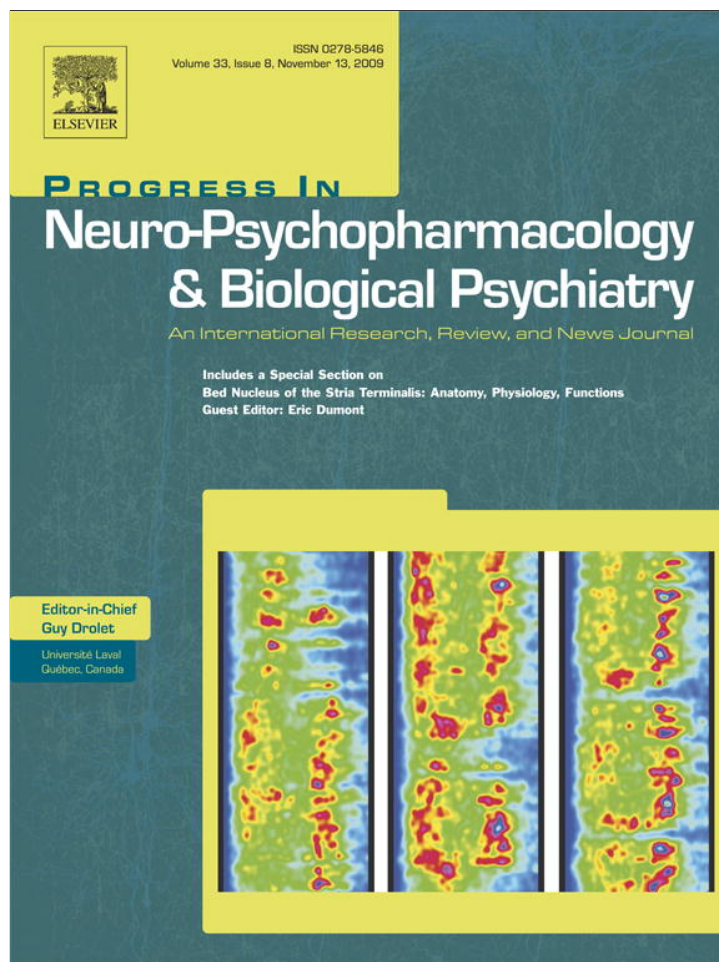


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Review article

The potential use of biomarkers as an adjunctive tool for staging bipolar disorder

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ABSTRACT

Recent data show that biomarkers differ in early and late-stage bipolar disorder (BD). Here we propose a model of staging for bipolar disorder that emphasizes the potential use of biomarkers for differentiating early and late-stage BD patients in the inter-episodic period. The proposed model includes a *Latent phase*: patients at “ultra-high-risk” for developing BD, characterized by a family history of BD, temperament traits, mood, and anxiety symptoms as well as genetic vulnerability for developing the disorder; *Stage I*: patients who return to their baseline level of functioning when mood episodes resolve; *Stage II*: biomarkers and functioning impairment are related to comorbidities or rapid-cycling presentations; *Stage III*: persistent cognitive and functioning impairment in the inter-episode period as well as changes in biomarkers; and *Stage IV*: same findings as in Stage III associated with extreme cognitive and functioning impairment, to the point that patients are unable to live autonomously. Empirical testing will determine the ability of the present model to inform patients and clinicians about both prognosis and response to treatment.

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1. Introduction

Staging models have well-recognized value for treatment and management of malignancies and many other medical diseases (Blechacz et al. 2009; Kameyama et al. 2009; Kyrtsolis et al. 2009; Rami-Porta et al. 2009). It has been suggested that clinical staging may be suitable to psychiatric disorders (McGorry et al. 2007) such as

Abbreviations: BD, bipolar disorder; BDNF, brain derived neurotrophic factor; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders — 4th edition; IL-6, interleukin-6; MRI, magnetic resonance imaging; NT3, neurotrophin-3; NT4, neurotrophin-5; TBARS, thiobarbituric acid reactive substances; TNF-alpha, tumoral necrosis factor-alpha.

