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Editorial

The concept of staging in bipolar disorder: the role of BDNF and TNF-alpha as biomarkers

Bipolar disorder (BD) is a highly recurrent and disabling illness. Recent evidence suggests a more deleterious course than previously thought. Episode recurrence itself may be a part of illness progression. Stressors and other environmental influences may complicate this, and contribute to a process of accumulating neurobiological alteration. For instance, a greater number of episodes is associated with a declining response to both psychotherapy and pharmacotherapy, and with increasing episode number, the inter-episodic interval typically becomes shorter. Moreover, contrary to previous suggestions that individuals with BD are asymptomatic between episodes and return to baseline levels of social functioning, recent studies have shown a much less satisfactory picture of the long term outcomes (1). These findings raise a possibility of staging BD based on a continuum of severity and incorporation of neurobiological features, both of which will allow a necessary shift in the diagnostic and treatment approach to BD.

Indeed, staging models, whereby a disorder is characterised according to severity, extension and features, have achieved wide currency in medicine but are still neglected in psychiatry. These models are useful when the disorder seems to follow a specific course, from an initial presentation which has a higher probability of response and recovery that leads to more chronic and difficult-to-treat stages. The current categorical psychiatric classification tells us little about the prognosis of the disorder in each particular patient. Recent research findings in the field could lead to a more informative classification, with course being a potential specifier, analogous to staging methods used in medical illness, in addition to the current axial classification (2). In this context, the initiative to develop a suitable staging method for BD is receiving increasing attention (3).

There are a variety of temporal courses and patterns in BD (4). This trajectory often includes progressive impairment in various areas of functioning, such as cognition, insight and social relationships. These deficits may better indicate illness severity when they persist during remission of mood symptoms. Two staging models have been proposed (1,3), the first emphasising the early stages of the disorder, and by implication, the potential for early intervention, and the second staging model emphasises the inter-episodic period as the most adequate window to perform staging assessment. The stages in the first model are: Stage 0: asymptomatic, at risk, Stage 1, the prodrome, Stage 2, the first episode, Stage 3 recurrence, divided into sub-threshold, threshold and multiple recurrence and Stage 4 is the stage of resistance. The model proposed by Kapczinski includes: Latent Stage: patients at ultra-high risk for developing BD; Stage1: Patients who have the diagnosis of BD and return to their baseline level of functioning when episodes resolve; Stage 2: Mild impairment in functioning due to enduring sub-syndromal BD symptoms or confined to comorbidities; Stage 3: Moderate impairment in functioning due to enduring sub-syndromal BD symptoms which are not resolved with therapy and/or clinically relevant cognitive and functioning; Stage 4: Patients unable to take care of themselves without assistance of family or day-care centres due to unremitting symptoms and/or severe cognitive impairment owing to the disorder.

These models need to be validated using a variety of clinical and biological markers. Recent research suggests that in addition to inter-episodic clinical impairment, neurobiological changes are persistent and even progressive in BD. Biochemical markers have been used in medicine for disease characterisation and diagnosis for decades. They are factors that are objectively measured and evaluated as indicators of normal biological processes or pathogenic processes, and can be very valuable in the diagnosis and prognosis of a medical condition for which a specific therapy is intended. BD has been associated with

abnormalities in some biomarkers, such as brain-derived neurotrophic factor (BDNF) and cytokines such as tumour necrosis factor alpha (TNF-alpha), which may be related to neuronal and glial dysfunction. These abnormalities may be the basis for the long-term poor outcomes in BD but these neurobiological changes have not been prospectively examined at different stages in BD (5,6). However, there is one recent study which suggested that late-stage bipolar patients, i.e. with 10 or more years of illness, are more likely to present lower BDNF serum levels, and higher levels of TNF-alpha when compared with patients in the early stages, defined as a recent first episode (7,8). On the basis of these findings, one can speculate that these biomarkers may be useful for validating the staging model of BD. Notwithstanding the clear difference between BDNF and TNF-alpha levels in the early and at late stages of BD, these changes were not examined in distinct stages of BD, according to most recent proposed models. To further explore this possibility, we conducted a reanalysis of BDNF and TNF-alpha levels at early and late stages of euthymic BD patients (7,8), which showed the ability of both markers to discriminate the late and early stages. For instance, in a receiver operating characteristics (ROC) curve, BDNF had an accuracy of 95% in discriminating the late from the early stages, for a suggested cut-off of 0.62 pg/ml or less, with sensitivity of 100% [95% confidence interval (CI) 88–100%] and specificity of 89% (95% CI 70–98%). Similarly, TNF-alpha had an accuracy of 91% for a suggested cut-off of 20.36 pg/ml or more to identify the late from the early stage, with sensitivity and specificity of 97% (95% CI 83–100%) and 85% (95% CI 65–96%), respectively (Fig. 1). These results make BDNF and TNF-alpha attractive potential biomarkers, with a clinical relevance if replicated with an adequate classification of staging. Staging could become a tool to guide the most suitable treatment to each patient. If correct staging ultimately results in better outcomes, biomarkers may initiate a new era in diagnosing and treatment in psychiatry.

