Published in final edited form as:
Biol Psychiatry. 2011 October 1; 70(7): 600–601. doi:10.1016/j.biopsych.2011.08.007.

Challenges Associated with Application of Clinical Staging Models to Psychotic Disorders

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Previously, McGorry and colleagues (1, 2) proposed the application of clinical staging models to psychiatric disorders, with a focus on psychoses and severe mood disorders. In this issue, Wood and colleagues expand on this staging model for psychotic disorders, using pathophysiological data and treatment response data to evaluate key predictions associated with a valid staging model (3). The staging model proposed uses clinical criteria to define illness severity stages that progress from relatively few, mild, and non-specific symptoms to an increasing number of more severe symptoms, including psychotic symptoms, neurocognitive impairments, comorbid conditions, and functional decline, culminating in the persistent disabling symptoms of chronic schizophrenia. Each stage is associated with an elevated risk for progression to the next stage. Although some patients progress through all of the stages, progression is not considered inevitable.

Wood and colleagues evaluate their clinical staging model by examining the extent to which pathophysiological data, largely drawn from neuroimaging studies, as well as treatment response data, differentiate between three major clinical stages: ultrahigh risk for psychosis (i.e., putatively prodromal) (Stage Ib), first episode psychosis (Stage II), and chronic persistent schizophrenia (Stage IV). Based on their review of the literature, the authors conclude that neuroimaging and treatment studies provide initial support for three key predictions of their staging model: 1) Structural and, to a lesser degree functional, brain imaging measures are more abnormal in later stage patients than in earlier stage patients 2) Structural brain imaging abnormalities progressively worsen as patients advance from earlier to later stages, and 3) Treatments, including relatively benign treatments such as essential fatty acid supplementation, are more effective in earlier stage patients than in later stage patients. While the authors' current focus is on how their clinical staging model maps onto pathophysiological data, their discussion points toward the longer term goal of staging

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psychotic disorders based on underlying causal pathophysiological measures rather than the descriptive clinical criteria employed in their current model.

In considering the application of clinical staging models to psychiatric disorders, it is instructive to consider how clinical staging has been defined in medicine, as well as the classes of disease to which staging has been applied most fruitfully. According to one definition (4), "Staging defines discrete points in the course of individual diseases that are clinically detectable, reflect severity in terms of risk of death or residual impairment, *and posses clinical significance for prognosis and choice of therapeutic modality*" (p. 637; italics added). The earliest and most important applications of staging models have been in clinical oncology (5). Staging models for other medical diseases have been developed (4), but their clinical utility is not as clear as it is for cancer (5). This is not for lack of evidence of pathophysiological progression of medical illnesses; the natural history of many medical illnesses involves a prodromal period followed by active illness with worsening sequelae, cumulative organ damage, and end stage impairment or mortality. Thus, the fact that an illness is progressive does not in and of itself guarantee that staging models will be useful. Rather, the value of staging models depends on their ability to define illness stages associated with distinct prognoses and treatment choices.

Implementation and widespread use of clinical staging models in psychiatry, including the model for psychotic disorders described by Wood et al., will require overcoming some significant challenges, many of which are considered by Wood et al. in their review. One significant challenge in connection with earlier pre-psychotic illness stages is that clinical ultra-high risk patients may be quite heterogeneous with respect to the pathophysiology and pathogenesis of psychotic disorders. Retrospective data from the North American Prodromal Longitudinal Study indicated that only 35% of clinical high-risk patient convert to a psychotic disorder within 2.5 years (6). Given this, it remains a challenge to distinguish between two alternative hypotheses. One hypothesis is that the pathophyiological processes underlying the development of psychotic disorders, and more specifically schizophrenia, are only present in the subgroup of patients who go on to convert, with the remaining non-converters constituting clinical "false-positives" or "phenocopies". The other hypothesis is that most clinical high-risk patients have reached this illness stage via a common pathogenic pathway that progresses, arrests, or remits depending on other moderating factors such as substance abuse, psychosocial stress, or early intervention. Given this ambiguity, it is difficult to know whether findings of intermediate brain pathology in Stage Ib ultra-high risk patients, relative to Stage 0 asymptomatic at-risk patients and Stage II first episode patients, reflects intermediate pathology in all Stage Ib patients or an admixture of more severe pathology in patients experiencing a true psychosis prodrome and essentially no pathology in patients whose symptoms simply mimic the prodromal syndrome. From the standpoint of staging, it therefore remains unclear whether all Stage Ib patients should be considered to have the same prognosis and treatment response, or whether a useful classification of this early stage must await the development of more precise clinical and/or neurobiological criteria to define a more homogeneous stage with respect to underlying disease processes, prognosis, and treatment.

