# Children and Bipolar Disorder: Recognizing Early Onset CME/CE

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**Release Date: April 28, 2005**; **Valid for credit through April 28, 2006**

## Target Audience

This activity is intended for psychiatrists, pediatricians, primary care nurse practitioners, and other clinicians involved in the treatment of children with bipolar disorder.

## Goal

This activity will help clinicians improve their ability to differentially diagnose and treat bipolar disorder in children.

## Learning Objectives

Upon completion of this activity, participants will be able to:

1. Recognize bipolar disorder in children.
2. Order laboratory tests to corroborate or rule out that diagnosis.
3. Prescribe appropriate medications.
4. Adjust or change medications depending on responses of individual patients.

## Credits Available

Physicians - up to 1.0 AMA PRA category 1 credit(s);
Registered Nurses - up to 1.2 Nursing Continuing Education contact hour(s)

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Participants should claim only the number of hours actually spent in completing the educational activity.

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This activity is supported by an educational grant from Janssen.




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Children and Bipolar Disorder: Recognizing Early Onset

## Presentation

AB, an 11-year-old boy with a long history of behavioral problems and attention deficit/hyperactivity disorder (ADHD), is brought to a clinic by his mother for evaluation of worsening behavior and "mood swings." AB's mother reports that his mood and behavior have gotten worse in the previous 2 years. He is now irritable more than half the time when he is at home. Simple requests to do his homework or chores or the withholding of permission to go over to a friend's house will send him into a "rage attack." In these attacks, AB will scream, throw things, and often destroy his own toys. He sometimes becomes physically aggressive, and in the past has punched and kicked his mother. He once even threatened his parents with scissors. He usually calms down in 20 minutes to an hour. After these episodes, he will often cry in his bed and make such statements as "I wish I were dead" and "everybody hates me." These attacks can occur 1-3 times/day and 1-5 days/week.

1. **Survey** - What is the differential diagnosis? (Check all that apply.)
   - ☐ Depression
   - ☐ ADHD
   - ☐ Opposition/defiance disorder (ODD)
   - ☐ Bipolar disorder

**Explanation:**

Children who are depressed often present with irritability instead of or along with sad mood. Suicidal ideation is not uncommon and should be carefully assessed. It is unusual but possible to see this degree of mood dysregulation (extreme rage) in a child who has unipolar depression.

ADHD also can present with irritability, but it is not a cardinal symptom. That is, ADHD requires symptoms of hyperactivity, impulsivity, and inattention, starting before age 7 years, to make the diagnosis. While the child has a history of ADHD diagnosis, these anger attacks are unusual for uncomplicated ADHD.

A diagnosis of ODD is made when the child demonstrates a repeated pattern of oppositional and defiant behavior, including purposely irritating others. Losing of the temper is considered a symptom of ODD as well, but in this case the child feels remorse and cries after these episodes, making a mood disorder more likely.

Extreme irritability is one hallmark of children with bipolar disorder, especially in those younger than 12 years old. Furthermore, children with bipolar disorder at this age usually have a history of ADHD (in 90% to 95% of cases). Further history needs to be obtained to narrow down the diagnosis.

**2. Survey** - In your experience, which of the following is the largest barrier to the optimal and timely management of adolescent mood disorders?

- Diagnosis of mixed symptoms
- Patient adherence
- Comorbid substance abuse
- Effectiveness of therapies

**3. Survey** - How confident are you that you are up to date on the most recent data related to the diagnosis and management of adolescent mood disorders?

- Not at all confident
- Somewhat confident
- Confident
- Very confident

## Further History

Further history reveals that while the child's irritability is fairly constant, it varies considerably in intensity. The periods of most acute irritability can last 3 to 10 days, during which he will also stay up later than usual (until 12-1 am), but still wake up at 6 am and go to school without being tired. During these times, he also often becomes silly and giddy, singing at the top of his voice, and shouting "I am the king, king of the world!" While usually creative artistically, during these times he will also collect items such as bottlecaps or magazines and make large collages. Sometime he works on these projects for hours and is unwilling to stop to go to sleep. During these periods, he has high levels of energy -- "bounces off the walls" -- speaks fairly quickly, and has many ideas that can come out in rapid bursts. When asked, he admits to having "many thoughts in my head" at these moments. He occasionally makes inappropriate sexual comments and at times almost seems to be "groping" his mother; so much so that she avoids giving him a shower or letting him see her in the bathroom.

