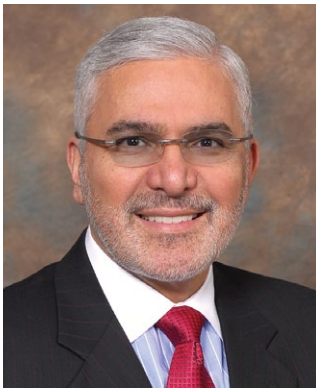
Staging psychiatric disorders: A clinico-biologic model



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Staging of medical illness is common in oncology and cardiology, but not in psychiatry. Staging can provide important information about illness severity, appropriate therapeutic intervention for that stage, treatment outcomes, and long-term prognosis.

In psychiatry, clinicians generally give a DSM label to a disorder once symptoms emerge and if it persists, simply categorize it as chronic. It's time for psychiatry to adopt a clinically meaningful staging schema for its major disorders. Several researchers already have proposed such staging models.

The momentum for staging major psychiatric disorders such as schizophrenia, bipolar disorder (BD), and major depressive disorder is being stoked by 2 major research advances: 1) accelerating recognition and characterization of the prodrome as a preclinical stage of psychiatric disorders, and 2) rapidly accruing neurobiologic discoveries about the deleterious biochemical and neural changes that evolve with each successive episode. However, early attempts and current proposals for staging psychiatric disorders are broadly clinical and descriptive.[1-4]

Clinical staging

McGorry et al[5] have proposed the following staging model:

Stage 0: Increased risk of psychotic or mood disorders, although no symptoms are present.

Stage 1a: Mild, nonspecific symptoms.

Stage 1b: Moderate, subthreshold symptoms.

Stage 2: Onset of first episode of a psychotic or mood disorder.

Stage 3a: Incomplete remission from the first episode.

Stage 3b: Recurrence or relapse of a psychotic or mood disorder.

Stage 3c: Multiple relapses, worsening of clinical severity and impact of illness.

Stage 4: Severe, persistent, or unremitting illness.

Although this is a good start, it does not incorporate the emerging neurobiologic findings of progressive psychotic and mood disorders from the preclinical stage to chronic deteriorative state. These pathologies include inflammation, oxidative stress, loss of neurotropic growth factors, and impaired neuroplasticity, all of which result in deleterious neuropathologic progression of damage to key brain circuits. Acute psychotic or mood episodes are recognized to have serious neurotoxic effects, just as myocardial infarction damages the myocardium. This is why patients who experience a first episode of psychosis, mania, or depression must be protected from relapsing: evidence is mounting that second (and certainly subsequent) episodes can be more damaging to the brain than first

It's time for psychiatry to adopt a staging schema based on clinical progression and neurobiology

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episodes and would require more aggressive treatment, similar to more advanced cancer stages. This has been well documented clinically, with excellent response to medication and remission in two-thirds of patients with first-episode schizophrenia,[6] but far lower remission rates after multiple relapses.

Consider the following advances about the adverse neurobiologic events associated with psychotic or mood episodes at various stages of the illness:

In utero, the risk genes, copy number variations, and random mutations in the thousands of genes involved in brain development probably account for smaller brain volume and hypoplasia of certain brain regions.

In the **premorbid phase** (childhood and early adolescence), negative symptoms and low cognition are evident as asociality and mediocre grades.

In the **prodrome phase** (mid-to-late adolescence), cortical changes and cognitive decline as well as mood symptoms are more apparent. Only omega-3 fatty acids—but not atypical antipsychotics—prevented a switch to psychosis better than placebo.[7] This suggests the emergence of a neuroinflammatory process that may respond to omega-3 fatty acids.

In the **first psychotic episode**, a stunning new finding[8] reveals brain edema, with a swollen brain and smaller ventricles, caused by water diffusion into extra cellular space of both gray and white matter. Such water diffusion can trigger neuroinflammation and the beginning of serious tissue damage, which can be slowed down by antipsychotics. Increased dopamine activity is associated with an increase of free radicals (oxidative stress) and suppression of growth factors. Glutamate hypofunction, another putative factor in schizophrenia, may be associated with cognitive decline and impaired neuroplasticity.

In the **second episode** of psychosis, recurrent water diffusion and continued neuroinflammation lead to axonal damage and more serious neurodegeneration.[8] This confirms the observation of more serious clinical and functional deterioration after the second episode compared with the first, and becomes much worse if the patient does not adhere to treatment and relapses. Drug response also declines, possibly because of neurodegeneration and further oxidative stress,[9] inflammation, breakdown in white matter, disruption in neuroplasticity, and further dysconnectivity across brain regions.[10]

In the **treatment-resistant or refractory phase**, clozapine is the only agent that has been shown to improve persistent psychotic symptoms. Although its exact mechanism of action remains unknown, recent studies indicate it may be exerting some of its effects by inhibiting microglial activation,[11] which is the main pathway for neuroinflammation in degenerative brain disorders.

Ultimately, after multiple episodes the chromosomal telomere becomes shorter in BD and schizophrenia,[12] which is known to predict mortality. This may explain premature death in chronically mentally ill patients (apart from cardiovascular risk factors caused by obesity).

Based on the above, I propose the following clinico-biologic staging model:

Stage 0: Abnormal brain development in utero due to genetic and non-genetic factors.

Stage 1a: Poor premorbid function in childhood (asociality, mediocre school performance).

Stage 1b: The prodrome, with noticeable negative symptoms, cognitive dysfunction, and gray and white matter changes.

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Stage 2: First psychotic episode, with delusions and hallucinations, increasing negative symptoms, and marked cognitive decline, accompanied by frontal, parietal, and hippocampal volume losses, white matter pathology, brain edema, inflammatory markers, oxidative stress, and decreased neurotropic growth factors.

Stage 3: Second psychotic episode, with more intense psychotic and negative symptoms, cognitive dysfunction, and worsening social and vocational functioning. Biologic signs include neuroinflammation, oxidative stress and impaired neuroplasticity biomarkers, axonal degeneration and further brain tissue loss, and slower response to antipsychotics.

Stage 4: Several psychotic episodes (subchronic phase), with residual positive and negative symptoms and continued cognitive impairment especially in memory, executive function, attention and verbal learning, accompanied by glial cell death, decline in dendritic spines, retraction or neurite extension, and low response to antipsychotics, with a Global Assessment of Functioning (GAF) score of 30 to 40.

Stage 5: Refractory, unremitting psychosis (chronic phase), with poor response to antipsychotics, severe clinical, social, and functional deterioration, inability to care for oneself, severe neurodegeneration (widespread brain atrophy and dysconnectivity), and GAF score ≤30.

This staging model implies that early intervention to prevent the first or second episode may be the best approach to arrest (and perhaps reverse) psychobiologic deterioration and modify the trajectory of serious psychiatric brain disorders. More can be done to prevent a downhill course in psychosis, and emphasizing the clinical and neurobiologic features of each stage of illness may serve as a roadmap for aggressive treatment approaches early in the illness course. Until a cure is found, prevention and early intervention are the best approaches. Staging models should be incorporated in future versions of the DSM so that psychiatric practitioners can implement the optimal treatment algorithm at the earliest stage possible. Readers' opinions are welcome!

Emphasizing the clinical and neurobiologic features of each illness may serve as a roadmap for aggressive treatment approaches early in the illness course

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