Biomarkers and staging of bipolar disorder: a systematic review

Dos biomarcadores ao estadiamento do transtorno bipolar: uma revisão sistemática

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Abstract

Introduction: A growing body of evidence suggests that bipolar disorder (BD) is a progressive disease according to clinical, biochemical and neuroimaging findings. This study reviewed the literature on the relationship between specific biomarkers and BD stages.

Methods: A comprehensive literature search of MEDLINE and PubMed was conducted to identify studies in English and Portuguese using the keywords biomarker, neurotrophic factors, inflammation, oxidative stress, neuroprogression and staging models cross-referenced with bipolar disorder.

Results: Morphometric studies of patients with BD found neuroanatomic abnormalities, such as ventricular enlargement, grey matter loss in the hippocampus and cerebellum, volume decreases in the prefrontal cortex and variations in the size of the amygdala. Other studies demonstrated that serum concentrations of neurotrophic factors, inflammatory mediators and oxidative stress may be used as BD biomarkers.

Conclusions: The analysis of neurobiological changes associated with BD progression and activity may confirm the existence of BD biomarkers, which may be then included in staging models that will lead to improvements in treatment algorithms and more effective, individually tailored treatment regimens. Biomarkers may also be used to define early interventions to control disease progression.

Keywords: Bipolar disorder, neuroimaging changes, neurotrophic factors, inflammation, oxidative stress, staging.

Resumo

Introdução: Níveis crescentes de evidência sugerem que o transtorno bipolar (TB) exibe um caráter progressivo, em nível tanto clínico, quanto bioquímico e neuroimagiológico. Este estudo revisa a literatura existente sobre a relação entre biomarcadores específicos e estágios do TB.

Métodos: Uma busca extensa da literatura nas bases de dados MEDLINE e PubMed foi conduzida para identificar estudos publicados em inglês e em português utilizando as palavras-chave biomarker (biomarcador), neurotrophic factors (fatores neurotróficos), inflammation (inflamação), oxidative stress (estresse oxidativo), neuroprogression (neuroprogressão) e staging models (modelos de estadiamento), em referência cruzada com o termo bipolar disorder (transtorno bipolar).

Resultados: Estudos morfométricos em doentes bipolares mostraram a existência de alterações neuroanatômicas, tais como o alargamento dos ventrículos, a perda de substância cinzenta no hipocampo e no cerebelo, a diminuição do volume de determinadas áreas do córtex pré-frontal e variações no tamanho da amígdala. Além disso, outros estudos apontam para a potencialidade do uso dos valores séricos dos fatores neurotróficos, de mediadores inflamatórios e de estresse oxidativo como biomarcadores do TB.

Conclusões: O conhecimento das alterações neurobiológicas, associadas à progressão e atividade do TB, é fundamental para a identificação de biomarcadores. A incorporação de biomarcadores nos modelos de estadiamento do TB poderá permitir um aperfeiçoamento dos algoritmos terapêuticos, possibilitando a elaboração de esquemas de tratamento mais personalizados e eficazes, com destaque para a importância da intervenção precoce na atenuação da progressão da doença.

Descritores: Transtorno bipolar, alterações neuroimagiológicas, fatores neurotróficos, inflamação, estresse oxidativo, estadiamento.

Introduction

Bipolar disorder (BD) is a chronic, often serious psychiatric disease with a prevalence of 1% to 3% worldwide.[1] According to the World Health Organization, BD is the 12th most important cause of disability in the world,[2] and its morbidity and mortality are significant. The reduction of mean life expectancy in BD is the result of the high rate of suicides, clearly associated with mood disorders,[3] and the increased prevalence of medical comorbidities, such as heart disease, diabetes, obesity and thyroid dysfunction,[4] found in over 80% of the patients.[5]

