

30 - 31.12b Early Onset Bipolar Disorder

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Newton AS, Hamm MP, Bethell J, Rhodes AE, Bryan CJ, Tjosvold L, Ali S, Logue E, Manion ID. Pediatric suicide-related presentations: A systematic review of mental health care in the emergency room department. *Ann Emerg Med*. 2010;56:649-659. Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, Borges G, Bromet E, Bruffaerts R, de Girolamo G, de Graaf R, Florescu S, Gureje O, Haro JM, Hu C, Huang Y, Karam EG, Kawakami N, Kovess V, Levinson D, Postada-Villa J, Sagar R, Tomov T, Viana MC, Williams DR. Cross-national analysis of the associations among mental disorders and suicidal behavior: Findings from the WHO World Mental Health Surveys. *PLoS Med*. 2009;6:1-13. Olfson M, Shaffer D, Marcus SC, Greenberg T. Relationship between antidepressant medication treatment and suicide in adolescents. *Arch Gen Psychiatry*. 2003;60:978. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. *Biol Psychiatry*. 2005;57(1):21. Von Knorring AL, Olsson GI, Thomson PH, Lemming OM, Hulten A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006;26:311. Wagner KD. Pharmacotherapy for major depression in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:819. Wagner KD, Brent DA. Depressive disorders and suicide in children and adolescents. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Vol. 2. Lippincott Williams & Wilkins; 2009:3652. Whittington CJ, Kendall T, Fonagy P, Cotrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet*. 2004;363:1341. Zalsman G. Timing is critical: gene, environment and timing interactions in genetics of suicide in children and adolescents. *Eur Psychiatry*. 2010;25:284-286.

31.12b Early-Onset Bipolar Disorder Early onset bipolar disorder has been recognized in children as a rare disorder with greater continuity with its adult counterpart when it occurs in adolescents than in prepubertal children. Over the last decade there has been a significant increase in the diagnosis of bipolar I disorder made in youth referred to psychiatric outpatient clinics and inpatient units. Questions have arisen regarding the phenotype of bipolar disorder in youth, particularly in view of the continuous irritability and mood dysregulation and lack of discrete mood episodes in most prepubertal children who have received the diagnosis. The

“atypical” bipolar symptoms among prepubertal children often include extreme mood dysregulation, severe temper tantrums, intermittent aggressive or explosive behavior, and high levels of distractibility and inattention. This constellation of mood and behavior disturbance in the majority of prepubertal children with a current diagnosis of bipolar disorder is nonepisodic, although some fluctuation in mood may occur. The high frequency of the above symptoms in combination with chronic irritability has led to the inclusion of a new mood disorder in youth in the Fifth Edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5) called Disruptive Mood Dysregulation Disorder, which is discussed in the next section (31.12c). Many children with nonepisodic mood disorders often have past histories of severe attention-deficit/hyperactivity disorder (ADHD), making the