When asked about depressive symptoms, AB reported that he has often thought that no one loved him and that he wished he were dead. However, these thoughts mostly occurred after anger outbursts. He has never attempted suicide but has hit his head against the wall in anger and frustration. He has brief periods of low energy, where he prefers to be in his room, and sometimes tell his mother he feels like crying during those

times. After falling asleep for a few hours, AB then returns to his normal high-energy state. His appetite has always been constant and slightly below normal since beginning methylphenidate treatment at age 7 years. He does not report a history of feeling guilty, but does feel that he is "a bad person" and wishes he were taller and "not so angry."

Even when his mood is even, AB has a hard time sitting completely still. He stares out the window and daydreams often during class. He will sometimes impulsively blurt out comments during class and has a hard time waiting in line. He often leaves his backpack on the bus and forgets homework assignments.

*What is the diagnosis?*

This patient meets the criteria for bipolar I disorder. He has a euphoric and irritable mood, lasting at least a week, during which he also has: (1) grandiosity, (2) distractibility, (3) psychomotor agitation (extreme hyperactivity), (4) pressured speech, (5) racing thoughts, (7) hypersexuality, and (8) decreased need for sleep. (1), (5), (7), and (8) are considered "cardinal" symptoms of mania because they rarely appear in any other disorders.[1]

*How often is ADHD comorbid with pediatric bipolar disorder?*

In adolescents, the rate of comorbidity is 50% to 60%; in children, the rate is 90% to 95%. Although there are overlapping criteria between ADHD and bipolar disorder, it is clear that the majority of children will meet both diagnostic criteria. It may be that the earlier in life the presentation of bipolar disorder, the more often it includes ADHD symptoms, usually as a precursor to mood symptoms. There is some evidence that ADHD in these children signals an early-onset form of bipolar disorder that is familial.[2,3]

## Past Developmental/Psychiatric History

### Early Development

AB was born at 38 weeks in a normal spontaneous vaginal delivery without complications. He began walking at 12 months and was speaking words by 13 months. Temperamentally, he was somewhat "colicky" and a "difficult child" in that he cried frequently and had difficulty self-soothing. During preschool, he had difficulty sitting still for "circle-time" and was aggressive at times with other children. In kindergarten, he was noted to be fidgety, impulsive, and easily angered. This behavior extended to the home, where he lived with his mother, father, and sister 2 years younger than him. In the first grade, he began losing friends due to his behavior in school. He was noted to have some fine motor skill problems (writing especially) but was verbally gifted. His language was normal, as were his eye contact and mannerisms.

### Relevant Family History

There was no history of significant trauma, including physical or sexual abuse. The parents have a good relationship, but have been feeling stress because of the difficulties of AB. His mother has a history of major depression, including a postpartum depression, and is taking sertraline, which has helped. AB's father is without psychiatric history but has a brother with bipolar disorder, with onset in his 20s. There are other relatives, including a paternal grandfather, who had difficulty with quick tempers, substance abuse, and depression. However, these family members were never formally diagnosed or treated.

**Medication History**

At age 7 years, at the request of his teacher, AB was evaluated by his pediatrician and placed on methylphenidate for ADHD. He responded fairly well, having increased attention and somewhat decreased hyperactivity. However, he needed escalating doses over the next 3 years to control his behavior in class. At age 10 years, after a prolonged rage attack during which he continually repeated his desire to be dead, he was referred to a child psychiatrist, who felt he was depressed and prescribed sertraline. After 2 days on sertraline 50 mg, AB became increasingly hostile, belligerent, and hyperactive, so the medication was stopped. The only medication he is currently taking is 36 mg of methylphenidate every morning.