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depressive disorders and alcohol dependence (Fekadu et al. 2009; Jockers-Scherubl et al. 2007; Langenbucher and Chung 1995) and bipolar disorder (Berk et al. 2007a,b). Staging models are useful when the disorder seems to follow a specific course, from an initial (apparently milder) presentation to a more severe and difficult-to-treat stages. This situation is common in many psychiatric disorders, including BD (Berk et al. 2007a).

A growing body of evidence indicates that BD has a much less favorable long-term outcomes than previously thought, with incomplete symptomatic recovery and persistent cognitive impairment (Martinez-Aran et al., 2004a,b) as well as significant overall functional impairment (Martinez-Aran et al. 2007; Rosa et al. 2007). The current model of staging in bipolar disorder (Berk et al. 2007a,b) suggests a progression from prodromal to more severe and refractory presentations engendered by the cumulative exposure to acute episodes. In addition, recent advances in the understanding of the pathophysiology of BD suggest a differentially patterned presentation of peripheral biomarkers between early versus late-stage BD (Andreazza et al. 2009; Kauer-Sant'Anna et al. 2009a). Such data were very important in suggesting a mechanistic pathway to neuroprogression (Berk 2009). A staging approach that includes the use of biomarkers to differentiate early and late-stage BD patients would bring psychiatric disorders closer to general medical models and help with the development of more targeted treatments (Kapczinski et al. 2009).

2. Clinical evidence of distinct stages in BD

In recent articles, Berk et al. (2007a,b) have put forward a staging model designed to account for not only the cross-sectional phenomenological changes used in the classification of BD but also some meaningful information about the course of the illness. Even though BD has a complex course the longitudinal trajectory is frequently clear with a progressive combination of disability, lack of insight (Dias et al. 2008), and functional impairment (Rosa et al. 2007). As proposed by Berk et al. (2007a) a staging model for BD includes an important course specifier component. However, the course of BD is not uniform: some patients present with greater severity right from the illness onset, whereas other patients may attain recovery periods even after several mood episodes (Berk et al. 2007a; Kapczinski et al. 2009). This diversity may be explained in part by differential vulnerability and resilience patterns (Caspi and Moffitt 2006). Thus, the number of episodes may not be the sole factor determining the stage; instead, factors like the degree of deterioration, which is more reliably assessed in the inter-episode period, may play an important role. This would take into consideration those patients who have a worse outcome from early stages of illness as well as those who present complete recovery even after many mood episodes.

Cognitive deficits are now known to be present among many BD patients. These deficits occur not only during episodes of mania or depression but also during euthymia (Martinez-Aran et al., 2004a,b), probably constituting a trait-related neuropsychological deficit (Torres et al. 2007). Furthermore, cognitive deficits seem to be related to the severity of the disease (Martinez-Aran et al. 2007), being more evident in patients who have experienced multiple episodes (Torres et al. 2007). In the same vein, despite adequate treatment, a significant proportion of BD patients have persistent symptoms that are predominantly depressive (Post et al., 2003a,b; Vieta et al. 2008). Even with intense monitoring and aggressive treatment, a considerable degree of residual illness-related morbidity usually persists (Post et al., 2003a,b). Subclinical symptoms, particularly depressive ones, may be predictors of poor functioning and role impairment (Kauer-Sant'Anna et al. 2009b). Even modest changes in the severity of depression are associated with significant disability (Simon et al. 2007a). Such residual symptoms are highly prevalent, correlate with maladjustment, and carry an increased risk of relapse (Huxley and Baldessarini 2007).

Besides subsyndromal symptoms and cognition, psychiatric comorbidity is also a determinant of severity in BD. Comorbid conditions in BD are the rule rather than the exception: substance abuse, medical illnesses, anxiety, and personality disorders are all common in bipolar patients (Sherwood Brown et al. 2001; Otto et al. 2006). These patients differ from those without comorbidities in terms of disease severity and functional recovery. Extensive data show that both anxiety and substance (including nicotine) abuse comorbidity are associated with worse outcomes, higher rates of suicide attempts, longer times to achieve remission and a higher risk for relapse (McElroy et al., 2001; Sherwood Brown et al. 2001).