diagnosis of bipolar disorder even more complicated. Family studies of children with ADHD have not revealed an increased rate of bipolar I disorder. Children with “atypical” bipolar disorders, however, are frequently seriously impaired, are difficult to manage in school and at home, and often require psychiatric hospitalization. Longitudinal follow-up studies are under way with groups of children diagnosed with subthreshold bipolar disorders and nonepisodic mood disorders, to determine how many will develop classic bipolar disorder. In one recent study of 140 children with bipolar disorder not otherwise specified (that is, the presence of distinct manic symptoms but subthreshold for manic episodes), 45 percent developed bipolar I or bipolar II illness over a follow-up period of 5 years. In another study, 84 children who were labeled with “severe mood dysregulation” (that is, a persistent nonepisodic negative mood along with severe anger outbursts) who also exhibited at least three manic symptoms (either pressured speech, agitation, insomnia, or flight of ideas) plus distractibility (also common to ADHD), followed for approximately 2 years, found that only one child experienced a hypomanic or mixed episode. Although childhood severe mood dysregulation has been found to be common in community samples—one study reported a lifetime prevalence of 3.3 percent in youth 9 to 19 years of age—its relationship to future bipolar disorder remains questionable. A longitudinal community-based study that followed children and adolescents with nonepisodic irritability over a 20-year period, found that these children were at higher risk to develop depressive disorders and generalized anxiety disorder, rather than bipolar disorders over time. Among adults and older adolescents with bipolar disorder who present with classic manic episodes, a major depressive episode typically precedes a manic episode. A classic manic episode in an adolescent, similar to in a young adult, may emerge as a distinct departure from a preexisting state often characterized by grandiose and paranoid delusions and hallucinatory phenomena. According to DSM-5, the diagnostic criteria for a manic episode are the same for children and adolescents as for adults (see Table 8.16). The diagnostic criteria for a manic episode include a distinct period of an abnormally elevated, expansive, or irritable mood that lasts at least 1 week or for any duration if hospitalization is necessary. In addition, during periods of mood disturbance, at least three of the following significant and persistent symptoms must be present: inflated self-esteem or grandiosity, decreased need for sleep, pressure to talk, flight of ideas or racing thoughts, distractibility, an increase in goal-directed activity, and excessive involvement in pleasurable activities that may result in painful consequences. According to the DSM-5, in contrast to DSM-IV-TR, diagnostic criteria for bipolar disorder now include changes in both mood and activity or energy level. Furthermore, whereas previously, full criteria for both mania or hypomania and major depressive disorder were required to make a diagnosis of a mixed episode, in DSM-5, this requirement no longer applies; instead a specifier, “with mixed features,” has been added. This specifier can be applied to a current manic episode, hypomanic episode, or depressive episode.

Thus, for example, in order to add the “mixed features” specifier to a manic or hypomanic episode, three of the following symptoms must be present during the majority of days of the current or most recent episode of mania or hypomania: prominent depressed mood, diminished interest in most activities, psychomotor retardation nearly every day, fatigue or loss of energy, feelings of excessive guilt or worthlessness, or recurrent thoughts of

death. To apply the “with mixed features” specifier to a full major depressive episode, three of the following hypomanic/manic symptoms must be present: elevated or expansive mood, grandiosity, pressured speech or increased speech, flight of ideas, increased energy, or decreased need for sleep. When mania appears in an adolescent, there is a high incidence of psychotic features including both delusions and hallucinations, which most typically involve grandiose notions about their power, worth, and relationships. Persecutory delusions and flight of ideas are also common. Overall, gross impairment of reality testing is common in adolescent manic episodes. In adolescents with major depressive disorder destined for bipolar I disorder, those at highest risk have family histories of bipolar I disorder and exhibit acute, severe depressive episodes with psychosis, hypersomnia, and psychomotor retardation.

EPIDEMIOLOGY The prevalence rates of bipolar disorder among youth vary depending on the age group studied, and on whether the diagnostic criteria are applied narrowly, restricting it to discrete mood episodes or more broadly, to include nonepisodic mood and behavioral states. In younger children, bipolar disorder is extremely rare, with no cases of bipolar I disorder identified in children between the ages of 9 years and 13 years by the Great Smokey Mountain Study. However, severe mood dysregulation, often a prominent feature in prepubertal children receiving a diagnosis of bipolar disorder, was found in 3.3 percent of an epidemiological sample. In adolescents, bipolar disorder is more frequent, found to range from 0.06 to 0.1 percent of the general population of 16-year-olds in studies using a narrow definition of bipolar I disorder. Prevalence of subthreshold symptoms of bipolar illness was found to be 5.7 percent in one study to at least 10 percent in another. Follow-up studies into adulthood revealed that the subthreshold manic symptoms predicted high levels of impairment with progression to depression and anxiety disorders, not bipolar I or II disorders. Community use of the diagnosis of bipolar disorder in youth has increased markedly over the last 15 years in both outpatient and inpatient psychiatric settings. A recent survey indicated a 40-fold increase in the diagnosis of bipolar disorder in youth being treated at outpatient clinics from the mid-1990s to the mid-2000s. Furthermore, from 2000 through 2006, the rate of youth hospitalized with a primary diagnosis of bipolar disorder increased from 3.3 per 10,000 to 5.7 per 10,000.

