A Systematic Review of Rates and Diagnostic Validity of Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder

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Objective: Adult attention-deficit/hyperactivity disorder (ADHD) is increasingly recognized and reported to frequently coexist with bipolar disorder. Concurrent diagnosis of adult ADHD and bipolar disorder remains controversial. In this study, we conducted a systematic review to examine the rates and diagnostic validity of the concept of comorbid adult ADHD and bipolar disorder.

Data Sources: MEDLINE, Embase, PsycInfo, and Cochrane databases were searched for articles published before March 30, 2007, using the keywords *manic*, *bipolar*, *attention deficit hyperactivity*, and *adult*. The computer search was supplemented with bibliographic cross-referencing.

Study Selection: Exclusion criteria were studies with only pediatric subjects, childhood ADHD only but not adult ADHD, and either bipolar disorder or ADHD only, but not both; review articles, case reports; letters to the editor; and book chapters. Of the 262 citations found, 12 studies met our inclusion criteria.

Data Extraction: Specific diagnostic validating criteria examined were phenomenology, course of illness, heredity, biological markers, and treatment response. There were 6 studies on comorbid rates, 4 on phenomenology, 3 on course of illness, 2 on heredity, none on biological markers, and 1 on treatment response.

Data Synthesis: The proposed comorbid syndrome is fairly common (present in up to 47% of adult ADHD and 21% of bipolar disorder populations), with a more severe course of illness compared with that of bipolar disorder alone, and high rates of comorbidity with other psychiatric disorders. Its treatment appears to require initial mood stabilization.

Conclusions: Comorbid adult ADHD and bipolar disorder has been insufficiently studied, with more emphasis on comorbidity rates and few data on course, neurobiology, heredity, and treatment. The diagnostic validity of adult ADHD/bipolar disorder as a true comorbidity is not well-established on the basis of this equivocal and insufficient literature. More studies are greatly needed to further clarify its diagnostic validity and treatment approach.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder of inattention, hyperactivity, and impulsivity that affects 8% to 12% of children and adolescents worldwide.[1] A growing body of literature suggests that ADHD is more persistent than previously thought, which has led to an increasing recognition of the diagnosis of adult ADHD.[2] Of those with childhood ADHD, 15% were found to meet full DSM (III and IV) criteria for adult ADHD, according to a meta-analysis of studies of children with ADHD being followed up to an average age of 25 years.[3] The National Comorbidity Survey Replication (NCSR) reported that 36.3% of the adults (aged 18–44 years) with a retrospective diagnosis of childhood ADHD met DSM-IV criteria for adult ADHD.[4] The estimated prevalence of adult ADHD in the U.S. was 4.4%, according to the latest NCSR.[5] Frequently, adult ADHD is reported to coexist with bipolar disorder.

Bipolar disorder is a frequent, severe, recurrent affective disorder with a lifetime prevalence of 1.3% to 1.6% and mortality rate of 2 to 3 times higher than that of the general population.[6] Considerable symptom overlap occurs between ADHD and the manic phase of bipolar disorder: talkativeness, distractibility, increased activity or physical restlessness, and loss of normal social inhibitions. There are also differences between adult ADHD and bipolar disorder. First, ADHD symptoms tend to be chronic while bipolar disorder symptoms tend to be episodic. Second, ADHD patients do not have increased productivity like bipolar disorder patients, despite having high energy level. Third, ADHD patients do not have decreased need for sleep or inflated self-esteem like symptomatic manic bipolar disorder patients. Fourth, there might be psychotic

symptoms such as hallucinations or delusions in severe cases of bipolar disorder that are absent in ADHD. Nonetheless, concurrent diagnosis of adult ADHD and bipolar disorder in adults remains controversial. Questions have been raised about whether the diagnosis of adult ADHD is an artifact of its symptom overlap with bipolar disorder, or vice versa. Clinically, it has been observed that bipolar patients have more awareness of their cognitive symptoms and lack insight into their manic symptoms.[7] As a result, they are more likely to complain of attentional problems and underreport or deny manic symptoms, contributing to the challenges of diagnosing bipolar disorder in the patient population with neurobehavioral problems. In addition, the comorbidity of adult ADHD and bipolar disorder makes treatment approach more challenging since medications for ADHD, stimulants or selective antidepressants, may destabilize or exacerbate bipolar disorder symptoms.[8–10]

