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Clinical implications of a staging model for bipolar disorders

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A model of staging in the field of bipolar disorder (BD) should offer a means for clinicians to predict response to treatment and more general outcome measures, such as the level of functioning and autonomy. The present staging model emphasizes the assessment of patients in the interepisodic period and includes: latent phase: individuals who present mood and anxiety symptoms and increased risk for developing threshold BD; Stage I – patients with BD who present well established periods of euthymia and absence of overt psychiatric morbidity between episodes; Stage II – patients who present rapid cycling or current axis I or II comorbidities; Stage III – patients who present a clinically relevant pattern of cognitive and functioning deterioration, as well as altered biomarkers; and Stage IV – patients who are unable to live autonomously and present altered brain scans and biomarkers. Such a model implies a longitudinal appraisal of clinical variables, as well as assessment of neurocognition and biomarkers in the interepisodic period. Staging facilitates understanding of the mechanisms underlying progression of the disorder, assists in treatment planning and prognosis and, finally, underscores the imperative for early intervention.

KEYWORDS: biomarker • bipolar disorder • gene–environment • neurocognition • neuroimaging • staging • treatment

A growing body of evidence indicates that bipolar disorder (BD) has a much less favorable long-term outcome than previously thought, with incomplete recovery and cognitive impairment [1,2], as well as significant overall functional impairment, even during remission periods, for many individuals [3,4]. In fact, there is evidence that the duration of euthymia in interepisodic periods shortens as the number of episodes increases [5,6]. Furthermore, patients with a longer duration of illness or those with more than three mood episodes are less likely to respond to treatment, particularly to lithium [7].

The current model of staging in BD [8] suggests a progression from a latent (at-risk) period to more severe and refractory presentations engendered by the cumulative exposure to acute episodes, drugs of abuse, life stress and inherited vulnerability [9]. Apart from the effect of cumulative mood episodes, certain clinical variables, such as rapid cycling or drug dependence, indicate a worse prognosis and less favorable response to treatment. In addition, recent advances in the understanding of the pathophysiology of BD suggest a differential pattern

regarding peripheral biomarkers between early- and late-stage BD [10,11]. These late findings were key in suggesting a mechanistic pathway to the process of neuroprogression of the disorder [12]. A staging approach including neurobiological parameters would bring psychiatric disorders closer to general medical models and help with the development of more targeted treatments.

Genetic underpinnings of staging model in BD

Although gene–environmental (G×E) interaction models for etiology and pathogenesis of recurrent unipolar depression are commonly assumed, these models are less well explored in the onset, development and progression of BD [13]. At this point, *BDNF*, *5-HTTLPR*, *COMT*, *MAO-A*, *SLC6A4*, *TPH2*, *DRD4*, *SLC6A3*, *DAOA*, *DTNBPI*, *NRG1* and *DISC1* genes are known to be involved in BD [13–15]. Some of these genes are also clearly related to G × E models of psychiatric disorders [16–18].

The G × E interaction assumes that environmental pathogens are the cause of the disorder and that genes influence susceptibility to them. The G × E

perspective suggests that there is no necessary expectation of a direct gene–behavior association in the absence of the environmental pathogen (FIGURE 1) [19]. The individual differences originating in the DNA sequence bring about differences in the resilience or vulnerability to the environmental stress [16].

Given this, the concept of a $G \times E$ interaction in BD (FIGURE 1) is in line with a staging model. This complex interaction might include susceptibility genes, a coherent signaling neural network related to neuroprotective and neurotoxic pathways, as well as the fact that stress is not a specific causal agent but does place genetically and biologically vulnerable individuals at risk for a more pernicious course of BD [9,20,21].

