

Defining Clinical Phenotypes of Juvenile Mania

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Objective: The authors suggest criteria for a range of narrow to broad phenotypes of bipolar disorder in children, differentiated according to the characteristics of the manic or hypomanic episodes, and present methods for validation of the criteria.

Method: Relevant literature describing bipolar disorder in both children and adults was reviewed critically, and the input of experts was sought.

Results: Areas of controversy include whether the diagnosis of bipolar disorder should require clearly demarcated affective episodes and, if so, of what duration, and whether specific hallmark symptoms of mania should be required for the diagnosis. The authors suggest a phenotypic system of juvenile mania consisting of a narrow phenotype, two intermediate phenotypes, and a broad phenotype. The narrow phenotype is exhibited by patients who meet the full DSM-IV diagnostic criteria for hypomania or mania, in-

cluding the duration criterion, and also have hallmark symptoms of elevated mood or grandiosity. The intermediate phenotypes include 1) hypomania or mania not otherwise specified, in which the patient has clear episodes and hallmark symptoms, but the episodes are between 1 and 3 days in duration, and 2) irritable hypomania or mania, in which the patient has demarcated episodes with irritable, but not elevated, mood. The broad phenotype is exhibited by patients who have a chronic, nonepisodic illness that does not include the hallmark symptoms of mania but shares with the narrower phenotypes the symptoms of severe irritability and hyperarousal.

Conclusions: The presence of distinct episodes and hallmark symptoms can be used to differentiate clinical phenotypes of juvenile mania. The utility and validity of this system can be tested in subsequent research.

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Juvenile mania has been a topic of considerable discussion and debate as the field grapples with how the diagnosis can be made reliably and validly (1–3) and whether (and how) the presentation of hypomania or mania may differ between children and adults (4). In particular, there is considerable disagreement about the most appropriate diagnosis for children with a constellation of chronic and severe irritability, hyperactivity, and abnormal mood (usually sadness and/or anger). Some psychiatrists would give such children a diagnosis of “mixed mania” or rapid-cycling bipolar disorder, while others would not (1). To address this problem, a panel of experts recently recommended that researchers in the field define “narrow” and “broad” phenotypes for juvenile mania so that children meeting the criteria for each phenotype could be assessed systematically and followed longitudinally (5).

The distinction between narrow and broad phenotypes is important from both a clinical and a research perspective. From the clinical perspective, it is important to know whether children who exhibit some manic symptoms respond to treatment differently than do those who meet the full diagnostic criteria for a manic episode (6). From the research perspective, the distinction between narrow and broad phenotypes is important because pathophysiologi-

cal and genetic studies require clearly defined inclusion criteria that will yield homogeneous groupings. This paper suggests a method for defining a range of phenotypes from narrow to broad, presents the rationale for the phenotype criteria, and outlines a research plan to validate the proposed phenotypic classification.

The controversy regarding the diagnosis of early-onset mania stems from disagreement on 1) whether the diagnosis of mania should require the presence of clearly defined episodes; 2) if so, what the minimum duration of these episodes should be; and 3) whether there are specific hallmark symptoms of mania that should be required for the diagnosis. In light of these questions, we suggest distinguishing four groups of children, only some of whom may ultimately suffer from an illness that is pathophysiologically similar to adult bipolar disorder. (In this phenotypic system, we follow DSM-IV [6] in that the criteria for hypomania and mania differ in minimal episode duration [4 versus 7 days, respectively] and in level of impairment but are otherwise identical. Throughout this paper, we use the term “(hypo)mania” to denote “hypomania or mania.” The suggested phenotypes are 1) the narrow phenotype, exhibited by patients who meet the full DSM-IV diagnostic criteria for (hypo)mania, strictly construed, with the hallmark

FIGURE 1. DSM-IV Criteria for Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance, three or more of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
 - (1) inflated self-esteem or grandiosity
 - (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
 - (3) more talkative than usual or pressure to keep talking
 - (4) flight of ideas or subjective experience that thoughts are racing
 - (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
 - (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 - (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The symptoms do not meet criteria for a mixed episode.
- D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hypothyroidism).

symptoms of elevated mood or grandiosity (7, 8) and clear episodes meeting the duration criteria (Figure 1 and Figure 2); 2) two intermediate phenotypes, exhibited by patients who have a clearly episodic illness but fail to meet strict criteria for (hypo)mania either because their episodes are, by the DSM-IV criteria, too short (we have named this phenotype “[hypo]mania not otherwise specified”) or because they lack the hallmark (hypo)manic symptom of elevated mood (we have named this phenotype “irritable [hypo]mania”) (Figure 3); and 3) the broad phenotype, exhibited by patients who have a chronic, nonepisodic illness that lacks the hallmark symptoms of (hypo)mania but that shares with the narrower phenotypes the symptoms of severe irritability and hyperarousal (Figure 4).

