Diagnosing bipolar disorders: recent challenges from the studies of offspring

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ABSTRACT

The initial steps towards creating the construct of bipolar disorder, as we apply it today, were taken after 1850. And it was naturally Kraepelin who formulated the concept more fully, even though not without opposition. Because of psychiatry's shared roots with neurology, the diagnosis has since been crafted mostly using symptoms. Influenced in particular by the advances of biological psychiatry, the "neoKraepelineans" revived some of Kraepelin's thinking since 1970s. Lately, with the confluence of multiple forces, the broadened notion of bipolar spectrum disorder was created.

In recent years, the findings from longitudinal studies of children of bipolar and psychotic parents have been reported and point to the limitations of the symptom-based approach to diagnosis. It turns out that the early manifestations of bipolar disorder include a nonspecific variety of psychopathological manifestations, and evidence is accumulating that, in a sequence of stages, this panoply of symptoms develops into bipolar disorder.

There is also growing confirmation that identifying the early stages of bipolar and psychotic disorders has important implications for successful treatment and stabilization. These observations pose a new and important challenge for the creators of improved versions of DSM and ICD.

SOUHRN

Jak diagnostikovat bipolární poruchu: problémy, ktere přinesly studie potomků

Počáteční kroky k vytvoření konstruktu bipolární poruchy tak jak jej používáme dnes, byly podniknuty po roce 1850. A byl to přirozeně Kraepelin, jenž zformuloval úplný koncept, ačkoliv se setkal s určitým odporem. Díky společným základům psychiatrie s neurologií byla od té doby diagnóza založena povětšinou na základě symptomů. Zejména pod vlivem pokroků biologické psychiatrie v 70. letech “neo-kraepeliniáni” oživili některé Kraepelinovy myšlenky. Nedávno se na základě souběhu mnoha sil vytvořil rozšířený pojem poruchy bipolárního spektra.

V posledních letech byly publikovány výsledky longitudinálních studií dětí bipolárních a psychotických rodičů, které ukazují na limity diagnostického přístupu založeného na symptomech. Ukazuje se, že časné projevy bipolární poruchy zahrnují nespecifickou rozmanitost psychopatologických obrazů a přibývá důkazů o tom, že tato plná výzbroj příznaků se v postupných fázích rozvíjí do bipolární poruchy.

Stále častěji se také potvrzuje, že identifikace časných fází bipolární a psychotické poruchy má významné důsledky pro úspěšnou léčbu a stabilizaci. Tato pozorování představují novou a důležitou výzvu pro autory vylepšených verzí DSM a MKN.

Klíčová slova: bipolární porucha, diagnóza, děti bipolárních rodičů, děti psychotických rodičů, longitudinální studie, časný průběh.

Bipolar disorders and classification

The concepts of mood disorders in general, and bipolar disorders (refer to as BD) in particular have reflected the history and development of psychiatric classifications. The desire for categorization similar to other scientific and medical disciplines often clashed with psychodynamic convictions that each patient has many individual, uncategorizable features and that the borders between normal and abnormal in psychiatry are actually not that sharp. Thus, each diagnostic classification has attracted controversy and criticism.

The way bipolar disorders have been diagnosed in psychiatry reveals changes in classification over time. For example, both the DSM-I and the DSM-II reflected the predominant psychodynamic psychiatry, symptoms of disorders were not specified in detail and explicit separation between normal and abnormal was not stressed. DSM-III and -IV, on the other hand, provided "neo-Kraepelinian" (1) categorical classification and assumed a particular pattern of symptoms in each category. A controversy regarding abandonment of the construct of neurosis, a cornerstone of psychoanalytic thinking was resolved through a political compromise, by reinserting the term in parentheses. DSM-IV was published in 1994, a product of 14 committees and 20 advisers who created 297 disorders and included, also for BD, a criterion of clinically significant distress or impairment to many categories.

DSM and ICD are dominant but by far not the only classifications. There is and always was arbitrariness in a symptom-based organization. For example, from a similar set of psychopathological manifestations, several tens of classifications have been constructed during the past one hundred years.