A growing body of evidence suggests that BP is a progressive disease.[6-8] In 1899 Emil Kraepelin found that the intervals between mood episodes become successively shorter as the number of previous episodes increases. The same author described that, after a certain number of recurrences, episodes tend to occur more spontaneously, in contrast with initial episodes, which are usually triggered by psychosocial stress factors.[7,9,10] The increase of the number of mood episodes is associated with poorer responses to psychopharmacological treatment.[6,8,11-13] Moreover, changes in cognitive functions are more marked in advanced stages of the disease than in controls and in patients in the initial phases of this psychiatric disorder.[8] Recent studies also showed that cognitive dysfunction and functional deterioration persist even during the euthymic periods in the advanced stages of the disease.[14,15] These clinical findings may be understood as a result of the neuroprogressive events that occur during the long course of BD. Neuroprogression involves a pathologic reorganization of the central nervous system (CNS) and is, therefore, associated with structural and functional changes of the neural substrate, which is involved in mood regulation.[8] Several studies have demonstrated that, in addition to the progression of clinical presentations, there are also biochemical and structural changes that confirm neuroprogression, as biological and neuroimaging patterns are different between the initial and the final phases of BD.[6,16]

The identification of neurobiological and neuroimaging changes associated with BD progression and activity is fundamental for the definition of biomarkers. Together with a clear understanding of the clinical course of the disease, the definition of biomarkers is fundamental for the development of staging models. BD staging models should be based on the progression from an at-risk to a more severe and refractory presentation and should classify patients according to different stages (I to IV). A staging system should be used in clinical practice to select the most appropriate treatment and define early interventions that may control BD progression.[17]

This study reviewed the literature about neuroimaging and neurobiological abnormalities in patients with BD as potential BD biomarkers. The analysis of neurobiological changes will focus on the role of neurotrophic factors, inflammatory mediators and oxidative stress in BD physiopathology, activity and progression, and the importance of BD staging will be reviewed.

Methods

A comprehensive literature search of MEDLINE and PubMed was conducted to identify studies in English and Portuguese using the keywords biomarker, neurotrophic factors, inflammation, oxidative stress, neuroprogression and staging models cross-referenced with bipolar disorder. One hundred and fifty-two articles published from 1899 to 2013 were retrieved. Selection for inclusion was based primarily on the information found in the study abstracts. Moreover, the bibliographies of the selected articles were analyzed. Finally, studies published by experts in this area were also examined. Two articles were excluded because they were written in a language other than English or Portuguese. Other studies were excluded because they did not investigate serum or imaging biomarkers and BD staging.

Results

Potential BD biomarkers

According to the definition adopted by the Biomarkers Definitions Working Group, a biomarker is a "characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[18] Biomarkers may be genes, proteins or other molecules, as well as morphological characteristics, associated with physiological or biological mechanisms.[19] They may be used for several purposes, such as defining prognosis and risk of developing a disease, monitoring response to treatment, establishing new therapeutic targets and elucidating unclear physiopathological processes.[19-21] In BD, biomarkers seem to be important to evaluate disease activity and progression associated with different moods (mood biomarkers), as well as to identify specific characteristics of the disease (trait biomarkers).[19,22]

Serum biomarkers have several advantages: easy collection, low cost, wide availability and possibility of use in large-scale studies.

Studies that investigated serum biomarkers of BD found that neurotrophins, inflammatory factors and

oxidative stress are potential candidates. At the same time, neuroimaging studies found that certain changes in patients with BD might be potential BD biomarkers.

Potential BD neuroimaging biomarkers

The existence of changes in the brain structures of patients with BD has been largely reported in several studies. Morphometric studies of patients with BD found enlargements of the lateral and third ventricles.[23,24] However, abnormal ventricular volumes are not evident from the onset of the disease and are often found only after several mood episodes. In fact, Strakowski et al. reported that the volume of ventricles in patients with BD during the first manic episode was similar to that of healthy individuals, whereas enlarged ventricles were a significant finding only in multiple-episode patients. Eight years after disease onset, lateral ventricles were 122% larger than at the time of the first episode.[24] The same study found that first-episode patients had a larger putamen than healthy individuals, although the difference from multiple-episode patients was not significant. The authors concluded that changes in putamen volume were not associated with BD progression. Nevertheless, studies should investigate whether this may be a neuroanatomic marker of BD traits or vulnerability, particularly if this finding is replicated in family members not affected by the disease.[24]

Other studies found a progressive decline in hippocampal and cerebellar gray matter density in people with BD. As the volume of these structures is smaller in patients with multiple mood episodes than in first-episode patients, the decline in hippocampal and cerebellar gray matter density may be a marker of disease progression.[25] In the same line of investigation, Brambilla et al. found an inverse correlation between cerebellar vermis volume and number of BD episodes.[26]

