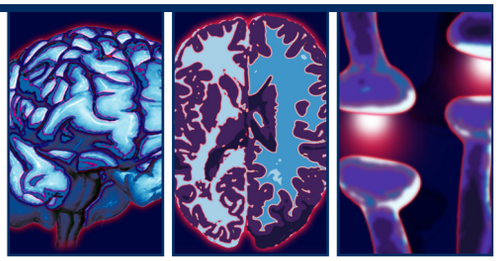

Should bipolar disorder be considered a systemic illness?

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Practice points

- Apart from the core features related to mood dysregulation, bipolar disorder correlates with cognitive deterioration, psychiatric comorbidities and poor physical health.
- The concept of allostatic load offers a means to bridge the burden of recurrent mood episodes and the neural and bodily wear and tear that take place among a large number of patients with bipolar disorder.
- Early and effective treatments hold the potential to protect patients from more severe clinical presentations, which include cognitive decline, psychiatric comorbidities and poor physical health.
- While novel treatments based on the concept of allostatic load are awaited, the use of currently available drugs for the cross-sectional treatment of subthreshold depressive symptoms and the prevention of further manic episodes are warranted.
- Psychoeducation, promotion of healthy habits and cognitive remediation techniques may provide useful means to reduce the allostatic load associated with bipolar disorder.

SUMMARY Recent evidence suggests that bipolar disorder is associated with increased rates of medical comorbidities as well as reduced life expectancy. The concept of allostatic load has been instrumental in bridging mental and physical illness and may help us understand the medical burden of bipolar disorder. We review the work of our group and others on this topic and put forward the notion that systemic pathophysiological changes may occur in parallel with the course of bipolar illness.

Bipolar disorder (BD) is one of the world's ten most disabling conditions, diminishing years of health functioning [1]. The prevalence of the classic manic–depressive disorder is approximately 1% across all populations [2] and that of bipolar spectrum disorders is 4.4% in the USA [3]. The cost of BD involves not only the expenses directly associated with psychiatric

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treatment but also enormous medical care costs associated with general clinical care [4], as well as indirect costs related to inability to work, work loss [5] and intangible costs such as family burden [6,7], which may be reflected on a elevated tax of single marital state [8]. Moreover, despite similar levels of education, BD patients have lower social and occupational function than the general population, which is related to persistence of low-grade depressive symptoms [8–10].

This is due not only to manic or depressive episodes of the illness, but also to cognitive impairment as well as psychiatric and medical comorbidities. Evidence suggests that BD patients may have cognitive impairment [11]. Such cognitive impairment may be evident during manic and depressive episodes as well as in euthymia [12–15]. The persistent cognitive deficits during euthymia may include functions such as attention, executive function and verbal memory impairment [14–17].

In addition, psychiatric comorbidities have been reported among 27.4% of euthymic BD patients [18] or even higher when noneuthymic patients are considered [19].

More recently, attention has been drawn to medical comorbid conditions commonly associated with BD. The most common of such comorbidities are cardiovascular disease (CVD), diabetes mellitus, obesity and thyroid disease [20]. Independently from pharmacological treatment, patients with BD have been shown to be at high risk for obesity, hypertension, diabetes and cardiovascular mortality [1,21–23].

The systemic burden of BD can be studied in light of the concept of allostatic load (AL) [24]. Allostasis, defined by McEwen and Stellar, is the ability to achieve stability through change produced by adaptive mechanisms that help us to deal with daily life situations, such as being awake, asleep or hungry [25]. AL refers to the cumulative, multisystem view of the physiologic toll that is required for adaptation. Within limits, mechanisms related to allostasis are adaptive to demands [26]. However, out of them, AL can increase causing systemic extra load [27].

The concept of AL helps bring together differential dimensions, such as cognitive dysfunction, psychiatric comorbidities and medical comorbidities, reported among patients with chronic mental disorders such as BD **(Figure 1)**. Here we review evidence of systemic illness in BD in the light of the concept of AL.

