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COMMENTARY (INVITED)

Course in Diagnosis of Psychotic Disorders: Research Agenda

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This article examines a proposal to include course features in Diagnostic and Statistical Manual of Mental Disorders, sixth edition (DSM-6) for classification of psychotic disorders. We review current knowledge on this topic including course typologies proposed in the literature and empirical studies of illness course. We also consider whether types can capture variability in patient's trajectories and discuss an alternative approach. Our review reveals that fundamental questions remain unanswered about course of psychotic disorders due to limitations of available research. We outline study designs needed to fill these gaps.

Cohen and Ongur[1] provided an incisive overview of the role illness course plays in the nosology of psychotic disorders. They made a compelling case that diagnostic systems limited to signs and symptoms are incomplete, and course patterns provide essential information not captured by symptom-based classifications. Furthermore, they proposed that diagnoses should include both symptom and course features.

This proposal should be seriously considered in the upcoming DSM-6. The key question is what course patterns are established, and what remains to be learned about psychotic disorders. Premature deployment of diagnostic guidelines that do not correctly represent psychopathology can result in poor reliability, validity, and clinical utility.[2-6] Arguably, reputation of prior editions of the Diagnostic and Statistical Manual of Mental Disorders suffered from inclusion of elements that proved to be incorrect, such as 10 personality disorders.[4] Likewise, classic schizophrenia subtypes—paranoid, disorganized, catatonic, undifferentiated, and residual—offered such poor diagnostic stability, reliability, and validity that they were eliminated from Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).[7] As a particularly relevant example, DSM-5 uses illness course to distinguish persistent depressive disorder (PDD) from major depressive disorder (MDD), with 2 years of continuous depression required for PDD. PDD is distinct from MDD in etiology, outcome, and treatment response.[8] Unfortunately, persistent type excludes cases of highly recurrent depression, although they are much more similar to PDD than to single-episode MDD.[9,10] Empirical evidence indicates that a more valid typology would combine persistent and recurrent depression variants,[11,12] which DSM-5 has not done. These examples caution against accepting face-valid typologies without empirical vetting, as alternative classifications may be much more valid and reliable.

A number of course typologies have been proposed for psychotic disorders. Kraepelin distinguished 2 types: chronic-progressive course (ie, dementia praecox) and episodic (ie, manic-depressive illness).[13] Strauss and Carpenter[14] elaborated this to 3 types: chronic, residual, and episodic. Ciompi[15] proposed a typology that combines mode of onset (acute vs chronic/insidious), course pattern (episodic vs continuous), and end state (recovered vs non-recovered), yielding a comprehensive system of 8 possible patterns. Of note, this was an extension of 7 types introduced earlier by Manfred Bleuler.[16] Watt et al[17] proposed a system of 4 types based on number of episodes (single vs multiple) and inter-episode functioning (no impairment vs impaired). DSM-5 and ICD-11 use an elaborated version of this system, characterizing course by single vs multiple episodes and remission status (acute, partial, or full). Another approach was inspired by success of staging models in other medical fields such as oncology. It classifies people according to illness progression rather than symptom profile. The leading clinical staging model for psychotic disorders specifies 5 major stages: 0 (no symptoms), 1 (subthreshold symptoms), 2 (first onset), 3 (incomplete remission or relapse), and 4 (severe unremitting illness).[18]

All aforementioned approaches were outlined rationally based on face-valid characterizations of course. Optimal course patterns can be identified using statistical methods for grouping people by their trajectories. Multiple techniques have been established for trajectory analyses. They can be categorized as either Latent Class Growth Analysis (LCGA), which assumes that all people in a given class follow the same trajectory, or Growth Mixture Modeling (GMM), which allows variability among trajectories within a class.[19,20] GMM assumptions are more realistic, but both methods are widely used. Some studies used other techniques such as latent class analysis or cluster analysis. These methods also explicate groups, but they are blind to time and not able to model trajectories. Hence, they are not recommended for longitudinal data.

Numerous studies applied LCGA and GMM to course of psychotic disorders. However, they varied widely in design. We focused on the most informative studies, those with >3 assessment points, >1 year of follow-up, and sample size >300 participants. Seven studies fit these criteria.[21-27] They followed cohorts with clinical high risk for psychosis, first-episode psychosis, or chronic psychotic disorders. The follow-up ranged from 2 to 20 years, with 4-10 assessments. These studies examined several dimensions of psychotic disorders. For general psychopathology, they found either 2 groups[24] or 4.[21] For positive symptoms, they found 2 groups (low vs high)[24,25] or another 2 (rapid vs gradual improvement)[21] or 5.[26] For negative symptoms, they found 2 groups[24,26] or 3[25] or 4.[21] For functioning, they found 2 groups[24,25] or 3[21] or 4 (high, moderate, low, and very low)[27] or another 4 (high, high worsening, low improving, and low)[22] or 5.[23]

