that BD is associated with whole brain and prefrontal lobe volume reductions, along with volume increases of the lateral ventricles. There is evidence that these and related brain abnormalities in BD are associated with both cognitive [88] and psychosocial decline [89]. Taken together, these studies suggest a stress-related cognitive, neurological, and psychosocial decline in people with BD who suffer from a more severe course of illness.

From a broader perspective, the link itself—between illness severity and neurocognitive decline—may aggravate the direct effects that each of these factors have on psychosocial functioning in BD. Thus, a more severe course of illness reduces psychosocial functioning in BD and simultaneously decreases neurocognitive functioning, which then also directly lowers functional outcomes. Thus, the two factors that have the strongest direct effect on psychosocial functioning in BD may be looped together in a way that accelerates functional decline.

5. Anxiety

BD has a particularly high rate of comorbid anxiety disorders estimated at over 50% in several studies [90, 91]. Intense anxiety in BD predicts a more severe course of illness and poor prognosis [92, 93]. A number of studies found that people with BD who suffer chronic anxiety tend to have a younger age of onset, longer and more frequent mood episodes [94, 95], higher prevalence of substance use disorders [96], decreased response to lithium and anticonvulsant medication [92, 94, 97], and increased suicidal ideation and attempts [98]. Coupled with illness severity, comorbid anxiety disorders strengthen the prediction of poor functional outcome in BD, as indicated by lower GAF scores, decreased social role functioning, poorer quality of life, and minimal employment [95, 99, 100].

Anxiety, which may reflect a natural emotional reaction to the instability that inheres in severe psychiatric disorders, may also exacerbate illness severity and functional deterioration through relatively underinvestigated pathways. One such pathway may involve the potentially negative impact of anxiety on cognitive functioning [101]. High levels of anxiety can significantly compromise attentional control and decision making even in nonpsychiatric populations [102, 103]. Well-designed studies indicate that neuropsychological test scores, across 6 cognitive domains, tend to be particularly sensitive to hypothalamic-pituitary-adrenal (HPA) axis dysregulation and elevated levels of cortisol [103, 104]. The HPA axis in BD can be dysregulated across all clinical states, including euthymia [105, 106], and may

affect cognitive functioning. Thus, HPA axis dysregulation can lead to debilitating cognitive impairment not only through the neurotoxic effects of inordinate allostatic loads, but more directly through excessive sympathetic arousal, triggered by the cognitive challenges of daily living. In short, it seems feasible to hypothesize that acute anxiety may compromise cognition in BD. Anxiety can potentially make baseline cognitive impairment circumstantially more acute and thereby further decrease functional abilities.

Another pathway in which anxiety may compromise psychosocial function in BD could be related more specifically to the encounter between cognitive impairment and demand in psychosocial contexts. This encounter may produce anxiety, especially when the person is unable to meet expectations in highly visible social circumstances. Thus, while anxiety compromises cognition, cognitive challenges in a cognitively compromised state can trigger anxiety. Even in nonpsychiatric populations, cognitive challenges significantly increase anxiety and physiological arousal [101]. Physiological anxiety in nonpsychiatric subjects increases during cognitive testing and rises even further when subjects make errors [107]. These effects are more intense in people who suffer from mental illness or substance use disorders, even during remission or abstinence [108, 109].

Since the most common behavioral reaction to anxiety is avoidance [110], people with BD who experience cognitive impairment may tend to withdraw from psychosocial demands that evoke anxiety to decrease their experiences of social failure. More broadly, the encounter between cognitive impairment and demand in daily life can create anxiety that exacerbates cognitive deficits, limits functional ability, reduces motivation, and leads to avoidance of psychosocial engagement. In schizophrenia research, several studies suggest that an avoidant coping style mediates the link between neurocognitive impairment and psychosocial functioning [111, 112]. Although there is little direct evidence that psychosocial avoidance plays a similar role in people with BD, this hypothesis remains viable, given the similarities between cognitive impairment in BD and schizophrenia [111, 113]. In summary, the interplay between anxiety and cognitive impairment may further limit functional capacities and exacerbate psychosocial decline in BD.

6. Diathesis-Stress

Various diathesis-stress [86, 114] and related models [115, 116] in BD research highlight the interactions between genetics and environmental stress as important predictors of illness onset and severity. These models broadly hold that cumulative environmental stressors trigger a person's genetic predisposition to experience mood disturbance and affect the progression of the illness after onset [117, 118]. In a recent review, Bender and Alloy [114] examined evidence for three of these models—the kindling hypothesis of illness progression in BD [119], the behavioral approach system (BAS) dysregulation model [120], and the social rhythm disruption (SRD) model [121].

The kindling hypothesis asserts that major stressful life events (SLEs) are required to trigger initial episodes in BD, but then, subsequent episodes become progressively uncoupled from stressors, to the point that future episodes may appear to occur independent of life stress. The kindling model is supported by multiple studies that found major SLEs occurring particularly in the year before the first episode of mood disturbance [114, 115, 121] or early on in the course of illness [122]. However, Bender and Alloy [114] found that many of these studies were methodologically flawed and offer only limited support to the widely cited kindling hypothesis.

The BAS dysregulation model is based on research showing that behavior is regulated by goals and rewards (when faced with goal-related cues) and a behavioral inhibition system (BIS) that triggers avoidance when a person is faced with cues related to threat or punishment [114, 120]. There is some evidence that in persons with BD, the BAS may be hyper-sensitive such that goal-related cues may trigger hypomanic behavior, while threat-related cues may trigger depression [114, 120].