Children exhibiting the broad phenotype may ultimately prove to be a heterogeneous group. Some may eventually meet the strict criteria for (hypo)mania; the course of others’ illness may be consistent with dysthymia, major depressive disorder, or some form of disruptive behavior disorder; and still others may prove to have a syndrome that is not well captured by the current diagnostic system. Family history may be a particularly important variable in defining more homogeneous subgroupings. For the present, we have defined a broad but clearly operationalized phenotype, identified by using the child’s symptoms, in order to facilitate the systematic study of children whose symp-

FIGURE 2. Criteria for the Narrow Phenotype of Juvenile Mania: (Hypo)Mania, With Full-Duration Episodes and Hallmark Symptoms

Modification to the DSM-IV criteria for manic episode
The child must exhibit either elevated/expansive mood or grandiosity, while also meeting the other DSM-IV criteria for a (hypo)manic episode (7).

Guidelines for applying the DSM-IV criteria

Episodes must meet the full duration criteria (i.e., ≥ 7 days for mania and ≥ 4 days for hypomania) and be demarcated by switches from other mood states (depression, mixed state, euthymia).

Episodes are characterized by a change from baseline in the patient’s mood (DSM-IV criterion A) and, simultaneously, by the presence of the associated symptoms (DSM-IV criterion B). For example, the distractibility of a child with ADHD would count toward a diagnosis of (hypo)mania only if his/her distractibility worsened at the same time that he/she experienced mood elevation.

Decreased need for sleep should be distinguished from insomnia (i.e., nonspecific difficulty sleeping, which is associated with fatigue).

Poor judgment per se is not a diagnostic criterion for (hypo)mania; the poor judgment must occur in the context of “increased goal-directed activity” or “excessive involvement in pleasurable activities that have a high potential for painful consequences.”

toms resemble those of the narrower phenotypes but whose nosologic status is unclear.

Longitudinal studies of children exhibiting each of the phenotypes are, of course, crucial. But ultimately the diagnosis of (hypo)mania, as of other psychiatric illnesses, will rest on an understanding of pathophysiology. At this point, when such understanding remains limited, careful phenomenological studies should inform the inclusion criteria for studies of brain function, and physiological studies should in turn yield data with implications for diagnostic criteria. In an attempt to facilitate this iterative process, we describe the proposed phenotypes while reviewing the problematic issues that complicate the diagnosis of (hypo)mania in children.

Narrow Phenotype: (Hypo)Mania (Full-Duration Episodes, Hallmark Symptoms)

As noted in the previous section, the most problematic issues in the diagnosis of juvenile mania involve questions about the presence and duration of episodes and the identification of hallmark symptoms of mania. Our narrowest phenotype requires that a child exhibit clear episodes that meet the full DSM-IV criteria, including duration (Figure 1), and hallmark symptoms of mania (elevated/expansive mood or grandiosity) (6, 7). Figure 2 shows the criteria for the narrowest phenotype as well as guidelines for the application of the DSM-IV criteria for (hypo)mania. The requirement of clearly defined episodes stems from the fact that, since early descriptions of mania (9), clinicians have observed that classic mania is characterized by demar-

FIGURE 3. Criteria for the Intermediate Phenotypes of Juvenile Mania

(Hypo)mania not otherwise specified
 The child meets the criteria for the narrow phenotype of juvenile mania except that his/her (hypo)manic episodes are between 1 and 3 days in duration.