Most noteworthy is the lack of consistency between studies. No classification clearly received more support than alternatives for any of these dimensions. Also, none of the rational course typologies described above emerged in these studies. Indeed, empirical research found a different number of classes than proposed by theorists. Moreover, these classes were defined by their starting point (intercept) and direction of change (slope) rather than the number of episodes—the focus of many rational systems. Also, class trajectories were gradual and nearly all linear, so no class could be interpreted as episodic. Likewise, none of the trajectories showed distinct stages. Overall, lack of consistency makes it doubtful that classes identified to-date are ready for inclusion in the DSM-6.

A larger question is whether course of psychotic disorders can be accurately represented by types or differences between patients are continuous and gradual. All studies reviewed above found 2 or more classes for every construct considered. However, LCGA and GMM are prone to identifying multiple classes even when in reality there is just one.[28,29] These methods require large sample sizes for accurate performance (eg, 500-2400 people)[30] and decisions about number of classes are often uncertain due to disagreements between model fit statistics. Most importantly, LCGA and GMM assume that variables in the analysis are normally distributed, but psychopathology measures are often skewed. Models cope with the skew by adding artifactual classes.[28] For example, numerous studies examined trajectories of PTSD symptoms following trauma and typically found 4 classes: low, high, worsening, and improving symptoms.[31] However, symptom scales were substantially skewed in this research. The largest investigation to-date followed 12 822 people for 20 years after the trauma, with up to 17 assessment points, and observed the expected 4 classes using standard methods.[32] However, when analyses addressed skew using generalized mixed-effects model with log-link, a single-class model showed best fit to data, indicating that the 4 trajectories were an artifact of skew.

Consequently, it remains possible that differences in the course of psychotic disorders are continuous in nature, and existing course types are due to inaccurate assumptions of theorists or analytic techniques. If true, this may have major implications for how illness course is characterized. Table 1 outlines concepts used to describe such continuous distributions of trajectories. Each patient has a trajectory defined by its individual starting point, direction, and speed of progression (linear or nonlinear). These characteristics can be estimated with as a few as 4 assessments. With greater number of follow-ups, more detailed characteristics can be added such as peak, cyclicity, variability, and inertia. They can be estimated with as few as 10 assessments, although 50 assessment points produce much more accurate estimates.[33,34] Multiple dimensions can be analyzed jointly to calculate correlations between symptoms for each person. For example, coupling of psychosis and depression may range from a strong negative correlation (ie, these symptoms occur at different times) to strong positive (ie, psychosis is limited to episodes of depression). Lagged effects can be examined to understand how symptoms influence each other (eg, worsening drug use leads to exacerbation of psychosis) or how symptoms are shaped by external factors such as life events and treatment. Such interplay can be critical for prognostication, explication of etiology, and as treatment targets.

Table 1 draws parallels between continuous and categorical descriptors. Some descriptors align closely (eg, peak and worst period) and others more loosely (eg, variability and recurrent vs single-episode). Some categorical descriptors are not present under continuous conceptualization (eg, onset, age of onset, remission, number of episodes), but they can be derived by applying a clinical threshold to trajectories. Overall, robust sets of descriptors are available whether course is organized into classes or continua, but it is important to determine which approach is correct.

More research is needed to address this fundamental question and to explicate specific course characteristics, which would support their inclusion in the DSM-6. Table 2 outlines our recommendations for designing studies that can fill these gaps. We recommend fairly

Table 1. Comparison of Course Features Under Dimensional and Categorical Models

Dimensional (individual trajectories)			**Categorical**
Concept	**Statistic**	**Description**	
Basic features			
Trajectory level	Person's mean	Mean symptom burden across time	Chronic vs episodic
Direction of change	Person's slope of time, sign	Direction of the trend in symptom burden over time	Deteriorating vs improving
Rate of change	Person's slope of time, magnitude	How quickly the trajectory worsens or improves	Acute vs insidious onset
Timepoint on trajectory	Person's model-implied score for given time	Symptom severity at a particular time after minimizing random noise	Acute/partial remission/full remission; Outcome (good, intermediate, poor)
Peak	Person's maximum	Time when trajectory was at highest point	Worst period
Cyclicity	Person's mean period between trajectory crossing mean level	Frequency with which trajectory rises and falls (if regular pattern is present)	Waxing and waning
Variability	Person's standard deviation	How much symptoms vary around person's temporal trend	Recurrent vs single-episode
Inertia	Person's autocorrelation	How quickly symptoms change over time	Episode duration
Symptom coupling over time (eg, psychosis and depression)	Person's correlation of 2 symptoms over time (slope of one symptom on another)	For example, degree to which changes in psychosis tracks changes in depression	Mood disorder with psychosis/schizoaffective disorder/psychosis with comorbid mood episodes
Lagged symptom interplay (eg, change in drug use predicts change in psychosis)	Person's symptom regressed on another lagged symptom, controlling for autocorrelation	For example, degree to which changes in drug use predict changes in psychosis	Secondary symptoms, symptom cascades, vicious circles
Derived features			
		Upward trajectory crossed clinical threshold	Onset
		Downward trajectory crossed clinical threshold	Remission
		Age when trajectory first crossed clinical threshold	Age of onset
		Times upward trajectory crossed clinical threshold	Number of episodes