3. Neurobiological evidence of distinct stages in BD

A staging model for BD should also differentiate the neurobiological correlates of the disorder's distinct stages (Berk et al. 2007a,b; Kapczinski et al. 2009). Biochemical changes in BD are now receiving greater attention, and their inclusion in forthcoming editions of the official classifications of mental disorders is currently under consideration (Phillips and Vieta 2007). However, the use of such correlates is hampered by their relatively low sensitivity and poor specificity. MRI changes in brain volume in cortical and subcortical regions, olfactory deficits, genetic variables, and other endophenotypic markers that reflect the progression or greater severity of the disorder could also be included in a staging model for BD (McGorry et al. 2007).

Biological factors thought to increase the risk of a poor disease outcome include white matter hyperintensities, with cortical lesions being associated with a worse prognosis (Moore et al. 2001; Silverstone et al. 2003). Morphometric studies have demonstrated enlargement of the third and lateral ventricles (Soares et al. 2005), reduced gray matter in the hippocampus and cerebellum (Moorhead et al. 2007), and reduced volumes in some areas of the prefrontal cortex (Blumberg et al. 2006; Soares et al. 2005). An increased size of the amygdala has also been reported (Blumberg et al. 2006). Strakowski et al. (1993) reported larger ventricles and differences in the gray/white matter distribution in BD patients at the time of their first manic episode compared to healthy controls. Further, reductions in brain volume are more pronounced in patients with multiple episodes (Strakowski et al. 2002). Non-biological factors, including personality, illness behavior, premorbid intelligence, social support, life events, and the availability and quality of treatment, play a major additional role in prognosis (van Os et al. 2007; Van Riel et al. 2008).

These anatomical changes could be a reflection of changes in neurotrophic factors and increased pro-apoptotic routes. For instance, BDNF (Cunha et al. 2006), NT3 (Walz et al. 2007), NT4 (Walz et al. 2009), and GDNF (Rosa et al. 2006) levels are altered in BD mood episodes. Recent findings from our group showed that biochemical markers may change significantly from the early to late stages of BD (Kauer-Sant'Anna et al. 2009a; Andreazza et al. 2009); for instance, TNF-alpha and IL-6 cytokines were shown to be increased in early and late stage of BD compared to controls, whereas BDNF levels were decreased in the late but not early stage of BD (Kauer-Sant'Anna et al. 2009a). The levels of the anti-inflammatory cytokine IL-10 also declined in the late-stage disorder (Kauer-Sant'Anna et al. 2009a). These and other findings (Cunha et al. 2008) indicate that patients with BD are likely to be in a pro-inflammatory state (Brietzke and Kapczinski 2008; Brietzke et al. 2009), which worsens in the later stages of the illness. Furthermore, an accelerated aging process has been suggested in BD, as indicated by increased telomere shortening (Simon et al. 2006) and greater age-related decreases in BDNF levels in bipolar patients compared to controls (Yatham et al. 2009). In addition, some parameters of oxidative stress, such as 3-nitrotyrosine, are altered in the early stages of BD; others, such as glutathione S-transferase (GST) and glutathione reductase (GR), differ from controls only in those patients with multiple episodes in later stages of BD

Table 1
Biomarkers and clinical staging in bipolar disorder.