Several studies also found a reduction in the volume of some areas of the prefrontal cortex.[23,27] However, the results of several other studies do not always confirm it.[19] López-Larson et al. found that although the volume of the prefrontal lobe of patients with BD is similar to that of healthy individuals, there are differences in volume of gray matter in both the right and left prefrontal cortex. Their findings also showed that disease duration may be correlated with a smaller volume of gray matter in the left inferior prefrontal cortex.[28]

In addition to the neurostructural abnormalities mentioned above, an increase in the size of the amygdala was also found in adults with BD.[29] However, studies with children and adolescents with BD have found a decline in amygdala volume.[30,31] According to Hallahan et al., the size of the amygdala is smaller in patients after the first mood episode and in patients not treated with lithium.[32] Therefore, the increase in amygdala volume, the focus of several studies,[33-36] seems to be associated with treatment with lithium.[32,37]

Finally, numerous studies have documented the existence of white matter hyperintensities in individuals with BD. The presence of these abnormalities in deep white matter is about 2.5 times more likely to be found in individuals with BD than in healthy individuals.[38] Gulseren et al. reported that the number of total brain hyperintensities increases with the number of manic episodes. The same authors suggested that these lesions should be used as a biological BD marker because white matter hyperintensities are frequent findings in family members that do not have BD.[39]

Potential serum BD biomarkers

Neurotrophic factors

Neurotrophic factors are a family of essential growth factors for neurogenesis and neuronal differentiation and survival. Neurotrophins also play an important role in synaptic plasticity and modulation of neuronal excitability.[40,41] To this date, more than 50 neural growth factors have been identified.[42] Some other important neurotrophins are the neuronal growth factor, brain derived neurotrophin factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4).[43]

BDNF, the most abundant neurotrophin in the CNS, has a particularly high expression in the amygdala, hippocampus and prefrontal cortex, brain areas associated with the regulation of emotion and several cognitive functions, such as attention, memory and executive functioning.[19,44,45] The role of BDNF in BD pathogenesis has been extensively investigated.[41,44] Recent studies suggested that BDNF might also be used as a biomarker of this mood disorder. Some of these studies showed evidence of promising properties of serum BDNF as a biomarker of BD state. The meta-analyses conducted by Lin and Fernandes et al. indicated that patients in the manic or depressive phase had lower blood concentrations of BDNF than healthy individuals, and that serum BDNF concentrations in euthymic patients were not significantly different from those found in controls.[45,46] These results suggest that serum BDNF may be a potential biomarker of acute episodes. Additionally, preliminary studies by Fernandes et al. found that serum BDNF concentrations differentiate patients in a manic or depressive state from those in a euthymic phase, at a sensitivity of 90% and a specificity of 85%.[45]

In contrast, a recent study found that laboratory measurements of serum BDNF concentrations may distinguish bipolar from unipolar depression at a

diagnostic accuracy of 88% for values equal to or lower than 0.26 pg/mL. The authors compared plasma BDNF concentrations of patients with BD in a depressive state with patients with unipolar depression, and found that the first group expressed lower levels of BDNF.[47] Clinically, the difference between bipolar and unipolar depression remains challenging,[47] as the BD diagnosis can only be made if the patient has at least one manic or hypomanic episode.[48] Therefore, blood BDNF concentrations may be an important element to establish the differential diagnosis between these diseases.[47]

Other studies suggest that BDNF may be a biomarker of disease progression and severity. In this sense, BDNF values are inversely correlated with severity of symptoms of patients with BD.[49,50] To explore the potential of blood BDNF to discriminate advanced and initial BD states, Kapczinski et al. raised the hypothesis that serum BDNF concentrations may discriminate patients with BD for less than 3 years from patients that have had it for over 10 years,[45] at a sensitivity of 100%, specificity of 88% and accuracy of 95% for values equal to or lower than 0.62 pg/mL.[51]

Another potential application of serum BDNF concentrations is the prediction of response to treatment and the control of pharmacological efficacy. In fact, Tramontina et al. found that there is a normalization of blood BDNF levels after appropriate treatment of acute mania.[52,53] Rybakowski and Suwalska, in turn, found that patients with an excellent response to lithium had higher plasma BDNF levels than patients refractory to treatment with this drug.[54]