The SRD model of diathesis stress is supported by several studies finding that SLEs, in combination with genetic differences, predict manic and depressive symptom recurrence [123] and delay in functional recovery [124] over the course of illness. On the side of genetics, Hosang et al. [125] found that for the worst depressive episodes in BD, stressful life events (SLEs) were significantly moderated by BDNF genotype—Val⁶⁶Met polymorphism. On the side of environmental stress, diminished perceived social support and psychosocial stress appear to be particularly predictive of mood instability in BD [123, 126–128]. In this regard, there is evidence that SRD and disruption to the attainment of psychosocial goals are associated with the number of reported manic episodes [121, 129]. In addition, social rhythm irregularity predicts time to affective relapse [121], and there is some evidence that persons diagnosed with BD experience higher numbers of SLEs and greater SRD than people without psychiatric illness [130]. Taken together, these studies point to the possible development of a reciprocal loop between SRD and mood symptoms, in which SRD aggravates the genetic propensity toward mood disturbance, and mood symptoms in turn exacerbate SRD.

In sum, these findings suggest that genetics carry an important influence on illness severity in BD, that SRD is a particularly destabilizing source of stress for people with a genetic predisposition toward BD, and that people with BD experience more psychosocial stress than people without mental illness. These factors may be central to understanding functional decline in BD. SRD alone, by definition, disrupts psychosocial functioning. Its effects in BD, however, might be compounded by the association between SRD and the recurrence of genetically triggered mood instability, which imposes a powerful and direct impediment to psychosocial development.

7. The Integrated Model

Previous research illuminated many aspects of illness progression in BD, including factors that contribute to

morbidity and psychosocial disability. This paper examines the effects of illness severity, cognitive impairment, anxiety, genetics, and psychosocial stress on functional outcome in BD. The interplay among these factors may be complex and involve reciprocal pathways. Figure 1 presents 13 possible interconnected pathways that potentially trap people with BD in a malignant cycle that accelerates psychosocial decline. The numbers that appear on the arrows in the figure match those of the pathways described below.

Pathway 1. There is a strong genetic component in BD that influences the onset, severity, and progression of the illness.

Pathway 2. The symptoms of BD have a direct impact on psychosocial functioning. Recurrent mood disturbance, lingering residual symptoms between episodes, hospitalizations, comorbid substance use disorders, and psychosis disrupt the consistency of psychosocial engagement required for functional development.

Pathway 3. Recurrent episodes of mood disturbance result in chronic physiological stress related to the hyperarousal of the autonomic nervous system and HPA axis.

Pathway 4. The physiological effects of stress are neurotoxic and lead to cognitive decline over time.

Pathway 5. Cognitive impairment in general, and executive dysfunction in particular, hampers the ability to meet psychosocial demand.

Pathway 6. The difficulty in meeting psychosocial demand creates disruption to social rhythm and increases environmental stress.

Pathway 7. Environmental stress in general, and psychosocial stress in particular, aggravates the phenotypic expression of mood disturbance, leading to a more severe course of illness.

Pathway 8. The consequent intensification in symptoms and their recurrence exacerbate the disruption to social rhythm and environmental stress.

Pathway 9. Psychosocial stress contributes to chronic hyperarousal of the autonomic nervous system and HPA axis.

Pathway 10. Repeated experiences of psychosocial failure intensify anxiety related to psychosocial demand.

Pathway 11. Anxiety has acute effects on cognitive functioning during psychosocial challenges. Superimposed on cognitive impairment, anxiety further compromises attentional control and executive functions.

in fact, aggravate it [133, 134]. Although medication can improve psychosocial functioning in BD in general by ameliorating affective symptoms [135], pharmacological interventions alone may not have sufficient power to overcome the destabilizing effects of psychosocial demands that exceed the person's functional capacities [7].

People with BD who strive to flourish against a current of psychosocial demand that is too stressful for their genetic level of stress tolerance may ultimately experience exhaustion, intense anxiety, and decompensation [7, 136]. Hospitalization may help to temporarily alleviate this experience. In this process, the chemical effects of pharmacology often reduce mood symptoms within the custodial environment of inpatient care. However, discharging the person into the same unworkable situation may result in recurrent decompensation and a sizable increase in the number and dose of prescribed medications over time.

To remain stable under these circumstances, many people with BD may choose to disengage from the natural pursuit of psychosocial development and seek the protective benefits of disability. Initially, this may bring some relief; however, trading psychiatric symptoms for psychosocial disability may become problematic over time. The stagnancy and social marginalization that may be created by disability can be detrimental to a person's identity and self-esteem [66, 137–139]. As time passes, the developmental gaps from the person's cohort widen, and the consequent changes to the person's identity and belief system diminish the probability of reversing the trend from psychosocial decline to growth [140].

Aside from medication, psychosocial interventions and support groups are also vital to improving functional outcome in BD. Support groups and psychotherapy offer a context in which people can experience acceptance, appreciation and meaningful interpersonal connections. Some interventions such as interpersonal and social rhythm therapy (IPSRT) may also enhance psychosocial competence in BD [141].

At the same time, these efforts may not be powerful enough to override a misfit between genetic vulnerability to stress and psychosocial demand. If people are unable to maintain consistent social and professional growth that is commensurate with their potential outside therapeutic settings, their lives remain limited by psychiatric illness and functional disability.

To overcome this problem, clinicians working with BD may need to develop expertise in helping people identify psychosocial contexts that facilitate growth. Learning to conduct, or at least interpret, cognitive assessments with ecologically valid interpretations would likely be fundamental to this process [142]. Clinicians who understand the interplay between a given profile of cognitive deficits and particular environments may be able to guide people toward settings that increase the likelihood of psychosocial success. Clinicians may also be able to provide persons with BD ongoing guidance with respect to goal-related expectations, pace of progress, and workload [143, 144].

