psychiatry, namely whether we need models for different disorders if their trajectories (especially early on) overlap in so many ways (e.g., genetics, neuropsychological profile, oxidative stress, sleep–wake cycle).[15] Pluripotential outcomes, transdiagnostic risk factors that could explain mental and physical comorbities, age at peak onset and transitions of subthreshold syndromes often defy classification under current schema, but are likely to be a key part of the new psychiatry.[16] If we decide to adopt clinical staging models, whichever version we choose will challenge us all, as it is not just a case of putting old wine into new bottles (or young wine into old ones!).

Jai Shah, MD, MSc; Jan Scott, MB BS, PhD

Affiliations: From the PEPP-Montreal, Douglas Mental Health University Institute, ACCESS Open Minds, Department of Psychiatry, McGill University, Montreal, Que., Canada (Shah); and the Institute of Neuroscience, Newcastle University, & Centre for Affective Disorders, IPPN, King's College, London, UK (Scott).

DOI: 10.1503/jpn.160196

References

1. Alda M, Kapczinski F. Staging model raises fundamental questions about the nature of bipolar disorder. *J Psychiatry Neurosci* 2016;41:291-3.
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. Kim-Cohen J, Caspi A, Moffitt TE, et al. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 2003;60:709-17.
4. Shankman SA, Lewinsohn PM, Klein DN, et al. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry* 2009;50:1485-94.
5. Wright JR. Albert C. Broders' paradigm shifts involving the prognostication and definition of cancer. *Arch Pathol Lab Med* 2012;136:1437-46.
6. Gonnella JS, Hornbrook MC, Louis DZ. Staging of disease. A case-mix measurement. *JAMA* 1984;251:637-44.
7. Bechdolf A, Ratheesh A, Cotton SM, et al. The predictive validity of bipolar at-risk (prodromal) criteria in help-seeking adolescents and young adults: a prospective study. *Bipolar Disord* 2014;16:493-504.
8. McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry* 2006;40:616-22.
9. Scott J, Hickie IB, McGorry P. Pre-emptive psychiatric treatments: Pipe dream or a realistic outcome of clinical staging models? *Neuropsychiatry* 2012;2: 263-6.
10. Liu P, Parker AG, Hetrick SE, et al. An evidence map of interventions across premorbid, ultra-high risk and first episode phases of psychosis. *Schizophr Res* 2010;123:37-44.
11. Vallarino M, Henry C, Etain B, et al. An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. *Lancet Psychiatry* 2015;2:548-63.
12. Lønning PE. Breast cancer prognostication and prediction: Are we making progress? *Ann Oncol* 2007;18(Suppl 8):viii3–7.
13. Tabák AG, Herder C, Rathmann W, et al. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012;379: 2279-90.
14. McGorry P, Keshavan M, Goldstone S, et al. Biomarkers and clinical staging in psychiatry. *World Psychiatry* 2014;13: 211-23.
15. Bellivier F, Geoffroy PA, Scott J, et al. Biomarkers of bipolar disorder: Specific or shared with schizophrenia? *Front Biosci (Elite Ed)* 2013;5:845-63.
16. Insel TR. Translating scientific opportunity into public health impact: a strategic plan for research on mental illness. *Arch Gen Psychiatry* 2009;66:128-33.

Author response

We are thankful to Drs. Shah and Scott for their comments on our editorial. Their letter gives us an opportunity to expand on and clarify the most relevant points. Our main argument has been that the staging model may not be as fully developed as to be ready for clinical application, but it has had healthy stimulating effect on our field, and we see the letter by Shah and Scott as a testimony to that.

It was not our intention to focus just on stages in fully manifest illness. The importance of recognizing clinical heterogeneity of bipolar disorder is supported by studies of prodromal stages as well. We have been involved in some of the longitudinal high-risk studies of young people at risk for bipolar disorder.[1–3] These studies, among others, described early stages of the illness and their comorbidities[4] as well as neuropsychological functioning[5] and structural brain findings.[6] Based on these studies as well as on observations of other authors, we believe that the point of heterogeneity of bipolar disorder and the need to separate it from the concept of uniformly progressing illness are equally applicable in the early stages as in the latter ones. The prodromes may appear nonspecific and uninformative with respect to future illness trajectories when viewed through the prism of current diagnostic classification. But an alternate phenotypic characterization may identify well circumscribed and more homogeneous subgroups of illness that are continuous with the later stages. This is exemplified by the studies of children of lithium-responsive and nonresponsive parents, showing concordance of the patterns of clinical course (as well as treatment response) between generations.[4,7]

Another point raised by Shah and Scott pertains to the risk:benefit ratio of treatments in different stages, considered more favourable early on. We agree that this is a reasonable assumption, but it remains to be tested, and such testing may not be easy to carry out. A recent review lists a handful of studies, some showing short-term relief of clinical symptoms in young people (frequently treated with medication).[8] However, the lower risk:benefit ratio of these mostly psychosocial treatments is implicitly assumed rather than derived from appropriate comparisons.

We agree with Drs. Shah and Scott that more attention needs to be paid to the early stages of major psychiatric disorders. We also believe that the staging concept is important for psychiatry heuristically as it challenges some of the basic concepts of bipolar disorder. However, before it can be applied clinically, the staging model deserves deeper scrutiny and more support from longitudinal studies.

Martin Alda, MD; Flavio Kapczinski, MD, PhD

Affiliations: From the Department of Psychiatry, Dalhousie University, Halifax, NS, Canada (Alda); and the Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ont., Canada (Kapczinski).

DOI: 10.1503/jpn.160197

References

1. Duffy A, Alda M, Kutcher S, et al. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. *Am J Psychiatry* 1998;155:431-3.
2. Duffy A, Alda M, Hajek T, et al. Early stages in the development of bipolar disorder. *J Affect Disord* 2010;121:127-35.
3. 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.
4. Duffy A, Alda M, Kutcher S, et al. A prospective study of the offspring of bipolar parents responsive and non-responsive to lithium treatment. *J Clin Psychiatry* 2002;63:1171-8.
5. MacQueen GM, Grof P, Alda M, et al. A pilot study of visual backward masking performance among affected versus unaffected offspring of parents with bipolar disorder. *Bipolar Disord* 2004;6:374-8.
6. Hajek T, Cullis J, Novak T, et al. Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. *Biol Psychiatry* 2013;73:144-52.
7. Duffy A, Alda M, Milin R, et al. A consecutive series of treated affected offspring of parents with bipolar disorder: Is response associated with the clinical profile? *Can J Psychiatry* 2007;52:369-76.
8. Vallarino M, Henry C, Etain B, et al. An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. *Lancet Psychiatry* 2015;2:548-63.