Staging model raises fundamental questions about the nature of bipolar disorder

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The concept of clinical staging is commonly applied in the management of various medical conditions, including cancer, hypertension, kidney disease or diabetes. In these conditions, the individual stages can be differentiated by clinical presentation and/or by specific biological markers, and they typically inform stage-specific treatment and prognosis. In psychiatry, the model proposes that mental disorders can be described in stages characterized by illness progression. The model further implies increasingly poor clinical course, more severe and refractory illness, and associated impairment in brain function, sometimes accompanied by structural brain changes. Among the first to propose a staging model for psychiatric disorders were Fava and Kellner.[1] Intuitively, the staging hypothesis not only makes sense, but also offers testable assumptions.[2] Its appeal is understandable as current psychiatric practice pays little attention to the longitudinal course of psychiatric disorders. Adding clinical stages provides a perspective that has not been addressed sufficiently in the current nosology, and it may address some of its idiosyncrasies.[1] At the same time, attributing clinical and research observations to illness progression is only one out of several alternative explanations. In this editorial we examine some of the contentious facets of the staging model as related to bipolar disorder.

Staging and heterogeneity in bipolar disorder

The stages of bipolar disorder have been conceptualized by several authors who all agree on certain key points: the illness moves from an at-risk phase (identifiable by family history of the illness) to early nonspecific symptoms to mild mood symptoms.[3] The first full mood episodes of mania and depression are usually followed by remissions, but later on symptoms persist between the episodes, and this more chronic course is often associated with structural and functional brain impairment.[4,5]

The most common argument supporting the staging model for bipolar disorder is the perception that longer duration of illness leads to more pronounced clinical and pathological changes. These include treatment refractoriness, structural brain changes with a loss of grey matter, cortical thinning and ventricular enlargement, neuropathological changes in postmortem studies (reduced glial density) as well as neuropsychological deficits.[4,5]

Clinical and pathophysiological heterogeneity represents an alternative or perhaps complementary concept to uniform progression of bipolar disorder from early to late stages. When heterogeneous groups of patients are examined cross-sectionally they may appear to comprise individuals at different disease stages. Clinical heterogeneity of severe mood disorders has been long recognized; for instance, Kraepelin noted that the majority of patients with manic depressive psychoses had episodic recurrent courses, but there was a recognizable minority of those who had a chronic course of illness with a gradual interepisode deterioration.[6] Arguably, differentiation of the subtypes of bipolar disorder is difficult, and even more so if one adopts only a cross-sectional view of the illness. Thus, staging and heterogeneity may be viewed as complementary aspects of classification. This leads to the question of whether we are looking at illness progression or typology of the illness with distinct patterns of clinical course — at the most basic level an episodic and chronic long-term course. Genetic studies also support the notion of heterogeneity. While genome-wide association studies are finding a number of loci of small effects (which is what these studies are designed to look for), sequencing studies not infrequently report unique families in which the illness cosegregates with genes of large effects.[7]

The gradual shift from conceptualizing bipolar disorder as a recurrent disorder to one that is more chronic and/or recurrent but with significant residual symptoms has been an important development that cannot be overlooked. As the diagnostic criteria for bipolar disorder expanded, the prevalence of bipolar disorder also increased,[8] leading to a more significant impact of heterogeneity. This shift in diagnostic concept of bipolar disorder is exemplified by blurring of the boundaries between a disorder characterized by distinct episodes of mania and depression and one characterized by

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DOI: 10.1503/jpn.160151

"mood swings." It could be that these conditions characterize 2 distinct types of mood dysregulation — 1 with abnormal, refractory mood during affective episodes and 1 with labile, reactive mood. The former might correspond more closely to the historical concept of "manic depressive illness," whereas the latter might be more consistent with the concept of "bipolar spectrum."[9] But any historical comparison is difficult as changes in various aspects of the illness and its management, such as treatment, recognition of cognitive problems, or increased use of brain imaging technologies, are taking place against the background of the changing definition of the illness.

