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Do the Trajectories of Bipolar Disorder and Schizophrenia Follow a Universal Staging Model?

Les trajectoires du trouble bipolaire et de la schizophrénie suivent-elles un modèle de stadification universel ?

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Abstract

Objective: The purpose of this study is to address the question of whether a universal staging model of severe psychiatric disorders is a viable direction for future research by examining the extant literature.

Method: A narrative review was conducted of the relevant historical, conceptual, and empirical literature pertaining to the clinical trajectory of bipolar disorder and schizophrenia and issues relevant to staging.

Results: There is substantive evidence that classic recurrent bipolar disorder is separable from schizophrenia on the basis of family history, developmental and clinical course, treatment response, and neurobiological findings. However, because of the intrinsic heterogeneity of diagnostic categories that has been amplified by recent changes in psychiatric taxonomy, key distinctions between the groups have become obfuscated. While mapping risk and illness markers to emerging psychopathology is a logical approach and may be of value for some psychiatric disorders and/or their clinical subtypes, robust evidence supporting identifiable stages per se is still lacking. Presently, even rudimentary stages such as prodromes cannot be meaningfully applied across different disorders and no commonalities can be found for the basis of universal staging.

Conclusions: Advances in the prediction of risk, accurate early illness detection, and tailored intervention will require mapping biomarkers and other risk indicators to reliable clinical phases of illness progression. Given the capricious nature of mood and psychotic disorders, this task is likely to yield success only if conducted in narrowly defined subgroups of individuals at high risk for specific illnesses. This approach is diametrically opposite to that being promulgated by proponents of a universal staging model.

Abrégé

Objectif : Savoir si un modèle de stadification universel des troubles psychiatriques graves est une direction viable pour la recherche future en examinant la littérature existante.

Méthode : Une revue narrative a été menée de la littérature historique, conceptuelle et empirique pertinente concernant la trajectoire clinique du trouble bipolaire et de la schizophrénie, et les enjeux ayant trait à la stadification.

Résultats : Des données probantes substantielles indiquent que le « trouble bipolaire récurrent classique » est séparable de la schizophrénie selon les antécédents familiaux, le cours développemental et clinique, la réponse au traitement, et les résultats

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neurobiologiques. Mais, en raison de l'hétérogénéité des catégories diagnostiques qui a été amplifiée par les récents changements de la taxonomie psychiatrique, les principales distinctions entre les groupes sont devenues obscurcies. Bien que la cartographie des marqueurs de risque et de maladie d'une nouvelle psychopathologie soit une approche logique et puisse être valable pour certains troubles psychiatriques et/ou leurs sous-types cliniques, il manque encore des données probantes fiables qui soutiennent les stades identifiables *en soi.* Présentement, même les « stades » rudimentaires comme les prodromes ne peuvent être sensément appliqués à différents troubles et on ne peut trouver de points communs pour la base de la stadification universelle.

Conclusions : Les progrès de la prédiction du risque, de la détection précoce exacte de la maladie, et de l'intervention sur mesure nécessiteront de cartographier les biomarqueurs et d'autres indicateurs de risque aux stades cliniques identifiables de la progression de la maladie. Étant donné la nature capricieuse des troubles de l'humeur et psychotiques, cette tâche ne peut probablement être réussie que si elle est menée dans des sous-groupes étroitement définis de personnes à risque élevé de maladies spécifiques. Cette approche est diamétralement opposée à celle promulguée par les proposants d'un modèle de stadification universel.

Keywords
staging, bipolar disorder, psychotic disorders, mood disorders, biomarkers, clinical course, risk syndromes, prodromes, heterogeneity

Clinical Implications

1. Understanding the natural history and mapping markers of illness activity onto emerging psychopathology may advance risk prediction and early detection and contribute to the identification of novel early intervention targets for a limited number of psychiatric illnesses or subtypes.
2. The heterogeneity of individual diagnostic categories and the well-established differences in family history, developmental course, clinical course, and treatment response between bipolar and psychotic disorders make the prospect of developing a universal staging model implausible based on present-day knowledge.

Limitations

1. Staging is variably defined, and there is limited evidence to inform its development at present; hence, this is not a systematic review. Consequently, it is likely that some perspectives may not have been fully captured.
2. A paucity of longitudinal studies of psychopathology and multilevel risk markers in genetically at-risk individuals identified from well-characterized subgroups of parents with stable diagnoses means that a definitive answer to the possibility of staging psychiatric illnesses cannot yet be determined.

