Bipolar Disorder and Attention-Deficit/Hyperactivity Disorder Comorbidity in Children and Adolescents: Evidence-Based Approach to Diagnosis and Treatment

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The relationship between bipolar disorder and attention-deficit/hyperactivity disorder (ADHD) has received considerable attention in psychiatric research. Elevated rates of bipolar disorder–ADHD comorbidity among youth and coaggregation within families raise questions as to whether co-occurring bipolar disorder and ADHD represent (1) a more severe subtype of bipolar disorder, (2) related disorders with a shared genetic predisposition, or (3) separate though frequently comorbid disorders. Regardless of etiology, co-occurrence of bipolar disorder and ADHD has been associated with adverse illness outcomes in both disorders,[1,2] consistent with bipolar disorder–ADHD comorbidity being a marker for poorer prognosis and thus a more severe subtype.

Course of Co-Occurring Bipolar Disorder and ADHD

Bipolar disorder is characterized by recurrent debilitating episodes of depression and mood elevation (euphoria and/or irritability), with a similar prevalence in males and females and onset typically in adolescence or young adulthood.[3] However, childhood-onset bipolar disorder also occurs and may be diagnostically more complex than adult bipolar disorder, potentially involving a more chronic than episodic course and more irritable than euphoric mood.[4]

In contrast to the typical demographic and clinical profile of bipolar disorder, ADHD has onset during childhood,[5] is more prevalent in males,[6] and is characterized by prominent difficulties with sustaining attention and/or organizing and completing tasks, possibly in combination with hyperactive and/or impulsive behavior.

Data suggest that having both bipolar disorder and ADHD yields a more severe illness course than having either disorder alone. Youth with bipolar disorder–ADHD comorbidity were shown to have earlier age at bipolar disorder onset,[7,8] greater bipolar disorder and ADHD symptom severity,[2] poorer functioning,[2,8] and more psychiatric comorbidities[2] than those with bipolar disorder alone. Adolescent bipolar disorder patients with compared to without ADHD were less likely to recover from manic/mixed episodes within 12 months of index hospitalization.[1] ADHD patients with compared to without comorbid bipolar disorder had increased comorbid anxiety disorders,[9–11] other disruptive behavior disorders,[9–11] and substance and alcohol use disorders[10,11]; poorer functioning[2,9,10]; and higher rates of psychiatric hospitalization.[2,10]

Epidemiology

In clinical studies of youth with bipolar disorder, rates of comorbid ADHD ranged from 22%–98%,[12] much higher than the ADHD pediatric population prevalence of 7.2%.[13] Notably, one study[8] found that comorbid ADHD was more than twice as prevalent in youth with chronic compared to episodic bipolar symptoms (55.6% vs 22.6%, respectively), although the latter ADHD rate was still substantially higher than the general pediatric population prevalence. Similarly, studies of children and adolescents with ADHD found rates of comorbid bipolar disorder ranging from 7%–22%,[12] considerably higher than the bipolar disorder pediatric population prevalence, which ranges from 0.1%–2.5%.[14,15]

Taken together, these data suggest that bipolar disorder and ADHD may be related disorders that increase the risk of one another, consistent with evidence of familial aggregation of the combined bipolar disorder–ADHD phenotype[16] and increased risk for both disorders in first-degree relatives of bipolar disorder[17] and ADHD[18] youth. Alternatively, it may be that symptom overlap leads to misdiagnosis of co-occurring bipolar disorder and ADHD in individuals in whom only 1 disorder is present.

Diagnosis

While the clinical profiles of bipolar disorder and ADHD differ in important ways, especially regarding the core requirement of disturbed mood for bipolar disorder but not ADHD, there remain several overlapping symptoms (eg, distractibility, psychomotor agitation, talkativeness, impulsivity). Moreover, while diagnostic criteria distinguish the more episodic nature of bipolar symptoms from the more persistent nature of ADHD symptoms, this distinction may be less evident in pediatric bipolar disorder, which can present with more chronic mood symptoms.[9] Together, these issues can complicate efforts to differentiate bipolar disorder from ADHD in children and adolescents.