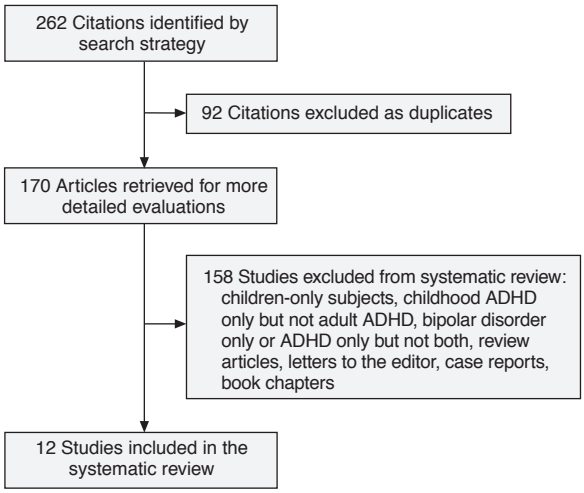
This systematic review aimed to assess the comorbidity rates and diagnostic validity of comorbid adult ADHD and bipolar disorder using the Robins and Guze approach[11] as further developed in the psychiatric epidemiologic literature.[12]

METHOD

We conducted a systematic literature search on MEDLINE, Embase, PsycInfo, and Cochrane using the keywords *manic*, *bipolar*, *attention deficit hyperactivity*, and *adult*. Exclusion criteria were studies with only pediatric subjects, childhood ADHD only without adult ADHD, either bipolar disorder or ADHD only, but not both; review articles; case reports; letters to the editor; and book chapters. The computer search was supplemented with bibliographic cross-referencing. The search included articles published before March 30, 2007. Thus, we included studies only if they included adults with ADHD and bipolar disorder. Some studies, particularly in genetics, also included children, but they were not excluded if they also included adults with ADHD. If genetic ADHD studies ONLY involved children (no adults with ADHD and adults with bipolar disorder), they were excluded.

We used the Robins and Guze approach[11] as further developed in the psychiatric epidemiologic literature[12] to assess diagnostic validity. Specific validating criteria examined were phenomenology, course of illness, family history, biological markers, and treatment response. We examined these lines of evidence to determine if an adult ADHD/bipolar disorder clinical construct is identifiable, and if so, which of the following diagnostic concepts best explain that clinical picture: (1) a comorbidity of 2 diseases (adult ADHD and bipolar disorder), (2) a clinical subtype of bipolar disorder, (3) a clinical subtype of ADHD, or (4) a separate disease entity.

Figure 1. Selection of Reported Studies for the Systematic Review



RESULTS

Our search strategy identified 262 citations, from which duplicates were removed and 170 articles were retrieved for further review. Of these 170 articles, 12 studies were identified as suitable for inclusion in the systematic review (Figure 1).

Comorbidity Rates

Six studies assessed the rates of coexisting adult ADHD and bipolar disorder in adult ADHD samples and bipolar disorder samples (1 study assessed rates in both samples). Three studies of bipolar disorder samples reported comorbid adult ADHD rates of 9.5% to 21.2% (Table 1).[5,13,14] Four studies of adult ADHD samples reported comorbid bipolar disorder rates of 5.1% to 47.1% (Table 2).[5,15–17]

Phenomenology

Four studies[13–15,18] examined phenomenology, 1 on the overlap of ADHD and bipolar disorder symptoms, and 3 on gender distribution, bipolar subtypes, and comorbid rates with other psychiatric disorders.

Regarding symptom overlap, there are 2 levels of overlapping. The first is the overlap of the symptoms within the DSM-IV diagnostic criteria for ADHD itself (Table 3). For instance, (1) easily distracted, (2) difficulty sustaining attention, and (3) failing to give close attention to details are 3 separate criteria; or (1) interrupting/ butting in uninvited, (2) blurting out answers, (3) difficulty awaiting turns are another 3 separate criteria; or (1) fidgeting, (2) difficulty remaining seated, (3) running or climbing around inappropriately, (4) difficulty engaging in leisure activities quietly are 4 separate diagnostic criteria. The

Table 1. Rates of Comorbid Adult Attention-Deficit/Hyperactivity Disorder (ADHD) in Bipolar Disorder Samples