Moving from assessment to implementing recommendations regarding psychosocial adjustment for persons with BD will require clinicians to pay particular attention to the

anxiety related to psychosocial demand. The fear of repeated psychosocial failure can lead to the avoidance of functional challenges and to feelings of helplessness and hopelessness. Helping people with cognitive impairment and mood instability overcome the impediments these factors create may require a great deal of expertise and potentially even more highly specialized programs—for instance, an intervention may combine elements of IPSRT with vocational counseling tailored to BD [145], cognitive remediation [146], and other interpersonal therapy. Traditional practices of vocational counseling alone may not suffice.

The delivery of psychosocial interventions aimed at improving social and occupational outcomes needs to be particularly sensitive to cognitive impairment and residual symptoms. As previously noted, longitudinal studies show that two key predictors of future social and occupational functioning in BD are subsyndromal depressive symptoms and cognitive deficits, particularly in executive functioning [25, 31, 147]. Cognitive impairment and residual depressive symptoms in BD have also been found to correlate with each other, independent of other outcomes [148]. Manic and depressive residual symptoms that are present during early remission from a mood episode also predict relapse [149], while cognitive dysfunction impedes the effectiveness of psychosocial interventions designed to improve functioning [145, 150] and reduces treatment adherence [151].

Given the impact of both residual symptoms and cognitive impairment on functioning, and the correlation between them, a thorough assessment of each should be included as part of the standard of care in BD. With respect to cognitive functioning, patient reports may not provide a sufficient indication of cognitive status, as these show weak correlations with objective assessments [152]. To adequately identify cognitive dysfunction in BD, assessment using a standard neuropsychological battery may need to become routine, as cognitive deficits in BD typically do not present when evaluated with the minimal status exam (MMSE) [55] commonly used by clinicians.

In the future, identified cognitive deficits may be addressed to some degree with direct interventions including compensatory [146] and restorative cognitive remediation programs [153] both manualized [154] and computerized [155]. Meta-analyses have found small-to-medium effect sizes for improving cognition using restorative cognitive remediation programs in several psychiatric conditions including schizophrenia [153] and substance use disorders [155]. In BD, findings so far are limited to a small, uncontrolled study involving a compensatory cognitive skills training program [146]. This study found that traditional CBT aimed at reducing residual depressive symptoms, combined with sessions teaching compensatory cognitive skills, resulted in significant improvement in occupational outcomes for eighteen people with BD. Several clinical trials aimed at determining the efficiency and occupational outcomes of restorative cognitive remediation and pharmacological interventions in BD are ongoing [156, 157] and await conclusion.

Even when not directly targeted, cognitive deficits in BD may require that psychosocial interventions such as psychoeducation be delivered in a highly structured manner

that accommodates cognitive disability [145, 158, 159]. Multiple findings indicate that psychoeducational interventions aimed at relapse prevention are effective and may improve functioning in BD, highlighting the need for these interventions to be accessible to the cognitively impaired [159]. Finally, psychoeducation regarding cognitive impairment itself may help persons with BD learn supportive techniques and strategies to compensate for such deficits in occupational settings [146].

After clients take action to re-engage in occupational pursuits, counselors may need to help them persevere in the face of the natural frustrations that accompany efforts to obtain psychosocial accomplishments on an alternative schedule. Counselors may also need to assess and monitor the person's stress effectively. Taking significant steps toward psychosocial development in BD is desirable but can increase stress, and thus lead to relapse. Clinicians will likely be challenged to help clients manage the stress without abandoning their quest for psychosocial growth or resigning themselves to a state of disability.

Given all of these challenges, progress toward psychosocial growth in BD may well be inconsistent. In many cases, a successful outcome of counseling would be to keep the growth from being eliminated completely in the face of recurring symptoms. Ultimately, a positive trend in psychosocial growth may be more important than measuring any one sizable change in outcome. Mild but valued movement toward growth with manageable stress may prove to be an effective mood stabilizer. Conversely, the absence of psychosocial growth may lead to a malignant decline in functioning.

Finally, further advances in functional outcomes for persons with BD will probably require changes in the social climate. At present, few mainstream environments accommodate the special needs of people with BD. Moreover, stigma and discrimination against people with mental illness in the workplace remain major obstacles for psychosocial growth in BD [66, 68, 137, 160, 161]. Consequently, in most settings, the intensity of functional demands and inhospitable atmosphere may be too stressful to negotiate with sufficient long-term consistency. In the absence of ongoing support, the chronic mismatch between the functional limitations of persons with BD and the environmental demands they face greatly impedes their psychosocial adjustment and development. Developing effective support for psychiatric disability in mainstream settings may, therefore, improve clinical and functional outcomes. More broadly, mainstream support and an inclusive shift in social climate may be essential for curbing the downward psychosocial spiral that so many people with BD experience after illness onset.

In conclusion, the factors that contribute to psychosocial impairment in BD may be looped together in intricate ways, creating an effect that traps people in a course of functional decline. Altering this downward trajectory may require both searching for and actively creating psychosocial environments that are hospitable to the specific needs of people who suffer from BD. In basic conception, psychosocial disability is environmentally dependent and not a constant. For this reason, in addition to medications and conventional forms

of therapy, a strategic approach that enhances the goodness of fit between persons with BD and their psychosocial environment may change their possible functional outcomes. Most importantly, improving this fit may shift the lifelong path of persons with BD from malignant psychosocial decline to growth.