Since the 19th century until late after the 2nd World War, Psychiatry as a specialty was fused with Neurology, and the diagnosis has since been crafted mostly using symptoms. As Neurology with the aid of symptoms can identify focal abnormalities, also the psychiatric diagnostic approach based on symptoms seemed to make sense. However, in 2001 Helen Mayberg (2) showed convincingly, by integrating a large body of clinical and neuroimaging observations that abnormal mood regulation is far from focal and includes a very complex brain system.

A bit of bipolar history

While the terms such as melancholia or mania have been used since at least Hippocrates, their meaning kept changing as the understanding of the various causes of behavioral disorders kept advancing (3). The initial steps to creating the construct of BD, as we apply it today, were taken after 1850 (4;5).

And it was naturally Kraepelin (6) who formulated the concept more fully, even though not without opposition. Many alternative nosologies were proposed, particularly after Kraepelin's death. The influence of psychoanalysis and psychodynamic psychiatry was noticeable particularly in North America. Manic-depressive patients were "disappearing" (7). In the

US-UK study of 1970, researchers showed that American psychiatrists diagnosed many conditions they saw in New York as schizophrenia, based on liberal definitions within the neurosis-psychosis continuum, while British psychiatrists in London, using Kraepelinean approach, were identifying these same conditions as mood or anxiety disorders.

An epoch that led to the reactivation of the Kraepelin's ideas began, when lithium was introduced for the treatment of manic-depressive illness, neuroleptics for the managements of psychosis, and antidepressants for the treatment of depression. Thus Kraepelin's ideas became viable also therapeutically.

Lately, with the confluence of multiple forces the broadened notion of bipolar spectrum disorder has become established. This reflects the observations that hypomania can present as a subjective experience and is much more common than presumed (8), reflecting the pressure to accommodate treatment with atypical antipsychotics under the bipolar umbrella. How things change! The concept of schizophrenia seemed extremely broad in 1950's and 60's and now, paradoxically, four decades later the same fate has affected the concept of BD.

Thus, BD started majestically as manic-depressive illness encompassing all remitting mood disorders and decades later shrunk into BD requiring both low and high polarities. Now BD seems heading into a category of bipolar spectrum disorder that may include, regardless of clinical course, a wide variety of patients with diverse comorbidities, and many with recurrent depressions plus subjectively experienced hypomanias.

Studies of children of bipolar parents

In most localities adult and child psychiatry represent two different universes, and two distinct ways of thinking. But in recent years several adult and child specialists have joined forces in order to investigate the populations of young people at high risk for BD and came up with the same basic findings in regard to the early clinical course (9-13).

BD definitely has a robust genetic contribution. The longitudinal study of children of affected parents is an important research strategy to characterize the illness in its full clinical evolution. Children with one bipolar parent, and the other one unaffected, have a relatively high lifetime risk of developing a major mood disorder. However, this risk varies substantially in individual families and appears higher in our selected sample.

We (Duffy et al.) have over the years studied the children of BD parents and developed a high-risk study designed to reduce the confounding issues of heterogeneity and assortative mating (9;14-17). A large high-risk cohort was identified from well-characterized families based on many years of careful prospective observation and using parental response and non-response to lithium. This approach improves homogeneity of the subgroups, as adult parents with unequivocal stabilization on lithium monotherapy share a characteristic clinical profile, replicated genetic linkage and neurobiological findings. We also expanded this study by adding a comparison group of offspring of well parents. This large, longest

high-risk study in the world has provided novel and important findings about the early natural history of BD.

First of all, we made the unprecedented observation that psychopathology of BD evolves in clinical stages. We described a predictable sequence of development from non-specific childhood disorders to minor mood problems in early adolescence, and then to major depressive disorder in later adolescence. The childhood history of anxiety or sleep disorder more than doubled the later development of a major mood episode (18).