4. **Survey** - What tests are necessary to make the diagnosis? (Check all that apply.)
   - ☐ Thyroid panel
   - ☐ Liver panel
   - ☐ Magnetic resonance imaging (MRI)
   - ☐ Electroencephalogram (EEG)

**Explanation:**

The thyroid panel is a useful test to obtain. Hyperthyroidism, or thyroid storm, could mimic a manic episode. Hypothyroidism can lead to depression or exacerbate rapid cycling of mood in bipolar disorder.

Liver panel is not commonly needed to rule out other medical causes. However, copper metabolism disorders (Wilson's), while rare, can cause inappropriate psychosis and may cause elevated liver transaminases.

Brain MRI should be obtained for any first-break psychotic or manic episode to rule out tumor or mass. However, in this case, symptoms gradually presented. If there are no other focal or general neurologic signs (impairment of consciousness, headaches, focal neurologic findings), then MRI is not indicated. No brain imaging can currently aid with psychiatric diagnoses, except perhaps for early Alzheimer's using positron emission tomography.

An EEG should be obtained if there are any neurologic findings (as above) or other signs of possible seizure focus (abrupt onset of behavior, repeated mannerisms, staring spells, loss of consciousness or change in mental status consistent with postictal state after rage episodes). Temporal lobe epilepsy can occasionally present with anger outburst episodes that can be confused with mania. Otherwise, EEG is usually not helpful in making the diagnosis.

**5. Survey** - You diagnose bipolar I disorder, ADHD. What are necessary interventions? (Check all that apply.)

- ☐ Pharmacologic
- ☐ Psychotherapeutic
- ☐ Educational
- ☐ Residential treatment

**Explanation:**

In almost every case, bipolar disorder requires medication, often chronically administrated.

Psychotherapeutic intervention is also indicated in all cases of pediatric bipolar disorder despite a lack of empirical evidence. Educational intervention is also indicated.

It is too early in the evaluation and treatment, however, to be certain that residential treatment is warranted. Usually the child with bipolar disorder first has educational interventions, then if necessary progresses to a therapeutic day school before residential treatment is sought. However, if home environment is unsuitable, or if the child cannot be maintained safely at home, then residential treatment is warranted.

**Past Developmental/Psychiatric History (Continued)**

**Psychopharmacologic Treatment**

Worried that the stimulant may be exacerbating irritability, you begin by discontinuing methylphenidate. AB continues to exhibit the same mood and behavior problems, but now he is more hyperactive and distractible.

**6. Survey** - What would you add?

- ○ Citalopram
- ○ Lithium
- ○ Divalproex
- ○ Carbamazepine

**Explanation:**

As this child does not have major depression or anxiety, citalopram is not the treatment of choice. Serotonin reuptake inhibitor monotherapy may actually worsen or cause mania in children with bipolar disorder.

Lithium is a reasonable choice. Open published data suggest a 66% response rate in monotherapy in children with bipolar disorder.[4] However, it is less studied in prepubertal children.

Divalproex is also a reasonable choice. Published data of open studies have reported approximately a 65% response rate in monotherapy.[4] However, response does not indicate remission, and often additional medication may need to be added.

There are very few data to support the use of carbamazepine in pediatric bipolar disorders at this point. Due to potential adverse effects (rash, agranulocytosis) and drug-drug interactions, this is a second- or third-line drug.

## Past Developmental/Psychiatric History (Continued)

You add divalproex 250 mg/day and gradually increase to 1250 mg/day. Serum valproate level is 98 mcg/mL. AB improves with less frequent irritability/anger attacks, and when they do occur they are usually less intense. However, he continues to have brief periods of decreased sleep, increased projects, giddiness, and racing thoughts. In addition, you now elicit a history of auditory hallucinations: when he is manic, AB experiences voices telling him "you are powerful" as well as "you are a lousy kid." These voices are not his own or his parents. He tells you that when he was younger, he used to also see shapes and people in his backyard when no one else did. Since AB has been on this treatment regimen for less than 5 days, you wait to see if there will be continued improvement. However, the symptoms do not improve, and you decide to add another agent. You consider increasing the dose of divalproex to raise serum valproate levels to the upper therapeutic range (110-120 mcg/mL). You also consider also adding lithium to manage the continuing manic symptoms, but decide instead that the psychosis (auditory hallucinations) requires addition of an atypical antipsychotic (which would also presumably treat the residual mania).