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Review Article

Self-Referential Thinking, Suicide, and Function of the Cortical Midline Structures and Striatum in Mood Disorders: Possible Implications for Treatment Studies of Mindfulness-Based Interventions for Bipolar Depression

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Bipolar depression is often refractory to treatment and is frequently associated with anxiety symptoms and elevated suicide risk. There is a great need for adjunctive psychotherapeutic interventions. Treatments with effectiveness for depressive and anxiety symptoms as well as suicide-related thoughts and behaviors would be particularly beneficial. Mindfulness-based interventions hold promise, and studies of these approaches for bipolar disorder are warranted. The aim of this paper is to provide a conceptual background for such studies by reviewing key findings from diverse lines of investigation. Results of that review indicate that cortical midline structures (CMS) appear to link abnormal self-referential thinking to emotional dysregulation in mood disorders. Furthermore, CMS and striatal dysfunction may play a role in the neuropathology underlying suicide-related thoughts and behaviors. Thus, combining studies of mindfulness interventions targeting abnormal self-referential thinking with functional imaging of CMS and striatal function may help delineate the neurobiological mechanisms of action of these treatments.

1. Introduction

The neurobiology of bipolar spectrum disorders is incompletely characterized [1]. Further, current medication treatments are only partially effective [2], and 73% of patients receiving pharmacotherapy relapse within 5 years [3]. Thus, there is a compelling need for effective adjunctive psychotherapy interventions [4, 5]. Cognitive-behavioral therapy is an effective intervention for depression [4, 6–9] but seems to be of less benefit for bipolar spectrum illness [10]. Bipolar disorder is highly comorbid with anxiety [11, 12], and therefore interventions that also target anxiety might be of particular benefit [13]. Mindfulness-based psychotherapies are being increasingly used to target both depressive and anxiety symptoms in a variety of clinical populations [14–16]. However, few studies [17–19] have investigated these

interventions for bipolar spectrum disorders. Furthermore, an integrated conceptual framework for such studies has not been published.

Mindfulness interventions target aberrant self-referential thinking [20]. Increasing evidence suggests that alterations in self-referential thinking may be associated with a number of mood and anxiety spectrum disorders. For example, investigations indicate an association between aberrant self-concept and/or self-schemas and unipolar depression [21–25], generalized anxiety disorder [26], obsessive-compulsive disorder [27, 28], PTSD [29–31], social phobia [32, 33], and panic disorder [34]. There is evidence that anomalous self-referential thinking is also associated with bipolar spectrum disorders [35–40]. Many studies also indicate that negative self-concept is associated with suicidal behavior [41–51]. One specific brain region, much of the medial

cortex, is associated with self-referential processing [52, 53]. Some studies have found aberrations in this region to also be associated with suicide [54–57]. Thus, functional abnormalities in medial cortex may be particularly relevant for both self-directed thinking and suicidal behaviors in bipolar spectrum disorders. Studies of this region may be important to completely characterize the neurobiology of these conditions. Furthermore, treatment interventions that target self-referential thinking may have the potential to be efficacious for both decreasing mood symptoms and preventing suicidal behavior. This paper provides an overview of relevant key studies. The goal is to integrate results from diverse lines of investigation and provide a conceptual framework for future studies of self-referential thinking and mindfulness-based interventions in bipolar spectrum disorders.

2. Self-Focused Thinking and Mood Disorders

There is evidence that the processing of self-referent information is abnormal in both unipolar and bipolar spectrum illness [35, 39, 58, 59]. For example, anomalous self-schemas (beliefs and ideas about self) form the basis for Beck's classic approach to depression [60]. These cognitive theories suggest that psychological symptoms can occur as a result of dysfunctional schemas [61–63]. Schemas are believed to be lasting cognitive structures held in memory that organize thoughts, emotions and behaviors into stable patterns [61]. It has been hypothesized that dysfunctional self-schemas could lead to negative beliefs about self and thus mood symptoms. Multiple studies have focused on the relationship of negative self-esteem and/or schemas to depression [21–25, 58, 64–73], and the effectiveness of interventions targeting negative schemas through cognitive therapy is well established [4, 6–9]. Finally, self-criticism is associated with depression [74–76]. In regard to bipolar spectrum disorders, many [35–38], but not all [77], investigations indicate that aberrant self-concept/schemas are also a characteristic of these conditions. Altered self-esteem persists during remission [35, 39] including instability of self-concept [36], which may represent a vulnerability to mood episodes. Finally, a recent study found that higher self-esteem corresponded to better prognosis in refractory bipolar disorder [40].

In addition to abnormalities of self-concept, other facets of self-referential thinking are associated with affective disorders. One of these is the amount of time spent thinking about self. Individuals with unipolar illness have increased self-focused thinking [78, 79]. The association between the extent of thinking about self and depressive symptoms is undoubtedly complex, and cause and effect relationships may be difficult to determine. However, excessive self-focus in general is associated with negative affect [80], and high levels of self-focus are thought to contribute to depressive pessimism [81]. Finally, cognitive impairment in depression may be associated with increased self-focus [82]. Therefore increased time spent thinking about self might directly contribute to depressive symptoms, at least in unipolar illness.

We are not aware of any studies that have directly addressed this question in bipolar spectrum illness.

In contrast to the extent of self-referential thinking, there is strong evidence that a particular type of thinking about self contributes to dysphoria in general and unipolar depression. Specifically, analytical self-focused rumination (thinking analytically about self and symptoms) is maladaptive [83]. This cognitive style is associated with overgeneral autobiographical memory [84], global negative self-judgments [85], greater negative future thinking [86], and dysphoria [87, 88]. Furthermore, there is compelling evidence that ruminative self-focus is associated with both the severity and duration of depressive symptoms [89–95] as well as relapse of illness [96]. There is less research investigating the role of rumination in bipolar spectrum illness, but some evidence suggests that rumination is associated with these conditions as well [97, 98]. Importantly, one study [97] found that rumination predicted the number of depressive episodes, which suggests that treatments targeting rumination might be effective for relapse prevention in bipolar spectrum illness.