Latent phase

There is an effort to highlight the importance of early intervention by identifying individuals at high risk for developing BD [8,22]. However, especially in younger individuals, the index episode of the illness is characteristically depression and a formal the diagnosis of BD can only be established after the occurrence of a (hypo) manic or mixed episode, which creates an important issue: the psychiatric diagnostic systems frequently fail in identifying BD before mania becomes apparent. This issue has led some authors to advocate the use of several criteria for the identification of latent bipolarity [23], while others have proposed the identification of illness-specific neurocognitive phenotypes for BD [24]. In this regard, specifically executive and memory dysfunctions have been considered potential markers of familial vulnerability to BD [KAPCZINSKI *ET AL.*, MANUSCRIPT SUBMITTED] [25–27]. However, there is no obvious pattern of cognitive impairment that specifically characterizes BD, and both the sensitivity and specificity of cognitive changes are poor.

Early signs of bipolarity can be observed among children of BD parents and often take the form of subsyndromal presentations [21]. Thus, the presence of prodromal symptoms, indicating an increased risk for the development of BD, could be understood as a latent stage according to our staging model [KAPCZINSKI *ET AL.*, MANUSCRIPT SUBMITTED]. The few studies that have followed at-risk youths into adulthood found

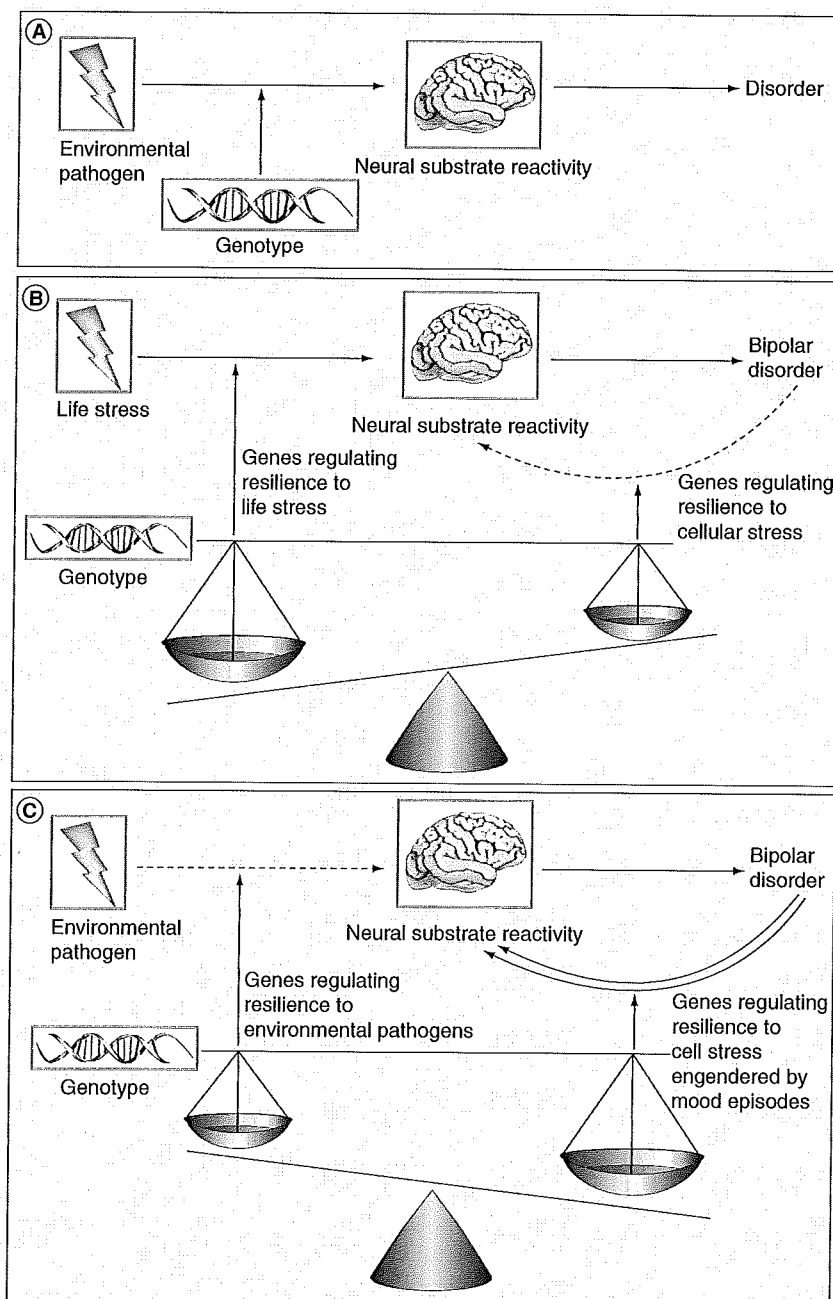


Figure 1. Gene and environment in bipolar disorder. (A) Demonstrates the model of 'gene–environment' interaction described by Caspi and Moffitt [16]. This perspective suggests that there is no necessary expectation of a direct gene–behavior association in the absence of the environmental pathogen. (B) Recurrent and progressive disorder. In early phases of the disorder, changes in the neural substrate occur owing to the effect of the pathogen, and the genes that regulate the impact of the pathogen in the neural substrate are the main factor for developing the disorder. However, the dotted line demonstrates that, in bipolar disorder, recurrent episodes may themselves change the neural substrate. (C) Shifting focus from environmental pathogens to cell stress. In late-stage phases of the disorder, the emphasis is placed on cellular resilience to the deleterious effect of cumulative episodes. Changes induced by recurrent episodes, such as decreased levels of brain-derived neurotrophic factor and increased oxidative stress, trigger proapoptotic cascades that may initially lead to loss of synapses and ultimately result in cell death.