7. **Survey** - Which antipsychotic would you use?
   - Olanzapine
   - Risperidone
   - Quetiapine
   - Ziprasidone

**Explanation:**

Data in adults support the use of olanzapine adjunctive to divalproex for the treatment of mania. In children, there are case reports only to support this approach.[5,6] In this patient, starting at 2.5 mg/day is reasonable, and dosing at bedtime is preferred, as olanzapine is usually sedating and may help restore sleep.

In one retrospective chart review, risperidone was found to be helpful in children and adolescents with mania when added to other medications.[7] Dosages ranging from 0.5 mg to 3 mg/day, divided twice a day or 3 times a day have been reported useful.

Quetiapine added to divalproex was found to be superior to divalproex alone in a placebo-controlled study of acutely manic adolescent inpatients.[8] While this patient is slightly younger, this is a good choice. Dosing typically would start at 50-100 mg/day, given at bedtime to help with sleep, then increased by 50-100 mg/day to clinical improvement of a target dose of 200-400 mg/day.

There are no studies currently to support the adjunctive (or monotherapy) use of ziprasidone in pediatric bipolar disorder. Therefore, it is recommended that one of the other agents be tried first.

## Past Developmental/Psychiatric History (Continued)

After adding risperidone, titrated up to 0.5 mg 3 times a day, AB improves gradually, with fewer manic symptoms, and less frequent anger attacks. However, now in school he is doing poorly, with problems paying attention, forgetfulness, and putting his head down on his desk during class. Sedation is a common adverse effect of risperidone, as well as most atypical antipsychotics. However, before making the decision to decrease the dose of risperidone, you decide to rule out depression (which can cause fatigue, lack of interest in school, and social withdrawal) and/or ADHD (which can cause distractibility and inattention). The patient denies sedation or other symptoms of depression, but teachers, parents, and the patient himself testify to his inattention, forgetfulness, and distractibility. You decide that ADHD treatment would probably help his school performance and start him on methylphenidate. By treating the ADHD after mood stabilizers are on board, you have decreased the risk of worsening mood or the return of frank mania.[9]

AB does well with methylphenidate added to his medication regimen, with improved behavior and focus in class. He finishes the school year in a special education class and gets mostly As and Bs. He remains relatively well until the next winter, when at age 13 years, he begins experiencing more depressive symptoms, including depressed mood, fatigue, increased sleeping, and social withdrawal.

8. **Survey** - What should you check for now? (Check all that apply.)

- ☐ Substance abuse

- [ ] Thyroid panel
- [ ] Valproate level
- [ ] Suicidal thoughts

**Explanation:**

Certainly, substance abuse is a common (40%) comorbidity in adolescents with bipolar disorder.[10] This should be assessed for by interview and, if necessary, urine toxicology screen.

Hypothyroid states can lead to depression. The patient is not taking lithium, which can cause hypothyroidism in up to 24% of children,[11] so this would be a rare occurrence, but could be checked anyway.

Measuring serum levels of valproate, and lithium or carbamazepine if the patient is taking these medications, is recommended every 6 months, along with a complete blood cell count and liver transaminase levels. Serum levels could change with age and change in liver metabolic rates and body mass index. If the patient's valproate level is relatively low, increasing the dose to reachieve therapeutic levels could resolve depressive (or breakthrough manic) episodes.

Suicidal ideation is very common in children and adolescents with bipolar disorder -- perhaps 25% of patients have this symptom at any time.[12] Thus, suicidal ideation should be carefully assessed at every appointment, and particularly during depressive episodes.

**9. Survey** - All laboratories are normal, and AB is not abusing substances. He continues with his depressive symptoms. What medication would you consider adding?

- ○ Fluoxetine
- ○ Bupropion
- ○ Lamotrigine
- ○ Olanzapine

**Explanation:**

Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, may induce mania in children with bipolar disorder, perhaps at higher rates than in adults.[13] However, it is less clear if the risk is decreased by adjunctive mood stabilizer treatment. Nonetheless, fluoxetine has the longest half life of the SSRIs, so would continue to be present in the body long after discontinuation in case of a manic reaction, potentially continuing to "fuel" the mania. Other SSRIs (sertraline, citalopram) could be considered, while monitoring the patient carefully for any new onset manic symptoms.