A second challenge is to establish the incremental clinical utility of discrete stage classifications relative to viewing illness progression as a continuum highly correlated with illness duration. This issue is somewhat more relevant in connection with the transition from first-episode psychosis (Stage II) to chronic schizophrenia (Stage III). To be sure, there are clinical features that, on average, tend to characterize first episode psychosis more than chronic schizophrenia, such as the likelihood that patients will show a more robust treatment response to low dose antipsychotic medication (7) and will more likely experience substantial resolution of their psychotic episode. Likewise, as Wood et al. note, brain abnormalities are more severe in chronic patients relative to first episode patients, suggesting that clinical progression is associated with pathophysiological progression. However, it not clear that staging affords any clear advantage relative to consideration of illness duration as a continuous measure from the perspective of prognosis and treatment choices. Moreover, relative to some neurodegenerative disorders such as Alzheimer's dementia, the progressive clinical course of schizophrenia is accompanied by, and perhaps overshadowed by, waxing and waning symptoms that flare in relation to life stress, medication non-adherence, drug and alcohol comorbidities, and other factors that remain to be elucidated. In this sense, once the illness has set in, prognoses and treatment choices are dictated more by the particular patient's acute presentation qualified by his/her history of illness severity and treatment response and less so by illness duration or the degree of progression through illness stages.

A third challenge is associated with transitioning from clinical to pathophysiological stage definitions. Despite advances in neuroimaging methods that provide multimodal assessments of brain structural and functional integrity, there is no compelling evidence that the pathophysiological data produced by these methods directly reflect the primary pathophysiology that causes illness progression in schizophrenia. For example, to date it has been difficult to demonstrate robust and replicable relationships between brain abnormalities in schizophrenia patients and the severity of their clinical or neurocognitive impairments. Similarly, longitudinal data documenting progressive worsening of brain abnormalities have not been consistently associated with clinical or neurocognitive progression. The tenuous relationships between pathophysiological and clinical data in schizophrenia, and the limitations of current neuroimaging measures to inform prognoses and treatment decisions, are perhaps most obviously illustrated by findings of ventricular enlargement in schizophrenia. As replicable as this finding has been, it can easily be argued that ventricular size *per se* does not regulate symptom severity, clinical progression, or responsiveness to specific treatments. This argument is equally applicable, although perhaps less obvious, for other brain measures that are closer to the structure and function of neural tissue (e.g., gray matter volume, fractional anisotropy of white matter tracts, or task-related brain activity). Thus, while current data are insufficient to support pathophysiological staging of psychotic disorders, the “roadmap for future research” described by Wood et al. wisely suggests that such data will most likely be generated by research examining neurodevelopmental changes during adolescence, the period where the transition to psychosis most often occurs.

Although the neuroimaging evidence reviewed by Wood and colleagues supports their clinical staging model, these data are equally supportive of a continuous progressive

pathophysiology model in schizophrenia, (which itself continues to be a point of some controversy (8-11). Perhaps more relevant to evaluating a staging model for psychosis is whether it can guide prognosis and treatment decisions in manner that approaches the role of staging in clinical oncology. Staging models have been widely adopted in oncology because stages are defined by clear pathophysiological boundaries associated with discrete changes in mortality risk and treatment choices (e.g., whether or not to administer radiation or chemotherapy). However, variation in cancer severity within a stage (e.g., tumor size or number of metastases) has fewer implications for prognosis and treatment than variation between stages, supporting the incremental utility of staging models over continuous progression models. While these characteristics of staging models have yet to be demonstrated for psychotic disorders, the proposal by McGorry and colleagues (1, 2) represents a well-reasoned start.

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