A developmental approach to psychiatric disorders that is likely to yield major gains has refocused attention on early identification and intervention efforts.[1-3] By describing the natural history of severe mental illnesses such as schizophrenia and bipolar disorder (BD), and considering early risk syndromes and prodromal clinical features, strategic opportunities for early intervention have been outlined and proposed. Concurrently, the developmental clinical phases of these illness have been subsumed within a broader framework, namely, that of staging.[4-7] However, evidence for stages of psychiatric illnesses is lacking, and yet this fundamental consideration has been overlooked as the field enthusiastically shifts its focus to the development of a single "universal" or "transdiagnostic" staging model.[8-11] Remarkably, the latter attempts to subsume all severe mood and psychotic disorders under one construct, even though prototypical schizophrenia and BD have clearly proven to adhere to Kraepelinian partitioning—founded and supported by differences in clinical course, separate familial segregation patterns, and distinct psychological and neurobiological correlates.[12,14]

Thus, on the basis of present knowledge, these disorders cannot be meaningfully staged let alone mapped onto a common framework. Even those aspects that lend themselves to rudimentary staging per se cannot be neatly aligned across disorders, making the prospect of a single universal staging model not only premature but perhaps ultimately impossible. Surely, such an approach would be a regressive step taking us backward over a century to the then-popular concept articulated by Wernicke and others that "insanity" does not possess different "forms" but only different "stages."[15] It is important that we generate models and formulate hypotheses, but this requires stepwise deliberation—in other words, a staged process of eliciting and evaluating the evidence.

To understand the evidence and find support for a staging model for specific psychiatric disorders, a number of difficulties need to be overcome, and a particular approach needs to be adopted.[16] It is important to note that psychiatric illnesses such as schizophrenia and BD are by nature heterogeneous, and clinical diagnosis is generally prone to change; hence, the concept of a prodrome is highly variable, and this needs to be clearly defined—in particular its specific prognostic value. Finally, the clinical course of psychiatric disorders needs to be carefully mapped against biological and clinical markers, but this is once again dependent on accurate diagnosis of the illness and its subtypes.

Heterogeneity of Psychiatric Disorders

A key but often ignored fact is that current diagnostic categories are heterogeneous and encompass many different illness subtypes, which vary across classifications and are often modified through successive iterations within taxonomies. For instance, the *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition*, supplanted manic depressive illness with the current BD concept by shifting the emphasis from a longitudinal perspective, in which the recurrence of mood episodes (depressive or manic) was important, to solely that of polarity, in which episodes viewed in cross section came to the fore.[17] This was notwithstanding the substantial evidence supporting the differentiation of manic depression from psychosis on the basis of course and outcome.[13,18] It also ignored the fact that manic-depressive illness or the classic lithium responsive subtype of BD is characterized by a prominence of depressive episodes—often from the onset.[19-22] At the same time, the concept of major depression was expanded[17,23] to include a range of problems from mild mixed anxiety and depressive syndromes (neurotic depression) to severe melancholic episodes, which may include psychotic features. It is therefore not surprising that rates of response to stabilizing lithium treatment have shifted from the majority to an estimated 30% of bipolar cases.[24]

This broad clinical picture of mood disorders reflects heterogeneity among phenotypes in terms of associations and risk. For example, family studies have shown that relatives of BD patients are at an elevated risk of recurrent depressive disorder, cyclothymia, and various forms of bipolar spectrum disorders (BDNOS, BDII).[25-27] In fact, major depression in first-degree relatives of BD patients has an estimated >80% chance of reflecting the BD diathesis, especially if recurrent.[28,29] This is further supported by evidence of paradoxical worsening[30] and treatment emergent switching into mania with antidepressant treatment,[31,32] dexamethasone suppression test positivity,[33] and shared genetic findings in patients with BD and recurrent unipolar depression.[14,25] On the other hand, relatives of patients with schizophrenia manifest a different spectrum of chronic disorders including neurodevelopmental disorders (autism spectrum), Cluster A personality, and schizoaffective disorders.[14,34,35] Recent studies demonstrate specificity of familial aggregation of manic and depressive episodes in BD, further supporting the need for more refined phenotypes[36] and strong familial specificity across psychotic and mood disorders.[37]

Clinically, treatment response is often viewed as diagnostic confirmation, and in this vein, it has been posited that lithium's specificity of action can be used to carve the mood disorders spectrum.[38] This has been exemplified to some extent by our research, in which prophylactic response to lithium was used to identify a homogeneous subtype of BD.[22,39,40] Lithium-responsive BD has been shown to have a characteristic episodic course with spontaneous remission, no apparent worsening or shortening of interepisode intervals over the long-term course, an increased risk of episodic mood disorders but not chronic psychosis in family members, and defining neural correlates and genetic findings that do not overlap with schizophrenia.[39,41-44] In fact, a recent preliminary study using stem-cell neuronal models suggests differential neuronal activation specific to the lithium-responsive BD subtype.[45]