developmental discontinuities from childhood to adulthood [21], suggesting the possibility that BD expression may be mediated by an abnormal maturation of brain structures involved in cognitive processes [25]. In summary, the first phase is related to prodromal symptoms and a cognitive pattern observed before the onset of BD and is probably related to specific endophenotypes.

Clinical stages

The staging model proposed by our group includes a latent stage and four clinical stages (TABLE 1) [KAPCZINSKI *ET AL.*, MANUSCRIPT SUBMITTED]. Stage I includes the earlier stages of illness: at this stage, the genotype modulation of the effects of environmental pathogens (life stress) on neural substrate reactivity becomes significant. Neural substrate reactivity is used in this perspective to emphasize that experiences, episode-related dysfunction and gene expression may change the way brain circuits react to further inputs [14]. The impact of neurochemical changes (cell stress) elicited by each single mood episode in the neural reactivity initiates the development of a recurrent disorder, where episodes take place without the presence of external triggering factors or of progressive disorder (FIGURE 1). Stage II derives from the clinical observation that even early stage patients who present rapid cycling or certain psychiatric comorbidities have a more guarded prognosis and less favorable responses to treatment (FIGURE 1). Stage III

is characterized by an overt autonomic course of the disorder with unequivocal cognitive and functioning impairment. The basic feature in Stage III is that the more pronounced G × E is between genotype and cell resilience to the challenges engendered by cumulative mood episodes (FIGURE 1).

The impact of recurrent episodes, life stress and lack of adequate coping leads to a bodily and progressive neural dysfunction engendered by cumulative mood episodes resulting from chronic overactivity or inactivity of physiological systems that are involved in the adaptation to environmental challenges [25]. The use of the allostatic load concept in BD offers an important clue as to why patients who undergo recurrent mood episodes are clinically perceived as less resilient [9]. In other words, a state of prolonged response to stress could generate a state of inadequate recovery from this environmental influence (progressive coping impairment). At this point, the individual's chronically activated neural substrate and their inability to make use of their cognitive resources to manage stress, give room for kindling processes to take place. The process of kindling and sensitization offers a heuristic basis for important issues in BD, such as episode recurrence, cyclicity and the development of tolerance to treatment [2]. Nevertheless, the phasic nature of the episodes, as modeled using the kindling/sensitization paradigm, would not account for the stochastic, nonlinear association of the cognitive impairment

