Introduction to New Research: Understanding the Issues in Child and Adolescent Bipolar Disorder

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Introduction

Debate still exists in the psychiatric field over whether pediatric bipolar disorder is a valid diagnosis. Many clinical features of this disorder distinguish it from the well-established criteria that define adult-onset bipolar disorder. Perhaps the most salient of these is the high prevalence of irritability as the major presenting symptom as opposed to the euphoria more often seen with the adult disorder. In addition to irritability, pediatric bipolar disorder tends to present with a mixed or continuous presentation of mania in contrast to the discrete manic episodes classically described for bipolar disorder.[1] Research in adults has revealed that bipolar disorder causes high morbidity, with patients symptomatically ill for 47% of the weeks in their life following diagnosis.[2] Depressive symptoms and subsyndromal depression predominate a patient's life with this disorder.

Natural History

Because little is currently known about the natural history of pediatric bipolar disorder, Biederman and colleagues[1] sought to examine patterns of persistence and remission in pediatric patients. An average age of onset of 6.3 ± 4.7 years was found in a cohort of 22 patients, with 55% having an onset of younger than 6 years. Assessment of the children was performed using several standard indices, including the KSADS-E (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Episodic version), GAF (Global Assessment of Functioning), and SAICA (Social Adjustment Inventory for Children and Adolescents). The study was performed using an accelerated longitudinal design in which children with a wide age range were assessed at baseline, thereby providing a broader view of the disorder than could otherwise be found during the timeline of the study. Estimations of the course and duration of pediatric bipolar disorder were made by calculating age of onset and remission for patients of different ages at baseline.

Remission

Remission was defined in one of several ways: (1) symptomatic, (2) syndromal (remission of full diagnostic criteria for bipolar disorder), (3) functional (symptomatic remission plus a GAF score of less than 65), or (4) euthymia (failure to meet criteria for mania or depression). Using these varying definitions of remission instead of only evaluating syndromal remission led to the observation that only 20% of patients functionally remitted and only 7% of patients achieved euthymia. Thus, although syndromal remission appeared to show high rates of recovery from the disorder, it is clear that most patients never achieve a euthymic state and experience bipolar disorder throughout adolescence. These data indicate that pediatric bipolar disorder shows a chronic, protracted course. Although 50% of patients remitted from the full syndrome, 80% never got completely well. Similarly, Lewinsohn and colleagues[3] found that, compared with adolescents with major depressive disorder or who were never mentally ill, bipolar children exhibited significant functional impairment and high comorbidity with other psychiatric disorders.

Characteristics of the Disorder

Although there is a growing consensus that bipolar disorder exists in children, there is continuing disagreement over the defining characteristics of the disorder. This is largely due to the lack of clearly defined manic and depressive episodes in the pediatric cohort and the large overlap with

patients with attention-deficit/hyperactivity disorder (ADHD). In an effort to develop a more complete profile of this syndrome, Mick and colleagues[4] performed a meta-analysis of the Child Behavior Checklist (CBCL) data from several studies. They used CBCL scores to analyze data from different sources using a common metric; the CBCL is standardized across different studies and is well known. Although the authors concede that the CBCL would be a poor diagnostic tool for bipolar disorder, it is useful as a means of bridging data from studies that would otherwise be disparate. Items of the CBCL that relate to bipolar disorder are spread out but can be chosen and analyzed to observe trends in bipolar patients. The authors observed that, compared with subjects without bipolar diagnoses, bipolar patients had significantly higher scores for anxiety and depression, attentional problems, and aggressive behavior.

Although irritability appears to be a major presenting feature of pediatric bipolar disorder, there remain questions regarding the specificity of this symptom. Some insist that irritability is an ADHD symptom and therefore not a good means for defining pediatric bipolar disorder, since these are often comorbid for this age group. However, irritability is not actually included in the diagnostic criteria for ADHD. In addition, the authors believe that the irritability associated with bipolar disorder is more severe and persistent than the frustration commonly found with ADHD. Data from the MTA (Multimodal Treatment Study of Children with ADHD) lend credence to irritability as a marker for bipolar disorder and not ADHD. The MTA study is essentially a nonbipolar sample of 289 ADHD subjects. Only 10% of this population showed irritability, and the probability of meeting full criteria for mania for patients exhibiting explosive irritability was approximately 45%.[5]

