# Mania and Attention Deficit Hyperactivity Disorder in a Prepubertal Child: Diagnostic and Treatment Challenges

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In rare cases, the first beginnings can be traced back even to before the tenth year.

—Kraepelin, 1921

Early-onset bipolar illness is historically an understudied area. Increasing awareness that prepubertal mania may occur more frequently than has been previously recognized has led to greater attention to bipolar disorder in the young (1). However, while there is widespread agreement that bipolar disorder may have its onset during adolescence, the diagnosis in children—and to a lesser extent, preadolescents—remains controversial (2, p. 187).

*"He shouted that he wanted to kill himself and attempted to stick his arm in the garbage disposal while it was running."*

Manic and depressive symptoms resembling those seen in adolescents and adults have traditionally been considered rare in prepubertal youth. In a study of more than 900 subjects, Kraepelin (3) observed that 0.4% of his patients experienced onset of their illness before age 10. Utilizing criteria that emphasized classical clinical descriptions of mania in adults—which are now thought to be suboptimal for classifying childhood bipolar illness—Anthony and Scott (4) discounted 96% of the cases with prepubertal onset in their review of the psychiatric literature between 1884 and 1954.

A contemporary shift away from the classical conceptualization of bipolar illness in children toward a more developmentally defined bipolar variant syndrome of childhood has since occurred (5). Key features of the prepubertal bipolar variant include a nonepisodic presentation of chronic mixed mania or continuous rapid cycling, marked irritability as the predominant mood abnormality, extreme, protracted temper tantrums or "affective storms," and near-ubiquitous comorbidity with attention deficit hyperactivity disorder (ADHD) (6–8).

It is not surprising that this shift has generated considerable controversy as well. With such widening of the diagnostic schema, some reports have suggested prevalence rates for mania as high as 16% in children seen in specialized child psychiatric settings (9). Critics have argued that the prepubertal diagnosis likely subsumes children with heterogeneous psychopathology. Furthermore, the unremitting course of prepubertal mania is antithetical to the cyclical nature of bipolar illness. Critics have also emphasized the lack of longitudinal data verifying that children diagnosed with prepubertal mania continue to meet criteria for bipolar disorder into adulthood (10).

In the contemporary literature, childhood bipolar illness is pervasively comorbid with other psychiatric disorders (9, 11, 12). Whether these findings represent "true" comorbidity of prepubertal mania with other, independent disorders or "artifactual" comorbidity due to symptom overlap between nondiscrete diagnostic categories is also debatable (13, 14). This controversy, in turn, reflects tensions between a hierarchical approach to psychiatric classification, embodied to some extent in the World Health Organization's ICD system, which encourages the formulation of a single major diagnosis, and a relatively nonhierarchical approach, advocated within APA's DSM system, which encourages multiple diagnoses (15). Within the DSM-IV framework, then, the complex, pleomorphic symptom profiles observed in childhood mania are conceptualized as multiple co-occurring psychiatric disorders. In clinical practice, however, some experts caution that this approach may lead to unnecessary polypharmacy when multiple diagnoses, and a medication for each, are given (16).

In adults with bipolar disorder, the prevalence of mixed mania, rapid cycling, and a chronic course of illness has been reported to be 40%, 15%, and 6%, respectively (2, p. 149; 17). In contrast, mixed mania, rapid cycling, and a chronic, unremitting course of illness have been reported in over 70% of prepubertal children with bipolar disorder (9, 11, 12). Such "atypical" presentations, therefore, constitute the rule rather than the exception in prepubertal bipolar disorder.

Children currently diagnosed with prepubertal-onset mania—who appear with complicated, and often disabling, pictures of severe affective and disruptive behavioral symptom profiles—are among the most challenging children to diagnose and treat in child psychiatry (18). This report describes the longitudinal course of a young boy diagnosed with prepubertal mania. In the discussion, we emphasized the evolution of this child's clinical presentation, the diagnostic and therapeutic complexities represented by this case, and the implications for future research.

## Patient Description

Adam (a pseudonym), age 9, was hospitalized on a psychiatric ward for young children. (Identifying information has been altered in this report to disguise patient identity.) Before this initial inpatient admission, Adam had lived with his parents and two siblings and had just completed fourth grade. He had received no prescribed or over-the-counter psychotropic medications. For several weeks preceding his hospitalization, Adam had become increasingly distressed over lack of contact with his father, who was working at two jobs. He had also become more irritable and aggressive, fighting frequently with his siblings and peers. After his father canceled an outing planned for the two of them, Adam, threatening suicide, jumped out of a window at his home. Although Adam was uninjured, his parents were alarmed by the recent deterioration in his behavior and brought him to the emergency room, where he was subsequently admitted for inpatient evaluation.