Course of Recurrent Mood Disorders and Schizophrenia

The seminal distinction proposed by Kraepelin between mood and psychotic disorders on the basis of differences in clinical course has survived examination.[12,18] However, the recent emphasis on the presence of mania and the altered perspective of what constitutes a "manic episode" (irritability, anger, mood-incongruent psychosis) have substantially changed course descriptions from a recurrent to a neuroprogressive illness.[46,47] In studies of classic manic depressive illness, chronicity was estimated to occur in as much as 15% of patients followed longitudinally,[19,20] and the weight of clinical and neurobiological evidence supports that intermediate presentations such as cycloid psychosis and schizoaffective illness belong to psychotic spectrum disorders.[48] In contrast, the course of prototypical schizophrenia is typically chronic or chronic fluctuating, with a small proportion of patients having a remitting course punctuated typically by significant residual symptoms.

While recent genome-wide association and linkage studies have identified some overlap in genetic factors,[49-51] a synthesis of the genetic findings[14] supports the fundamental dichotomy between psychotic spectrum disorders and episodic mood disorders.[14] A recent study reported dissociation between BD without psychosis and psychotic disorders based on a paternal age effect on risk.[52] Similarly, the aggregate findings from studies support that neural structural and cognitive differences in psychotic patients are not generally characteristic of BD.[42,53,54] In fact, accruing evidence suggests that cognitive and neural correlates associated with BD are not reliably present until later in the course of full-blown illness and likely reflect burden-of-illness effects associated with metabolic disease, substance use, and untreated episodes rather than a progressive primary illness course.[55,56]

Post[57] proposed a "kindling theory" in which both the phenomenology and pharmacologic responsiveness worsen over the course of BD—implicating alterations in underlying neurobiology. The concept of kindling has proven difficult to substantiate and is incompatible with observations on the lithium-responsive BD subtype as its course does not exhibit a progressive worsening nor a shortening of the interepisode interval predicted by kindling theory.[13,22] For example, according to the kindling model, if a patient is fully stabilized for 10 years and lithium is then stopped, a much milder course of the illness should ensue—but instead, the previous pattern of illness reemerges.[58,59] Furthermore, the outcome

of long-term treatment does not appear to be associated with latency in onset of treatment in narrowly defined BD.[60]

Genetic High-Risk Studies: Clinical, Cognitive, and Neural Trajectories

Given the high clustering of BD in families,[61] children of affected parents are an important identifiable high-risk population. More than 2 decades ago, we started to systematically describe the clinical manifestations in offspring of well-characterized BD parents.[62] An important aspect of this study was that the diagnosis in the parent was stable over prospective observation of up to 40 years. Furthermore, affected parents had been systematically treated by us with lithium in accordance with a research protocol.[22,63] In this way, we were able to reliably differentiate 2 high-risk subgroups: offspring of parents with either a lithium-responsive or lithium–nonresponsive BD. The aim of this design was not to generalize to a heterogeneous clinical population of real-world patients but rather to describe the emerging trajectory of illness and determine the associated risk factors in each subtype identifying points of overlap and difference.[64]

Evidence from this ongoing study have demonstrated that, although on the surface there is some overlap in early risk syndromes between the high-risk subgroups, there are substantial differences including the presence of neurodevelopmental disorders, poorer academic and social functioning, and quality of remission in the offspring of lithium nonresponders compared with the offspring of lithium responders.[7,65,66] This observation is consistent with different underlying pathophysiological processes. Further, early risk syndromes predict a different outcome in the high-risk subgroups; that is, offspring of lithium responders develop episodic mood disorders, while offspring of lithium nonresponders develop poorly remitting mood and psychotic disorders.[5] This suggests that despite some early overlap in clinical features, the clinical trajectory is different between the 2 subgroups: one exemplifying a classical episodic mood disorder and the other a chronic psychotic spectrum illness.[7,67]

These findings are convergent with reported observations of cognitive, motor, and social deficits in children who later develop schizophrenia, typically not characteristic of children who develop BD.[68-71] By contrast, cognitive deficits in BD seem more related to burden-of-illness effects, and based on school performance and quality of early social functioning, it is difficult to differentiate children at familial risk of BD from the general population.[72,73] Interestingly, the offspring of psychotic spectrum BD parents nonresponsive to lithium appear to overlap developmentally with descriptions of children at risk for psychosis.[74]

Prodromal Features

Over the past 16 years, McGorry and others have attempted to define "ultra-high risk states" predicting the onset of full-blown psychotic episodes with the aim of preventing illness onset and mitigating illness progression.[75-78] Despite the logical appeal of earlier identification and intervention, studies show that only a minority of high-risk youth convert to psychosis.[4] Further, a recent meta-analysis pointed to significant heterogeneity across defined high-risk groups in conversion rates.[79] Meta-analysis of conversion risk to psychosis associated with early interventions have highlighted problems with treating false-positive cases and the need for more specific subgroups of ultra-high-risk patients based on validated indicators of treatment response.[78]