Stage	Clinical features	Biomarkers
Latent	At-risk for developing BD, positive family history Mood or anxiety symptoms without criteria for threshold BD	Polymorphisms that confer susceptibility to BD
I	Well defined periods of euthymia without overt psychiatric symptoms	↑ TNF-alpha ↑ 3-Nitrotyrosine ↑ IL-6, IL-10
II	Symptoms in inter-episodic periods are mainly related to comorbidities	↑ TNF-alpha ↓/- BDNF ↑ 3-Nitrotyrosine ↑ IL-6, IL-10
III	Marked impairment in cognition and functioning	↑↑ TNF-alpha ↓↓ BDNF ↑ 3-Nitrotyrosine ↓ IL-6, IL-10
IV	Unable to live autonomously due to cognitive and functional impairment	↑↑ TNF-alpha ↓↓ BDNF ↑↑ Glutathione reductase and S-transferase ↑ 3-Nitrotyrosine ↓ IL-6, IL-10

(Andreazza et al. 2009). Emerging data also suggest that the lowering of BDNF levels in acute episodes occurs in parallel with increased oxidative stress, suggesting that such changes occur in an orchestrated fashion (Kapczinski et al. 2008a). The utility of the glutathione precursor N-Acetyl cysteine reinforces the role of these pathways (Berk et al. 2008a) (Table 1).

4. Latent Stage – “Ultra-high risk” for developing BD

Since the diagnosis of BD can only be established after the occurrence of a (hypo)manic or mixed episode, one can argue that the psychiatric diagnostic systems fail in identifying BD before pathophysiological changes become apparent. We and others have made an effort to highlight the importance of early intervention by identifying cases of depression at high risk for developing BD (Berk et al. 2007c). Similar to the model proposed by Berk and colleagues, the mood symptoms that occur before the diagnosis of BD can be made are included in the present staging model in the Latent Stage (Kapczinski et al. 2009).

The Latent Stage is defined by the presence of prodromal symptoms indicating an increased risk for the development of BD. Symptoms are most commonly atypical and include hypersomnia, hyperphagia, seasonal pattern, psychomotor retardation, mood lability, and irritability. In addition, a family history of BD and hyperthymic/cyclothymic temperament traits (Mazzarini et al. in press) should also be considered when determining the pre-clinical stage (Ferrier et al. 2004). In terms of biomarkers, the latent-stage patients would be the ones that carry gene polymorphisms that have been related to the subsequent development of BD (Carter 2007; Craddock and Forty 2006; Mandelli et al. 2007). In addition, this stage may be especially important for the development of preventive strategies, including a strong emphasis on the avoidance of substance misuse.

5. Stage I – Inter-episode period devoid of relevant impairment

The first episode may be a critical time window for appropriate and early intervention and a particular challenge for accurate diagnosis. There is some evidence that the structural brain changes seen in the disorder are progressive from relative normality at the first episode (Strakowski et al. 2002). Patients in Stage I have had their first episode of (hypo)mania, and they usually return to their previous functioning level after treatment. However, the majority (two-thirds) of bipolar patients do not make a functional recovery after a first episode (Conus

et al. 2006), and many predictors of outcome (e.g., age, gender, and substance use) may be fixed at disease onset.

Monotherapy with a mood stabilizer could be appropriate for symptomatic control and maintenance of clinical remission. Moreover, appropriate psychosocial and pharmacological treatment in Stage I could be potentially neuroprotective. There is some evidence that lithium may be less effective if it is not started early in the course of the disorder (Swann et al., 1999).

Psychotherapy, namely adjunctive psycho-education and cognitive-behavioral interventions, could be especially useful in this stage (Scott et al. 2006; Vieta and Colom 2004). The objective of psychotherapy in Stage I would be to help the patient accept and understand the disorder, improve treatment adherence, and help the patient to cope with the medical, financial, and personal consequences of the mood episode(s). It is important that people maintain the ability to meet age-specific developmental, social, vocational, and educational tasks (Berk et al. 2008b).

6. Stage II – Clinical and biomarker changes in the inter-episode periods

Impaired functioning may be due to symptoms confined to comorbidities (drug/alcohol abuse/dependence and axis II disorders, especially anxiety disorders) or rapid-cycling presentations. Detected comorbidities should be treated without delay, because they are a potential factor of destabilization and are related to an unfavorable prognosis. After adequate treatment, remission may be achieved and patients could be classified as Stage I patients once more. Clinically, there may be no evidence of cognitive impairment; however, neuropsychological tests may reveal a decline in task performance. It is necessary to emphasize that comorbidity is typically present as early as the prodromal period. In terms of biomarkers, the same changes described below for Stage III may be present, but would tend to resolve once comorbidities are effectively treated.