Cognitive dysfunction in BD

Bipolar disorder is associated with significant neurocognitive deficits across all mood states [Vieta E, Popovic D, Rosa A *et al.*: The clinical implications of cognitive impairment and allostatic load in bipolar disorder (2011), Submitted] including euthymia. However, this impairment increases during mood episodes [13]. Such dysfunction seems to be related to the severity of disease as well as the presence of psychotic symptoms, longer duration of illness and higher number of manic episodes [17]. The importance of neurocognition resides in its correlation with functional outcome, even in the absence of residual symptoms [16]. Performance on executive tasks has shown a positive relationship with occupational status and a negative one with longer illness duration, higher number of hospitalizations, suicide attempts and greater number of previous manic episodes [13]. Poor functional outcome in BD has also been associated with poor premorbid functioning, prominent major or minor depressive morbidity, less educational level and training, drug abuse, weak social support and poverty [28,29].

During euthymia, persistent cognitive deficits may include executive function, verbal memory and attention [12,14,15]. These cognitive dysfunctions may reflect abnormal activation patterns in the brain [30,31], implicating the prefrontal cortex in the etiopathogenesis of bipolar illness and suggesting cortical–subcortical–limbic dysfunction in BD [32]. Such deficits may not be specific to the disorder. In fact, the pattern is qualitatively quite similar to the one found in schizophrenia, albeit overall less severe [33,34]. It is not yet clear if deficits in executive function and verbal memory are related one to another [Vieta E, Popovic D, Rosa A *et al.*, Unpublished Data]. Moreover, the putative existence of premorbid cognitive deficits is being researched. Several investigations have studied cognitive impairment in a large cohort of children or youths and analyzed the profile of those who would develop BD or schizophrenia [35,36]. On the whole, those who were diagnosed with schizophrenia suffered from severe deficits that were not detected in those diagnosed with BD [Vieta E, Popovic D, Rosa A *et al.*, Unpublished Data] [35–37], with the possible exception of visuospatial reasoning [38].

The differentiation between BD type I (BD-I) and type II (BD-II) is described in the Diagnostic and Statistical Manual, Fourth

Edition, Text Revision (DSM-IV-TR) [39]. Studies report that patients with BD-II tend to present a more chronic course of illness with more frequent depressive episodes and shorter euthymic phases as well as more rapid cycling [40,41]. This evidence suggests that BD-II may not simply be a milder form of BD-I [42,43]. Cognitive impairment has been described in both BD-I and BD-II. Cognitive performance tends to be better in BD-II than in BD-I but it is worse overall in patients as compared with controls [44–46]. BD-I patients tend to present a more widespread cognitive dysfunction both in pattern and magnitude and a higher proportion have clinically significant cognitive impairment [45]. The best predictors of poor psychosocial functioning in BD-II seem to be the presence of subthreshold depressive symptoms, early onset of illness and poor performance on executive functions [46].

Evidence suggests that multiple episodes, particularly manic and psychotic episodes, would lead to more severe cognitive impairment [13,17]. These findings have been corroborated by neuroimaging studies, where patients with multiple episodes are more likely to have enlarged ventricles and gray matter atrophy than first-episode patients [47]. While depressive symptoms may have a greater cross-sectional impact on cognition, in the long term it is the manic episodes that count most, implying that the treatment of current depressive symptoms, even when mild, and the prevention of further manic episodes, would be some of the most effective tools to avoid the progression of cognitive impairment.

The role of iatrogenic factors, such as long-term pharmacotherapy or polypharmacy, on neurocognitive dysfunction is under investigation [48]. Most of the current data come from cross-sectional studies that retrospectively assess the clinical course of illness and thus, limit the possible inferences that can be drawn on causality **(Figure 1)** [49].

Psychiatric comorbidities in BD

Substantial clinical and community data indicate that BD co-occurs with substance use, anxiety, personality, eating and impulse-control disorders [3,50–53]. The prevalence of comorbid psychiatric disorders is elevated in BD [19] and its presence is associated with worse prognosis, earlier onset, lower remission rates, suicidal behavior, lower response to treatment, worse functioning and quality of life [Vieta E, Popovic D, Rosa A *et al.*, Unpublished Data] [18,19,54–56] . The most frequent comorbidities are substance use and anxiety disorders [3,54].

