The clinical staging and the endophenotype approach as an integrative future perspective for psychiatry

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In their paper, McGorry et al advocate the international introduction of a clinical staging model into clinical diagnosis in the different mental health care systems.

For the early course of psychotic disorders, three stages with different implications for diagnosis and therapy are distinguished: a) the ultra-high risk stage according to the criteria developed by the Melbourne working group, b) the first-episode psychosis and c) the most crucial first 2-5-year period following the first diagnosis of psychosis.

Elsewhere (1), the staging model has already been extended to depressive and bipolar disorders and subdivided into eight different stage definitions. According to this more differentiated model, one more stage (Ia) with mild or non-specific symptoms, including neurocognitive deficits and mild functional changes or decline, precedes the ultra-high risk states in psychotic and severe mood disorders (Ib). Even prior to these, an increased risk stage (0) without symptoms might exist. Furthermore, the critical period (stage III) after first-episode psychosis (stage II) is subdivided into stages of incomplete remission (IIIa), recurrence or relapse (IIIb) or multiple relapses (IIIc), and a stage IV is identified for persistent or unremitting psychotic and severe mood disorders.

Any early intervention strategy, however, presupposes available retrospective and/or prospective findings on the early course and a clinical staging model re-

lated to these. In the German Research Network of Schizophrenia (GRNS, 2), for example, the early detection and intervention projects (3) proceeded from studies which had already aimed for a thorough characterization of the initial prodromal stages prior to first-episode psychosis with optimized retrospective (4,5) and prospective (6) methodologies. These studies had revealed a duration of the initial prodrome of 5-6 years on average and, within this phase, had identified some syndrome sequences, from nonspecific symptoms, via cognitive-perceptual basic symptoms, attenuated and transient psychotic symptoms, to first-episode psychosis (7). These early cognitive-perceptual basic symptoms had shown a good predictive accuracy, with a transition rate of 63% within the average 9.6-years follow-up (6). Thus, in combination with available data on transition rates for ultra-high risk criteria, a subdivision of the prodromal phase into an early initial and a late initial prodromal state has been proposed, that is quite similar to the above differentiation between stages Ia and Ib. This model has been the basis for the early detection and intervention projects in the GRNS (8) and, slightly modified, the multinational prospective European Prediction of Psychosis Study (EPOS, 9).

The EPOS results confirmed an emerging problem that the Melbourne group has described for its own ultra-high risk approach, i.e., that the short-term transition rates are lower in recently collected samples compared to the initially studied ones. As a solution to the resulting problem of increased false-positive predictions of first-episode psychosis, the EPOS group has proposed a two-step procedure: first, the combination of the more late prodrome-aligned ultra-high risk criteria with the more early prodromal-related basic symptom criteria will allow a more sensitive and more specific allocation to the initial prodromal risk stage. Second, new prognostic indices could be calculated, which, for each individual, determine the probability and the time expected to pass until transition into first-episode psychosis. Thereby, the clinical staging could be combined with an individual risk estimation.

The clinical staging model differs from the endophenotype approach (10,11). The clinical staging model assumes that at-risk subjects develop their first mild symptoms already in adolescent years. Depending on a variety of neurobiological, social and personal risk as well as protective factors, these can increase and transgress thresholds of more severe stages. Therefore, it is essential to prevent this progress as early as possible. This, in turn, requires detailed knowledge of the patient's stage of the disease and the risk and protective factors relevant to this stage. The endophenotype approach focuses on heritability, familial association, co-segregation and even state-independence. Candidate markers are regarded as constant traits, which are present at all clinical stages and, most importantly, even at the non-clinical at-risk state.

Within the GRNS, the two approaches have been combined. Substantial interest has been paid to possible changes of the neurobiological correlates during a person's transition across different stages from 0 to IV. The differentiation between early initial and late initial prodromal states, with its diagnostic and therapeutic implications, has been included in the new German Clinical Practice Guidelines. However, despite all progress, both the clinical staging and the endophenotype approach still require consolidation by further research, before they can be sensibly implemented in international diagnostic systems.

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