### *Background*

Adam was born after a full-term pregnancy and normal delivery. His mother had smoked up to a pack of cigarettes daily during the pregnancy. Adam reached developmental speech and motor milestones within normal time limits. During the toddler years, Adam's unusually high activity level and frequent temper tantrums became a concern. In preschool and kindergarten, Adam was noted to have a short attention span and to have difficulty settling down during quiet times and remaining seated. His play was often rough, and he displayed a low tolerance for frustration with his peers. Adam's social and behavioral problems persisted into elementary school.

### *Medical and Family History*

Adam was in good general health. There was no history of physical or sexual abuse or head trauma. The results of physical and neurological examinations were unremarkable. The results of blood chemistries, a liver panel, a CBC, tests of thyroid function, a urinalysis, an ECG, and an EEG were normal. No other brain imaging studies were completed. At the time Adam was originally assessed, pertinent family psychiatric history was limited to reports of "anger problems" in Adam's brother and father. Over time, however, it became clear that Adam's father, who had not received psychiatric evaluation or treatment, experienced periods of moodiness with volatile temper outbursts, intermittent alcohol binges, and an unstable work history. Of note, his mother developed an initial major depressive episode about 9 months after Adam's first hospitalization.

## First Hospitalization

When he was first examined, Adam was a somewhat overweight young boy who avoided eye contact but was otherwise cooperative. He appeared moderately depressed. His thought processes were goal-directed, and he reported no auditory hallucinations or racing thoughts. On the Children's Depression Inventory (19)—a self-report scale of depressive symptoms for children ages 6–18 that is similar to the Beck Depression Inventory (20)—Adam endorsed a prominent depressed mood, anhedonia, negative self-esteem, and the feeling of being unloved at the time of admission. His T score was 95 on this self-report scale, on which a score above 69 is considered to be clinically significant for depression. Upon projective testing with the Thematic Apperception Test, his responses emphasized feelings of personal ineffectiveness, vulnerability, and social isolation. Adam's score on the Children's Global Assessment Scale (GAS) (21)—an adaptation of the adult GAS (22)—was 31. His score on the ADHD Rating Scale (23), retrospectively completed by a physician on the basis of ward and classroom observations, was 39. In a normative community sample of 9-year-old boys, mean parent and teacher scores on this measure were 13.4 (SD= 12.4) and 14.0 (SD=10.4), respectively.

During an initial period of observation, Adam partially responded to the ward's highly structured behavioral milieu. While his initial suicidal ideation quickly disappeared, he continued to appear sad, withdrawn, and anxious. Adam was diagnosed with a major depressive episode, possibly comorbid with ADHD. Paroxetine, 10 mg/day, was initiated to target his depressive symptoms. Additional interventions included individual therapy and social skills group therapy for Adam, as well as psychoeducation and parent training sessions for Adam's mother. Adam's clinical condition improved, and he was discharged after a 2-week inpatient stay. His Children's Depression Inventory score was 14, his Children's GAS score was 50, and his ADHD Rating Scale score was 36. Follow-up, to include psychotherapy, ongoing monitoring of antidepressant response, and evaluation of need for additional ADHD pharmacotherapy, was planned.

## After First Hospitalization

Adam's depressive symptoms improved while he was taking paroxetine, 10 mg/day, after his return home, which coincided with the summer months and his return to school in the fall. Despite sustained improvement of his depressive symptoms, Adam continued to experience multiple, impairing symptoms of ADHD at school and at home. Therefore, methylphenidate, 5 mg t.i.d., was added to Adam's antidepressant regimen to target his inattentiveness, distractibility, and hyperactivity. Before treatment with methylphenidate, Adam's Children's GAS score was 55; his ADHD Rating Scale score was 36. One week after he began taking methylphenidate, his ADHD Rating Scale score was 19.

After 8 months of paroxetine and 1.5 months of methylphenidate treatment, Adam's mood deteriorated in a pattern suggestive of possible manic-like symptoms. His teachers observed that he was more bossy, intrusive, and aggressive with peers. His classroom behavior was more disruptive, and he had become increasingly defiant toward teachers, refusing to accept corrections on assignments.