Additional confounders

The stages of bipolar disorder are described in terms of severity of symptoms and quality of remissions as well as associated cognitive and functional impairment. These are often related to one another and to the severity of mood symptoms, and they also may be reversible. In a recent systematic review Strejilevich and colleagues found little systematic evidence of progressive deterioration of cognitive functioning.[10] The staging concept also needs to be reconciled with the notion of cognitive impairment as an endophenotype of severe mood disorders — a presence of functional changes in unaffected family members of bipolar probands.

Psychiatric and medical comorbidites also likely play a role. Psychiatric comorbid conditions are common and contribute to less favourable treatment response and long-term outcome. This effect may be related to illness subtypes for some forms of comorbidities, such as anxiety, or to poor treatment adherence as well as direct drug effects on the brain, such as in substance abuse. But comorbidities seem to be distributed unevenly among bipolar disorder subtypes.[9] Another set of concerns relate to the presence of metabolic disturbances in people with bipolar disorder. Obesity, insulin resistance, and type II diabetes have been all viewed as correlates of poor outcome; their prevalence increases with age and they seem to be related to bipolar disorder in a complex, likely bidirectional way.[11]

Finally, one needs to consider the possibility that iatrogenic effects may create the impression of worsening clinical course and progression from early to later stages. Iatrogenic factors are practically impossible to study systematically for obvious reasons. Yet, clinical observations as well as some case reports suggest that inappropriate treatments may at best prevent recovery and at worst aggravate the clinical course and lead to more chronic illness on the one hand or induce rapid cycling or mixed states on the other hand. This is especially relevant in the prodromal and early stages of bipolar disorder.[12,13] Several brain imaging studies also hint at differences with respect to the effects of various long-term medications on the brain structure, such as volumes of specific brain regions and/or cortical thickness. It will be interesting to see if the observed shift toward anticonvulsants or atypical antipsychotics will lead to an increased prevalence of chronic course and structural brain changes on a population level.

Testing the hypothesis

The staging concept of bipolar disorder is still relatively young, and most tests of the hypothesis have not been performed. Reviewing the predictions proposed by Scott and colleagues,[2] we note the following.

The first testable prediction stipulates that response to treatment in the early stages is more favourable than in later stages. The data in this respect are mixed. Indeed, several trials found patients with longer duration of illness to be more refractory. Examples include the analysis of antimanic response to valproate and lithium[14] and Berk and colleagues'[15] re-analysis of olanzapine maintenance data. Similarly, in a trial of cognitive behavioural therapy only patients who had fewer than 12 episodes of illness improved.[16] The picture is quite different with respect to lithium. Although there are studies suggesting that treatment delay could lead to worse outcome, a number of investigations in typical patients with an episodic course found no such effect[17–19] (see also the review by Calkin and Alda[20]). When viewed in the context of heterogeneity, these observations correspond with the concept of 2 forms of bipolar disorder — 1 that is nonprogressing, recurrent and responsive to lithium and 1 that is more chronic and requires antipsychotic treatment with a better response early on.

The second assumption suggests that the risk:benefit ratio is better in early treatments. In other words, treatments in early stages should be "less noxious" than those applied later. To our knowledge, there is insufficient evidence to refute or support this claim.

Third, it is expected that early interventions will have detectable effects on distribution of later stages among people with the illness. Thus, successful interventions would reduce the prevalence of more advanced stages across populations. Several prospective studies are currently underway that include interventions; an example is the FORBOW project in Halifax, Nova Scotia, Canada.[21] However, early interventions will need to be adopted by a considerably larger number of programs to result in a detectable effect.

The same can be said about the fourth prediction — that early interventions will modify the risk of disease progression within patients. One study in support of this claim is the earlier cited study by Berghofer and colleagues[19] showing that patients stabilized on lithium remained well in follow-up extending up to 20 years with no apparent increase in morbidity in later years of treatment. This hypothesis is also amenable to testing in high-risk studies and may well represent the key test of the staging model.

Finally, it is suggested that the clinical stages will be possible to characterize with biomarkers. Such discovery would indeed strengthen the overall staging concept. But such work will require more precise clinical differentiation of the illness stages before such markers can be developed and tested. And studies validating stage-specific biomarkers will need to consider the alternative explanations as outlined here. For instance, it will be critical to account for medication effects, acknowledging that most treatments for bipolar disorder are not assigned at random.