Patients in Stage II may need vocational rehabilitation, since hospitalization, moral exposition, delay in obtaining complete relief of the symptoms, or adverse effects of medications might have had a devastating effect in their occupational and social lives. There are currently no definite conclusions regarding randomized controlled trials of different psychosocial interventions, but cognitive-behavioral and family-based approaches may be beneficial for patients in Stage II (Justo et al. 2007; Reinares et al. 2008; Scott et al. 2006). Nevertheless, both the temporal stage of the illness and the level of illness burden are potentially important predictors of the response to psychotherapy (Scott et al. 2006).

7. Stage III and IV – Severe impairment in the inter-episode periods associated with changes in biomarkers

These patients may present inter-episodic subsyndromal BD symptoms and/or evidence of clinically relevant cognitive impairment. The duration of the inter-episodic period of euthymia usually shortens as the number of episodes increases (Kessing et al. 1998), and patients may experience persistent subsyndromal mood symptoms of either a depressive or manic nature, irritability, dysphoria, anxiety, or anguish despite adequate treatment. Some patients may not present significant subsyndromal symptoms but will have clinical evidence of cognitive impairment or a marked impairment in functioning. By marked impairment, we are referring to patients who are unable to work or who have a working status much inferior to what would be expected from their level of education or previous degree of achievement. Substance use comorbidity increases significantly, as does the risk of suicide attempts, due to problems with continuing illness burden, insight into losses, substance abuse, or anxiety disorder (Simon et al. 2007b).

In general, patients at Stage III have gone through multiple treatments. The occurrence of repeated episodes increases the probability of cognitive impairment and structural changes that can be detected with neuroimaging scans (Strakowski et al. 2002). Attention should be drawn not only to gray matter atrophy and ventricular enlargement, which may not be severe, but also to white matter hyperintensities that have been overlooked due to their lack of specificity. Stage III patients may present abnormalities in biomarkers related to neuronal and glial dysfunction. As a correlate of late-stage illness, preliminary data from our laboratory suggest that patients in Stage III are more likely to present an increased activity of key enzymes in the glutathione pathway, glutathione reductase (GR) and glutathione S-transferase (GST) compared to early-stage patients and controls; in contrast, the glutathione peroxidase (GPx) did not show alteration either in early or late-stage patients, when compared to controls. In addition, in a recent study we showed that protein carbonyl levels did not differ between early or late-stage BD, however the 3-nitrotyrosine levels were increased in both stages of BD patients, but not in controls (Andreazza et al. 2009). This data suggests the involvement of a compensatory system related to oxidative stress in BD, and add to the notion that a longer duration of illness and multiple mood episodes may have a cumulative effect (Kapczinski et al. 2008b; Post, 2007). In addition, higher levels of lipid peroxidation markers like TBARS (Andreazza et al. 2007a), an increased frequency of DNA damage (Andreazza et al. 2007b), telomere shortening (Simon et al. 2006), and higher levels of mediators of inflammation like TNF-alpha (Brietzke and Kapczinski 2008) have been reported. Kauer-Sant'Anna et al. (2009) have reported low serum BDNF levels in the late stage of BD; in this study, BDNF levels were negatively correlated with illness duration. In contrast, IL-6, IL-10 and TNF-alpha were increased in the early stages of BD, compared to controls. While TNF-alpha and IL-6 continued to be significantly higher than controls in the late stages of BD, IL-10 did not. There was a significant decrease in BDNF and IL-6 in the later stage of BD as compared to early-stage patients; TNF-alpha showed a significant increase in the late stage (Kauer-Sant'Anna et al. 2009a; Andreazza et al. 2009).