Irritable (hypo)mania
 The child meets the DSM-IV criteria for (hypo)mania with irritable, not elevated or expansive, mood.
 Consistent with the DSM-IV criteria for (hypo)mania, the child's irritable (hypo)mania must occur in distinct episodes meeting the duration criteria.

cated time periods of disturbed mood accompanied by behavioral and cognitive symptoms. However, the controversy surrounding the diagnosis of mania in children has been fueled in large part by disagreement concerning the definition and minimum length of an episode (1). In classic mania, manic episodes are discrete events long enough to be differentiated clearly from depressive and euthymic periods. Some investigators have argued that, while prepubertal children with mania have distinct episodes, these episodes are shorter than those of adults and remit less completely, so that fewer euthymic periods exist to demarcate affective episodes (8, 10–13). Other investigators have described the presentation of early-onset mania as relatively chronic, with very brief episodes characterized by an acute but short-lived worsening superimposed on an impaired baseline (1).

Several methodological and conceptual issues complicate the discussion of episodicity in childhood-onset mania and thus fuel the controversy. The first is that the available data are retrospective. Research has shown that adults perform poorly when asked to report retrospectively the duration and frequency of mood states, placing undue emphasis on the most recent and severe negative mood (14). For children with psychopathology, data indicate that neither parents nor children can date reliably the onset of symptoms beginning more than a few months before the interview (15). Thus, it may be extremely difficult for children with bipolar disorder, their parents, or even adults with bipolar disorder to give accurate retrospective reports of cycle length, since frequent mood switches occur in children (or adults) with bipolar disorder (7, 16).

A second methodological issue concerns the tendency to characterize patients with affective episodes in terms of the longest episode(s) that they have ever experienced and/or in terms of the typical duration of their episodes. Studies of adults with bipolar disorder have tended to place greater diagnostic weight on the duration of a patient's longest episodes. For example, the terms rapid, "ultra-rapid," and "ultradian" cycling, often used to describe children with bipolar disorder (10), are derived from the literature on adults with bipolar disorder (17). In Dunner and Fieve's original description of rapid-cycling bipolar disorder (18), and in most subsequent research, the researchers

FIGURE 4. Criteria for the Broad Phenotype of Juvenile Mania: Severe Mood and Behavioral Dysregulation

Inclusion criteria
 Age 7–17 years, with the onset of symptoms before age 12.
 Abnormal mood (specifically, anger or sadness) present at least half of the day most days and of sufficient severity to be noticeable by people in the child's environment (e.g., parents, teachers, peers).
 Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness.
 Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week for the past 4 weeks.
 The symptoms noted in the previous three items are currently present and have been present for at least 12 months without any symptom-free periods exceeding 2 months in duration.
 The symptoms are severe in at least in one setting (e.g., violent outbursts or assaultiveness at home, at school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.

Exclusion criteria
 The individual exhibits any of these cardinal bipolar symptoms: elevated or expansive mood, grandiosity or inflated self-esteem, episodically decreased need for sleep.
 The symptoms occur in distinct periods lasting more than 4 days.
 The individual meets the criteria for schizophrenia, schizophreniform disorder, schizoaffective illness, pervasive developmental disorder, or posttraumatic stress disorder.
 The individual has met the criteria for substance use disorder in the past 3 months.
 IQ <80.
 The symptoms are due to the direct physiological effects of a drug of abuse or to a general medical or neurological condition.

required that adults with bipolar disorder experience four affective episodes that meet the full duration criteria in a year. We recommend that the same convention be used for children. It is noteworthy that Dunner and Fieve (18) and subsequent researchers found that, in addition to having had full-duration episodes, most adult patients with rapid-cycling bipolar disorder also experienced shorter episodes.

In the literature on juvenile mania, however, researchers often do not specify the duration of the longest manic (or depressive) episodes patients have experienced. Such data would allow comparisons with adult patients. In addition, prospective longitudinal observation of children presenting with manic symptoms is an important complement to retrospective reports. Using both retrospective and prospective data, we found that most children with well-demarcated episodes and hallmark symptoms of mania have lifetime histories of episodes meeting full duration criteria (although most of their episodes are considerably shorter) and therefore may be categorized as having the narrow phenotype rather than as having (hypo)mania not otherwise specified (see the next section) (19).