To examine the potential contribution of diagnostic overlap to the higher than expected bipolar disorder–ADHD comorbidity rate, some investigators utilized a subtraction method, eliminating overlapping symptoms from the *DSM-III-R* criteria for bipolar disorder and ADHD (psychomotor agitation, overtalkativeness, and distractibility) and reassessing youth previously diagnosed with both disorders.[9,19] After applying the subtraction method, 95%–100% of patients retained an ADHD diagnosis, whereas only 47%–50% of patients retained a bipolar disorder diagnosis.[9,19] More recent approaches, however, favor counting overlapping symptoms toward bipolar disorder diagnosis if they increase in severity during mood episodes.[4] The studies cited above[9,19] applied more stringent criteria, eliminating overlapping symptoms from consideration without assessing changes in symptom severity during mood episodes, and thus may have underreported bipolar disorder rates within their samples.

Other investigators utilized semistructured interviews and/or *DSM-IV* criteria to compare the prevalence of specific symptoms in patients with bipolar disorder and/or ADHD. Elevated mood, insomnia/decreased need for sleep, and inappropriate sexual behavior were significantly more prevalent in youth with bipolar disorder compared to ADHD, whereas hyperactivity and decreased attention/distractibility were less helpful in differentiating children and adolescents with bipolar disorder from those with ADHD.[20,21] Table 1 summarizes these and other clinical features that may aid the clinician in differentiating bipolar disorder from ADHD.

Table 1. Differentiating Bipolar Disorder From ADHD

Clinical Feature	Bipolar Disorder	ADHD
Onset age[3,5]	Adolescence/ young adulthood	< 7 y
Gender[3,6]	Male = Female	Male > Female
Course	More episodic	More persistent
Suicidality, psychosis[21]	Common	Rare
Euphoria, decreased need for sleep, grandiosity, hypersexuality[20,21]	Common	Rare

Abbreviations: ADHD = attention-deficit/hyperactivity disorder.

Treatment

Beyond the inherent diagnostic challenges of co-occurring ADHD and bipolar disorder, pharmacologic management of youth with both disorders can prove complicated given that stimulants, which are first-line treatments for ADHD, have been associated with earlier age at bipolar disorder onset and stimulant-induced mania and psychosis.[22] Hence, clinicians may hesitate to use stimulants in children and adolescents with co-occurring bipolar disorder and ADHD despite the impaired functioning that could result from untreated/undertreated ADHD symptoms.

However, in contrast to retrospective analyses and case reports indicating potential adverse consequences of stimulant exposure in bipolar disorder patients, larger prospective studies suggest that the actual risk of mood worsening following stimulant exposure may be low in youth with bipolar disorder or subthreshold bipolarity.[22] Moreover, in a 6-year prospective study[7] of 81 children with ADHD (24 with first-degree family history of bipolar disorder), stimulant exposure did not predict subsequent switch to bipolar disorder, and a retrospective study[23] of 245 children and adolescents with bipolar disorder found no association of prior stimulant exposure with younger bipolar disorder onset age. Notably, ADHD youth with compared to without co-occurring manic symptoms demonstrated similar improvements in ADHD symptoms when treated with stimulants.[22] In studies of euthymic bipolar disorder youth already taking mood stabilizers or second-generation antipsychotics, adding stimulants or atomoxetine yielded improvement in ADHD symptoms without destabilizing mood.[22]

In summary, these findings suggest that (1) in youth with ADHD who have subthreshold bipolar disorder or familial risk of bipolar disorder, stimulants improve ADHD symptoms with little risk of acute mood worsening or later bipolar disorder development, and (2) in youth with co-occurring bipolar disorder and ADHD, first treating to euthymia with mood-stabilizing agent(s) prior to adding stimulants or atomoxetine can permit attenuation of ADHD symptoms without significantly increasing risk for mood destabilization. Nevertheless, more longitudinal prospective studies are needed to definitively assess whether stimulants in ADHD youth at risk for bipolar disorder will precipitate earlier bipolar disorder onset and/or more adverse bipolar illness outcomes.

Conclusions

Studies demonstrating increased rates of coaggregation of bipolar disorder and ADHD in individuals and families, and increased risk for both disorders in first-degree relatives of bipolar disorder and ADHD patients, support the possibility of a shared predisposition to these 2 disorders extending beyond mere diagnostic convergence. While the differentiation of bipolar disorder and ADHD in youth is challenging due to symptom overlap and pediatric mood disturbance that is commonly more continuous than episodic, careful attention to clinical features that are unique to bipolar disorder (eg, euphoria, decreased need for sleep, hypersexuality, suicidality, and psychosis) can enhance diagnostic accuracy. Moreover, outcomes in youth with co-occurring bipolar disorder and ADHD can be enhanced by first using mood-stabilizing agent(s) to yield euthymic mood prior to adding a stimulant or atomoxetine to address ADHD.