It is not clear if bupropion, an atypical antidepressant, is less prone to cause mania than SSRIs. Thus, it is an option, but may not necessarily be preferential to SSRIs.

There is some evidence for the efficacy of lamotrigine in adult[14] and adolescent bipolar depression.[15-17] However, no controlled studies have been conducted yet. Nevertheless, lamotrigine is a good option here, especially as it appears much less likely to trigger a manic episode.

Olanzapine was found to beat placebo in one study of adult bipolar depression.[18] In that study, olanzapine-fluoxetine combination was found to be more effective than either treatment. Thus, while either treatment would have some data to support it, neither medication has been studied in adolescents with bipolar depression.

## Past Developmental/Psychiatric History (Continued)

You decide to add lamotrigine. Serious rash is an uncommon but potential fatal adverse effect of lamotrigine, as it can lead to Stevens-Johnson syndrome. Such reactions can be minimized by starting at a low dose and gradually titrating upwards. The recommended dosing schedule in adults with bipolar disorder (and adolescents with epilepsy) who are not taking valproate or carbamazepine adjunctively is 25 mg/day x 2 weeks, then increase to 50 mg/day x 2 weeks, then increase to 100 mg/day. However, AB is taking valproate, which can double or triple serum lamotrigine levels. Therefore, you start him at 12.5 mg/day x 2 weeks, then 25 mg/day x 2 weeks, after which you then increase it to 50 mg/day.

AB does well after 4 weeks of lamotrigine at 50 mg/day, and the dose is eventually raised to 75 mg/day. Mood is stable, and functioning is good, but over 12 months since starting medication, the patient has gained 30 lbs. The patient is now 5'2" and weighs 160 lbs.

10. **Survey** - What do you do now?
    - Nothing
    - Add topiramate
    - Decrease risperidone dose
    - Decrease divalproex dose

**Explanation:**

Weight gain is a common adverse effect of many psychotropic medications, particularly mood stabilizers (lithium, valproate) and antipsychotics (clozapine, olanzapine, risperidone, quetiapine). Children taking these mediations may gain more weight proportionally than adults.[19] Weight gain to obese levels increases risk of several

medical conditions, including diabetes, metabolic syndrome, and cardiovascular illness. Weight gain may taper off after a few months of psychotropic treatment, but it can also continue chronically. Therefore, measures should be taken to reverse this process in AB.

Although it is unclear if topiramate is an effective mood stabilizer in children and adolescents (there have been 3 negative trials in adults with acute mania), there is some indication that it may suppress appetite and cause weight loss in some children.[20] Typically, doses range from 75-200 mg/day. Patients should be monitored carefully for possible cognitive disturbance (eg, word finding difficulties) with higher doses of topiramate.

Decreasing risperidone is a possibility, as a common adverse effect of risperidone is weight gain. If the patient were unstable from a mood standpoint, this might be risky. However, the patient is stable, and also has had lamotrigine added since the risperidone was added. Therefore, it is unclear if the patient would remain stable on just lamotrigine, or would require risperidone and/or divalproex. This is a common route for patients with behavior disorders taking multiple medications. At appropriate junctures (when adverse effects occur and when the patient is relatively stable psychiatrically), it is a good idea to consider tapering off medications, while monitoring closely for possible worsening of mood and for improvement in adverse effects.

Decreasing the divalproex dose is also a possible action, for all the reasons noted for decreasing risperidone, above.

**11. Survey -** The patient remains stable through the rest of 8th grade. Even though he is well, what should you monitor? (Check all that apply.)

- ☐ CBC, AST, ALT
- ☐ Renal panel, TSH
- ☐ Fasting glucose, lipid profile
- ☐ Heart rate, blood pressure

**Explanation:**

Along with serum valproate level, CBC, AST, and ALT should be obtained every 6 months while the patient is taking divalproex.