To be classified as having our narrowest phenotype, a child has to experience not only full-duration (hypo)manic episodes but also hallmark symptoms of (hypo)mania (elevated mood and/or grandiosity). While specificity is a serious problem in psychiatric nosology generally, and in childhood-onset disorders particularly, (hypo)mania is one of the few psychiatric illnesses that has a pathognomonic presentation: the episodic, hyperaroused, euphoric state (20). However, some of the symptoms of (hypo)mania are nonspecific, and a major cause of the controversy regarding juvenile (hypo)mania stems from criterion overlap with attention deficit hyperactivity disorder (ADHD) (21). Such overlap is present in the following criteria: “pressure to keep talking” ([hypo]mania) and “often talks excessively” (ADHD), psychomotor agitation ([hypo]mania) and “often runs about or climbs excessively” (ADHD), and distractibility (both [hypo]mania and ADHD) (6). To make the differential diagnosis with confidence, clinicians can rely on episodicity (since ADHD is not an episodic illness [22]) and on the identification of symptoms that occur only in (hypo)mania.

Geller et al. (8) found that grandiosity, elated mood, flight of ideas, decreased need for sleep, hypersexuality, and increased goal-directed activity (along with other symptoms not included in DSM-IV) differentiated children with bipolar disorder from those with ADHD. These univariate analyses should be complemented by multivariate techniques and receiver operating characteristics analyses (23). In addition, longitudinal and family history data can contribute to the identification of cardinal symptoms of (hypo)mania. Prospective epidemiological studies could identify developmental norms for symptoms such as euphoria, grandiosity, and irritability, and clarify the extent to which childhood irritability predicts adult pathology.

The analysis by Geller et al. (8) of symptoms differentiating youth with ADHD from those with bipolar disorder found that, of all the symptoms, elated mood and grandiosity were best able to distinguish the two groups. Therefore, in subsequent studies her research group required the presence of one of these classic symptoms of (hypo)mania for inclusion in the narrow phenotype group. We believe that this is a reasonable approach, and we have incorporated it into our definition of a narrow phenotype (Figure 2). However, in applying this criterion, it is important to note that, just as depressed children may report sadness when their parents are aware only of the child's irritability, the parents of (hypo)manic children may be aware of the child's irritability but not of his/her concurrent euphoria. Therefore, it is important to interview both the parent and the child to ascertain the presence of elevated mood.

Intermediate Phenotypes

(Hypo)Mania Not Otherwise Specified (Short Episodes, Hallmark Symptoms)

How short can a (hypo)manic episode be? The question is important, because researchers have suggested that chil-

dren with (hypo)mania tend to have shorter episodes than adults with (hypo)mania (10, 24). In our system of phenotypes, the distinction between children with (hypo)mania and those with (hypo)mania not otherwise specified stems from a difference in the length of their mood episodes. According to our definition, those with (hypo)mania must meet the full DSM-IV duration criteria (1 week for mania and 4 days for hypomania), whereas those with (hypo)mania not otherwise specified have episodes that last between 1 and 3 days. Our approach therefore differs somewhat from that of Geller et al. (7, 25), who include in the narrow phenotype group those children whose symptoms last for at least 4 hours/day. In contrast to Geller's approach, our approach distinguishes (hypo)mania from (hypo)mania not otherwise specified (thereby increasing homogeneity) and sets a minimum duration of 1 day in order to ascertain the presence of criterion B symptoms (see the next paragraph). While we have adopted the DSM-IV duration criteria to distinguish (hypo)mania from (hypo)mania not otherwise specified, more research is needed on this question, since the criteria are based on nosologists' clinical judgment, rather than on data. Depending on the diagnostic system, the required duration for (hypo)mania has ranged from “none specified” to 2 weeks (26, 27, DSM-III).

Meanwhile, in the absence of data validating a minimum episode duration, an episode could theoretically be defined as lasting only hours. However, a major problem with successively shorter definitions of an episode is that, when examining a span of hours rather than weeks or days, it is considerably more difficult to discern whether the reported shifts in mood are *accompanied by changes in behavior*, as required by criterion B for (hypo)mania. Thus, the clinician becomes more dependent on subjective measures of mood and less able to use objective variables such as hours of sleep, weight loss or gain, or amount of schoolwork accomplished to ascertain whether a significant state change is occurring.