At home Adam was restless, agitated, and increasingly oppositional. His extreme refusal to accept adult directives at home and at school had a possible grandiose quality, as if "the rules did not apply" to him. His speech was pressured, he began using sexually graphic profanity, and he was caught stealing from his grandmother. Adam also began to defy his bedtime limits, staying up past midnight playing computer games. According to his mother, he was sleeping about 2–3 hours less than usual at night and was not napping during the daytime. Finally,

Adam was suspended from an after-school program after he attempted to choke a peer. When his parents attempted to discipline him for this suspension by taking away his television privileges, he shouted that he wanted to kill himself and attempted to stick his arm in the garbage disposal while it was running. After this incident, Adam was readmitted to the child inpatient service.

## Mental Status Examination

At his second admission, 8 months after his first hospitalization, Adam appeared in an agitated state, stating, "My motor's going so fast. I'm about to explode." He described his mood as angry and exhibited labile affect, pressured speech, intrusive behavior, and unfounded suspiciousness toward peers. Once he was ensconced on the ward, his mood was also noted to be expansive, with periods of inappropriate giddiness alternating with extreme irritability and prolonged angry outbursts. Adam was observed to appear physically driven, with a degree of psychomotor hyperactivity that clearly exceeded the activity levels observed during his first hospitalization. There were numerous episodes of physical aggression toward male peers and staff and inappropriate attempts to kiss female peers, resulting in multiple time-outs in open seclusion and one-to-one staffing for safety. In light of his intervening history and clinical presentation in the hospital, Adam was given a presumptive diagnosis of bipolar disorder.

His Children's Depression Inventory score was 10, his Children's GAS score was 20, and his ADHD Rating Scale score was 42. Adam's score on the Young Mania Rating Scale (24)—retrospectively completed on the basis of detailed multidisciplinary inpatient documentation—was 36. In adults, Young Mania Rating Scale scores greater than 12 suggest hypomania, while scores greater than 20 are usually consistent with mania. While normative data in children are not available for this measure, Fristad et al. (25) published an open pilot study on its use among 11 prepubertal subjects ages 6–12. In that study, the Young Mania Rating Scale distinguished manic children, whose scores ranged from 14 to 39, from children with ADHD, who received scores of 0–12.

On admission, Adam's methylphenidate and paroxetine doses were discontinued. Adam's acute agitation and paranoid ideation were treated with haloperidol, and he began taking lithium. After a 2-week stay, he no longer met criteria for inpatient treatment and was discharged while he was taking 600 mg/day of lithium (serum level=0.8 meq/liter) and 1 mg of haloperidol at bedtime. His Young Mania Rating Scale and Children's GAS scores were 15 and 50, respectively.

## After Second Hospitalization

Adam's mood instability, irritability, and aggression were better while he was taking lithium (serum levels= 1.0–1.2 meq/liter) and 1 mg of haloperidol at bedtime for several weeks. His frequent, prolonged temper tantrums and explosive agitation ceased. He was less aggressive toward other children and reported no suicidal ideation. However, about 1 month after Adam's return home, his mother appeared to develop clinical depression, identifying the death of Adam's maternal grandfather 6 months earlier, worsening marital conflict, and the stress of Adam's illness as possible precipitants. She was seen with fatigue, a depressed mood, hypersomnia, complaints of being "unable to cope" accompanied by impaired functioning, and passive suicidal ideation. Adam's clinical status rapidly deteriorated in the context of maternal impairment, parental discord, and the recent loss of his grandfather. He began to have numerous fistfights with peers, despite continued compliance with medication treatment.

A third hospitalization was precipitated when Adam was expelled from school for making homicidal threats that were accompanied by severe physical aggression toward peers and escalating behavioral dyscontrol at home. Upon rehospitalization, his score on the Young Mania Rating Scale was 31, and his Children's GAS score was 35. The addition of an anticonvulsant mood stabilizer to lithium was proposed. However, Adam's parents refused the addition of divalproex sodium and requested that lithium be withdrawn because Adam had experienced a 20-lb weight gain while taking lithium. Carbamazepine was therefore initiated and titrated, on the basis of clinical response, to a serum level of 10 μg/ml, while lithium therapy was gradually withdrawn. Adam responded well to carbamazepine, with marked reductions in irritability and mood lability observed after 2 weeks of treatment. However, he continued to experience multiple, impairing symptoms of distractibility and hyperactivity on the ward and in the classroom. His ADHD Rating Scale score was 35. Because of Adam's prior history of possible psychostimulant-associated mood destabilization, clonidine therapy was initiated to target residual ADHD symptoms. Adam was discharged from the hospital while taking carbamazepine (serum level=10 μg/liter), 0.05 mg t.i.d. of clonidine, and 1.5 mg/day of haloperidol. His Young Mania Rating Scale score was 11, his Children's GAS score was 55, and his ADHD Rating Scale score was 25.