ETIOLOGY Genetic Factors Estimates of the heritability of bipolar disorder based on adult twin studies range from approximately 60 to 90 percent, with shared environmental variables accounting for 30 to 40 percent and the nonshared environmental factors accounting for approximately 10 to 20 percent. High rates of bipolar disorder have been reported in the relatives of

the narrow phenotype of early onset bipolar disorder compared to young adult-onset of bipolar disorder. The high rates of comorbid ADHD among children with early onset bipolar disorder has led to questions regarding the co-transmission of these disorders in family members. However, children with the broader phenotype of bipolar disorder, that is, severe mood dysregulation without episodes of mania, have not been found to have higher rates of bipolar disorder in family members, which suggests that the narrow and broad phenotypes of bipolar disorder may be distinct and separate entities. Nearly 25 percent of adolescent offspring of families with probands with bipolar disorder experienced a mood disorder by the age of 17 years old, compared to 4 percent of

controls, with approximately 8 percent representing bipolar I, bipolar II, or bipolar disorder not otherwise specified. Most of the risk in the offspring, therefore, is for unipolar major depressive disorder. Disruptive behavior disorders were not found to be increased, in a longitudinal study, in the offspring of families with a bipolar proband, compared to controls. The combination of ADHD and bipolar disorder is not found as frequently in relatives of children with only ADHD compared with first-degree relatives of children with the combination. Although bipolar disorder appears to have a significant heritable component, its mode of inheritance remains unknown. A number of research groups have concluded that early onset bipolar disorder is a more severe form of the illness, characterized by more mixed episodes, greater psychiatric comorbidity, more lifetime psychotic symptoms, poorer response to prophylactic lithium treatment, and a greater heritability. The European collaborative study of early-onset bipolar disorder (France, Germany, Ireland, Scotland, Switzerland, England, and Slovenia) carried out a genome-wide linkage analysis of both the narrow and the broad early onset bipolar disorder. This group concluded that a genetic factor located in the 2q14 region is either specifically involved in the etiology of early onset bipolar disorder, or that a gene in this region exerts influence as a modifier of other genes in the development of bipolar disorder in this age group. Other linkage regions that were found by this collaborative did not find specific genome regions that pertained only to the early onset group of bipolar disorder, suggesting that there may be some genetic factors common to early-onset and adult-onset bipolar disorder. This is consistent with the increased incidence of adult-onset bipolar disorder among siblings of early onset disease. Further genome-wide studies are needed to elucidate the genetic etiology of early onset bipolar disorder. Neurobiological Factors Converging data suggest that early-onset bipolar disorder is associated with both structural and functional brain alterations in prefrontal cortical and subcortical regions associated with the processing and regulation of emotional stimuli. Structural magnetic resonance imaging (MRI) studies suggest that altered development of white matter and a decreased amygdalar volume are found more frequently in this population than in the general population. Functional MRI (fMRI) studies are important in that they can identify altered brain function in vulnerable populations such as youth with early-onset

bipolar disorder at baseline, and can also be utilized to elucidate functional changes toward normalization in brain functioning after various treatments, and potentially identify pretreatment neural predictors of good response to various treatments. A recent fMRI study of pediatric bipolar patients documented pretreatment brain activity and posttreatment effects of a trial of risperidone versus divalproex. This double-blind study included 24 unmedicated manic patients with a mean age of 13 years, randomized to either risperidone or divalproex treatment, and 14 healthy controls examined over a 6-week period. Prior to treatment, the patient group showed increased amygdala activity compared to healthy controls, which was poorly controlled by the higher ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal cortex (DLPFC), which are believed to exert influence on the amygdala to control emotional regulation and processing. Increased amygdala activity at baseline predicted a poorer treatment response to both the risperidone and the divalproex in the patient group. Patients were given an affective color-matching word task involving matching positive words (i.e., happiness, achievement, success), negative words (i.e., disappointment, depression, or rejection), or neutral words, with one of two colored circles displayed on a screen while fMRI was administered. Greater pretreatment right amygdala activity during a word task with positive and negative words in the risperidone group, and greater pretreatment left amygdala activity with a positive word task in the divalproex group, predicted

poor response on the Young Mania Rating Scale. Increased amygdala activity in early-onset bipolar patients is hypothesized to be a potential biomarker predicting resistance and poor treatment response to both risperidone and divalproex. Neuropsychological Studies Impairments in verbal memory, processing speed, executive function, working memory, and attention are commonly found in early-onset bipolar disorder. Data suggest that on tasks of working memory, processing speed, and attention, children and adolescents with comorbid bipolar disorder and ADHD demonstrate more pronounced impairments compared with those without ADHD. Other studies found that children with bipolar disorder make a greater number of emotion recognition errors compared with controls. They more frequently identified faces as “angry” when presented with adult faces; however, these errors did not occur when children’s faces were shown. Impaired perception of facial expression has also been reported in studies of adults with bipolar disorder.