Concepts column lists features of an individual's trajectory that can be used to capture dimensional differences between people in illness course. Statistic and Description columns elaborate the corresponding concept. Categorical column does not capture the same concept, but lists the closest concept available from the categorical nomenclature to highlight similarities and differences between the 2 approaches.

large samples, as statistical simulations showed their necessity.[30,35] Another consideration is the number of assessments, as even basic models require at least 4 time points. Reliable estimation of differences between people in trajectories requires 10 assessments for basic characteristics and 50 or more for complex characteristics.[34] Fortunately, greater number of time points reduces sample size requirements.[33] For example, an analysis that requires sample size of 900 people given 4 assessments may require only 250 people given 10 assessments to achieve 80% statistical power.[35] Follow-up length is also important to ensure sufficient time for differences in trajectory slopes to emerge.[35] Analyses of malleable dimensions (eg, positive symptoms) may need only one year of follow-up, whereas highly stable dimensions (eg, cognition) may require a decade. When designing new studies, we recommend conducting power analyses because of the multiple factors involved.

Fortunately, a number of collaborative projects have gathered data that exceed all of these requirements and are publicly available.[36-39] This is in addition to many single-site studies that gathered sufficient longitudinal data. Moreover, electronic health records can be mined to obtain useful data with numerous time points in large samples. In clinical practice and translational research, it may be difficult to collect numerous prospective assessments. Importantly, requirements outlined in Table 2 are for research that aims to explicate course characteristics. Once these features are identified and validated, it is likely that a single retrospective assessment can approximate target features sufficiently to be clinically useful.

Table 2. Recommendations for Design of Studies to Investigate Course Features

Sample size should be sufficient for accurate estimation of trajectories. If multiple classes are expected, then n ≥ 500 is minimum; presence of several classes would require n ≥ 1000.
Representativeness requires diverse, heterogeneous samples, with the broadest inclusion criteria possible.
Population. Patient samples are informative, and epidemiologic samples from community are especially valuable as they are underrepresented in the literature. If studying patients, it is optimal to begin at a common point such as the first episode.
Time points. At least 4 assessment points are necessary, and greater number increases statistical power and precision. Many features require at least 10 assessments to be estimated reliably and some require 50 or more.
Follow-up length should be long enough to reliably detect differences between people in the rate of change on the target measure. This length can be estimated based on reliability and temporal stability of the measure.
Psychopathology assessment should be as comprehensive as possible—optimally including various dimensions of symptoms, real-world functioning, and cognition—as course characteristics likely differ between these constructs and some course features require joint analysis of different symptoms.
Modeling considerations. Rigorously test for continuous vs discontinuous distribution of trajectories, including methods that account for skew of measured scores. Also, test non-linear effects such as trajectory slope changing over time (change may be gradual or abrupt).
Validate identified characteristics including their reliability and ability to explain risk factors, outcomes, and treatment response.

With regard to comprehensiveness of measurement, Cohen and Ongur[1] argued that 3-7 dimensions are sufficient to describe symptom profile of psychotic disorders. They further proposed that these characteristics change differently over time, and thus course patterns should be mapped for each. We can recommend a well-validated system that includes factor-analytically derived reality distortion, disorganization, inexpressivity, and avolition, alongside provisional mania, dissociation, cognition, and real-world functioning domains.[40,41] Multiple other dimensional systems are available. A critical consideration is that course modeling can identify a fairly large number of characteristics (Table 1), but it is likely that not all of them are clinically useful. Accordingly, reliability and validity of each feature should be thoroughly tested.

Course is undoubtedly critical to characterizing and treating psychotic disorders. It is striking that, despite century of research on this topic, much remains unclear. Fortunately, we now have the data and analytic methods capable of answering many outstanding questions about course of psychotic disorders. An essential part of this process is validation of features identified by statistical modeling. A concerted effort is needed to address current knowledge gaps and develop empirical basis for inclusion of course characteristics in the DSM-6.

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Conflicts of Interest

None declared.

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