## Outpatient Treatment

### *Placement in Therapeutic School*

Psychoeducational testing revealed that—despite an average cognitive ability (estimated full-scale IQ=96)—Adam's academic achievement lagged 2–3 years behind in most subjects, and he fulfilled criteria for a developmental reading disorder as well as a disorder of written expression. In addition, his numerous behavioral problems had handicapped his social adaptation. Ameliorating Adam's experiences of academic and social failure at school thus became one of the principal goals of his outpatient treatment. To achieve this goal, funding was ultimately obtained for Adam to attend a specialized day school for children with severe emotional disturbances and learning disabilities.

Adam's specialized school provided a safe, controlled environment, a highly structured behavioral program, remedial academic instruction, individual and family therapy, and intensive social skills training. In this therapeutic milieu, Adam was able to make progress both academically and socially; consequently, his self-esteem and conduct improved considerably. Indeed, both Adam and his mother considered placement in this "new school" to be one of the most effective interventions Adam had yet received.

### *Parent Guidance and Support*

**As shown during his first hospitalization, Adam was quite sensitive to the family environment. During his outpatient treatment, his mother was diagnosed with clinical depression and was referred for her own treatment. Initially resistant to psychiatric referral, she agreed when Adam's sensitivity to her psychological state was emphasized. Improvement in her clinical condition proved beneficial for Adam as well, who responded positively to her greater emotional availability when she was euthymic.**

**However, Adam also remained a highly vulnerable child who could decompensate quickly without the high level of intervention provided by his therapeutic school environment and his pharmacotherapy—or in response to significant familial and interpersonal stress. Initially, both he and his parents expressed a desire for short-term psychiatric treatment. Working toward a realistic acceptance of the long-term nature of his illness and the necessity for ongoing multimodal interventions proved to be a crucial component of Adam's treatment.**

**After his three hospitalizations and over the subsequent year of outpatient treatment, Adam's mood lability and ADHD symptoms remained improved. Adam did experience several, brief episodes of mild to moderate hypomanic-like activation; however, there were no further hospitalizations. At the time of termination, Adam was taking carbamazepine (serum level=7 μg/liter), 0.05 mg b.i.d. of clonidine and 0.1 mg at bedtime, and 1.0 mg of haloperidol at bedtime. His score on the Children's GAS was 61, his Young Mania Rating Scale score was 9, and his ADHD Rating Scale score was 22.**

## Discussion

This case illustrates at least three factors that make accurate diagnosis of bipolar disorder in children challenging. First, the "moving-target" nature of developmental psychopathology complicates differential diagnosis. Adam's early childhood history was suggestive of ADHD. "Premorbid" histories of childhood ADHD have been reported both in adolescents and adults diagnosed with bipolar disorder (26, 27). With childhood-onset bipolar disorder, ADHD symptoms have also been reported to precede the development of mania (28).

The predictive significance of early ADHD symptoms for the ultimate development of bipolar disorder is debatable. Some investigators have proposed that ADHD may represent an age-specific manifestation of bipolar disorder, while others argue that the two disorders are separate and comorbid, with perhaps one (ADHD) increasing the risk of development of the other (bipolar disorder) (29). A third possibility—that children with ADHD who go on to manifest mania-like symptoms have "bad" ADHD or a new diagnostic entity altogether—has also been proposed (30).

Adam started with a diagnosis of ADHD and then developed a depressive episode at age 9. Longitudinal data have suggested that the rates of switching to bipolar disorder are 20%–40% among children and adolescents diagnosed with severe major depression (31). Depressive episodes as the first manifestation of bipolar disorder have been reported in over 60% of adolescents in an epidemiological study (32). Children with bipolar disorder who have histories of major depression often experience the onset of major depression before the onset of mania (33).

Predictors of bipolarity are therefore particularly important for children and adolescents who are seen with clinical depression. In adolescents hospitalized for depression, several purported predictors—such as symptoms of psychomotor retardation, psychotic features, pharmacologic hypomania, and a family history of bipolar disorder—have been reported to increase the likelihood that a patient will develop bipolar disorder (34, 35).