Table 1. Clinical staging in bipolar disorder.

| Stage | Clinical features | Biomarkers | Cognition | Maintenance treatment | Prognosis |
|--------|--|---|--|---|--|
| Latent | At risk for developing BD, positive family history, mood or anxiety symptoms without criteria for threshold BD | Polymorphisms that confer susceptibility to BD | No impairment | ↓ Exposure to pathogens | Good prognosis when protected from pathogens |
| I | Well-defined periods of euthymia without overt psychiatric symptoms | ↑ TNF- α ↑ 3-nytrotyrosine | No impairment | Mood stabilizer monotherapy; psychoeducation | Good prognosis with careful prophylaxis |
| II | Symptoms in interepisodic periods related to comorbidities | ↑ TNF- α ↓ BDNF ↑ 3-nytrotyrosine | Transient impairment | Combined treatment (pharmacotherapy + psychotherapy; focus on the treatment of comorbidities) | Prognosis depends on how well comorbidities can be managed. Worse than stage I |
| III | Marked impairment in cognition and functioning | Morphometric changes in brain may be present ↑ TNF- α ↓ BDNF ↑ 3-nytrotyrosine | Severe cognitive impairment associated with functioning impairment (unable to work or very impaired performance) | Complex regimens usually required; consider innovative strategies | Reserved prognosis; rescue therapy required |
| IV | Unable to live autonomously owing to cognitive and functional impairment | Ventricular enlargement and/or white matter hyperintensities ↑ TNF- α ↓ BDNF ↑ Glutathione reductase and transferase ↑ 3-nytrotyrosine | Cognitive impairment prevents patients from living independently | Palliative; daycare center | Poor prognosis |

BD: Bipolar disorder; BDNF: Brain-derived neurotrophic factor.

to cumulative episodes. In terms of treatment strategies, these would have different targets according to the course and stage of BD. For example, stressful events are an important factor for the emergence of the initial episodes. As the disease progresses, the disorder acquires an autonomous motion and episodes are increasingly spontaneously triggered without a clear intervention from stressful events.

Progressive coping impairment

The response inhibition deficit appears to be a potential endophenotype of BD and a potential marker of prefrontal dysfunction. Such endophenotype markers of cognitive impairment in BD appear to involve frontotemporal and frontolimbic structures [27].

Consistent evidence suggests that coping is a key factor of the overall set of executive functions that are regulated by the prefrontal cortex [28]. According to a recent pathophysiological model of BD [9], coping abilities could modulate the relationship between stress and episode recurrence. At the same time, coping abilities could be directly impaired by the neurofunctional and neurostructural damage associated with the recurrent course of BD [29]. Given this, stress and adverse life events are likely to be important factors associated with illness onset and the early course of the disease [26].

With time, as the cyclic pattern of episodes appears to acquire an autonomous rhythm, stress factors become a less important triggering factor of new episodes. However, the cumulative effects of stress continue to exert a persistent deleterious impact. Coping could be observed as a possible target to psychosocial intervention, since there is a substantial and partially causal link between stress and BD [9]. These interventions could include preventive strategies to population subgroups that have a higher risk for BD development.

Differential changes in peripheral markers in early- versus late-stage BD

A staging model for BD should also differentiate the neurobiological correlates of the disorder's distinct stages [8,22]. Biochemical changes in BD are receiving greater attention, but their use is hampered by their relatively low sensitivity and poor specificity. Several recent studies have made efforts to investigate the involvement of growth factors, the inflammatory system, oxidative balance and related apoptotic pathways in BD patients.