In summary, considerable evidence indicates that alterations of self-referential thinking are associated with both unipolar and bipolar spectrum illness. One component is negative self-concept, which is likely associated with depression, regardless of diagnosis. Another facet is rumination about self. In particular, analytic self-focused rumination is maladaptive and may represent a treatment target for bipolar spectrum depression. The implications of this will be discussed in the sections that follow.

3. Self-Focused Thinking, Rumination, and Suicide-Related Behaviors

As described above, cognitive theories suggest that suicidal ideation, and other psychological symptoms, can occur as a result of dysfunctional self-schemas and thus negative self-focused thinking [61–63]. As with symptoms of depression, there is considerable evidence of an association between self-referential thinking and suicidal behaviors. Numerous studies have reported an association between self-concept and suicide-related behaviors in a variety of populations [41–51]. Most, but not all [99], suggest that low self-esteem and/or negative beliefs about self are risk factors for suicide or suicidal ideation. In contrast, evidence suggests that positive self-appraisals may confer resilience to suicide [100]. Additionally, individuals who attribute negative life events to external, transient, and specific factors are at decreased risk of suicidal ideation as compared to those who explain undesirable outcomes on internal, stable, and global self-characteristics [101]. However, the relationship is complex because there is evidence that self-esteem is decreased by suicide ideation and suicide attempt history [102]. Therefore a dynamic association may exist such that negative self-concept and suicidal behaviors are mutually reinforcing over time whereas positive self-referential thinking inhibits suicidal thinking/behaviors.

In addition to low self-esteem, other aspects of self-referential thinking patterns have been shown to be associated with suicide. For example, suicide has been posited to serve as an escape from awareness of self [103] and research provides support for this hypothesis [104–106]. According to this model, outcomes that fall short of one's standards and expectations for self are interpreted (self-criticism) as personal inadequacies. This attribution causes self-awareness to become painful and generate negative affect. Suicidal thoughts and behaviors can then occur in response to the individual's desires to escape from both self-awareness and the associated unpleasant affect. Thus, a personality trait of higher levels of self-criticism is likely a risk factor for suicide-related behaviors [104, 106].

Automatic self-associations are another important facet of self-referential thinking. Both automatic associations and explicit beliefs reflect aspects of dysfunctional self-schemas likely related to suicidal thinking. Automatic associations reflect simple associations in memory that activate links between self and specific concepts as opposed to the more complex development of explicit beliefs [107]. It has been shown that automatic self-associations of depression and anxiety are significantly related to both suicidal ideation and past suicide attempts [61].

Automatic self-associations are clinically relevant because they are associated with both symptom expression [108, 109] and uncontrolled behaviors [108]. Thus, these associations are thought to drive some spontaneous psychopathological behaviors and contribute to the persistence of psychopathological symptoms [61, 110]. The association between dysfunctional automatic self-associations and suicidal ideation [61] therefore suggests that these self-associations may contribute to the onset and maintenance of suicidal ideations as well as the difficulty of controlling these thoughts. Automatic associations of self with death are also associated with suicide [111], which suggests another link between this type of memory processing and suicidal thoughts and behaviors.

Finally as is the case for depressive symptoms, there is compelling evidence that rumination is directly associated with suicidal ideation [112–118]. Furthermore, ruminative thinking may partially mediate relationships between both self-criticism [117] and negative life events [118] with suicidality. Rumination leads to greater negative future thinking [86] which might also contribute to suicidal ideation.

The literature reviewed above provides strong evidence that aspects of self-referential thinking are related to suicidal ideations and behaviors in a variety of populations. Few studies have directly addressed this topic among subjects with bipolar spectrum disorders. However, some evidence indicates that facets of self-focused thinking are relevant to suicide in these conditions. For example, low self-esteem lasting into remission seems related to the expression of suicidality during depressive episodes of bipolar patients [119]. Another study suggests that increased ruminations may mediate the association between anxiety and suicidal ideation/behaviors [120]. Future studies are warranted, as it seems likely that self-referential thinking may be related to the expression of depressive symptoms and suicidality irrespective of diagnosis.

4. The Functional Architecture of Self-Focused Thinking in Mood Disorders

Most of the anterior and posterior midline cortex has been characterized as an anatomical and functional unit known collectively as the cortical midline structures (CMS) [52]. The CMS are thought to be important in affective disorders because of anatomical connectivity with the amygdala [121–125] and striatum [126], both of which are important for emotional processing. Further, the CMS has extensive involvement in both self-referential [52, 53] and emotional processing [127, 128], and these regions are components of the default mode network [129, 130].

Studies using a variety of methodologies suggest that functional alterations exist in the CMS in both unipolar [131–145] and bipolar [146–158] spectrum disorders. More importantly, a growing body of evidence directly links the CMS with both self-referential processing and emotional dysregulation associated with depression. A study of healthy controls demonstrated that self-referential processing activates the CMS and that this neural response is associated with negative affectivity [159]. In unipolar illness, studies indicate that abnormal self-referential processing is mediated by neural response in cortical and subcortical midline structures [134, 160]. Abnormal CMS neural response during emotional processing has also been demonstrated in unipolar illness [127, 160]. Furthermore, depressed subjects have increased neural activity during rumination in the CMS, amygdala, and other regions [161]. Finally, depressive symptoms are associated with the degree of CMS activity during a self-negative judgment task [160]. Thus, a growing body of evidence directly links CMS function to self-referential thinking and rumination in unipolar illness, and it appears likely that CMS structures play a key role in mediating the relationship between excessive self-referential thinking and negative affect.