There are limited data on predictors of the development of bipolar disorder in children. Post and colleagues (36) reported on a retrospective analysis of early symptoms that are highly predictive of childhood bipolar disorder. Children who exhibited a combination of three or more symptoms from a five-symptom model—consisting of shortened attention span, grandiosity, irritability, racing thoughts, and suicidal gestures—had an 80% or greater chance of developing bipolar disorder. This promising report merits prospective replication. Of note, Adam fulfilled three of five criteria from this early-onset model at the time of his first hospitalization (e.g., shortened attention span, irritability, and suicidal gestures.)

Furthermore, Adam's case illustrates the need to update family psychiatric histories on an open-ended basis, especially during the longitudinal follow-up of younger patients. The parents of children who are seen with affective illness are often, themselves, still within the age of risk for developing a de novo mood disorder, as did Adam's mother. The possibility that affected family members may have eluded formal diagnosis must also be kept in mind. Adam's father and brother appeared to have significant affective instability. Furthermore, the father's work schedule, as well as his history of episodic alcohol binges and periods of marked irritability and explosiveness, raised the possibility of a bipolar-spectrum illness. No definitive diagnosis of Adam's father, who refused formal assessment, could be made. Nevertheless, in the ongoing diagnostic and therapeutic formulation of Adam's illness, it was important to recognize the possibility of a bilineal parental history (i.e., a father and a mother with bipolar disorder and major depression, respectively), which may significantly increase a child's risk of developing bipolar illness (37, 38).

Second, there is considerable overlap between diagnostic criteria for mania and disruptive behavioral disorders, particularly ADHD. The considerable challenges posed by overlapping diagnostic boundaries have been described (39). ADHD and mania share common symptoms of hyperactivity, distractibility, and short attention span. Furthermore, symptoms exclusive to mania, such as euphoria and grandiosity—as well as clear-cut onset and offset of affective episodes—may be rare in children. Family history, age at onset, and the episodic course of mania and depression compared to the chronic nature of ADHD have all been suggested to be clinical clues that may assist diagnostic clarification in some instances (2, p. 190; 40).

Third, comorbidity may be the rule rather than the exception. Comorbidity with common childhood disorders may overshadow affective illness in children with prepubertal bipolar disorder and lead to underdiagnosis of mania (41). As stated earlier, studies of prepubertal-onset mania report high rates of comorbidity with other axis I disorders, including anxiety disorders, oppositional defiant disorder, and conduct disorder (42, 43). An association between early-onset bipolar disorder and comorbid substance dependence and alcohol abuse disorders has also been described in young adolescents (44, 45). Comorbid ADHD is universally reported in childhood-onset mania. In groups of children with prepubertal mania, the rates of comorbid ADHD consistently exceed 90% (46). The reason for the high rates of comorbidity observed in childhood-onset bipolar disorder is unknown but is likely to be multifactorial.

It should be noted that Adam was initially treated with an antidepressant for a major depressive episode and subsequently received a stimulant trial for residual ADHD symptoms. The possible role that these early pharmacological interventions may have played in the development of his manic symptoms is uncertain. Antidepressants and stimulants have been reported to precipitate mania in bipolar adults; however, the spontaneous rate of switching from depression to mania without exposure to medications is high (47–50).

Thus, attribution of a causal relationship between drug exposure and subsequent mania may in many cases be misleading. In children and adolescents, behavioral activation and (hypo)mania due to stimulant and antidepressant use have been reported (51–53) but have received little rigorous study. In two retrospective reports, Biederman and colleagues (54, 55) observed that selective serotonin reuptake inhibitors and tricyclic antidepressants, but not psychostimulants, increased the risk of mood destabilization in bipolar children and adolescents undergoing treatment for depression and ADHD, respectively. Given increasing rates of antidepressant and stimulant use during childhood (56), the risks of pharmacological (hypo)mania induction in youngsters require further elucidation.

## Treatment

There are few empirical data to drive medication treatment decisions in children with bipolar disorder. A naturalistic report suggests that—similar to Adam's experience—prepubertal mania may follow a chronic course characterized by high rates of relapse, psychiatric hospitalizations, chronicity, and the need for polypharmacy (57).

Similar lacunae exist in the study of psychotherapeutic interventions for childhood bipolar disorder. While Chang (58) reported some positive preliminary results of a group-therapy protocol for bipolar youth, psychosocial modalities for pediatric bipolar disorder, by and large, have not been scientifically evaluated. As this case exemplifies, however, comprehensive psychosocial treatment—for Adam and his family, efficiently delivered in the form of a therapeutic day school—is essential in the long-term clinical management of children diagnosed with prepubertal mania. More psychotherapeutic treatment studies of bipolar children and adolescents are needed.

