Should be cited as: Psychiatr. Pol. 2014; 48(2): 231–243
PL ISSN 0033-2674
www.psychiatriapolska.pl

Bipolar disorder: staging and neuroprogression

Aline André Rodrigues[1,4], Adriana R Rosa[1,3], Maurício Kunz[1,2], Bruna Ascoli[1,4], Flávio Kapczinski[1,2]

[1] Laboratory of Molecular Psychiatry, Universidade Federal do Rio Grande do Sul, Brazil;
[2] Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
[3] Department of Pharmacology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
[4] Graduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Summary

In bipolar disorder illness progression has been associated with a higher number of mood episodes and hospitalizations, poorer response to treatment, and more severe cognitive and functional impairment. This supports the notion of the use of staging models in this illness. The value of staging models has long been recognized in many medical and malignant conditions. Staging models rely on the fact that different interventions may suit different stages of the disorder, and that better outcomes can be obtained if interventions are implemented earlier in the course of illness. Thus, treatment planning would benefit from the assessment of cognition, functioning and comorbidities. Staging may offer a means to refine treatment options, and most importantly, to establish a more precise diagnosis. Moreover, staging could have utility as course specifier and may guide treatment planning and better information to patients and their family members of what could be expected in terms of prognosis. The present study reviews the clinical and biological basis of the concept of illness progression in bipolar disorder.

Key words: bipolar disorder, staging models, neuroprogression

Introduction

Bipolar disorder is a severe, recurrent mental and a major public health problem [1]. According to data published by the World Health Organization (WHO), bipolar disorder ranks sixth among conditions causing the greatest disability, defined as lost working years due to disability in young adults [2]. Moreover, patients with bipolar disorder may show difficulties in order functioning areas such as interpersonal relationships [3], finance, cognition, and autonomy [4-6].

The progression of bipolar disorder is frequently associated with a higher number of episodes [7-9], subclinical symptoms in the interepisodic period [10, 11], higher

rates of comorbidities [12], increased risk for suicide [13], higher number of hospital admissions [14] and poorer response to treatment [9]. Also, several studies have shown a strong association between number of mood episodes and unfavorable clinical outcomes, especially cognitive and functional impairment [15, 16]. From a different standpoint, however, the course of bipolar disorder is considerably heterogeneous: while some patients recover well even after several episodes, others show increased illness severity from the onset of symptoms [17, 18]. These contrasting findings may be due, at least in part, to different patterns of vulnerability and resilience found in this population [19-21].

Recent studies investigating the pathophysiology of bipolar disorder have suggested that in certain cases the disorder may follow a progressive pattern from initial towards more advanced stages, characterized by increased severity and functional impairment. This finding has motivated authors to suggest staging models for bipolar disorder [17, 18, 22, 23]. The staging models proposed for bipolar disorder is based on its progression from early, prodromal phases to more advanced, treatment-refractory stages. According to this model, better treatment responses and a better prognosis could be achieved if interventions are implemented earlier in the course of illness [22]. As observed in other medical fields, the rationale of staging in bipolar disorder relies on the fact that different illness stages require different treatment approaches, according to the physiological, structural, and symptomatic changes corresponding to each stage [24].

The objective of the present review is to describe the most important staging models currently available for bipolar disorder, as well as the biological basis involved in disease progression.

Clinical staging models

The value of staging models has long been recognized in many medical and malignant conditions [25-28]. Nevertheless, in bipolar disorder, only very recently has the use of a staging model been proposed as an illness course specifier [25, 29].

In 1992, Post proposed a neurosensitization model which indicates that permanent alterations in neuronal activity are occasioned by multiple episodes, implying a poorer response to medication and greater relapse liability [30].

Fava and Kellner propose a staging model in psychiatry [23]. McGorry et al. developed a staging model for psychotic and severe mood disorders. After that, different models have been suggested for bipolar disorder, always relying on the premise that the illness progresses from latent, asymptomatic stages to more advanced, chronic stages, in which symptoms do not completely remit [17, 18].

According to the model proposed by Berk et al. [31], bipolar disorder initiates with an asymptomatic phase [stage 0], which is directly associated with specific risk factors, e.g., family history of bipolar disorder and substance abuse. Stage 1 is divided

into 1a and 1b, characterized by the presence of mild, nonspecific mood symptoms, with the possibility of evolving to prodromal patterns. Stage 2 is where the first episode takes place, in either the manic or depressive phase – the latter being more common. Stage 3, divided into three phases, is characterized by the first relapse or the persistence of subclinical symptoms [phase 3a], by an illness course with borderline symptoms [3b], and by a remission and recurrence pattern [3c]. Finally, stage 4 refers to patients who do not achieve full remission of symptoms or are refractory to treatment.