To clarify the mechanisms that underlie the decline of BDNF levels in patients with BD, several studies have investigated the existence of polymorphisms in the *bdnf* gene. One of the most frequently investigated polymorphisms is a methionine substitution for valine at codon 66 (val66met) in the region of the promoter of the *bdnf* gene. However , studies found divergent results when investigating the association between the val66met polymorphism and BD development.[55-65] Differences in results may indicate that genetic alterations in different ethnic groups, races or populations may confer different levels of susceptibility to BD development.[41]

In addition to BDNF, other neurotrophins are also abnormal in the plasma of patients with BD. Patients with BD have higher serum NT-3 concentrations during mood episodes than euthymic patients or healthy individuals.[43,50,66,67] Neurotrophin 4/5 (NT-4/5) seems to be persistently higher in the blood of patients with BD, regardless of their mood state.[43,68]

Inflammatory factors

Inflammatory factors, also known as cytokines, are proteins or glycoproteins secreted by cells of the immune system in response to noxious stimuli. In the CNS, cytokines act in specific pathways and are associated with mood control, energy and activity.[69] Moreover, inflammatory factors interact with the neuroendocrine system, specifically the hypothalamus-hypophysis-adrenal axis, the autonomous nervous system and the system of neurotransmitters, which includes dopamine, serotonin and glutamate.[69,70]

In the last years, a growing number of publications have suggested that the immunoinflammatory system may be involved in BD physiopathology. In fact, recent studies with patients with BD confirmed the presence of chronic inflammation in this mood disorder.[5]

In general, mood episodes may be classified as proinflammatory states.[43] Brietzke et al. found that patients with BD in a manic state had higher inteleukin-2 (IL-2), IL-4 and IL-6 concentrations than controls, whereas in patients with BD in a depressive state, only the proinflammatory cytokine IL-6 was elevated. The same authors found that, during euthymic states, only the IL-4 levels were elevated.[71] These findings suggest that mania and depression, at a lower grade, are associated with a proinflammatory state.[72] Similarly, Kim et al. found that patients in a manic state have significantly higher concentrations of IL-6 and tumor necrosis factor alpha (TNF-α) than individuals without BD. After six weeks of treatment with mood stabilizing drugs, the same patients had normal IL-6 levels, but TNF-α concentrations remained high. Therefore, those authors suggested that IL-6 might be a marker of manic states.[70]

At the same time, preliminary studies found inflammatory biomarkers capable of discriminating bipolar patients in the initial stage of the disease from those in advanced stages.[61] According to Kauer-Sant'Anna et al., at advance BD stages, serum IL-10 concentrations declined and plasma TNF-α levels increase significantly.[16,73] Kapczinski et al. found that when TNF-α concentrations were equal to or greater than 20.36 pg/mL, patients with BD at advanced stages could be discriminated from patients in initial stages of the disease at an accuracy of 91% and sensitivity and specificity of 97% and 85%,[51] which indicates that TNF-α may be a potential biomarker of BD progression.

In addition to the changes in inflammatory cytokines described above, moderately elevated levels of C-reactive protein are found during manic episodes.[74] Increased concentrations of proinflammatory cytokines, found in patients with BD, may indicate an association with high rates of medical comorbidities, particular heart disease,[5] as these inflammatory changes may be risk factors for the development of obesity, hypertension, diabetes and atherosclerosis.[75] These findings stress the importance of medical evaluations and physical

control of patients with BD, as well as of the definition of adequate treatments to reduce early deaths associated with BD. Comorbidities seem to be not only a consequence of treatment and life style characteristic of individuals with BD, but also a symptom of this psychiatric disorder.[5] In fact, medical burden is part of the early stages of BD.[5] Over 70% of young individuals with BD are estimated to need treatment for chronic medical conditions.[76] Middle-aged individuals with BD, in contrast, develop heart disease and hypertension at a younger age than adults without BD.[77] Therefore, medical burden should be included in BD staging.

Oxidative stress

Oxidative stress is the result of imbalance between oxidant and antioxidant enzymes, which usually results in cell damage. Lower antioxidant levels and an increased production of pro-oxidant agents give rise to oxidative stress, which leads to changes in macromolecules, such as lipid, proteins, carbohydrates and DNA.[43,78] The CNS is particularly vulnerable to oxidative lesions, because the brain uses great amounts of oxygen, which promotes the formation of oxygen free radicals and oxygen reactive species. Moreover, the CNS has a limited antioxidant capacity, and glutathione is the main antioxidant in the brain.[43,79] The antioxidant system is composed of an enzyme, such as superoxide dismutase (SOD), catalase and glutathione peroxidase, and a non-enzyme component, such as glutathione.[43]