DIAGNOSIS AND CLINICAL FEATURES Early onset bipolar disorder is often characterized by extreme irritability that is severe and persistent, and may include aggressive outbursts and violent behavior. In between outbursts, children with the broad diagnosis may continue to be angry or dysphoric. It is rare for a prepubertal child to exhibit grandiose thoughts or euphoric mood; for the most part, children diagnosed with early onset bipolar disorder are intensely emotional with a fluctuating but overriding negative mood. Current diagnostic criteria for bipolar disorders in children and adolescents in DSM-5 are the same as those used in adults (see Tables 8.1-6 and 31.12b-1). The clinical picture of early-onset bipolar disorder, however, is complicated by the prevalence of comorbid psychiatric disorders.

Table 31.12b-1 DSM-5 Diagnostic Criteria for Bipolar II Disorder

Comorbidity with ADHD ADHD is the most common comorbid condition among youth with early onset bipolar disorder and has been reported in up to 90 percent of prepubertal children and up to 50 percent of adolescents diagnosed with bipolar disorder. One of the main sources of diagnostic confusion regarding children with early onset bipolar disorder is the comorbid ADHD, since the two disorders share many diagnostic criteria, including distractibility, hyperactivity, and talkativeness. Even when the overlapping symptoms are removed from the diagnostic count, a significant percentage of children with bipolar disorder continued to meet the full criteria for ADHD. This implies that both disorders with their own distinct features are present in many cases.

Comorbidity with Anxiety Disorders Children and adolescents with bipolar disorder have been reported to have higher than expected rates of panic and other anxiety disorders. In youth with the narrow phenotype of bipolar disorders, up to 77 percent have been reported to exhibit an anxiety disorder. Lifetime prevalence of panic disorder was found to be 21 percent among subjects with the broader phenotype of bipolar disorder compared with 0.8 percent in those without mood disorders. Patients diagnosed with bipolar disorder who have comorbid high levels of anxiety symptoms are reported as adults to have higher

risks of alcohol abuse and suicidal behavior. On the other hand, children who exhibit the broader phenotype of bipolar disorder are at higher risk to go on to have anxiety disorders as well as depressive disorders. Jeanie is a 13-year-old adopted teen who was admitted to the hospital after assaulting her adoptive mother, causing bruises on her arms and legs from Jeanie’s kicks and punches. Jeanie has had a long history of excessively severe tantrums, which include assaultive and self-injurious behavior since before she was adopted at the age of 3 years. Jeanie had always been a child who was irritable and explosive, with a short fuse, who could blow up with very little

provocation, even when things were going her way. Jeanie had become increasingly hard to manage at home, refused to go to school, yelled and screamed for hours on a daily basis, and often hit and kicked her adoptive parents by the time she was 10 years old. Jeannie had been placed in residential treatment for about a year and a half from age 11 and a half to almost 13, where she had been given a diagnosis of bipolar disorder and placed on lithium and citalopram. She was doing so well there after a year that Jeanie's adoptive mother decided to take her home. After a few weeks at home, however, Jeanie began to decompensate, having daily explosive tantrums during which she became aggressive and out of control. On multiple occasions she had hurt herself and her adoptive mother and father. Upon arriving at the hospital, Jeanie was calm by the time she was brought to her hospital room; however, her adoptive mother refused to consider taking her home until she had received a full psychiatric evaluation and something new was done to control Jeanie's unsafe behaviors. Jeanie was initially evaluated by the child and adolescent psychiatrist on-call, after which she was admitted to a pediatric inpatient unit, where she awaited a bed on a psychiatric adolescent inpatient unit. The psychiatrist learned that Jeanie had been born prematurely to a teenage mother and placed in multiple foster homes until she was adopted. Jeanie was a small girl who appeared younger than her stated age, although her demeanor was bossy and pedantic. Jeanie's biological family history was unknown, and although she had at least one stigmata of fetal alcohol syndrome, her IQ was in the average range and there was no other evidence to corroborate this possibility. On mental status examination in the hospital, Jeanie reported that things were fine, that she was not depressed, and that she did not get along with kids her own age but that she had a few friends. Jeanie admitted that she had a bad temper and that she did not remember what she did after she was in a rage. Jeanie's affect was odd, and she seemed to like having the psychiatrist as her audience. Jeanie denied suicidal ideation or past attempts, and she denied having been a danger to herself or her adoptive parents. Jeanie seemed annoyed when she was asked about the reasons for her placement in a residential facility, and she became irritable when questioned about the reasons for her current admission. Jeanie was referred for admission to an adolescent psychiatric inpatient unit with the following recommendations: Jeanie was referred for a trial of an atypical antipsychotic, such as