As previously mentioned, the pathophysiology of BD may be associated with impaired synaptic plasticity with consequent alterations of neurotrophins. In particular, brain-derived neurotrophic factor (BDNF) has received attention owing to its role in regulating neuronal survival, structure and function [30,31]. In addition, neurotrophins are essential to long-term memory [26]. Decreased serum BDNF levels have been reported in the manic phase [32,33], as well as in depressed BD patients [32]. There has been one study demonstrating decreased levels of BDNF [34], while two other studies found similar BDNF levels compared with healthy controls [DIAS VV *ET AL.*, MANUSCRIPT SUBMITTED] [32]. Interestingly, a negative correlation between serum BDNF levels and psychopathology scores has been found in BD individuals [32]. It is important to

emphasize that studies of normal aging have demonstrated that the expression of BDNF in the hippocampus decreases with age [35] and that these decreases might contribute to age-related cognitive impairments [36]. Recent findings from our group demonstrated that BD patients have an accelerated age-related decrease in BDNF levels compared with healthy subjects [37].

A recent study from our group compared BDNF in the early and late stages of BD, and found decreased BDNF levels in the later stages of the disorder (10–20 years of illness duration), but not in the early stage (1–3 years of illness duration) [10]. In the same cohort, Kauer-Sant'Anna and colleagues found increases in the levels of the proinflammatory cytokines IL-6 and TNF- α in both the early and late stage of the disorder, while the anti-inflammatory cytokine IL-10 was increased in the early stage but not in the later stages [10]. A number of recent reports have shown increased levels of TNF- α in acutely manic or depressed patients with BD [38–40]. Kim and colleagues prospectively examined the immune response in BD, demonstrating that IL-6 and TNF- α levels were increased during mania, but only IL-6 returned to baseline levels after 6 weeks of treatment with mood stabilizers, whereas TNF- α levels remained elevated [38]. These data suggest that TNF- α may represent a more enduring change in BD and indicate that patients with BD are in a proinflammatory state, which worsens in the later stages of the illness. In parallel, there is a decrease in the compensatory or protective mechanisms, as indicated by a reduction in BDNF levels, as well as anti-inflammatory cytokines. One could hypothesize that BDNF levels decrease during mood episodes; however, the restoration of normal levels may be less likely with multiple episodes of the disorder.

Furthermore, an accelerated aging process has been suggested in BD, as indicated by the alterations in diverse oxidative stress parameters [37,41–49]. Oxidative stress can result from diminished levels of antioxidants and/or increased production of reactive species from oxygen or nitric oxide (NO). It was recently shown that unmedicated manic patients have increased levels of serum thiobarbituric acid reactive species (TBARS) [43], a marker of lipid oxidative damage, and that these increases in serum TBARS are present across all phases of BD (manic, depressed or euthymic) [41]. Oxidative damage to lipids may damage membrane phospholipids, leading to alteration in the fluidity, which may in turn induce synaptic dysfunction and even cell death [50]. Supporting the involvement of oxidative stress in BD, several studies have shown increased levels of NO [42,44,45,51–53]. From these, three studies were in manic patients [42,52,53], one in depressed patients [44] and two in euthymic patients [45,51]. In addition, a recent meta-analysis demonstrated that TBARS ($p = 0.001$), as well as NO ($p = 0.02$), activity were significantly increased in BD, with a large effect size for TBARS and a moderate effect size for increase in NO [9].

Superoxide dismutase (SOD) activity appears to be elevated in BD patients [41,43,45,48,49]. Furthermore, Andreazza and colleagues found that this increase occurs during the manic and depressed phases of BD, but not in euthymia [41]. This was corroborated in part by Machado-Vieira *et al.* who reported increased activity of SOD in unmedicated manic patients [43]. However, Savas

et al. have identified increased SOD levels in 27 euthymic BD patients [45] and Gergerlioglu *et al.* reported a decrease in levels of SOD in 29 manic patients [42]. The catalase activity has been demonstrated to be decreased in euthymic patients [41] and increased in unmedicated manic patients [43]. Kuloglu and colleagues also found decreased levels of catalase in BD patients [48]. Moreover, glutathione peroxidase has also been reported in BD [47–49].