Some years later, Kapczinski et al. [18] proposed a new staging model that shifted the emphasis to functioning in the inter-episode as a means to assess staging. In this model, patients are classified into five stages, starting with a latent phase, in which individuals may experience mood and anxiety symptoms without overt presence of bipolar disorder. In stage I, patients already present a period of mania/hypomania and but present adequate functioning and absence of cognitive deficits in the inter-episode. In stage II, subclinical symptoms, comorbidities, and mild cognitive dysfunction are present in the inter-episode. In Stage III patients present with marked cognitive and functional impairment. Finally, stage IV includes individuals with severe cognitive and functional impairment, leading to loss of autonomy.

As also observed in other medical specialties, the relevance of staging models in psychiatry relies on the fact that therapeutic interventions adopted at early stages tend to be more effective and more likely to prevent illness progression than therapies implemented at more advanced stages [32]. From an early intervention that targets the first episode of disease, maybe it becomes possible to prevent the neuroanatomical, neuropsychological, clinical and functional consequences of the illness [33]. Reinares et al. have shown that the benefits of family psychoeducation for patients at early stages of bipolar disorder, with fewer relapses and longer periods euthymia when compared with patients who received the intervention at more advanced stages [34].

Staging and biomarkers: neurotrophins, inflammation, oxidative stress

Although Sterling and Eyer used the term allostasis in first place, it was McEwen and Wingfield who developed this idea in 2003. The term allostatic load has been used to describe the process of wear and tear in wich body and brain are submitted as a result of overactivity or inactivity of physiological systems in an attempt to adapt to stress [21, 35].

Several studies have shown important changes in biological markers, especially neurotrophins and markers of inflammation and oxidative stress, in patients with bipolar disorder. Brain-derived neurotrophic factor [BDNF] is an important neurotrophin involved in regulating neuron survival, functioning, and structure [36]. Clinical studies involving bipolar patients have shown a reduction in BDNF levels in the serum of manic and depressed patients, returning to normal patterns during euthymia [36-39]. Also, in patients at more advanced stages of bipolar disorder, BDNF levels are

reduced, differently from what is observed at early illness stages, further supporting the progression theory [40]. Similarly to BDNF, other neurotrophins, e.g., NT3, NT4 [42], glial cell line-derived neurotrophic factor [GDNF] and nerve growth factor [NGF] [REF] have been shown to be altered and possibly involved in the pathophysiology of bipolar disorder [41-43].

With regard to inflammatory markers, a recent meta-analysis of 30 studies on bipolar disorder has found a significant increase in the concentration of interleukins IL-4, IL-6, IL-10, soluble IL-2 receptor [sIL-2R], sIL-6R, tumor necrosis factor alpha [TNF-alpha], soluble TNF-alpha receptor, and IL-1 receptor antagonist in bipolar patients when compared with healthy controls [44] – some of these markers [TNF-alpha, IL-6] tended to normalize during euthymia. A previous study of our group has shown increased plasma levels of TNF-alpha and IL-6 in the serum of patients at both early and advanced stages of the illness, as well as a reduction in IL-10 levels in those at more advanced stages [40]. Moreover, changes have been reported in oxidative stress markers, especially nitrotyrosine levels, in early stages of bipolar disorder, as well as in the levels of antioxidant enzyme systems [glutathione] in advanced stages [45]. These findings are in line with another study, also involving patients with bipolar disorder, which found increased DNA damage in association with severity of depressive and manic symptoms [46].

Overall, the changes in biomarkers described above seem to be part of the progression mechanisms underlying bipolar disorder, as many of them are found to be more pronounced at more advanced illness stages. Future studies should investigate the neuroprotective role of early therapeutic interventions targeting biological markers associated with bipolar disorder [47].