Patients in Stage III are often treated in specialized centers (McGorry et al. 2007), and they most likely will need treatment in combination with mood stabilizers and atypical antipsychotics (Berk et al. 2007c). This reinforces the point that services should be focused in patients in early stages of disorder instead of focused on the most refractory cases (Conus et al. 2008; Van Riel et al. 2008). Patients in stage IV would present similar features to stage III. However in stage IV functioning impairment is more pronounced, to the point that patients are unable to live autonomously.

8. Limitations of the model

The main drawback of our proposal is that the neurobiological evidence of stages in BD is still limited. However, these progressive changes in biological markers have been shown in other neurodegenerative conditions. For instance, recent data suggest that there is a significant difference in BDNF levels between the early and late stages of Alzheimer's disease, as defined by memory performance scores. Furthermore, serum BDNF levels correlated with mini-mental examination scores in these patients (Laske et al., 2006a,b). Similarly, multiple sclerosis patients with a longer history of the disease and incomplete recovery after relapse show lower BDNF levels (Caggiula et al. 2005). Another limitation of this model is the dearth of evidence from long-term prospective studies regarding cognitive impairment and brain imaging.

The development of a staging model may be a starting point for future studies that would include a stage-dependent treatment approach and neurobiological investigation that validates and revisits this construct.

9. Conclusions

A staging model for BD should help to guide effective treatment according to the differential stages of the disorder. Early intervention is likely to be associated with a better response to treatment, the use of simpler therapies, and lower rates of progression to more severe phases of the disorder (Berk et al. 2007a). For example, lithium and other mood stabilizers may provide neuroprotection (Bearden et al. 2007; Chang et al. 2005; Sassi et al. 2004), and lithium response is probably greater in the early phases of the disorder (Franchini et al. 1999; Post et al. 2003b), and then declines with increasing numbers of episodes (Swann et al., 1999).

If the preliminary evidence that oxidative stress, immune dysfunction, and dysregulation of neurotrophins are confirmed, this evidence would support these areas as intervention targets. This is a critical issue, as bipolar disorder lacks a clear pathophysiology that presents targets for rational drug development (Berk 2009; Kapczinski et al. 2008b; Post 2008).

Adjunctive cognitive behavior psychotherapy (Scott et al. 2006) and rehabilitation (Vieta and Rosa 2007) may have significant benefits for bipolar patients. However, the timing for psychotherapy considered from the perspective of whether it is introduced during an episode or in a period of remission, as well as the individual's history of BD may produce different results. Adjunctive psychotherapy to individuals that have been euthymic for more than a year has been shown to significantly reduce the risk of relapse (Scott et al. 2006), but this does not seem to be the case for subjects who commence therapy at an early point during an acute episode (Scott et al. 2006). Moreover, individuals with a history of multiple relapses may have no additional benefit from adjunctive psychotherapy as compared to psychopharmacological treatment alone; this may be due to long-standing maladaptive coping strategies or to a greater degree of neurocognitive impairment and allostatic load (Kapczinski et al. 2008b; Scott et al. 2006; Kapczinski et al. 2009).

The severity of clinical impairment seen in patients with BD dictates that treatment strategies should be directed to prevention. In this context, a model that could guide the management of BD based on neurobiological changes before many mood episodes occur would be an important contribution to the field. One could argue that data are still limited to support the present staging construct. However, a staging model drawn from even preliminary evidence would provide the basis for future research and validation. In this way, incorporating the use of biomarkers for staging BD could provide a means to refine guidelines and algorithms, allowing treatment to be tailored into needs-based management (Berk et al. 2007a,b,c; Kapczinski et al. 2009).

Conflict of interest

Flávio Kapczinski is a NARSAD Independent Investigator and is supported by the Stanley Medical Research Institute, CNPq, INCT-TM, CAPES, FIFE-HCPA. Additionally, Kapczinski is a speaker and/or advisor and/or receives research support from Lilly, AstraZeneca, Janssen, Servier, and Roche.

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Dr. Vázquez has served as a consultant, advisor or member of the speaker bureau of AstraZeneca, Glaxo-Smith-Kline, Roche and Eli Lilly Corporations.

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