A recent study demonstrated increased activity of key enzymes in the glutathione pathway, glutathione reductase and glutathione S-transferase, in late-stage patients compared with early-stage patients and controls; while glutathione peroxidase did not demonstrate alterations either in early- or late-stage compared with controls [54]. In addition, this same study demonstrated that protein carbonyl levels did not differ between early- or late-stage BD; however, 3-nitrotyrosine levels were increased in the early and late stage of BD, but not in controls [55]. These data suggest the involvement of a compensatory system related to oxidative stress in BD and add to recent theories suggesting that longer duration of illness and multiple mood episodes may have a cumulative effect [9,26]. This is also in accord with the ideas of medical staging of BD.

Neurocognitive evidence of distinct stages in BD

Studies have reported generally normal [54] or superior [56], rather than impaired, function in some cognitive domains in children who subsequently developed BD. During adolescence and/or early adulthood, but before illness onset some degree of poor premorbid adjustment has been reported [57], with some authors arguing that cognitive dysfunction may predate illness onset. The existence of some cognitive deficits predating illness onset suggests their association with a familial, presumably genetic, vulnerability for BD [58], which appears to worsen as the illness progresses [59].

Early in the course of BD, some degree of neurocognitive impairment appears to be present in the majority of BD patients [60,61], especially on executive functions. Moreover, evidence suggests that cognitive function is negatively related to certain illness features, particularly the number of mood episodes, the number of hospital admissions and the duration of illness [62,63]. In fact, despite methodological limitations, the evidence points towards a robust association between impaired long-delay verbal memory and a greater burden of illness, with verbal memory and executive functions being the domains with greatest impairment [59]. Manic episodes appear to be more consistently related to delayed verbal memory and some measures of executive functions, whereas depressive episodes relate less consistently to a broader range of impairments [64]. A 4-year follow-up of BD patients and controls revealed a reduction in memory function and loss of gray matter volume in the medial temporal cortex that were associated with illness intensity [63]. Moreover, the risk of dementia appears to increase with the number of episodes in BD [65], lending some support to the hypothesis that cognitive impairment is a trait marker of the illness that worsens over time [59]. In fact, cognitive deficits are nowadays known to persist even during remission/euthymic phases of the disorder, especially in executive functions and processing speed [65].

Cognitive impairment appears to be related to a worse clinical course and poor functional outcome [2]; therefore, a better knowledge of the factors that determine disease course in BD may help devise ameliorative strategies for cognitive dysfunction and functional impairment, preventing patients from progressing to more severe stages of the disorder.

Staging & brain imaging

It has long been acknowledged that a better understanding of the neuroanatomical and neurofunctional correlates of psychiatric disorders is a critical step in the search for potential diagnostic tools [66]. To this we add that brain imaging may also help to determine the stage of illness by detecting the progression of morphometric and functional abnormalities in brain structures. Studies that have examined first-episode patients with BD suggested that structural changes in frontolimbic areas may be evident early in the course of the illness [67]. For example, a recent study found that patients hospitalized owing to first-episode affective psychosis (mainly manic) displayed a substantial decrease in gray matter content in the subgenual cingulate cortex at baseline and at 1.5 years of follow-up [68]. Considering that the subgenual cingulate cortex is associated with resolution of emotional conflict, presumably due to a top-down control over the amygdala [69], these studies provide evidence that abnormalities in emotional regulation are present early in the course of BD and suggest that the subgenual cingulate cortex is a potential target for early intervention. This is consistent with the fact that smaller amygdala volumes were found in children and adolescents with BD [70] and in first-episode BD patients [71], whereas amygdala volume is increased and hyper-reactive to emotional stimuli in adult BD individuals [72]. Interestingly, abnormal amygdala function is thought to be related to altered regulation of emotional memory observed in individuals with BD [10]. Long-term, longitudinal assessment using high-resolution MRI acquisition and validated volumetric measures are necessary to test this hypothesis. In addition, a study conducted with first-episode BD patients demonstrated a progressive gray matter loss in the anterior cingulate cortex after 2 years of follow-up [73], which suggests that amygdala-related dysfunction may be associated with abnormal top-down control from the anterior cingulate cortex [69,74].