When counting major mood episodes, in nearly all affected offspring BD began as Major Depressive disorder in mid-adolescence. Typically, hypomanic or manic episodes occurred several years after the first depressive episode, and were never diagnosed in either high-risk subgroup prior to age 12. The illness may manifest the first time at any stage, but then appears to follow the predictable sequence. This onset of BD at any stage may seem puzzling but is conceivable in disorders that strike because of complex interplay of oscillating neurobiological and varying psychosocial factors.

There were important differences between offspring subgroups in the natural course. First, offspring of lithium responders (LiR) developed mood disorders with an episodic fully remitting course, while offspring of lithium non-responders (LiNR) developed mood disorders with a chronic course. Offspring of LiNRs manifested a broader spectrum of childhood antecedents including neurodevelopmental disorders, ADHD, learning disabilities (LD) and Cluster A traits, not seen among the LiR offspring. In addition,

offspring of LiRs showed resolution of childhood anxiety or sleep disorders prior to the development of mood disorders in adolescence (sequential co-morbidity), while the offspring of lithium nonresponders tended to layer new manifestations on continuing earlier disorders (concurrent co-morbidity).

To date we have studied 87 controls and 307 high-risk offspring; of these 212 in a prospective study with blind diagnostic assessments and 95 in a naturalistic observation. The sample of 212 children is described in detail elsewhere (14-17). The offspring in the open observation have been followed earlier at McMaster University, Hamilton, Ontario, for 10 years and longer.

High-risk offspring with a BD diagnosis and requiring stabilizing treatment against recurrent mood episodes tended to respond to the same stabilizer as the bipolar parent. Moreover, preliminary evidence suggested that high-risk offspring affected with early stage psychopathology (sleep, anxiety disorders, minor mood disturbances) did not benefit from the treatment prescribed according to symptom-based, traditional diagnosis (9) but responded rather to the mood stabilizer that was effective in the parent.

These observations regarding clustering of treatment response even at the earliest clinical stages may have major therapeutic implications. If these early manifestations of BD are not recognized for what they are, and diagnosed and consequently treated the traditional way for the presenting diagnosis, the young patients may be harmed. Antidepressants given for depression may be destabilizing and induce a “switch” to a later stage, chronic hypnotics

for sleep disorder habit-forming and anxiolytics for anxiety disorders ineffective.

BD has in the past been considered a disorder of adulthood, with an occasional onset in adolescence. Both depressive and manic/hypomanic syndromes were considered essential for the diagnosis. However, based on recent studies of children of bipolar parents, this diagnostic construct of BD requires rethinking and adjustment. There are findings from these studies that are particularly troublesome for a symptom-based diagnosis: that BD develops in distinct stages, that early stages have nonspecific manifestations and that these nonspecific changes share important characteristics with full fledged BD, such as for example the nature of the clinical course (episodic vs non-episodic).

Studies of children of psychotic parents

This emphasis on high-risk children has not been limited to BD. In parallel, but independently, studies with the same focus on the early phase have mushroomed in psychotic disorders. Meta-analysis and systematic reviews demonstrated that a longer duration of untreated psychosis is associated with poorer response to antipsychotic treatment as evidenced by several psychopathological and functional outcomes as well as by greater neuroimaging changes (19). However, for most patients a prolonged period of attenuated symptoms and impaired functioning antecedes the first psychotic attack.

New clinical and research programs have been established around the globe aiming to identify individuals in the pre-psychotic stage of illness

who are at imminent risk of developing psychosis, driven by observations that early intervention might favorably alter the course of illness. Intervening during this stage may reduce the burden of disability and prevalence of full blown illness.

Strategies such as an ultra-high risk approach have been introduced to attempt to identify individuals in the prodromal phase. Ultra-high risk criteria are based on a combination of known trait and state risk factors for psychosis, including attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder. These criteria are valid and reliable for predicting psychosis onset in this population, as they are able to identify the transition to threshold psychotic disorder in up to 40% within one year (19;20).