Study	Bipolar Sample Size; Setting (age)	Rate of Comorbid Adult ADHD, %	Diagnostic Method for Bipolar Disorder	Diagnostic Method for ADHD	Weaknesses	Strengths
Nierenberg et al 2005[13]	919; outpatient clinic (28–53 y)	9.5	DSM-IV–based MINI, administered by trained clinical researchers	DSM-IV–based MINI, administered by trained clinical researchers. Adult ADHD (defined as lifetime ADHD in this study) required: 6/10 Criteria of the MINI by age 7 y 9/14 Criteria of the MINI in adulthood Symptoms caused significant problems in at least 2 settings Active symptoms within the past 6 mo	Recall bias	Large sample size Inclusive of bipolar disorder patients (bipolar I; bipolar II; bipolar disorder not otherwise specified; schizoaffective disorder, bipolar subtype; cyclothymia) Mostly psychiatrist raters
Kessler et al 2006[5]	Subset of 3199 respondents; representatives of 9282 household residents in the NCSR (18–44 y)	21.2	WHO CIDI (version 3.0), administered by clinical psychologists	Semistructured interview, administered by clinical psychologists. Adult ADHD diagnosis required: 6 Symptoms of either inattention or hyperactivity-impulsivity Symptoms occurred during the 6 mo before the interview At least 2 DSM-IV criterion A symptoms before age 7 y Some impairment in at least 2 areas of living during the past 6 mo Clinically significant impairment in at least one of these living areas	Recall bias Comprehensive assessment of adult ADHD was done only in the clinical reappraisal subsample Semistructured interview, not gold standard SCID	Large sample size Clinical psychologist raters
Tamam et al 2006[14]	44; outpatient clinic (19–58 y)	15.9	DSM-IV–based SCID, administered by psychiatrists	DSM-IV–based clinical interview by psychiatrist. Adult ADHD diagnosis required: Full diagnosis of childhood ADHD, according to DSM-IV criteria, by age 7 y Chronic course of ADHD symptoms from childhood to adulthood, existing outside of manic episodes Some level of impairment due to ADHD symptoms All symptoms of ADHD were observed independent of presence of any bipolar episode within the last month	Small sample size Recall bias Only patients with bipolar I were included	Diagnostic evaluation done by psychiatrists

Abbreviations: MINI = Mini-International Neuropsychiatric Interview, NCSR = National Comorbidity Survey Replication, SCID = Structured Clinical Interview for Axis I Disorders, WHO CIDI = World Health Organization Composite International Diagnostic Interview.

Table 2. Rates of Comorbid Bipolar Disorder in Adult Attention-Deficit/Hyperactivity Disorder (ADHD) Samples

Study	Adult ADHD Sample Size; Setting (age)	Rate of Comorbid Bipolar Disorder, %	Diagnostic Method for ADHD	Diagnostic Method for Bipolar Disorder	Weaknesses	Strengths
Wilens et al 2003[15]	51; referred adults to clinical trials of ADHD (18–59 y)	47.1	DSM-IV–based SCID, administered by assessment staff; interview data were reviewed blindly by psychiatrists and psychologists. Adult ADHD diagnosis required: Full DSM-IV criteria for ADHD by the age of 7 y Full DSM-IV criteria currently (within the past month) Chronic course of ADHD symptomatology from childhood to adulthood, existing outside of manic episodes Moderate or severe level of impairment attributed to the ADHD symptoms	DSM-IV–based SCID, administered by assessment staff; data were later reviewed by psychiatrists and psychologists	Small sample size Recall bias Trained interviewers performed SCID	Using SCID
McGough et al 2005[16]	79; outpatient clinic (41–44 y)	5.1	Clinical interviews conducted by clinical psychologists and trained interviewers Adult ADHD ("persistent ADHD" in this study) required: Full retrospective DSM-IV childhood criteria Full current DSM-IV criteria Evidence of impairment	SADS, administered by clinical psychologists and trained interviewers	Small sample size Recall bias Sample was derived from parents of ADHD children with the inclusion criteria of these parents having at least 1 child meeting full DSM-IV ADHD criteria and another child having a diagnosis of definite or probable ADHD, limiting the generalizability of the data	Clinical psychologists administered interviews
Kessler et al 2006[5]	Subset of 3199 respondents; representative of 9282 household residents in the NCSR (18–44 y)	19.4	A semistructured interview administered by clinical psychologists. Adult ADHD diagnosis required: 6 Symptoms of either inattention or hyperactivity-impulsivity during the 6 mo before the interview At least 2 DSM-IV criterion A symptoms before age 7 y Some impairment in at least 2 areas of living during the past 6 mo Clinically significant impairment in at least 1 of these areas of living	WHO CIDI, version 3.0, administered by clinical psychologists	Recall bias Adult ADHD was assessed comprehensively only in the clinical reappraisal subsample Semistructured interview is not quite gold standard as SCID	Large sample size Clinical psychologists rated patients
Faraone et al 2006[17]	127; outpatient clinic (26–47 y)	18	DSM-IV–based SCID and modules from K-SADS, administered by trained lay interviewers. Adult ADHD required: Full DSM-IV criteria for ADHD within the 6-mo period before the interview Onset of some symptoms before age 7 y	DSM-IV–based SCID, administered by trained interviewers	Recall bias Trained lay interviewers performed the SCID	Using SCID