This model would suggest specific, stage-orientated therapeutic approaches (7). Staging would predict that the earlier stages would be associated with better prognosis, a higher likelihood of response, and the need for simpler strategies that would be safer; in contrast, the later stages demand more complex and potentially risky treatments. Moreover, a staging model in BD may further emphasise the need for early intervention and preventive strategies. Early intervention is further associated with lower rates of progression to more severe phases of the disorder (1). In this way, a staging model for BD could augment guidelines and algorithms, refining treatment according to an individualised, needs-based management plan (1). Such differentiated strategies, with a special focus on neurobiological changes, could help preserve the young person's ability to meet

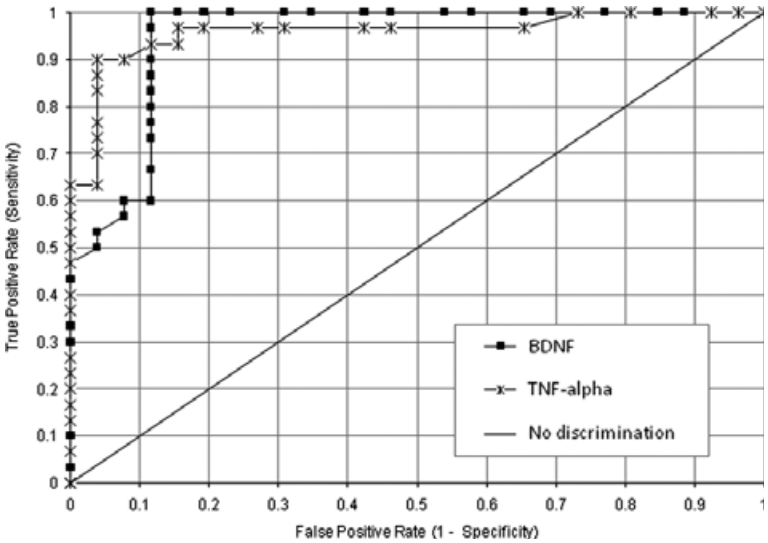

Fig. 1. Receiver operating characteristics curve (ROC curve) for brain-derived neurotrophic factor (BDNF) and tumour necrosis factor alpha (TNF-alpha) as biomarkers of late and early stages in bipolar disorder (BD). For BDNF, the area under the curve (AUC) is 0.95 [95% confidence interval (CI) 0.89–1.00, $p < 0.0001$]. Considering a suggested cut-off value of 0.62 pg/ml or less, the BDNF level as a biomarker of late-stage BD when compared with the early stage has a sensitivity of 100% (95% CI 88–100%) and a specificity of 88% (95% CI 70–98%). For TNF-alpha, the AUC is 0.96 (95% CI 0.91–1.00, $p < 0.0001$). Considering a suggested cut-off value of 20.36 pg/ml or more, the TNF-alpha level as a biomarker of late-stage BD when compared with the early stage has a sensitivity of 97% (95% CI 83–100%) and a specificity of 85% (95% CI 65–96%). Number of patients are 26 in the early stage, and 30 in the late stage.

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age-specific developmental, social, educational and vocational tasks (1).

Taking into account, the evolving knowledge on biomarkers in BD, the integration of a staging model, can assist in integrating evidence into clinical practice, and help to direct treatment options, as different stages may require specific treatment strategies.

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