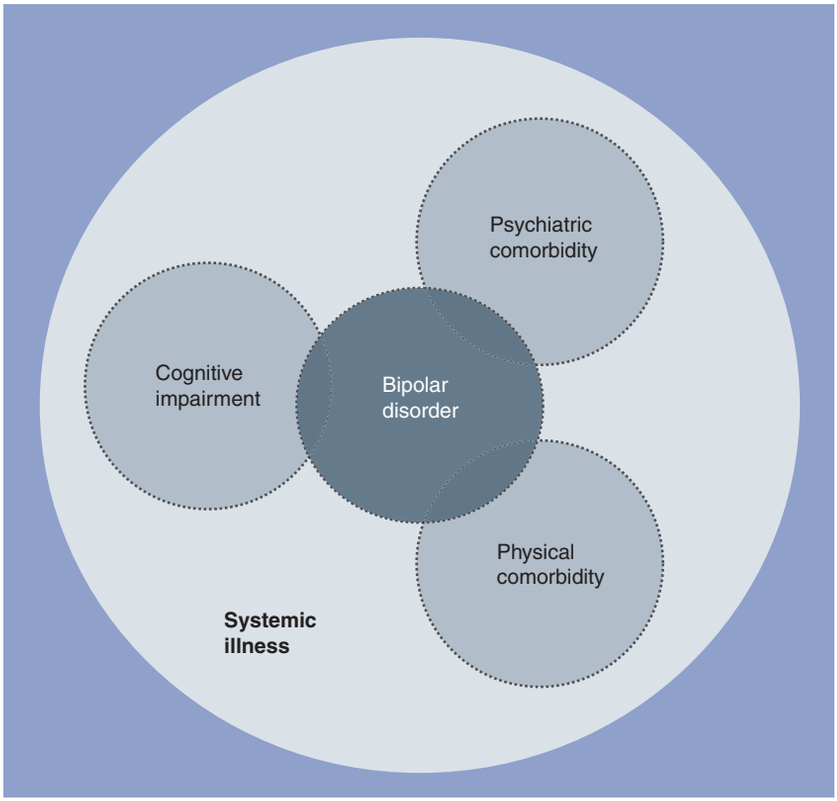

Figure 1. Patients with bipolar disorder may suffer from cognitive dysfunction, psychiatric and/or physical comorbidities.

In a recent study [57], suicidal behavior was evaluated in BD patients with and without alcohol use disorder. More than half of the respondents who met criteria for BD also reported alcohol use disorder. Those who reported both disorders were at greater risk for suicide attempts than those individuals without alcohol use disorder and were more likely to have comorbid nicotine dependence and substance misuse disorders. Ostacher *et al.* reported that BD patients with lifetime smoking were more likely to have an earlier age at onset of mood disorder, greater severity of symptoms, poorer functioning, history of a suicide attempt and a lifetime history of comorbid anxiety and substance use disorders [58]. Conversely, co-occurring substance use was also associated with poor response to mood stabilizers and cognitive impairment [59,60]. Ostacher *et al.* also reported that current or past substance use disorders were not associated with

longer time to recovery from depression but may contribute to greater risk of switch into manic, mixed or hypomanic states [58].

Evidence suggests a strong association between BD and anxiety disorders since they are significantly more frequent during the lifetime in individuals with BD than in the general population [51,54,61–63]. In a recent study conducted by Mantere *et al.,* it was shown that anxiety levels were associated with depression levels both cross-sectionally and longitudinally in BD [54]. The comorbidity with obsessive–compulsive disorder was more strongly associated with poor outcomes than other anxiety comorbidities [64]. Considering attention deficit/hyperactivity disorder, systematic studies of children and adolescents with a diagnosis of BD have shown comorbidity rates ranging from 60 to 90% [65,66]. In adults with BD, lifetime attention deficit/hyperactivity disorder is a frequent comorbid condition associated with a worse course of BD and greater burden of other psychiatric comorbid conditions [53,67]. Eating disorders have also been associated with BD. A large amount of patients with BD have referred suffering from anorexia nervosa, bulimia nervosa and binge eating disorders as well [52,68–70]. In the National Comorbidity Survey-Replication, BD-I and -II were reported to be associated with bulimia nervosa and binge eating disorder, but not with anorexia nervosa [71].