The potential role of the CMS in emotional dysregulation and self-referential thinking is not as well characterized in bipolar spectrum disorders. However, a number of function imaging studies using emotional activation paradigms suggest a relationship between CMS function and emotional dysregulation in depression [147, 148, 155], mania [156–158], as well as euthymia [162]. Most investigations have studied bipolar I disorder; however, our group recently reported evidence of CMS-mediated emotional dysregulation in bipolar II disorder [153]. Finally, there is also some evidence of changes in CMS activation associated with treatment response [152, 163–165]. To our knowledge, aberrant self-referential processing in bipolar disorder has not yet been investigated using functional neuroimaging methods.

In summary, compelling functional imaging evidence indicates that CMS dysfunction in unipolar illness is associated with self-referential thinking and emotional regulation in unipolar illness. Further, the CMS likely mediates interactions between self-focused cognitions and emotional symptom expression. In bipolar disorders, considerable evidence indicates that CMS function is related to emotional dysregulation. Neuroimaging studies of self-referential processing in bipolar spectrum conditions are warranted.

5. The Role of the Striatum and CMS in Suicide-Related Thoughts and Behaviors

A large literature documents the role of striatal and associated corticobasal ganglia circuitry dysfunction in affective disorders, see [166, 167] for recent reviews. Recent studies also implicate striatal dysfunction in the neurobiology of suicide-related thoughts and behaviors in both bipolar [168] and unipolar spectrum disorders [169–171] as well as among those with alcohol dependence [172]. In regard to the CMS, there is structural, functional imaging [54] and molecular [55–57] evidence that dysfunction in this region may also be related to suicide.

The striatum and CMS have extensive anatomical [126, 173] and functional [174] connectivity. Importantly, striatal-CMS connectivity has been shown to be disrupted in bipolar II depression [168]. Finally, aberrant functional connectivity of the striatum with the posterior medial cortex has been shown to correlate with depression severity [168].

Taken together, these studies suggest that both CMS and striatal dysfunction may be relevant for suicide. Future investigations of the potential role of these regions in suicide-related behaviors are warranted. In particular, additional investigations of functional connectivity between the two regions may provide important insights.

6. Implications for Studies of Self-Referential Processing and Suicide in Bipolar Spectrum Depression

A primary aim of this manuscript is to integrate results of diverse key studies in order to provide a conceptual framework for future investigations of bipolar depression. Conclusions from the investigations reviewed herein are summarized in Table 1.

It is now well established that aspects of aberrant self-referential thinking contribute to the symptoms of unipolar depression. The strongest evidence is for analytical self-focused rumination. However, the amount of time spent thinking about the self may also be relevant. Studies clearly demonstrate that CMS play primary role in self-referential thinking. Additionally, there is strong evidence the CMS dysfunction plays a direct role in emotional dysregulation in unipolar depression and likely mediates the relationship between self-focused thinking and emotional dysregulation in this disorder. Finally, abnormalities of both the striatum and CMS may contribute to suicide risk in affective illness and the functional connectivity between the new regions may be of particular relevance.

In regard to bipolar disorder, there is relatively strong evidence of aberrations of both self-referential thinking and CMS function. Further, CMS dysfunction appears to be associated with deficits of emotional regulation. It is unclear if self-focused thinking and emotion dysregulation are linked by the CMS, as is the case for unipolar depression. However, this possibility clearly warrants investigation. Studies of the potential roles of both the striatum and CMS in suicide are indicated as well.

Future studies, as suggested above, may enhance our understanding of the neurobiology of bipolar depression. More importantly, it is possible that a subregion of the CMS might mediate relationships between self-referential thinking, emotional dysregulation, and suicidality. Such a finding would likely be very relevant for the development of bio markers as well as treatment interventions.

7. Implications for Bipolar Depression Treatment Studies Using Mindfulness Interventions

The studies reviewed herein have implications for studying neurobiological mechanisms in bipolar depression as described above. More importantly, these investigations support studies of mindfulness-based treatment interventions that specifically focus on altered self-referential processing.

There is not yet complete consensus as to how the concept of mindfulness should be properly operationalized in Western psychology, and such lack of consensus is reflected into the multiplicity of definitions of mindfulness employed by different authors concerned with mindfulness-based interventions, for example [175]. However, mindfulness is usually described as a practice through which one learns to focus attention on moment-by-moment experience with an attitude of curiosity, openness, and acceptance. Practicing mindfulness is simply experiencing the present moment, without trying to change anything [20, 176]. During mindfulness, awareness is focused on external sensory inputs, such as auditory, olfactory, and visual stimuli, as well as internal sensations, such as proprioception and pain. Furthermore, attention is specifically focused on awareness of the internal workings of the mind [20].

Although an increasing number of mindfulness-based interventions are currently employed for a large variety of psychiatric disorders, two such interventions, mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), have proven to be particularly fruitful approaches for many of these conditions. The concept of mindfulness originated in Buddhist spiritual practices [177]; however, both MBSR and MBCT are secular, clinically based methods utilizing manuals and standardized techniques. MBSR was developed by Dr. Kabat-Zinn at the University of Massachusetts Medical Center [20]. MBSR includes education about stress as well as training on coping strategies and assertiveness in addition to mindfulness. The mindfulness component includes sitting meditation, a body scan (focusing on bodily sensations), and Hatha Yoga. MBSR involves the cultivation of a number of attitudes, including becoming an impartial witness to one's own experience and acceptance of things as they actually are in the present moment [20]. MBCT was developed by Segal et al. [178]. MBCT is based upon MBSR and combines the principles of cognitive therapy with those of mindfulness to prevent relapse of depression. MBCT, like MBSR, utilizes secular mindfulness techniques including seated meditation. The program specifically teaches recognition of deteriorating mood with the aim of disengaging from self-perpetuating

TABLE 1: Conclusions from studies reviewed.