Keeping these arguments in mind, it appears that the staging concept of bipolar disorder is not at the point where it could be applied clinically. At the same time, it has had a stimulating effect on clinical psychiatry and has directed much-needed focus on long-term clinical course of bipolar disorder and on studies of individuals at risk for the illness.

The role for staging in psychiatry

Overall, the concept of staging has challenged the field to adopt a more careful observation of the longitudinal course of illness. It has also helped to acknowledge that many cases of bipolar disorder are preceded by a prodromal period that often takes place in childhood and adolescence. These insights helped to bring colleagues from the field of adult and child psychiatry to work in an integrated fashion. Indeed, it may be in the field of prodromes and risk assessment that the concept of staging would provide clinicians with a more meaningful contribution. Thus, staging in psychiatry, and more specifically in the field of bipolar disorder, could be a means to emphasize preventative strategies, such as reducing exposure to illicit drugs and trauma and promoting the judicious use of antidepressants, in genetically vulnerable populations. For these reasons alone the staging model deserves our attention and more thorough study.

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Competing interests: None declared.

References

1. Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. *Acta Psychiatr Scand* 1993;87:225-30.
2. Scott J, Leboyer M, Hickie I, et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. *Br J Psychiatry* 2013;202:243-5.
3. Duffy A, Alda M, Hajek T, et al. Early stages in the development of bipolar disorder. *J Affect Disord* 2010;121:127-35.
4. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. *J Affect Disord* 2007;100:279-81.
5. Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. Clinical implications of a staging model for bipolar disorders. *Expert Rev Neurother* 2009;9:957-66.
6. Kraepelin E. *Manic-depressive insanity and paranoia* (English translation by RM Barclay). E. & S. Livingstone, Edinburgh; 1921.
7. Ament SA, Szelinger S, Glusman G, et al. Rare variants in neuronal excitability genes influence risk for bipolar disorder. *Proc Natl Acad Sci U S A* 2015;112:3576-81.
8. MacQueen GM, Hajek T, Alda M. The phenotypes of bipolar disorder: relevance for genetic investigations. *Mol Psychiatry* 2005;10:811-26.
9. Alda M. The phenotypic spectra of bipolar disorder. *Eur Neuropsychopharmacol* 2004;14(Suppl 2):S94-9.
10. Strejilevich SA, Samame C, Martino DJ. The trajectory of neuropsychological dysfunctions in bipolar disorders: a critical examination of a hypothesis. *J Affect Disord* 2015;175:396-402.
11. Calkin CV, Gardner DM, Ransom T, et al. The relationship between bipolar disorder and type 2 diabetes: more than just comorbid disorders. *Ann Med* 2013;45:171-81.
12. O'Donovan C, Garnham JS, Hajek T, et al. Antidepressant monotherapy in pre-bipolar depression; predictive value and inherent risk. *J Affect Disord* 2008;107:293-8.
13. Berk M, Dodd S. Are treatment emergent suicidality and decreased response to antidepressants in younger patients due to bipolar disorder being misdiagnosed as unipolar depression? *Med Hypotheses* 2005;65:39-43.
14. Swann AC, Bowden CL, Calabrese JR, et al. Mania: differential effects of previous depressive and manic episodes on response to treatment. *Acta Psychiatr Scand* 2000;101:444-51.
15. Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord* 2011;13:87-98.
16. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry* 2006;188:313-20.
17. Bratti IM, Baldessarini RJ, Baethge C, et al. Pretreatment episode count and response to lithium treatment in manic-depressive illness. *Harv Rev Psychiatry* 2003;11:245-56.
18. Baldessarini RJ, Tondo L, Baethge CJ, et al. Effects of treatment latency on response to maintenance treatment in manic-depressive disorders. *Bipolar Disord* 2007;9:386-93.
19. Berghöfer A, Alda M, Adli M, et al. Long-term effectiveness of lithium in bipolar disorder: a multicenter investigation of patients with typical and atypical features. *J Clin Psychiatry* 2008;69:1860-8.
20. Calkin C, Alda M. Beyond the guidelines for bipolar disorder: practical issues in long-term treatment with lithium. *Can J Psychiatry* 2012;57:437-45.
21. Uher R, Cumby J, MacKenzie LE, et al. A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. *BMC Psychiatry* 2014;14:344.