The role of oxidative stress in the physiopathology of BD has been investigated in several studies, which consistently reported changes in antioxidant enzymes, lipid peroxidation and levels of nitric oxide (NO), an important marker of oxidative stress.[19,80,81]

The meta-analysis conducted by Andreazza et al. concluded that some of the oxidative stress markers are elevated in plasma or blood cells of individuals with BD, particularly NO and thiobarbituric acid reactive substances (TBARS), markers of lipid peroxidation.[80] The analysis of blood TBARS concentrations in patients with BD revealed that they are elevated during all stages of BD.[82] These results suggest that lipid damage occurs all along the course of this mood disorder.[80] Therefore, these findings suggest that the levels of TBARS may be used as biomarkers of BD progression if future studies confirm that they increase with disease duration. In addition to TBARS, NO concentrations are also elevated in BD, regardless of mood state.[19,83] Andreazza et al. found that there are other oxidative stress markers, such as 3-nitrotyrosine (3-NT), that are elevated in the initial stages of BD.[84]

However, the results of studies about the antioxidant enzyme system are often discordant. Andreazza et al. and Kunz et al. found an increased SOD activity in patients during acute BD episodes, but not in euthymic patients.[43,82,85] Similarly, Machado-Vieira et al. reported an increase in the activity of this antioxidant enzyme in unmedicated patients with BD during a manic episode.[43,86] In contrast, other studies found a decrease in SOD activity during all BD phases,[43] whereas Raffa et al. did not find any differences in SOD levels between patients with BD and healthy individuals.[43,87]

One of the consequences of oxidative stress is DNA damage, and studies with patients with BD have shown an increase in the frequency of DNA damage.[19,43,88] Andreazza et al. described a positive correlation between manic and depressive symptom severity and increased DNA damage.[88] At the same time, DNA damage has also been associated with reductions in telomere length in lymphocytes of individuals with BD.[19,89] According to Saretzki and Von-Zglinicki, telomere shortening may be indicative of cumulative oxidative stress.[90] Moreover, a study with patients with BD concluded that the number of shortened telomeres and mean telomere length are associated with number of depressive episodes along life, but not with type of disease.[6,89] Telomere shortening physiologically occurs after each cell division as part of normal ageing. However, telomere shortening found in individuals with BD seems to be indicative of ageing acceleration in about 10 years. These data may explain the association between BD and early medical comorbidities associated with ageing.[91]

Another element to support the role of oxidative stress in BD is the evidence that antioxidant compounds, such as N-acetylcystein (NAC) are beneficial in the treatment of BD, according to several studies. NAC, a glutathione precursor, efficiently reduces depressive symptoms in patients with BD and improves their functioning and quality of life.[92,93]

Treatment effects of mood stabilizers seem to be associated with their action upon oxidative stress pathways.[19] Patients with BD treated with lithium have a significant reduction of TBARS concentrations and of the SOD/CAT ratio,[19,89] whereas healthy individuals exposed to lithium do not have the same changes.[19,94] These findings suggest that lithium has an antioxidant effect favorable for the treatment of BD.

To evaluate systemic toxicity in BD, Kapczinski et al. compared the concentrations of several markers in patients with BD, healthy individuals and patients with sepsis. One of their notable findings was the impressive magnitude of oxidative damage during acute BD episodes, as high as the level seen in patients with sepsis in some cases.[42,95]

The importance of BD staging

Staging is a widely used tool in Medicine, particularly in cancer and heart disease, and is the basis for the choice of adequate treatment and the definition of a prognosis.[96] However, only recently have the first models of staging of psychiatric disorders been developed.[97]

To build staging models, the course of the disease should be predictable along time,[96] and the disease at the initial stages should usually be associated with a better prognosis and simpler treatment requirements. In addition, treatment efficacy should also be greater in the beginning of the disease, and a subsequent progressive decline should be expected, culminating with resistance to treatment.[98] For this reason, staging models should be constructed in parallel to treatment algorithms, as several stages usually have different treatment needs. Therefore, staging should guide treatment plans and the definition of prognoses.[99]

In the last years, different staging models have been suggested for BD. In 2007 Berk et al. suggested that BD develops from an asymptomatic at-risk stage during which risk factors are active (stage 0). The next is the prodromal stage, during which symptoms are mild and nonspecific (stage 1). After this stage, the first mood episode, usually a depressive episode, occurs (stage 2). The first episode is usually followed by multiple remissions and relapses (stage 3). Finally, individuals with BD may experience a phase characterized by symptom persistence and resistance to treatment, without interepisode symptom remission (stage 4)[17,99] (Table 1).