Renal panel and TSH are important in patients taking lithium, which is renally excreted and can cause hypothyroidism.

Measuring fasting glucose and lipid profile is generally recommended in children before they begin taking mood stabilizers/antipsychotics and regularly thereafter (every 6-12 months, or when weight gain occurs). Rising fasting glucose levels may indicate a

developing type II diabetes or impending metabolic syndrome. Lipid profiles aid in determining degree of risk for future cardiovascular morbidity.

It is always a good idea to monitor heart rate and blood pressure in children taking stimulant medication or atomoxetine. These agents may increase these values slightly, and usually not within clinically important ranges. However, occasionally, greater increases are seen.

## Past Developmental/Psychiatric History (Continued)

Now the patient is entering the 9th grade and is 14 years old. He starts to have brief periods of anger and oppositionality at home. At school, he is doing well, but beginning to have decreasing grades. He enjoys being with his friends and says "they understand me, not like my parents." Upon further investigation, you hear that he has been sneaking out past his curfew at night, and his parents are worried that he might be drinking or smoking marijuana.

**12. Survey** - What do you do?

- Perform a urine toxicology screen
- Increase dose of mood stabilizers (divalproex or risperidone)
- Recommend family and/or individual psychotherapy
- Nothing, this is normal teenage behavior

**Explanation:**

While performing a urine toxicology screen may be important at some point to document and follow degree of substance use, at this point performing this test may alienate the teenage patient and prevent future honest communication.

It is not clear that the patient is experiencing breakthrough mania, so this should be assessed for. If more manic symptoms (than just irritability) are present, then one would consider increasing doses of mood stabilizers or antipsychotics.

AB's actions are consistent with adolescent development, in novelty seeking behavior and establishing independence from parents. However, this behavior can be problematic, especially in the context of bipolar disorder. Family and/or individual psychotherapy can be helpful in improving communication with parents, decreasing oppositional behavior, and improving family relations overall. Furthermore, educating the adolescents as to the potential harm of substances (alcohol, marijuana, LSD, ecstasy) in interacting with medications and destabilizing mood may lead to decreased use.

## Past Developmental/Psychiatric History (Continued)

### Psychotherapy

Psychotherapy is indicated, not alone but in conjunction with medication, in the treatment of children with bipolar disorder.[21] However, empirical evidence demonstrating the efficacy of adjunct therapy is scarce. Based on adult data, it would seem that a more cognitive/behavioral therapy with psychoeducation would be best. Family-focused therapy (FFT) has been shown to be effective in adults with bipolar disorder (controlled)[22], and efficacious in adolescents with bipolar disorder (open single-arm study).[23] FFT involves working with the child and family over 6 months, to educate, improve communication, and develop behavioral plans. Understanding the trigger for mood episodes and ways of reducing stress are important. The psychoeducational piece includes understanding the different mood episodes, understanding medications, and learning about causes of bipolar disorder. Other modalities, such as individual cognitive/behavioral therapy for adolescents, may also be useful in bipolar disorder.

### Educational Interventions

It is important to evaluate the child with bipolar disorder for any specific educational needs they may have. As children spend 30% to 50% of their time at school, school can either be a therapeutic environment or can actually worsen their condition. Thus, implementing accommodations for children with bipolar disorder is often necessary and helpful, not just for academic achievement, but also amelioration of bipolar symptoms and improved psychosocial functioning.

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Disclosure: Kiki D. Chang, MD, has disclosed that he has received grants from Abbott Laboratories, GlaxoSmithKline, National Institute of Mental Health, Heinz C. Prechter Foundation, National Alliance for Research in Schizophrenia and Depression, and Klingenstein Third Generation Foundation. He has also disclosed that he served as a consultant for Abbott Laboratories, AstraZeneca, Eli Lilly & Co., GlaxoSmithKline, Janssen Pharmaceutica, Shire UB, and UCB Pharma. Dr. Chang is on the speakers' bureau for Abbott Laboratories, AstraZeneca, Eli Lilly & Co., GlaxoSmithKline, and Ortho McNeil.

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Disclosure: David McNeel has no significant financial interests or relationships to disclose.

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