Researchers guided earlier only by observed symptoms have found that modern psychiatry's neglect of subjective experience has limited the efforts at prospective and early identification. Disturbance of the basic sense of self may be a core marker of psychotic vulnerability.

Most important in this research are the treatment implications. Transition rates can be significantly reduced even by relatively non-invasive therapies such as essential fatty acids or psychosocial interventions. Antipsychotic agents may not be necessary for individuals detected early with sub-threshold psychotic symptoms (19;21). However, broad-spectrum antipsychotics may also have a neuroprotective effect, reduce anxiety and depression, and may delay or prevent full-blown psychosis onset

But the early recognition of individuals at high risk of developing a psychotic disorder is again complicated by our current

diagnostic system which classifies only end-stage disorder, and by the lack of information about the earliest clinical manifestations. Similar to the situation with BD, to identify patients in the early stages the clinician had to focus on symptoms and features other than psychosis, such as high levels of depression, reduced attention, sense of self, family history of psychosis and significant decrease in functioning.

Discussion

The present diagnostic method, being over 100 years old, now shows signs of aging. This is to be expected in a construct that was conceived before the age of the light bulb, car and airplane and since then tweaked by committees and political compromises, rather than altered by solid research. Initially developed to serve primarily hospital statistics and the symptom description of hospitalized patients, it now fits less when used for the choice of treatment, for prognosis, for emotional problems in the community and for young people experiencing prodromes of major psychiatric disorders.

The findings from prospective studies of children of bipolar parents pose a new challenge for identifying correctly BD, particularly in their early stages: a similar underlying dysfunction can manifest in an ample variety of psychopathologies. An analogous problem is looming for psychotic disorders. But these obstacles should not come as a surprise. The traditional diagnostic system for BD was developed primarily from observations of intensely ill, hospitalized patients and reflected the illusion

of stable symptoms. It did not take a developmental approach and there was a lack of information about the early natural history of the disorder.

The symptom-based approach serves better when the clinician is dealing with a fully developed disorder, but has limited validity particularly for the initial stages when the harbingers of major mental disorders start manifesting. Sadly, this diagnostic approach is of no value when effective intervention may be needed most. Even obtaining approval from the Ethics committees for controlled trials for these conditions will be impossible until the illness has fully evolved and traditional labels can be applied. Unfortunately, as patients move through early stages of BD or psychosis, the traditional approach generates an illusion of multiple comorbidities and thus forces unnecessary polypharmacy.

The DSM-V is currently in preparation. How or if it will address these new challenges remains to be seen. The continuous supply of new medications makes refined diagnostic distinctions increasingly imperative. To make correct clinical decisions, a diagnosis of DSM or ICD type is important and necessary, but obviously not sufficient. There are other features to consider. Unfortunately, psychiatrists today often limit their approach to listing symptoms, diagnosing, and then prescribing long-term medication.

For both effective treatment and research, the variety of psychopathological prodromes, as it emerges from the high-risk studies, will require a broader diagnostic approach, paying attention not just to psychopathological symptoms and syndromes, but also to other aspects of clinical profile and to the stage of illness. Otherwise, the current

diagnostic categories in psychiatry will continue impeding progress in understanding illness evolution and identifying the most effective intervention strategies. More flexible useful tools are needed for guiding early intervention or treatment of people with less severe illness, or uncovering underlying pathological mechanisms.

The clinical staging model that draws a distinction between initial, milder clinical manifestation and those that characterize advancing illness has a particular utility (22). A welcome approach would also include the recognition that over time an individual patient may present with several clinical phenotypes, which may coalesce into subtypes with characteristic endophenotypes and biomarkers .

The findings from high-risk studies may also reactivate a nearly two centuries old, perennial question in psychiatry: Are there only stages and variations of one major disorder (“Einheitspsychose”) (23) or are there distinct, genuine disorders which one can delineate? This question now expands further: Can we determine if bipolar disorder, unipolar depression and psychosis share a common early phase? Can we reliably differentiate specific antecedents for mood disorders from the prodromes of psychotic disorders?

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