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Potential conflicts of interest: **Dr Chang** has been a consultant for GlaxoSmithKline, Bristol-Myers Squibb, Eli Lilly, and Merck (unpaid); has received grant/research support from GlaxoSmithKline and Merck; and has been on a data and safety monitoring board for Sunovion. **Dr Ketter** has received grant/research support from Agency for Healthcare Research and Quality, Sunovion, and Teva/Cephalon; has been a consultant for Allergan, Forest, Sunovion, and Teva/Cephalon; has received lecture honoraria from Abbott, GlaxoSmithKline, and Otsuka; and has received royalties from American Psychiatric Publishing. Dr Ketter's spouse (Nzeera Ketter, MD) is an employee of and stockholder in Janssen. **Dr Miller** reports no potential conflict of interest.
Funding/support: None reported.
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REFERENCES

1. DelBello MP, Hanseman D, Adler CM, et al. *Am J Psychiatry*. 2007;164(4):582–590.
2. Arnold LE, Demeter C, Mount K, et al. *Bipolar Disord*. 2011;13(5-6):509–521.
3. Merikangas KR, Akiskal HS, Angst J, et al. *Arch Gen Psychiatry*. 2007;64(5):543–552.
4. Leibenluft E, Rich BA. *Annu Rev Clin Psychol*. 2008;4(1):163–187.
5. Kessler RC, Berglund P, Demler O, et al. *Arch Gen Psychiatry*. 2005;62(6):593–602.
6. Gaub M, Carlson CL. *J Am Acad Child Adolesc Psychiatry*. 1997;36(8):1036–1045.
7. Tillman R, Geller B. *Dev Psychopathol*. 2006;18(4):1037–1053.
8. Masi G, Perugi G, Toni C, et al. *Bipolar Disord*. 2006;8(4):373–381.
9. Wozniak J, Biederman J, Kiely K, et al. *J Am Acad Child Adolesc Psychiatry*. 1995;34(7):867–876.
10. Biederman J, Faraone S, Mick E, et al. *J Am Acad Child Adolesc Psychiatry*. 1996;35(8):997–1008.
11. Wozniak J, Spencer T, Biederman J, et al. *J Affect Disord*. 2004;82(suppl 1): S59–S69.
12. Singh MK, DelBello MP, Kowatch RA, et al. *Bipolar Disord*. 2006;8(6): 710–720.
13. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep*. 2010;59(44):1439–1443.
14. Stringaris A, Santosh P, Leibenluft E, et al. *J Child Psychol Psychiatry*. 2010;51(1):31–38.
15. Merikangas KR, Cui L, Kattan G, et al. *Arch Gen Psychiatry*. 2012;69(9):943–951.
16. Faraone SV, Biederman J, Mennin D, et al. *J Am Acad Child Adolesc Psychiatry*. 1997;36(10):1378–1387, discussion 1387–1390.
17. Chang KD, Steiner H, Ketter TA. *J Am Acad Child Adolesc Psychiatry*. 2000;39(4):453–460.
18. Faraone SV, Biederman J, Wozniak J. *Am J Psychiatry*. 2012;169(12):1256–1266.
19. Milberger S, Biederman J, Faraone SV, et al. *Am J Psychiatry*. 1995;152(12):1793–1799.
20. Luckenbaugh DA, Findling RL, Leverich GS, et al. *Bipolar Disord*. 2009;11(4):441–451.
21. Geller B, Zimerman B, Williams M, et al. *J Child Adolesc Psychopharmacol*. 2002;12(1):11–25.
22. Goldsmith M, Singh M, Chang K. *Paediatr Drugs*. 2011;13(4):225–243.
23. Pagano ME, Demeter CA, Faber JE, et al. *Bipolar Disord*. 2008;10(2):334–341.

J Clin Psychiatry 2013;74(6):628–629 (doi:10.4088/JCP.13ac08565)