Staging and neuroimaging

Morphometric studies have shown important neuroanatomical changes in patients with bipolar disorder, including enlargement of lateral ventricles and of the third ventricle [49], loss of hippocampal, fusiform, and cerebellar gray matter [48], volume decline in prefrontal cortex areas [48, 50], and white matter hyperintensity [51, 52]. Also, enlargement of the amygdala has been identified in association with illness progression [50, 53, 54], contrasting with the smaller size of the structure at early stages. Volume deficits such as decreased white matter density, can also be found in bipolar patients [55]. Finally, loss of white matter in the prefrontal cortex can be observed as early as in the first manic episode, becoming more evident after multiple episodes [56-58]. A reduced anterior cingulate cortex volume [59], as well as reduced cingulate gray matter density [60], have also been reported. Basal ganglia have been reported to undergo shape [61] and volume alterations [53, 62], particularly in the striatum, at both early and late stages of bipolar disorder [61]. Recently, in a case series, we have shown a significant enlargement of ventricles in a patient at an advanced illness

stage compared with another patient at an early stage, underscoring the importance of achieving a better understanding of the biological basis of progression in bipolar disorder [63]. Neuroanatomical changes, especially those involving limbic structures [hippocampus, amygdala, and prefrontal cortex] are very likely to be directly related with the poor cognitive functioning observed in patients with bipolar disorder [48].

Staging, cognition, and functioning

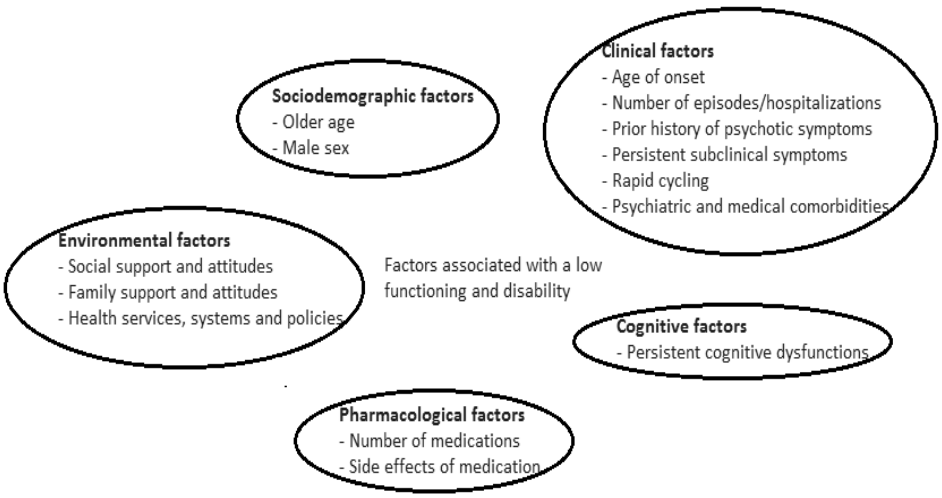
Evidence has shown that many patients with bipolar disorder present cognitive deficits. These deficits are primarily observed during acute episodes, but some of them persist, in a milder form, during clinical remission [5, 53]. The cognitive areas most commonly affected are executive functions and verbal memory; other domains, e.g., inhibitory control, sustained attention, psychomotor speed, and abstraction, may also be affected [15, 64, 65]. Olvet et al. assessing cognitive functioning in individuals at high risk for developing psychosis, showed similar intelligence quotient values in patients who developed bipolar disorder/schizophrenia and in those who did not develop such disorders [66]. Notwithstanding, several studies have shown a strong correlation between cognitive deficits and mood episodes [5]. One study conducted by Lopez-Jaramillo et al. observed worse cognitive performance in euthymic patients who had had at least three manic episodes vs. patients with one single episode [67]. In addition to mood episodes, the presence of subclinical depressive symptoms also seems to negatively affect cognition [68, 69] and psychosocial functioning [70, 71]. In this context, a study carried out by Bonnín et al. has shown that patients with subthreshold depressive symptoms [scores 4-7 on the Hamilton Rating Scale for Depression [HDRS]] had a higher degree of cognitive impairment, as assessed by the California Verbal Learning Test, than those with no symptoms [HDRS $\leq$ 3] [72]. Additional factors, such as number of hospital admissions, length of illness [15], and psychiatric comorbidities [73], also seem to play a role in the poorer cognitive functioning observed in this population [74].

Cognitive deficits, in turn, are related with a worse clinical course and poorer psychosocial functioning [72, 15, 75]. In particular, verbal memory and learning deficiencies have been identified as strong predictors of functioning in patients with bipolar disorder in a 4-year follow-up study [68]. In this context, some investigators have shown that patients with poorer executive functioning tend to face more difficulties performing daily activities [76, 77]. In a study by Martínez-Arán et al. the main differences between patients with high and low psychosocial functioning were memory deficits and executive dysfunction. These findings probably indicate that memory deficits lead to more significant difficulties remembering information in the long-term, which in turn could be directly associated with poorer social and occupational functioning [15].