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- (i) Abnormalities of self-referential processing are likely a general characteristic of mood disorders
 - (ii) Increased self-focused thinking may contribute to depressive symptoms
 - (iii) Analytical self-focused rumination clearly contributes to the manifestation of depression in unipolar illness and possibly in bipolar spectrum depression
 - (iv) Aspects of aberrant self-focused thinking (particularly rumination) likely contribute to suicide-related behaviors and thoughts in unipolar depression
 - (v) The cortical midline structures (CMS) play a key role in both self-referential thinking and emotional regulation
 - (vi) Functional abnormalities of the CMS are likely a characteristic of mood disorders in general
 - (vii) In unipolar illness, CMS function plays a role in dysregulation of both self-referential thinking and emotion and likely mediates the relationship between the two
 - (viii) Dysfunction of both the striatum and CMS are likely involved in the neurobiology of suicide-related thoughts and behaviors
 - (ix) Abnormal functional connectivity between the striatum and CMS may be relevant for both the expression of both depressive symptoms and suicide
-

patterns of ruminative, negative thought that contribute to relapse [178].

A very large literature supports the effectiveness of MBSR on several psychological outcomes. Examples include studies of social anxiety disorder [179], generalized anxiety disorder [180], insomnia [181], psychological functioning among individuals with a large variety of medical disorders [182–186] including fibromyalgia [187, 188], cancer [182, 186, 189–192], gay men living with HIV [193], and pain [183, 187, 194–197] as well as healthy individuals [198]. Evidence indicates that MBCT is beneficial for unipolar depression relapse prevention [199–204], generalized anxiety disorder [180], panic disorder [205], hypochondriasis [206], and social phobia [207]. The strongest evidence is for relapse prevention in unipolar illness. A recent meta-analysis [208] concluded that MBCT was significantly better than usual care for reducing relapses in those with three or more prior episodes. Additional conclusions were that effectiveness for relapse prevention was similar to antidepressants at one year and that augmentation with MBCT could be useful for reducing residual depressive symptoms. A subsequent study [204] provided compelling evidence confirming that for depressed patients, MBCT offers protection against relapse equal to that of maintenance antidepressant pharmacotherapy. Further, a recent review and meta-analysis [15] specifically addressed the effectiveness of MBSR and MBCT (and similar interventions) for reducing symptoms of anxiety and depression. The authors concluded that mindfulness-based therapy improves symptoms of anxiety and depression across a wide range of severity and even when these symptoms are associated with other disorders [15]. This study supports the use of these interventions for acute treatment as well as relapse prevention. Finally, there is evidence of effectiveness of MBCT for depression among both symptomatic and partially symptomatic patients [209].

These studies suggest that both MBSR and MBCT have broad-spectrum antidepressant and antianxiety effectiveness. Furthermore, preliminary evidence suggests that MBCT is feasible for use in bipolar disorder and may decrease symptoms of anxiety and depression [17–19]. Of note, one of these investigations [17] specifically studied

individuals who had previously experienced serious suicidal ideation. Finally, evidence is accumulating in support of the use of mindfulness interventions for suicide prevention [210–213], and additional research is ongoing [214].

The studies cited above indicate that additional trials of mindfulness interventions for bipolar spectrum disorders are warranted. In particular, studies of acute and maintenance treatment of depressive and anxiety symptoms as well as suicide prevention are warranted.

The possibility that mindfulness interventions may help prevent suicide is particularly intriguing. In bipolar spectrum disorders, severity of affective episodes [215] comorbid panic [216], and psychosocial stress [217] are suicide risk factors. Thus, mindfulness interventions might decrease suicide risk through more than one mechanism.

8. Neuroimaging of Mindfulness: Implications for Studies of Bipolar Depression

Neuroimaging studies of mindfulness add to the evidence supporting trials of mindfulness interventions for bipolar depression. Furthermore, these studies suggest specific investigations that could be aimed at exploring the neural mechanisms underlying any observed benefits.

As described above, the CMS play a key role in both self-referential and emotional processing [52, 53, 127, 128]. Further, evidence indicates that CMS structures play a direct role in mediating the relationship between self-referential thinking and negative affect in mood disorders [127, 134, 147, 148, 153, 155–162]. A number of structural and functional neuroimaging as well as electroencephalogram (EEG) studies have provided information about the neural processes underlying mindfulness practices. Some key findings are reviewed herein, for a more detailed recent review, see [218].

Zen meditation is a mindfulness practice that has been studied using neuroimaging methods. Zen is a traditional Buddhist approach to mindfulness [219, 220]. Zen primarily involves the practice of developing mindfulness by way of seated meditation [219, 220]. During meditation periods,

known as Zazen, practitioners sit silently without moving on either a cushion or in a chair [220]. It is important to note that while Zen meditation is a Buddhist practice, it is frequently practiced as a secular means to achieve mindfulness [221].

A number of investigations indicate that Zen meditation induces changes in brain function measurable by both functional MRI (fMRI) and EEG [222–228]. One fMRI study [228] of regular Zen practitioners and matched control subjects found that Zen practitioners displayed a reduced duration of the neural response linked to conceptual processing in regions of the default network, including a portion of the CMS. The authors concluded that that meditative training fosters the ability to control the automatic cascade of semantic associations triggered by a stimulus or, in other words, voluntarily regulate the flow of spontaneous mentation. This study suggests that the practice of Zen meditation may facilitate the ability to regulate self-referential thinking by consciously modulating the function of the CMS and other brain regions.