A Unique Diagnosis

Further evidence supporting pediatric bipolar disorder as a unique psychiatric entity comes from a family study performed by Wozniak and colleagues.[6] Of 262 children younger than 12 years who were referred to their clinic, 16% met criteria for mania. The mean age of manic subjects was 7.9 years, and patient evaluation revealed that the mania in most subjects had a preschool age of onset. For this reason, a study was designed to map the developmental course of pediatric bipolar disorder in the families of 107 bipolar probands with 296 first-degree relatives. Interviewers were blind to subject and family diagnoses. In addition to exploring clinical features in the children, the study was also used to assess the validity of the structured interview. There was high convergence found between the interview, which was performed by lay interviewers, and the clinical evaluation, which was performed by a panel of board-certified child and adolescent psychiatrists.[7]

In this cohort, the average age of mania onset was 5.4 years, with 75% reporting an onset of mania at younger than 5 years. For this population, the mean number of B symptoms of mania, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, was 6/7. This included 86% with irritability, 81% with grandiosity, 70% with racing thoughts, and 50% with hypersexuality; these figures indicate that, although pediatric bipolar patients present most often with an atypical presentation, this population still exhibits a variety of classic bipolar symptoms. A distinguishing feature of this pediatric population was that only 9% had pure manic episodes, whereas most had a mixed presentation of mania with depression. Comorbidity was high, with many patients diagnosed as having comorbid ADHD, conduct disorder, severe oppositional defiant disorder, severe major depressive disorder, multiple anxiety disorders, psychosis, tic disorders, and substance use disorders. In these subjects, the authors found a high proportion of ultrarapid cycling subjects (27%), with more than 20 manic episodes per year, and a unique group of ultradian cycling subjects, who reported more than 300 episodes per year.[6]

Bipolar Depression

Although understanding these distinguishing features of pediatric mania is important, it is also necessary to assess clinical characteristics of bipolar depression in children and how they

compare to adult populations. Depression in bipolar adults has been described as more "melancholic" than unipolar depression.[8] These melancholic features include the following[9]:

1. Psychomotor disturbance
2. Loss of interest
3. Indecisiveness
4. Nonreactive mood
5. Diurnal mood variation
6. Appetite/weight loss

Severity on the Hamilton Depression scale is often similar, but there are unique aspects of bipolar depression that differ from major depressive disorder. A study by Carlson and Kashani[10] identified that bipolar children had more anhedonia, diurnal variation, hopelessness, psychomotor retardation, and delusions than unipolar patients. Strober and Carlson[11] found that 20% of children assessed with unipolar depression went on to have bipolar disorder later in life. Predictors of bipolar disorder in this major depressive disorder population included rapid symptom onset and psychomotor retardation, consistent with previous findings.

A more recent study by Faraone and colleagues[12] compared children with unipolar depression to those with bipolar depression using boys and girls referred for a study on ADHD to determine whether a unique phenotype exists for bipolar depression. They found that severity of depression correlated with the likelihood of a bipolar diagnosis; 77% of bipolar patients had severely impairing major depressive disorder compared with 43% of unipolar patients. Bipolar patients were also more likely to admit to feeling both irritable (mad/cranky) and sad than unipolar patients (74% vs 54%). Consistent with the previous studies described, bipolar subjects had greater psychomotor disturbances and hopelessness or pessimism. They also presented with greater suicidality and a greater number of comorbidities.

Pediatric bipolar patients in this cohort and the previously described family study are a high-risk group of children, with 31% to 36% reporting prior hospitalization and overall high rates of cognitive impairment, as assessed by the need for tutoring, special classes, and repeated grades. Severe social dysfunction with parents, siblings, and peers and at school was also found for these subjects. It is imperative to diagnose the conditions of these patients accurately to alleviate some of the problems associated with this disorder. These recent studies serve to better define the syndrome of pediatric bipolar disorder, thereby aiding in more rapid diagnosis and intervention to prevent the myriad problems that affect bipolar children.

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New Research in Child and Adolescent Bipolar Disorder

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There was a significant amount of new research presented at the Annual Child and Adolescent Psychiatry Annual Meeting in Miami, Florida, October 14-19, 2003. Among other topics, there was a great deal of interest in bipolar disorder and its psychopharmacologic treatment, effects of medications on weight gain and metabolism, as well as detection of psychopathology in children that develops into psychiatric disorders.