Bipolar disorder has been initially thought to show functional recovery in inter-episode periods but most of the current studies point to marked cognitive deficiency even during euthymia. Impairment may affect various areas of functioning, e.g., autonomy, work, cognition, interpersonal relationships, and financial status [16, 78], and seems to take place already at the initial phases of illness, during the first mood episode [79], becoming more pronounced as the illness progresses [80]. Reed et al. in a large-scale longitudinal European study, reported higher rates of symptomatic and functional recovery in patients treated after the first mood episode than in those with multiple episodes [81]. Similar results have been found in a population of Spanish patients with bipolar disorder: more severe functional impairment [both overall and in specific domains] was found in individuals with multiple episodes vs. those with first episode [80]. Despite the large body of evidence showing the impact of a higher number of episodes on the functioning of patients with bipolar disorder, other markers of severity, e.g., presence of depressive subclinical symptoms, suicide attempts, and underdiagnosis, may also contribute to poorer psychosocial functioning [83]. Reinares et al. investigating the best predictors of prognosis in bipolar disorder, showed that four clinical features, namely episode density, residual depressive symptoms, estimated verbal intelligence, and inhibitory control, were strongly associated with a worse course of the illness [83].

In summary, all these studies seem to suggest that the frequency of mood episodes and the length of illness have a negative impact on the patient's cognitive and psychosocial functioning. This scenario underscores the need for new therapeutic strategies focused on preventing the progression of bipolar disorder, as well as on restoring the cognitive and functional ability of these patients.

Figure 1: Factors associated with poor psychosocial functioning



Adapted from J. Sanchez-Moreno et al., 2009 [73]

Neuroprogression and treatment response

Bipolar disorder progression is strongly related to poorer treatment response. For instance, a poorer response to lithium has been associated with a higher number of episodes [8, 84], and a more effective response to olanzapine, with earlier stages [85]. Some subgroups of patients tend to respond poorly to the use of lithium, including those with a rapid cycling course and dysphoric mania [86]. Patients with comorbid alcohol and drug abuse and those who do not have first-degree relatives with bipolar disorder are also included in this group [87]. Other predictors of poor response to treatment include at least three mood episodes in the past 3 years [88] and a diagnosis of borderline personality disorder [85]. In an observational study assessing 221 patients with bipolar I and II disorders, Pacchiarotti et al. identified factors associated with response to treatment with antidepressants. Respondents [those showing at least 50% reduction in relation to baseline HDRS scores after 8 weeks of treatment] included patients with previous response to antidepressants and with psychotic symptoms. Non-respondents, in turn, showed a higher number of antidepressant-induced manic switches in previous depressive episodes, history of atypical depression, in addition to a higher number of depressive and hypomanic episodes – but not of manic or mixed episodes – in comparison with respondents [89]. From a psychosocial point of view, changes have also been reported in association with a higher number of relapses, and may include a poorer response to cognitive-behavioral therapy [9] or family psychoeducation [33].

Despite the consistent body of research on the treatment of bipolar disorder, further studies are warranted to contribute new findings to the development of both pharmacological and psychotherapeutic interventions, specifically designed according to early or advance illness stages.

Conclusion

Biological, cognitive and functional impairment seem to be strongly related to the course of bipolar disorder. This supports the notion of the use of staging models in this illness. In these models, patients are classified according to a disease continuum that ranges from early, more favorable periods, to periods of incomplete remission. The literature suggests that early interventions are associated with an improved response to treatment, fewer relapses, and the possibility to prevent illness progression to more advance stages. Primary prevention could be used as a therapeutic tool in individuals at high risk for developing psychiatric illnesses and also in patients at stage I. In this context staging models for bipolar disorder may guide treatment planning and better inform patients and their family members of what could be expected in terms of prognosis.

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Financial & competing interests disclosures

Prof. Kapczinski has received grant/research support from Astra-Zeneca, Eli Lilly, Janssen-Cilag, Servier, CNPq, CAPES, NARSAD, and the Stanley Medical Research Institute; has been a member of the speakers` boards of Astra-Zeneca, Eli Lilly, Janssen and Servier; and has served as a consultant for Servier.
Dr. Rosa has served as speaker for Eli Lilly.
Dr. Kunz, Dr. Rodrigues and Dr. Ascoli declare that they have no competing interests.