In addition to functional changes, evidence also indicates that extended Zen practice is associated with changes in brain morphology. In one study [229], structural MRI scans were performed and pain tolerance was assessed in meditators and controls. Meditators had significantly lower pain sensitivity than controls. Furthermore, meditators were found to have thicker cortex in a CMS region (dorsal anterior cingulate) and other areas and more years of meditation experience was associated with thicker gray matter in the anterior cingulate. This study provides compelling evidence that a mindfulness practice can impact CMS structure in addition to effects on function as demonstrated by other studies [222–228]. Another study [230] examined how the regular practice of Zen meditation might affect the normal age-related decline of cerebral gray matter volume and attentional performance observed in healthy individuals. Structural MRI and a computerized sustained attention task were used to study regular practitioners of Zen meditation and controls. Control subjects displayed the expected negative correlation of both gray matter volume and attentional performance with age. However, in contrast, meditators did not show a significant correlation of either measure with age. The effect of meditation on gray matter volume was most prominent in the putamen. The authors conclude that these findings suggest that the regular practice of meditation may have neuroprotective effects and reduce the cognitive decline associated with normal aging.

Several studies of mindfulness and other meditation practices also indicate these methods impact CMS function [231–235]. For example, Vipassana is a mindfulness technique that has similarities to Zen meditation, but has a particular focus on introspection, contemplation, and the development of insight [236]. An fMRI study [235] of this practice also revealed differences in CMS activation among meditators as compared to controls.

In addition to the investigations described above, MBSR has also been studied using functional and structural neuro imaging. One study [237] found that prior to MBSR

training, experiential focus (mindfulness) was associated with decreased CMS activation as compared to narrative focus. After MBSR training, experiential focus resulted in marked and pervasive reductions of CMS activation along with increased engagement of other regions. Further analyses demonstrated uncoupling of right insula and CMS connectivity in response to MBSR. This study provides compelling direct evidence that neural process underlying mindfulness involves both CMS activation and connectivity with other regions. Another study [238] recently demonstrated that this practice resulted in altered connectivity between anterior CMS regions and sensory cortex, which may indicate greater reflective awareness for sensory experience as a result of MBSR. In regard to structural imaging, recent studies [239, 240] indicate that MBSR, like Zen, also alters brain morphology. One study [239] found changes in gray matter concentration in the CMS as well as left hippocampus, the temporoparietal junction and the cerebellum. Thus in addition to impacting the CMS, mindfulness practices may decrease emotional reactivity by modulating other mechanisms as well. At least two other studies also support this conclusion. A recent study [179] reported decreased amygdala activation as a result of patients receiving MBSR for social anxiety disorder. Another study indicated that reductions in perceived stress correlated positively with decreases in right basolateral amygdala gray matter density in response to MBSR [240].

As described above, compelling evidence now exists demonstrating that mindfulness practices impact both the structure and function of the CMS as well as other regions. Furthermore, sadness is associated with CMS activation and mindfulness training changes the neural response associated with this emotion [241]. Taken together, the studies reviewed herein suggest a hypothesis of the neural mechanisms underlying any beneficial effects mindfulness practices may provide for bipolar depression. Specifically, these interventions likely exert benefit, at least in part, by modulating CMS functions associated with both self-referential thinking and emotional regulation. Thus, studies of mindfulness practices for bipolar disorder may benefit from a functional imaging component aimed at exploring CMS activation and connectivity. Such studies should also evaluate striatal function because meditation impacts this region [230, 232] as well as the fact that dysfunction of this area is associated with both affective illness [166, 167] and suicide [54–57, 168–172].

9. Conclusions

Bipolar disorder is a disabling [242–244] and difficult to treat [245–248] condition. In particular, bipolar depression is a source of considerable suffering [249, 250] and is often associated with anxiety [251, 252] and increased suicidal risk [249, 250, 253, 254]. Current treatments are often only partially effective [2], and relapse is a common occurrence [2, 3]. Adjunctive psychotherapy approaches are needed that are effective for

depressive and anxiety symptoms as well as suicide prevention.

Converging lines of clinical evidence reviewed herein indicate that mindfulness-based interventions, such as MBSR and MBCT, hold great promise as psychotherapeutic interventions for bipolar depression. From the clinical perspective, there is compelling evidence that MBSR and MBCT have broad-spectrum effectiveness for anxiety and depressive symptoms [15, 179–209]. Additionally, evidence now specifically indicates that MBCT is feasible for use in bipolar disorder and decreases symptoms of both anxiety and depression [17–19]. Finally, evidence is accumulating in support of the use of mindfulness interventions for suicide prevention [210–213]. Thus, investigations of mindfulness-based interventions for bipolar spectrum disorders are clearly warranted as these approaches have the potential to decrease symptoms of depression and anxiety as well as suicide risk.

In addition to the clinical evidence, psychological and neurobiological studies come together suggesting a hypothetical mechanism of action for mindfulness practices in the treatment of bipolar disorders. Specifically, the processing of self-referent information is abnormal in affective disorders [35, 39, 58, 59]. The CMS play a key role in both self-referential [52, 53] and emotional processing [127, 128], and a growing body of evidence indicates that CMS structures play a direct role in mediating the relationship between self-referential thinking and negative affect in mood disorders [127, 134, 147, 148, 153, 155–162]. Mindfulness interventions target aberrant self-referential thinking [20], and neuroimaging studies indicate that mindfulness practices impact both structure and function of CMS [228, 229, 231–235, 237–239]. Thus, these interventions likely exert benefit, at least in part, by modulating CMS functions associated with both self-referential thinking and emotional regulation. Studies of mindfulness practices for bipolar disorder should include a functional imaging component aimed at exploring CMS activation and connectivity. These studies should also evaluate striatal function because meditation impacts this region [230, 232] as well as the fact that dysfunction of this area is associated with both affective illness [166, 167] and suicide [54–57, 168–172]. Such investigation could provide important insights into how mental training can affect the cognitive and emotional dysfunctions typically observed in patients with affective disorders.

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