The initial model described by Berk et al. was later developed by Kapczinski et al., who, in 2009, suggested the adoption of a staging model that included a latent phase followed by four stages (stages 1 to 4). This model describes the progression from a latent (at-risk) stage to a more advanced, treatment-refractory stage. The model developed by Kapczinski et al. requires the longitudinal evaluation of several clinical features, the study of comorbidities, functioning and neurocognition and the definition of biomarkers (Table 1).[17,100]

The staging models described by Berk et al. and Kapczinski et al. are based on the identification of individuals at risk of developing BD because early diagnosis and treatment may critically improve prognosis.[17] According to Berk et al., early interventions are fundamental for neuroprotection.[101] Therefore, the treatment during the initial stages of the disease should primarily focus on neuroprotective strategies, but treatment during more advanced stages should be palliative and rehabilitative to control the consequences of disease progression.[99] The importance assigned to neuroprotective strategies may take psychiatry to a new era of preventive psychopharmacology.[43]

Table 1 - Suggested staging models (adapted by permission)

Berk et al.[98]		Kapczinski et al.[73,100]		
Stage	Description	Stage	Description	Biomarkers
0	Increased risk for mood disorder, asymptomatic period during which a set of risk factors are active.	Latent	Mood change symptoms and anxiety; Increased risk of developing BD; No cognitive dysfunction.	Genetic polymorphisms may determine susceptibility.
1a	Mild or nonspecific symptoms.	1	Well-defined euthymic periods. No psychiatric morbidity between episodes. No cognitive dysfunction.	Serum concentrations: ↑ TNF-α ↑ 3-NT ↑ IL-6, IL-10
1b	Prodromal features: ultra-high risk.			
2	First major manic or depressive (more common) episode.	2	Inter-episode symptoms due to comorbidities. Transient cognitive dysfunction.	Serum concentrations: ↑ TNF-α ↑ 3-NT ↑ IL-6, IL-10 ↓ BDNF
3a	First relapse, subclinical symptoms.	3	Clinically relevant pattern of cognitive and functional impairment (unable to work)	Morphometric brain abnormalities may be present. Serum concentrations: ↑↑ TNF-α ↑ 3-NT ↑ IL-6, IL-10 ↓↓ BDNF
3b	First clinical relapse.			
3c	Subsequent pattern of remissions and relapses.			
4	Refractory to treatment, no symptom remission.	4	Loss of autonomy due to cognitive and functional impairment.	Ventricular enlargement and/or white matter hyperintensities. ↑↑ TNF-α ↑ 3-NT ↓↓ BDNF ↑↑ Glutathione reductase and transferase ↓ IL-6, IL-10

BDNF = brain-derived neurotrophic factor, IL = interleukin, TNF-α = tumor necrosis factor alpha, 3-NT = 3-nitrotyrsosine.

Conclusions

Although the physiopathological mechanisms of BD have not been fully clarified, several publications have suggested that neurotrophic and inflammatory factors and oxidative stress may play a role in the pathogenesis of this psychiatric disorder. Recent studies with individuals with BD pointed to the possibility of using plasma concentrations of neurotrophins, inflammatory factors and oxidative stress mediators as biomarkers of BD progression and activity. At the same time, neuroimaging studies of patients with BD also found structural abnormalities that may be potential BD biomarkers. The adoption of biomarkers to stage BD may improve treatment guidelines and algorithms and lead to the development of more efficient, individually tailored treatment regimens.[73] However, current literature also points to limitations that should not be ignored. To this date, most studies are cross-sectional, and very few are prospective. Moreover, other psychiatric disorders and neurodegenerative diseases present with biochemical and imaging abnormalities identical to those found in BD, which may compromise the use of isolated biomarkers. Therefore, different combinations of serum concentrations and neuroimaging biomarkers may have to be evaluated to improve their sensitivity and specificity. Finally, study findings should be replicated, and longitudinal studies should be conducted to confirm the clinical and scientific validity of biochemical and neuroanatomic abnormalities as biomarkers of BD.

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