Topiramate in Bipolar Disorder as an Adjunctive Treatment

Researchers investigated whether topiramate was both effective and tolerated in children during an acute manic or mixed episode.[1] They retrospectively reviewed data from more than 25 patients with a median age of 14 years. Individuals had to have a DSM-IV diagnosis of type I bipolar disorder and had to be given topiramate as a part of their medication regimen during their hospitalization. Many had coexisting diagnoses including attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder, oppositional defiant disorder (ODD), and others. Retrospective review categorized concomitant medications that were given to participants. More than two thirds were on atypical antipsychotics, about a half were on mood stabilizers, more than a third were on antidepressants, and one fifth were on stimulants. With the median final dose of topiramate around 150 mg/day and a range extending between 25-350 mg/day, around 70% of patients were much/very much improved with a Mania Clinical Global Impression Score of </= 2. Patients had significantly decreased mean total and mania scores on the Clinical Global Impression measure at discharge. Similarly, clinicians reported that this group of patients had a mean increase in their Clinical Global Assessment Scale of approximately 22 points. However, 1 patient stopped treatment because of irritability, 2 reported sedation, and 1 reported cognitive slowing. No other serious adverse events were observed. Further prospective, randomized, controlled, double-blind studies are indicated to confirm these preliminary positive findings.

Risperidone Monotherapy in Pediatric Bipolar Disorder

Currently, there is increasing interest in using atypical antipsychotics alone to stabilize mood in patients. Investigators studied the mood-stabilizing effects of a monotherapy with risperidone over 8 weeks in youths.[2] In this prospective, open-label trial, around 30 subjects met DSM-IV criteria for bipolar disorder with a manic, hypomanic, or mixed episode. This sample had more males and about a third of the subjects did not complete the study. Drop-out reasons included loss to follow-up, perceived lack of efficacy, or adverse events including agitation, dry mucous membranes with insomnia, and headaches with gastrointestinal and appetite changes. The participants were treated with a risperidone maximum dose of 2 mg/day in children younger than 12 years and up to 4 mg/day in adolescents. Results indicated an almost 15-point reduction in the Young Mania Rating Scale (YMRS) from their scale average of around 27 at baseline. Significant metabolic findings included prolactin increase and an average weight gain of around 2 kg. A notable feature of this study is that relevant metabolic variables, including cholesterol, lipoproteins, triglycerides, and glucose, are reported. Further placebo-controlled, double-blinded studies are needed not only to assess the effectiveness of risperidone monotherapy, but also to continue close monitoring of metabolic effects that are so critical in long-term health outcomes.

Neuropsychological Deficits and Predictors of Bipolar Onset

Several studies are investigating cognitive function in pediatric bipolar patients. Researchers sought to examine whether children with bipolar disorder have neuropsychological deficits similar to those found in adults with the disorder.[3] Around 20 bipolar youth and 20 normal controls with a normal IQ were included in the study if they were responding to treatment and considered euthymic (YMRS < 10). On average, the group was around 12 years old and mixed in gender. About half of the bipolar group was treated with more than 4 medications. Cognitive performance was assessed using the standardized, computerized Cambridge Neuropsychological Test Automated Battery (CANTAB). Results showed that bipolar youths had impairments on set-shifting and visuospatial memory such as the spatial span task. More significantly, they had lower performance on the computerized Wisconsin Card Sorting Task (WCST). The researchers recognized the limitations of comorbid ADHD, but their rates of comorbidity are similar to other bipolar samples. It is interesting to note that these neuropsychological deficits are different from those shown by the same tasks given to a pediatric ADHD population. Moreover, many research studies now include rather than exclude comorbidities in order to produce more clinically relevant data.

Another group of investigators presented data suggesting poor executive function tasks can be detected in individuals prior to a formal diagnosis or treatment of bipolar disorder.[4] These participants were part of a prospective longitudinal study of children who had mothers diagnosed with mood disorders. Of the more than 100 offspring, over 90 of them met criteria for inclusion in this study. They had completed a neuropsychological battery including the WCST at a regular interval follow-up between ages 11 and 19 years. Those who later met criteria for bipolar illness exhibited around a 67% impairment on the WCST in comparison with the children who had no mood disorder or unipolar depression (both < 20%). It was striking that the early attentional problems that preceded any of the other mood disorder diagnoses were not associated with impairment on the WCST. Even when controlling for age, gender, full-scale IQ, and premorbid attentional deficits, impairment on the WSCT appeared to be associated with the development of bipolar disorder. These data support growing evidence that point towards differences in ventrolateral prefrontal cortices of children with a diagnosis of bipolar disorder. Currently, we are far from a clear psychometric profile of children with many psychiatric disorders. These data are intriguing given the marked lack of insight and presumptive frontal impairment seen in bipolar youths.