A voxel-based study conducted with 70 adolescents with first-episode psychosis found that those with a diagnosis of BDI at 1-year of follow-up had lower gray matter content in the left medial prefrontal cortex, a brain region centrally involved in attention and inhibitory control [75]. This is in line with a study assessing the orbitofrontal cortex of children and adolescents with BD demonstrating decreased gray matter in males in contrast with increased gray matter in females [76]. Together, these studies suggest that subregions of the medial prefrontal cortex are also altered early in the course of BD. In adults, decreased gray matter content has been observed in the lateral orbital frontal cortex in medication-free individuals with BD [77]. A recent investigation of the white matter tracts in the orbitomedial prefrontal cortex, as assessed with diffusion-tensor imaging, found asymmetric fractional anisotropy, indicating abnormalities in neuronal connectivity in BD patients [78]. These brain imaging studies indicate

that a number of regions of the medial prefrontal cortex may be altered during the course of BD, which is consistent with neurocognitive studies suggesting that such dysfunction is present in manic, depressive and euthymic BD patients [68,79–81].

In summary, morphometric studies have shown that, in comparison with controls, patients with BD have changes in many brain structures [82–84] and that neuroanatomical changes tend to be more pronounced in patients with repeated episodes and longer illness duration [81,84,85]. Moreover, patients who recently had their first manic episode were shown to have minimal alterations in brain structures [86].

Clinical implications

In the available literature we found very few predictors of response to pharmacological or psychological interventions. The scarce literature assessing reasons for treatment failure in specific subgroups of patients points to the number of previous episodes as a powerful predictor of lack of response to drug treatment or psychotherapy [87–89]. Treatment using mood may achieve differential results according to the stage of BD. Lithium response is probably greater in the early phases of the disorder [87,88], declining with increasing numbers of episodes [7]. Response to lithium, but not to divalproex, was shown to decline in patients with higher numbers of episodes independently of rapid cycling or mixed-state presentations [7]. Recent evidence suggests that lithium and other mood stabilizers may provide neuroprotection [88,90–92], which could, in turn, positively influence cognitive function in the long term.

Concerning the choice of medication strategies by clinicians, a recent study has shown that these are influenced to a larger extent by the previous course of illness and history of poor response to treatment rather than by treatment severity [TOHEN *ET AL.*, MANUSCRIPT SUBMITTED]. In fact, although first-episode patients presented higher levels of psychopathology compared with multiepisode patients, the majority were prescribed with monotherapy, but were able to achieve remission and recovery more often than multiepisode patients [TOHEN *ET AL.*, MANUSCRIPT SUBMITTED]. This finding reinforces the notion that patients with a longer course of illness become progressively less responsive to pharmacological treatment [93].

The same phenomenon appears to occur with cognitive-behavioral therapy [89], where patients with more than 11 episodes prior to treatment implementation demonstrated no benefit of adding cognitive-behavioral therapy to standard pharmacological treatment. Interestingly, despite being a powerful and validated add-on therapy, group psychoeducation also demonstrated a similar phenomena, with 12 episodes prior to treatment implementation being the point where response to psychoeducation suddenly disappeared. Moreover, if we assessed the efficacy of psychoeducation by means of a more sensible measure, such as 'number of days fulfilling episode criteria', the prophylactic efficacy against mania disappeared for those patients with more than six previous episodes. In addition, authors were unable to find any overall prophylactic efficacy with patients having had more than 15 episodes [COLOM *F.*, UNPUBLISHED DATA]. In summary, early- versus late-stage BD patients differ in terms of biological markers and response to both psychological and pharmacological treatment.