risperidone or olanzapine, and a reconsideration of a return to a more structured school program, either a day program or residential facility. The diagnosis of bipolar disorder remained in question, as she did not meet the narrow phenotype for this disorder. **PATHOLOGY AND LABORATORY EXAMINATION** No specific laboratory indices are currently helpful in making the diagnosis of bipolar disorders among children and adolescents. **DIFFERENTIAL DIAGNOSIS** The most important clinical entities to distinguish from early onset bipolar disorder are also the disorders with which it is most frequently comorbid. Included are ADHD, oppositional defiant disorder, conduct disorder, anxiety disorders, and depressive disorders. Although childhood ADHD tends to have its onset earlier than pediatric mania, current evidence from family studies supports the presence of ADHD and bipolar disorders as highly comorbid in children, and the concurrence is not because of the overlapping symptoms that the two disorders share. In a recent study of more than 300 children and adolescents who attended a psychopharmacology clinic and received a diagnosis of ADHD, bipolar disorder was also evident in almost one third of those children with ADHD who had combined-type and hyperactive-types, and occurred with much less frequency (i.e., in less than 10 percent) in children with ADHD, inattentive-type. **COURSE AND PROGNOSIS** There are several pathways regarding the course and prognosis of children diagnosed with early onset bipolar disorder. Those who present with severe mood dysregulation at an early age, without discrete mood cycles, are

most likely to develop anxiety and depressive disorders as they mature. Youth who present in adolescence with a recognizable manic episode are most likely to continue to meet criteria for bipolar I disorder in adulthood. In both cases, the long-term impairment is considerable. A longitudinal study of 263 child and adolescent inpatients and outpatients with bipolar disorder followed for an average of 2 years found that approximately 70 percent recovered from their index episode within that period. Half of these patients had at least one recurrence of a mood disorder during this time, more frequently a depressive episode than a mania. No differences were found in the rates of recovery for children and adolescents whose diagnosis was bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified; however, those youth whose diagnosis was bipolar disorder not otherwise specified had a significant longer duration of illness before recovery, with less frequent recurrences once they recovered. About 19 percent of patients changed polarity once per year or less, 61 percent shifted five or more times per year, about half cycled more than ten times per year, and about one third cycled more than 20 times per year. Predictors of more rapid cycling included lower socioeconomic status (SES), presence of lifetime psychosis, and bipolar disorder not otherwise specified diagnosis. Over the follow-up period, about 20 percent of subjects who were

diagnosed with bipolar II disorder converted to bipolar I disorder, and 25 percent of the bipolar disorder not otherwise specified subjects developed bipolar I disorder or bipolar II disorder during the follow-up period. Similar to the natural history of bipolar disorders in adults, children have a wide range of symptom severity in manic and depressed episodes. The more frequent diagnostic conversions from bipolar II disorder to bipolar I disorder among children and adolescents, compared with adults, highlight the lack of stability of the bipolar II disorder diagnosis in youth. This is also the case with respect to conversion from bipolar disorder not otherwise specified to other bipolar disorders. When bipolar disorder occurs in young children, recovery rates are lower. In addition, a greater likelihood is seen of mixed states and rapid cycling, and higher rates of polarity changes compared with those who develop bipolar disorders in late adolescence or early adulthood.