Lithium and Divalproex in Treating Bipolar Youths

There has been a clinical trend toward combining medications at lower doses and minimizing side effects instead of medication monotherapy. Researchers are now examining the effectiveness of combining lithium with divalproex sodium (DVPX) in bipolar children.[5] More than 130 youths aged 5-17 years were entered in the study if they fulfilled diagnostic criteria for bipolar type I or II. They then were given up to 20 weeks of lithium at around 22 mg/kg/day along with DVPX at around 21 mg/kg/day. Comorbid diagnoses included more than 60% with ADHD, almost 30% with ODD, and more than 10% with conduct disorder. If they met *a priori* remission criteria for 4consecutive weeks (YMRS-C < 12.5, CDRS-R < 40, CGAS > 51), they continued the study by being randomized into the lithium or DVPX monotherapy groups. More than half of the participants did not meet the *a priori* remission criteria and exited the study. Some of these patients also withdrew because of medication intolerance. Compared with baseline, combined treatment of lithium and DVPX resulted in significant improvement on all 3 of the outcome measures seen at testing intervals at the end of week 4 and week 8. These preliminary data mark the early stages of exploring how combination therapies may be efficacious in treating children. Unlike adults, mania appeared to be more treatment resistant than depression. It is important to further explore the marked differences in symptom presentation that occur over the development of psychopathology and the subsequent treatment differences.

In adults, there has been considerable research exploring whether lithium or DVPX is better at preventing recurrence of bipolar symptoms. This follow-up, double-blind study examined whether either lithium or DVPX monotherapy was superior for maintenance treatment in bipolar youths up to 76 weeks.[6] Around 30 patients were randomized to each monotherapy after they had responded to combination therapy by demonstrating YMRS-C < 12.5, CDRS-R < 40, and CGAS > 51 for 4 consecutive weeks. Log survivor analysis revealed no significant differences in these monotherapies for the time until a mood event occurred. Further analysis revealed that time to drop out for any reason was also not significantly different. Risk for relapse was greater with younger age, and risk for withdrawal from the study was greater in participants who had a higher initial YMRS scores. Again, these results highlight how disorders in children may be different from adults in their course of depression and mania. If mania is more treatment-resistant in children than depression, lithium may not be better at maintenance therapy. Clinicians must be cautious when generalizing conclusions from data on adults to children. Further studies should both replicate and explore the risks and benefits of acute and maintenance combination therapy. Clinicians need to know how much combination therapy decreases side effects and results in subsequent medication compliance.

Metabolic Side Effects and Managing Weight Gain

With obesity as a national epidemic, weight gain with psychiatric drugs has become a new focus in clinical research. Childhood obesity and metabolic changes may place individuals at greater risk for long-term side effects resulting in increased morbidity and mortality. The goal of this study was to comparatively look at factors related to weight gain and metabolic abnormalities during the use of olanzapine, risperidone, and quetiapine in children.[7] This prospective, 12-week, naturalistic study followed more than 100 children between ages 5 and 18 years who were newly started on an atypical antipsychotic to target psychosis, mood, or aggressive behaviors. All 3 atypicals resulted in weight gain that corresponded with increase in body fat, often deposited abdominally. All groups showed metabolic increases in triglycerides and insulin resistance. However, changes in glucose, insulin, cholesterol, low-density lipoprotein, and high-density lipoprotein were not significant. When compared with baseline, only olanzapine showed a significant elevation of insulin resistance. Those who were treatment-naive and did not have concomitant treatment with stimulants were at greatest risk for weight gain, although low BMI was not an independent risk factor. All 3 drugs were associated with new-onset dyslipidemia in about one third of those treated. These authors recommend monitoring weight monthly, as well as lipids and fasting glucose every 3 to 6 months in youths treated with these antipsychotics. Longitudinal studies are needed to continue to monitor weight and metabolic risk factors in the development of medical complications such as diabetes and heart disease.

Clinicians have been seeking adjunctive treatments to minimize the weight gain that results from treatment with many common psychiatric drugs. A study was done to evaluate whether weight gain can be limited with the addition of topiramate to atypical antipychotics.[8] Around 30 bipolar children were followed in this prospective, open-label, 8-week trial. Participants were treated either solely with olanzapine or with a combined treatment of both olanzapine and topiramate (range 25-900 mg/day). The 2 groups did not significantly differ in age, drop-out rates, YMRS scores (baseline and end point), and end point olanzapine dose. Unfortunately, data were not presented about side effects such as cognitive slowing. The group with olanzapine gained an average 4.8 kg vs the 3.2 kg gained with the adjuvant topiramate therapy. The weight differences were not statistically significant, although this may be confounded by the small sample size and wide dose range of topiramate. This clearly indicates the need for further blinded, randomized, controlled studies of topiramate as well as other agents that may prevent iatrogenic weight gain in children.

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