Abbreviations: KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia, NCSR = National Comorbidity Survey Replication, SADS = Schedule for Affective Disorders and Schizophrenia, SCID = Structured Clinical Interview for DSM-IV Axis I Disorders, WHO CIDI = World Health Organization Composite International Diagnostic Interview.

Table 3. Comparison of DSM-IV Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder[a]

ADHD	Bipolar Disorder, Mania
Overlapping symptoms	
1. Talks excessively	1. More talkative than usual
2. Easily distracted/jumps from one activity to the next	2. Distractibility or constant changes in activity or plans
3. Difficulty sustaining attention	
4. Fails to give close attention to details/makes careless mistakes	
5. Fidgets	3. Increased activity or physical restlessness
6. Difficulty remaining seated	
7. Runs or climbs about inappropriately	
8. Difficulty engaging in leisure activities quietly	
9. On the go as if driven by a motor	
10. Interrupts or butts in uninvited	4. Loss of normal social inhibitions
11. Blurts out answers before questions have been completed	
12. Difficulty awaiting turns	
Non-overlapping symptoms	
13. Forgetful in daily activities	5. Inflated self-esteem/grandiosity
14. Difficulty organizing tasks and activities	6. Increase in goal-directed activity
15. Loses things	7. Flight of ideas
16. Avoids sustained mental effort	8. Decreased need for sleep
17. Does not seem to listen when spoken to directly	9. Excessive involvement in pleasurable activities with disregard
18. Difficulty following through on instructions/fails to finish work	for potential adverse consequences

[a]Adapted with permission from Kent et al.[19]

second is the overlap of symptoms between ADHD and the manic phase of bipolar disorder (Table 3). For example, talking excessively in ADHD and more talkative than usual in bipolar disorder; or difficulty sustaining attention in ADHD and distractibility or constant changes in activity in bipolar disorder; or fidgeting, difficulty remaining seated, on the go as if driven by a motor in ADHD and increased activity or physical restlessness in bipolar disorder; or interrupting or butting in uninvited, difficulty awaiting turns in ADHD and loss of normal social inhibitions in bipolar disorder.[19] Twelve of eighteen DSM-IV diagnostic criteria for ADHD overlap with the diagnostic criteria for bipolar disorder, manic episode.

The issue of overlap raises the question of whether the diagnosis of adult ADHD is an artifact of symptom overlap with bipolar disorder or vice versa. Only 1 study has evaluated this question.[18] In that study, in 14 adults with comorbid adult ADHD and bipolar disorder, overlap symptoms were assessed by 2 methods: "subtraction" and "proportion." The "subtraction" method removed any overlap symptoms, specifically distractibility, psychomotor agitation, and talkativeness. Excluding those symptoms from the endorsable symptoms for diagnostic criteria, 79% of the ADHD/bipolar disorder subjects retained their ADHD diagnosis, and 64% of the ADHD/bipolar disorder subjects retained their bipolar disorder diagnosis. The "proportion" method was a less stringent way to diagnose bipolar disorder or ADHD after removal of overlapping symptoms. It required that the observed proportion of symptoms in the reduced set of endorsable symptoms be at least as large as the proportion of symptoms required by the original criteria. The "proportion" method led to higher rates of retained diagnosis of these conditions: 86% of adult ADHD and 93% of bipolar disorder.