Expert commentary

The emerging data on stage-related changes in treatment response, cognition and neuroimaging suggest that BD is a condition where an active process of neuroprogression takes place [12]. The mechanisms underlying this are beginning to be understood [11,12], adding to the puzzle. Having an understanding of the underlying pathophysiology is critical for the development of rational therapies and the emergence of BDNF, oxidative stress and inflammatory cytokines as mediators of the disease process has changed the way that neuroprogression is understood. These mechanisms further advance our understanding of what existing treatments do, as many share effects on these targets and, additionally, they open the possibility of direct interventions at these pathophysiological targets. This is critical, as the development of pharmacotherapy for BD to date has been largely serendipitous.

This understanding additionally heralds the first illness episode as a critical target for early intervention, creating hope of being able to prevent some of the neuroanatomical, neuropsychological, clinical and functional consequences of the illness. A key implication of this model is that optimal pharmacotherapy and psychotherapy require implementation at the earliest stages of the disorder when they have the greatest efficacy. It also suggests that adherence and engagement need to be emphasized as a core intervention strategy.

The use of a staging model for BD, similar to that proposed in schizophrenia and other disorders [94,95], would aid in defining clinical needs, guide treatment choice and prognosis, and would add depth to clinical descriptors. These data support the case for the use of staging as a course specifier in *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* [96].

Five-year view

Future prospective studies may help to validate this staging model in the field of BD. It is of particular interest to identify which assessment tools would be the most appropriate to define staging. The definition of the latent phase of the illness would benefit from the identification of polymorphisms that are associated with increased vulnerability to develop BD. Genetics would also play a role in defining which genotypes would be more associated with decreased cell resilience during episodes and, thus, with a more rapid progression of the disorder and guarded prognosis. In terms of neurocognition, recent studies have pointed to emotional memory [97] and face recognition [98] as promising tools to assess BD patients. Even in terms of the well-established changes in executive functioning and verbal memory [1,2], more refined and specific tests could be developed and used in the routine assessment of BD patients. Regarding neuroimaging, new techniques to assess white/gray matter volumes, assessment of small structures (differential nuclei from amygdala and hippocampus) and functional neuroimaging offer new opportunities for staging BD. The field of peripheral markers has offered important clues in terms of physiopathology and is likely to clarify in part the pathways of illness progression [10], most likely being a valuable tool for the assessment staging. Overall, the ideal scenario to be pursued in the next 5 years is the clear definition of more proximal correlates of the changes in the neural substrate that occur in the context of the progression of BD (FIGURE 1). Such correlates of the degree of dysfunction of the neural substrate are not intended

to function as surrogates of clinical assessment. We understand that a sophisticated and longitudinal clinical assessment added to the assessment of cognitive functioning and peripheral biomarkers in the interepisodic period may offer a consistent set of data that, analyzed in the light of genomic and neuroimaging findings, may help to create a well-structured and clinically meaningful model of staging. Such staging model should be able to inform clinicians and patients of prognosis and treatment response. In the future, algorithms of treatment in BD may benefit from incorporating the concepts put forward in the present staging system.

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Key issues

- Community cohorts suggest that children who develop bipolar disorder (BD) later on in their lives do not have cognitive impairment.
- By the time of the first episode, many BD patients already present with a certain degree of cognitive impairment and neuroimaging changes.
- After multiple episodes, further changes in brain, neurocognition and biomarkers take place among BD patients.
- Staging models in BD may be useful tools to obtain information regarding prognosis and response to treatment.
- Given the difficulties of proper assessment of cognition and biomarkers during episodes, we have put forward the notion that the interepisode period is a better window for staging assessment in BD.
- The current notion of gene–environment interactions in the pathogenesis of psychiatric disorders suggests that highly vulnerable individuals would present a faster stage progression of illness irrespective of the number of episodes.
- Emerging data show that the use of medication, as well as psychotherapy and psychoeducation, may be more effective in the early stages of the illness.

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