It is known that recurrent episodes influence the outcome by increasing the vulnerability to subsequent episodes, as well as by reducing the response to therapy [72]. For example, lithium response is inversely correlated with number of episodes [73] and duration of illness prior to starting treatment [74]. Consistently, olanzapine was found to be more effective early in the course of BD [72]. The same findings were replicated in the field of psychosocial treatments, where patients with multiple recurrences do not seem to respond to adjunctive cognitive behavioral therapy [75] or family psychoeducation [76]. See **Figure 1**.

Medical comorbidities in BD

Bipolar disorder ranks as the sixth leading cause of disability in the world [77]. The healthcare utilization costs of BD patients are four-times greater than costs for nonbipolar patients [78] and a considerable part of this is assigned to medical illness [79]. It may be argued that the reasons for high medical comorbidity would be the inadequate access to quality care, poor lifestyle choices and adverse effects of treatment [80–82]. However, it is highly probable that the pathophysiology underlying BD fosters the development of a variety of medical disorders [49,83].

The medical problems that have most commonly been associated with BD are CVD, diabetes and obesity [84–88]. Apart from higher burden of general medical comorbidity, patients with BD suffer from them earlier [89]. One of the possible explanations for this could be accelerated aging. Simon *et al.* in a preliminary study for a chronic stress model of accelerated aging reported shortening of telomere length equivalent to 10 years of accelerated aging in BD patients compared with controls [90].

The most prevalent disorders reported in patients with BD are hypertension followed by hyperlipidemia and diabetes [87,88,91]. These do not only seem to be associated with increased morbidity and medical costs but also with increased mortality. Angst *et al.* studied the mortality rate of patients with mood disorders in the longest recorded prospective study of this kind, with a follow-up of 34–38 years [84]. They confirmed an increased risk of death by CVD and cerebrovascular disorders apart from suicide. In Sweden, the rates were twice those of the general population [92]. In particular, BD-I patients had a significantly higher mortality due to cerebrovascular diseases than BP-II patients. Conversely, medical burden has also been related to a worsened BD and a slow improvement throughout the course of treatment [93–95].

A high prevalence of metabolic syndrome in patients with BD has been widely reported around the world [21,96–102]. A third of patients with BD meet criteria for metabolic syndrome, a group of risk factors prominently associated with the development of heart disease, stroke and Type 2 diabetes [103,104]. Metabolic syndrome-related illnesses may be associated with more complex illness presentations and greater severity of mood symptoms. For instance, different studies have reported higher rates of depressive symptoms [105], more attempted suicides among patients with concurrent metabolic syndrome [104] or longer duration of illness and major disability [106]. Moreover, in patients with rapid-cycling BD who received lithium and valproate, medical comorbidities such as endocrine or metabolic diseases appear to be associated with greater depressive

symptom severity and poorer treatment outcomes [83]. Considering atypical antipsychotics, BD patients who received that treatment presented with metabolic syndrome rates similar to schizophrenia [107].

Considering obesity, clinical and epidemiologic studies reveal more than half of BD patients are either overweight or obese [83,108,109]. This finding appears to be independent of treatment [21]. Obesity may also involve a poorer treatment outcome [110] and increased lifetime number of depressive and manic episodes as well as more frequent relapses, particularly depressive episodes [85]. Adiposity disposition is also of concern, since women with BD seem to have more visceral fat in abdominal regions than in obese controls [111]. Visceral fat is metabolically active and secretes proinflammatory cytokines and other acute phase reactants that have been correlated with increased severity of depressive symptoms [112]. Elmslie *et al.* compared anthropometric characteristics of 89 patients with BD with controls matched for age and sex [108]. They described that obesity was more prevalent and body fat was more centrally distributed in pharmacologically treated BD patients than in matched population controls. In a later study [113], these authors evaluated the lifestyle of patients in order to identify causes of overweight and found that patients reported less physical activity than controls. They suggest that medication may change food preference and lead to excessive energy intake, such as high intake of sucrose and energy-rich beverages. At the same time, patients reported less physical activity than controls.