Left with only subjective mood measures, an observer can view the data at different levels of resolution, leading to different conclusions about episode duration. It is important to note that mood states are not completely consistent in manic patients, in depressed patients, or in comparison subjects. Even among patients with a diagnosis of euphoric mania, 20%–30% exhibit dysphoria (28). One might consider those brief time periods when a patient reports dysphoria to be switches out of mania into depression, or one might take a broader view and conclude that the patient is experiencing a pure manic episode with occasional, fleeting dysphoria. Similarly, a depressed subject might experience diurnal variation that, if one used a fine level of resolution, could be considered a switch from depression to euthymia and then back to depression the next morning, yielding 14 depressive and 14 euthymic episodes in a 2-week period. Alternatively, one could take a broader view, contrasting the 2-week period with the preceding months in which the subject never met criteria for depression and

concluding that the subject had one depressive episode lasting 2 weeks. We recommend the broader view because 1) it is more likely to be relevant to treatment decisions and 2) it allows one to ascertain whether subjective mood changes are accompanied by the vegetative and behavioral symptoms that are characteristic of mood disorders.

Since our system requires a minimum episode duration of 1 day to meet the criteria for (hypo)mania not otherwise specified, the question arises of how to characterize children whose (hypo)manic episodes are shorter than 1 day. As noted earlier, it is important in such cases to ascertain the child's longest lifetime episode and whether the duration criteria have ever been met. In addition, it is important to determine not only whether the child exhibits an episodic change in mood (criterion A, Figure 1) but also whether enough criterion B symptoms are present. If the mood changes are episodic and enough B criteria are met, the clinician must then determine what mood state is alternating with the very brief (hypo)manic episode. If the second mood state is euthymia, we would consider these mood fluctuations to represent the severe diurnal variation that is often seen in adults with rapid-cycling bipolar disorder (29). If, on the other hand, the second mood state is depression, then the patient would meet the DSM-IV criteria for a mixed episode (see the next section).

Irritable (Hypo)Mania (Full-Duration Episodes, No Hallmark Symptoms)

According to DSM-IV, a patient can be given a diagnosis of a (hypo)manic episode if he/she has elevated/expansive or irritable mood (Figure 1). In our phenotypic system, however, children who exhibit irritability only (concurrent with the criterion B symptoms of [hypo]mania) are differentiated from those who exhibit elation in that the latter are classified as having the narrowest phenotype, while the former are classified as having the intermediate phenotype of irritable (hypo)mania. The rationale for this distinction is that, while episodic elevated/expansive mood is unique to mania, episodic irritability can also be seen in depressed children, and chronic irritability is common in oppositional defiant disorder, ADHD, and some variants of pervasive developmental disorder. Given the uniqueness of manic euphoria versus the ubiquity of irritability in childhood psychopathology, we, like Geller et al. (7, 25), have elected to reserve the narrowest (hypo)manic phenotype for children with a lifetime history of euphoria, thereby dividing the DSM-IV diagnosis of (hypo)manic episode into irritable and pure (hypo)mania. According to the convention established earlier, a patient who met the criteria for irritable (hypo)mania with episodes of 1–3 days' duration could be categorized as having irritable (hypo)mania not otherwise specified. Furthermore, researchers might wish to add a modifier indicating whether children with irritable (hypo)mania have a lifetime history of retarded depression and/or agitated depression, since

course and response to treatment may differ with these variables.

In the child psychiatric literature, the term "mixed mania" is frequently applied to patients with irritability (rather than euphoria). In contrast, DSM-IV and most recent articles describing adult bipolar disorder patients use the term "mixed" for patients with dysphoric (i.e., depressed, sad) affect, rather than for patients with irritability only (30, 31). In part, this is because some degree of irritability occurs in approximately 80% of the adults who meet the DSM-IV criteria for mania, whereas dysphoria occurs in less than 50% (32). In any event, given this ambiguity in the use of the terms "mixed," "irritable," and "dysphoric" mania, it is important for researchers and clinicians to provide detailed phenomenological data for patients who are given this diagnosis. DSM-IV defines a mixed episode such that a patient is required to meet the full diagnostic criteria for both (hypo)mania and depression, and we recommend that children who meet such criteria receive the diagnosis of mixed episode. (In contrast, children who meet our criteria for irritable [hypo]mania would not meet the full criteria for depression.)