TREATMENT Treatment of early onset bipolar disorder incorporates multimodal interventions including pharmacotherapy, psychoeducation, psychosocial intervention with the family and the child, and school interventions to optimize a child's school adjustment and achievement.

Pharmacotherapy Two classes of medications—atypical antipsychotics and mood stabilizing agents—are the most well-studied agents that provide efficacy in the treatment of early-onset bipolar disorders. Eight randomized controlled trials have shown efficacy of atypical antipsychotic agents in the treatment of bipolar disorder in youth between the ages of 10 and 17 years. These studies compared an atypical antipsychotic to placebo, or compared an atypical antipsychotic to a mood stabilizer, or added an antipsychotic to a mood-stabilizing agent. The atypical antipsychotics included olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone. All five of the atypical antipsychotic studies demonstrated significant efficacy in the treatment of early onset bipolar manic or mixed states. A recent trial comparing quetiapine and valproate found that both were efficacious, but the quetiapine was superior in the speed of its effect. In another trial comparing risperidone and divalproex treatment for bipolar disorder in youth, risperidone was found to have a more rapid improvement and a greater final reduction in manic symptoms compared to divalproex. Mood-stabilizing agents have been used in open trials and anecdotally with early onset bipolar illness with little evidence of efficacy at this time. In trials using lithium or divalproex for treatment of early onset bipolar disorder, responses were less robust compared to results with atypical antipsychotics. Controlled trials have provided some evidence suggesting that

lithium is efficacious in the management of aggression behavior disorders. Although lithium has been approved for use in adolescent mania, more research is needed to know if lithium is effective for more classic forms of mania in adolescents. The Collaborative Lithium Trials (CoLT) established a set of protocols to

establish the safety and potential efficacy of lithium in youth, and to develop studies to provide evidence-based dosing of lithium for youth. A group of researchers recently studied the first-dose pharmacokinetics of lithium carbonate in youth and found that clearance and volume are correlated with total body weight in youth, and particularly with fat-free mass. Difference in body size was consistent with the pharmacokinetics of lithium metabolism in children and adults. An open-label trial of lamotrigine (Lamictal) in the treatment of bipolar depression among youth provides possible support for its use in children and adolescents. Current evidence suggests a faster response and more robust effect with atypical antipsychotics compared to mood-stabilizing agents in the treatment of early-onset bipolar disorder. However, given the severity and impairment of bipolar disorder in youth, when only partial recovery is achieved, consideration of adding an additional agent may be necessary. Psychosocial Treatment Psychosocial treatment interventions for early onset bipolar illness have included a family-focused treatment. This treatment consists of several sessions of psychoeducation, then sessions focusing on current stressors and mood management plan, and then several sessions of communication enhancement training and problem-solving skills training. The use of this type of intervention for youth diagnosed with bipolar disorder as well as youth at risk for the disorder by virtue of their family history or subthreshold conditions has been of value. Adjunctive family-focused psychoeducational treatment modified for children and adolescents has been shown to reduce relapse rate. Children and adolescents treated with mood-stabilizing agents in addition to a psychosocial intervention showed improvement in depressive symptoms, manic symptoms, and behavioral disturbance over 1 year. A year-long trial of a modified Family Focused Treatment-High Risk in youth with bipolar disorder showed significant improvement in mood disturbance, especially depressive mood and hypomania, and improved psychosocial functioning. Family-focused treatment for high-risk youth is a promising intervention that deserves further investigation as a longitudinal follow-up to determine the course of youth at risk to develop bipolar disorder. REFERENCES Axelson DA, Birmaher B, Strober M, Goldstein BI, Ha W, Gill MK, Goldstein TR, Yen S, Hower H, Hunt JI, Liao F, Iyengar S, Dickstein D, Kim E, Ryan ND, Frankel E, Keller MB. Course of subthreshold bipolar disorder in youth: Diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry*. 2011;50:1001-1016. Carlson GA. Bipolar disorder and mood dysregulation. *Proceedings; AACAP 2011 Psychopharmacology Update Institute: Controversies in child and adolescent psychopharmacology*. 2011;257-284. Carlson GA, Myer SE. Early-onset bipolar disorder In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Vol. 2. Lippincott Williams & Wilkins; 2009:3663. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult

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