In recent years, the focus has shifted to applying this same approach to identify high-risk states preceding the onset of severe mood disorders.[6,80,81] Given the substantial morbidity and mortality associated with BD already evident in adolescence[82] and the estimated substantial delay for an accurate diagnosis in help-seeking patients,[83] this line of research seems justifiable. Some researchers have attempted to characterize high-risk states and predict conversion to BD either from health or major depression. This includes retrospective studies of prodromal symptoms temporally associated with subsequent first episode (typically psychotic) mania[84,85] and prospective studies of help-seeking youth identified through criteria validated in studies of conversion to psychosis.[86-88]

While these studies have been informative for identifying prodromes to first-episode psychotic mania, there are limitations to the interpretation and relevance for typical mood disorders. For example, a 10-year follow-up study of first-episode manic patients reported substantial diagnostic instability, with half of the changed cases being diagnosed on the schizophrenic spectrum.[89] Predictors of change to psychotic disorders in manic adolescents included childhood psychopathology, insidious onset, poor premorbid adjustment, and psychotic symptoms in childhood.[90] Convergent evidence from independent high-risk offspring studies show that the first and subsequent initial major mood episodes related to BD are typically depressive and not manic,[5,91-94] although this is not consistent across all studies.[95] This means that focusing on predicting and preventing the onset of psychotic manic-like episodes does not adequately address the aim of predicting and preventing the onset of BD.

To wit, major depressive episodes in genetically at-risk youth occur on average 4 to 5 years prior to the first activated episode, are debilitating, and are often associated with a high risk of substance misuse and suicidal behavior.[82,94,96] Therefore, focusing only on conversion to mania represents a small portion of the larger challenge in early identification of risk in BD that for many high-risk youth is too little far too late. For others manifesting a related subtype (recurrent major depression in the context of a family history of BD), the manifestation of a manic episode may never happen. This uncertainty is compounded by hypomania and the diagnosis of BDII, affective instability, and treatment-emergent affective switching. The nature of these conditions is poorly understood, and even seemingly distinct depressive and

manic states can be coloured by mixed features—the diagnostic and prognostic significance of which remains unclear.[31,97,98]

Conclusions

Anticipated major breakthroughs in understanding the patho-aetiology of BD and identifying novel early treatment targets have failed to materialize. For example, even though BD has the highest estimated heritability of all psychiatric illnesses, no genes of major effect have been identified and no reliable validated risk indicators or biomarkers beyond a confirmed family history for any stage of illness have been described. Prospective studies have provided evidence that most major psychiatric illnesses manifest early in life and that identified early-risk syndromes are often nonspecific or heterotypic in nature.[99] Early accurate diagnosis reliant on symptoms is an imprecise science especially in the absence of identified biomarkers. While the Research Domain Criteria approach[100] argues that symptoms may map to neurobiological correlates, this is yet to be proven and runs counter to the experience in the rest of medicine, in which chasing biomarkers of nonspecific symptoms such as cough or headache without a clinical context (including course and familial risk) would be considered nonsensical.

This means that staging at this juncture is difficult and likely to be possible for only validated subtypes of specific psychiatric illnesses. Furthermore, important differences in the early developmental course, academic/cognitive realm, nature of the clinical course, the spectrum of illnesses in family members, and phase or sequence of psychopathology separate BD from schizophrenia—supporting that the pathophysiology is likely substantially different. Therefore it is unlikely that forcing the early clinical patterns of these different illnesses to fit into a single universal model will be possible or useful.

In sum, while staging has worked for some medical diseases predicting risk, planning treatment, and gauging illness progression, even here it has limitations and cannot be applied universally. For example, breast cancer is now conceptualized as several different diseases each with specific biomarkers and differential treatment response.[101] The likelihood of developing similar clinical staging for psychiatric disorders is much less, simply because to be useful, staging requires a predictable progression of a disease process both at clinical and biological levels. However, psychiatric disorders are notoriously capricious in initial presentation and subsequent course—even within the same diagnostic categories.

Clearly the way forward requires increased specificity and reduction of heterogeneity. Longitudinal study of well-defined subgroups of genetic and clinical high-risk youth is an important contributor to the effort of mapping biomarkers to emerging psychopathology—reducing heterogeneity and separating cause from effect. While the results from such detailed studies in selected, validated subgroups will not generalize to real-world clinical populations, it is the only viable approach to understanding patho-aetiogical mechanisms. Thus, while some form of staging may be possible for certain psychiatric illness subtypes, the current enthusiasm for the development of a universal staging solution that can be applied across the spectrum of heterogeneous psychiatric disorders is an ill-conceived step in the wrong direction that is cause for concern and should prompt careful reevaluation of extant data and future research directions.

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