We know of no placebo-controlled trials of mood-stabilizing agents among children or preadolescents with bipolar disorder. The literature on lithium therapy in children with bipolar disorder is the most extensive (59), although most studies lack control groups. One well-controlled study (60) demonstrated the superiority of lithium over placebo in 25 adolescents with bipolar disorder or major depression with purported predictors of latent bipolarity, complicated by secondary substance dependency. While the mean age of the subjects treated in this study was 16.3 years (SD=1.2), their mean age at the onset of bipolar disorder was 9.6 (SD=3.9), suggesting lithium's therapeutic potential for patients with prepubertal-onset bipolar disorder (60).

Children with bipolar illness frequently have features that predict a small lithium response in adults, such as dysphoric mania and rapid cycling (61, 62). The potential utility of anticonvulsant mood stabilizers in the treatment of prepubertal bipolar disorder is thus of considerable clinical interest. The benefit of divalproex sodium for children and adolescents with bipolar disorder—many of whom were lithium nonresponders—has been documented in at least three case reports (63–65), one retrospective chart review (66), and six open studies (67–72).

While we know of no double-blind, placebo-controlled trials involving pediatric bipolar disorder, Donovan et al. (73) reported that divalproex sodium was superior to placebo in 20 children and adolescents with a disruptive behavior disorder who also met operationalized criteria for explosive temper and mood lability—a constellation of symptoms that overlap with prepubertal mania.

Several case reports have documented carbamazepine's utility in treating adolescent mania that is refractory to lithium therapy (74–76). A comparative open trial of lithium, divalproex sodium, and carbamazepine in 42 children and adolescents with bipolar disorder reported statistically equivalent response rates of 38%, 52%, and 38%, respectively (77). However, more than half of the subjects in this study failed to respond to monotherapy with any of the three mood stabilizers. The use of combination mood stabilizers, atypical antipsychotic agents, and/or stimulants was anecdotally reported to be of benefit in patients with refractory illness.

The treatment of ADHD in early-onset bipolar disorder is controversial. The use of psychostimulants to treat ADHD in children with mania has led to clinical concerns about these drugs' potential risk for triggering affective episodes in vulnerable children (78). Koehler-Troy et al. (52) reported a case of methylphenidate-induced mania in a prepubertal boy who was seen with severe hyperactivity and a history of maternal bipolar disorder. In that report, stimulants were used without a concomitant mood stabilizer. However, clinical experience to date, although limited, suggests that stimulants in combination with one or more mood stabilizers may be safe and effective in the

treatment of prepubertal mania complicated by ADHD (79, 80).

In preclinical studies, however, repeated administration of dopaminergic agonists, such as methylphenidate, have led to progressive and enduring increases in locomotor hyperactivity and stereotypic behavior in a phenomenon known as behavioral sensitization (81). A pathoetiologic process analogous to behavioral sensitization has been hypothesized to occur in patients with bipolar disorder (82). How or whether this process is relevant to children with ADHD who develop bipolar disorder is unknown. In animal models, lithium blocks the behavioral sensitization associated with cocaine-induced hyperactivity and stereotypy (2, p. 407). Divalproex sodium has also been reported to block behavioral sensitization in methylphenidate-exposed rats (83). These antisensitization properties may also provide protection against the stimulant-sensitization phenomenon. In adult human subjects, lithium has been observed to attenuate mood elevation and behavioral activation after challenges with methylphenidate and amphetamines (84, 85).

In line with this evidence, preliminary reports in children with bipolar disorder and ADHD have suggested that the concurrent use of stimulants and mood stabilizers may result in therapeutic improvement of ADHD symptoms without mania exacerbation (86, 87). Carlson et al. (88) reported that the treatment combination of lithium (serum levels=0.7–1.1 meq/liter) and methylphenidate (5–10 mg b.i.d.) was superior to use of either agent alone on measures of attention and hyperactivity in a placebo-controlled, double-blind crossover trial of children (N=7) who were seen with disruptive behavioral disorders and either bipolar disorder or major depressive disorder. Three of the seven children had first- and second-degree relatives with bipolar disorder. While this pilot report was limited by its small size (N=7), its crossover design, and the subjects' diagnostic heterogeneity, it suggested the potential for combination treatments in children and adolescents with bipolar disorder that is comorbid with ADHD. The efficacy and safety of combined regimens of mood stabilizers and anti-ADHD treatments in childhood-onset bipolar disorder that is comorbid with ADHD warrant further systematic study.

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