From a clinical perspective, it is important that particular care be given to assessing anxiety and subtle forms of paranoia in children with irritable (hypo)mania or mixed episodes, especially those who exhibit aggressive behavior. Two recent factor analyses of symptoms in adult mania found that irritability loaded onto a factor with paranoia and aggression, while anxiety loaded onto a separate factor with dysphoric or depressed items (28, 33).

Broad Phenotype: Severe Mood and Behavioral Dysregulation

In developing inclusion and exclusion criteria for the broad phenotype (Figure 4), we had two major goals: 1) to encompass the clinical description of the patients' symptoms, which is reasonably consistent although not formally operationalized in the literature (1, 34), and 2) to exclude children who fit the criteria for the narrower (hypo)manic phenotypes. The clinical descriptions of the broad phenotype emphasize the children's increased reactivity to negative emotional stimuli in the form of severe rages, as well as chronic hyperarousal (motor hyperactivity, distractibility, etc.). These symptoms, which are also seen in the narrower (hypo)manic phenotypes, form the core of our inclusion criteria. In addition, the criteria specify that the child exhibit abnormal mood between rages, in the form of sadness or anger, and that the symptoms are chronic and cause impairment in at least two settings. We exclude from the broad phenotype group children with the hallmark symptoms of elevated/expansive mood and grandiosity, those with distinct episodes of abnormal mood, and those who exhibit episodically decreased need for sleep. Our rationale for the latter is that, of all the symptoms of mania, decreased need for sleep is the one that has been

TABLE 1. Criteria for and Research Strategies to Establish Reliable and Valid Phenotypes of Juvenile Mania^a

Criterion	Description	Research Strategy
1	Consistent clinical description	The reliability of Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) modules and rating scales for (hypo)mania, depression, and the broad phenotype is established. The results of cluster analyses are used to revise the phenotypic criteria.
2	Consistent findings in physiologic/neuropsychological studies	Neuropsychological function and physiologic measures in response to standardized emotional stimuli and structural neuroimaging are used to assess subjects with different phenotypes and comparison subjects. The results are used to design functional neuroimaging paradigms.
3	Clear delimitation from other disorders	Children presenting in clinics for mood disorders and attention deficit hyperactivity disorder are assessed with the K-SADS, the new K-SADS module, and rating scales to ascertain that doubtful cases can be excluded reliably.
4	Consistent clinical outcomes found in follow-up studies	Children with different phenotypes are followed into adulthood, and their clinical course/ diagnostic outcomes are compared.
5	Increased prevalence in relatives found in family and genetic studies	Parents are interviewed to ascertain first-degree relatives' phenotypes. If heritability is established, and other criteria are met, genetic studies can be undertaken.

^a Criteria for establishing reliability and validity adapted from Robins and Guze (38).

shown to have pathophysiological significance (35). However, it is important to distinguish the decreased need for sleep characteristic of (hypo)mania from nonspecific insomnia (only the latter is accompanied by tiredness), as well as from the stimulant-induced insomnia, initial insomnia, or chronically decreased need for sleep that may be seen in ADHD (36).

In collaboration with J. Kaufman, Ph.D., we developed modifications to the Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (37) to ensure that the broad phenotype can be diagnosed reliably. We will be testing these modifications both in our research setting and (in collaboration with Paramjit Joshi, M.D.) in tertiary care clinics. We expect that many subjects who meet the criteria for the broad phenotype will also meet the criteria for one or more DSM-IV diagnoses, such as major depressive disorder, ADHD, conduct disorder, and/or oppositional defiant disorder. However, the controversy about how to establish a diagnosis for these children has arisen in part because none of the DSM-IV diagnoses captures a relatively homogeneous population of patients with mood disturbance, hyperarousal, and decreased frustration tolerance. Therefore, it is reasonable to begin with a clearly operationalized description of the broad phenotype and to treat DSM-IV diagnoses as descriptive data rather than as inclusion or exclusion criteria.