Visceral adiposity coupled with insulin resistance and associated with hypercortisolemia can act synergistically to worsen cardiovascular outcome and augment risk for development of Type 2 diabetes mellitus and hyperglycemia [114]. Diabetes mellitus is extremely prevalent in BD [96,115] and is associated with a worsening evolution of the disorder and more lifetime psychiatric hospitalizations **(Figure 1)** [86].

AL, cognitive decline & comorbidities

The concept of AL has provided a link between apparently separated dimensions such as cognitive dysfunction and bodily 'wear and tear,' which have been reported among patients with chronic mental disorders such as BD [24]. AL refers to the cumulative, multisystemic view of the physiologic toll that is required for adaptation. On the one hand, adaptive mechanisms are protective but on the other hand, adaptation is the price to pay for this forced re-setting of parameters, particularly when allostatic processes become extreme or inefficient [116]. For instance, this may take place when mediators of allostasis are not turned off once stress is over, when they are not turned on adequately during stress or when they are overused by many stressors [117]. An example of the trade-off related to allostasis is provided by the physiology of glucocorticoids. Acutely, they promote allostasis by regulating the availability of energetic compounds. However, chronic elevated levels of glucocorticoid may induce a 'domino effect' on interconnected biological systems that overcompensate and eventually collapse themselves, leaving the organism susceptible to stress-related diseases [117,118]. Chronic elevated levels of glucocorticoids may induce insulin resistance, diabetes, obesity, atherosclerosis, hypertension and increase risk for physical and cognitive decline [119,120]. These disorders are also described in patients with the highest AL [119–125].

Allostasis is regulated by the brain, the major regulator of the neuroendocrine, autonomic and immune systems, as well as behavior. Alterations in brain function due to chronic stress can, therefore, have direct and indirect effects on the cumulative AL. The brain exerts an integrative role in the process of stress response, as it orchestrates the action of a series of primary mediators such as stress hormones, cytokines, oxidative stress and neurotrophins, which intervene in the cardiovascular, metabolic and immune adaptive systems. Moreover, alterations in limbic circuitry have been detected in BD patients [27]. Findings suggest that the amygdala and its related circuits seem to be overactive but dysfunctional in patients with BD [126,127].

The more chronic psychosocial stress and emotional dysregulation exists, the more AL increases, resulting in a wear and tear of the organism as a whole [121]. Hence, AL translates into cognitive impairment, psychiatric and medical comorbidites [49]. Impairment in cognitive function has been demonstrated in manic, depressed and euthymic BD patients [17,128]. Comorbid psychiatric disorders, particularly substance abuse and anxiety disorders, are described in BD patients [19] and increased prevalence of diabetes mellitus, hypertension,

ischemic heart disease and stroke has also been documented in BD patients, as well as twofold mortality rates from CVD compared with the general population [84]. In this sense, AL offers a theoretical connection between the effects of systemic effects in BD.

Conclusion

The concept of AL has been operational in bridging BD and cognitive dysfunction, psychiatric comorbidities and systemic deterioration that is often found among BD patients [24]. The implication of increased AL in BD may contribute to cognitive and functional impairment [13–15], psychiatric [129] and medical [1,22,130,131] comorbidities and mortality [84]. For this reason, early intervention in BD is of critical importance in order to prevent malignant transformation to rapid cycling, spontaneous episodes and refractoriness to pharmaceutical treatment, and to reduce medical comorbidity [132].

Future perspective

Recent evidence suggests that BD is related to differential psychiatric and medical dimensions beyond mood dysregulation. Recent studies show that the cognitive impairment related to BD may be attenuated using medications that do not primarily target mood stabilization, such as mifepristone [133]. In addition, recent data from clinical trials suggest that treatment with antioxidants, such as *N*-acetyl-cysteine [134], may be helpful in patients with BD. In this sense, treatments developed to target the systemic dimension of BD may provide a new avenue for preventing the neuroprogression that may take place among patients with BD [135].

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