While the population defined by these criteria should be more homogeneous than populations defined by DSM-IV diagnoses, it is nonetheless likely to be heterogeneous. Subgroups may be distinguishable by family history of bipolar disorder, DSM-IV diagnoses, and/or the relative severity of their mood symptoms, psychotic symptoms, hyperarousal, or behavioral dyscontrol. Longitudinal studies that examine the relationship between such variables (particularly, family history of bipolar disorder) and ultimate course are crucial. If the broad phenotype is actually a phenotype of (hypo)mania, but children with this phenotype do not meet the DSM-IV diagnostic criteria for (hypo)mania because the criteria are developmentally insensitive, then one might expect the children's symptoms

to evolve as they age and to eventually approximate a more classic presentation of (hypo)mania. Alternatively, children classified as having the broad phenotype may never develop a classic (hypo)manic presentation but may nonetheless follow a clinical course in the "bipolar spectrum" (38).

Conclusions

Research on the pathophysiology and treatment of children with mania and related syndromes would be advanced by the definition of relatively homogeneous clinical subgroupings. To test the validity of this and other phenotypic definitions, collaborative research efforts are needed so that questions about the minimum duration of an episode, the diagnostic criteria for a mixed state, and the identification of cardinal symptoms of (hypo)mania can be resolved empirically.

Within this phenotypic system, an important area of research concerns the extent to which the diagnostic criteria for the broad phenotype are reliable and valid. Robins and Guze (39) suggested that a valid syndrome should meet the following criteria: 1) a consistent clinical description; 2) consistent evidence from diagnostic laboratory studies; 3) clear differentiation from other, clinically similar entities; 4) evidence from follow-up studies indicating that patients have relatively similar clinical outcomes or, at least, do not eventually fit diagnostic criteria for another entity; and 5) evidence from family studies indicating increased prevalence in relatives.

The application of these criteria to the proposed phenotypes is shown in Table 1 (with Robins and Guze's criteria 2 and 5 [39] updated). With regard to clinical description (Robins and Guze's criterion 1), it is possible to test the reliability of the K-SADS-PL interview in differentiating the phenotypes and to test the ability of the broad phenotype module to identify children who meet the criteria for this phenotype (and who may or may not also meet the criteria for ADHD, major depressive disorder, oppositional defiant disorder, etc.). Such a test of reliability would demonstrate

that the phenotypes have clear boundaries (criterion 3). In addition, since the K-SADS-PL does not include severity ratings, it is important to develop reliable and valid rating scales for the broad phenotype as well as for (hypo)mania in children and adolescents, since the available adult (hypo)mania rating scales have not been validated in younger patients. Cluster analyses of the symptoms reported by patients and parents can be used to revise the diagnostic criteria shown in Figure 4. Children can be followed longitudinally to ascertain clinical course, prognosis, and diagnostic stability (criterion 4). To ascertain the heritability of the phenotypes (criterion 5), parents can be interviewed about their own symptoms by using the Structured Clinical Interview for DSM-IV with an additional module designed to ascertain past and present symptoms of the broad phenotype. And finally, to address Robins and Guze's criterion 2 (the identification of physiological findings distinguishing patients with the syndrome), patients' neuropsychological functioning, as well as their neurophysiologic response to standardized emotional stimuli, can be studied and compared across phenotypes and relative to comparison subjects. The results of these studies can then be used to design paradigms for eventual use in functional neuroimaging studies.

Clear phenotypic definitions can be used to optimize treatment, since it is helpful for clinicians to know the degree to which patients classified as having a given phenotype are likely to respond to a specific intervention. Multi-site clinical trials could ascertain whether a patient's phenotype predicts his/her clinical response to a given treatment. For example, it is conceivable that children with the narrow phenotype resemble adult patients with bipolar disorder, in which case mood stabilizers would be the medications of choice and stimulants and/or antidepressant treatments might precipitate mania or rapid cycling (40, 41). On the other hand, very preliminary evidence indicates that children with the broad phenotype may respond well to stimulants (42). Given the phenomenological differences between the narrow and broad phenotypes, it is possible that their optimal treatment algorithms are not identical.

The diagnosis and treatment of early-onset (hypo)mania pose considerable challenges to clinicians and researchers alike. The heterogeneity of the illness and the effect of developmental factors on its clinical presentation tax the limits of the current diagnostic nosology, leading investigators to suggest the definition of a more detailed and comprehensive phenotypic system. In suggesting one such system, along with a research program to test its reliability and validity, we hope to contribute to the field's progress in understanding and treating this disabling illness.

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