Three studies[13–15] assessed clinical characteristics of comorbid adult ADHD and bipolar disorder: gender distribution, bipolar subtypes, the type of first episode, and comorbidity with other psychiatric illnesses (Table 4).

Most of the data are driven by 1 large study.[13] Nonetheless, it appears that in adult ADHD/bipolar disorder patients there was a higher percentage of males than females, the bipolar subtype was much more commonly type I, the onset mood episode in bipolar disorder was more likely to be a major depressive episode, and there was a high rate of comorbidity with alcohol and substance dependence as well as with other psychiatric illnesses.

Course of Illness

Three studies[13,14,20] assessed age at onset and severity of illness of comorbid adult ADHD and bipolar disorder. Two studies[13,14] suggested that adult ADHD/bipolar disorder patients had a significantly earlier age at onset of bipolar disorder compared with that of bipolar disorder only patients (mean ± SD = 13.9 ± 7.8 vs. 18 ± 8.6 years).

One study found that adult ADHD/bipolar disorder patients had a much higher likelihood of developing substance addiction in their adolescent years compared with adult ADHD patients or bipolar disorder patients, or non-ADHD/non–bipolar disorder patients (90% vs. 38% vs. 33% vs. 30%, respectively).[20]

With regard to severity of illness, adult ADHD/bipolar disorder patients compared with bipolar disorder patients had significantly more lifetime episodes of mania (41%

Table 4. Clinical Characteristics of Comorbid Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder

Characteristic	Wilens et al 2003[15] (N = 51)	Nierenberg et al 2005[13] (N = 919)	Tamam et al 2006[14] (N = 44)
Gender, %			
Male	75	64.4	29
Female	25	35.6	71
Bipolar subtype, %			
I	12	82.8	100[a]
II	88	13.8	
Other	None	3.5	
Type of first episode, %	Not provided		
Mania		31.0	29
Depression		47.1	71
Mixed		21.8	None
Comorbid condition, %			Not provided
Panic with agoraphobia	Not provided	16.1	
Panic without agoraphobia	18	10.3	
Agoraphobia without panic	23	14.9	
Social phobia	28	35.6	
Generalized anxiety disorder	23	26.7	
Obsessive-compulsive disorder	9	13.8	
Posttraumatic stress disorder	Not provided	28.7	
Alcohol abuse/dependence	72	60.9	
Drug abuse/dependence	37	48.3	
Psychotic disorders	Not provided	3.5	
Bulimia	Not provided	9.2	
Anorexia	Not provided	6.9	
Antisocial personality disorder	41	Not provided	

[a]Only bipolar I disorder patients were included in this study; all other bipolar types were excluded.

vs. 30% with > 20 lifetime episodes of mania, p = .037),[13] more affective episodes (mean ± SD = 7.6 ± 4.2 vs. 3.8 ± 1.6, p = .05),[14] more lifetime history of suicide attempts (46% vs. 33%, p = .022),[13] higher rate of lifetime violence (40% vs. 19%, p < .0001),[13] and higher rate of legal problems (42% vs. 22%, p = .00007).[13]

Heredity

Two studies[21,22] examined familial transmission of comorbid ADHD and bipolar disorder, ADHD only, and bipolar disorder only. The studies had similar design and sample size, except that the first study[21] included both boy and girl probands and the second study included only girl probands. First-degree relatives (parents and siblings) and probands were directly interviewed with the Structured Clinical Interview for DSM-III-R. Controls were probands without ADHD or bipolar disorder. The first study[21] found that probands with ADHD/bipolar disorder had a significantly elevated risk of having relatives with ADHD/bipolar disorder (risk ratio [RR] = 14.2; 95% CI = 7.6 to 26.7) or relatives with ADHD alone (RR = 3.5; 95% CI = 1.3 to 8.9), but similar risks of having relatives with bipolar disorder alone (RR = 2.1; 95% CI = 0.6 to 8.1), compared with controls. The second study[22] found that ADHD/bipolar disorder probands had a significantly elevated risk of having relatives with ADHD/bipolar disorder (RR = 5.5; 95% CI = 2.1 to 14.3), relatives with ADHD alone (RR = 3.6; 95% CI = 1.4 to 9.0), or relatives with bipolar disorder alone (RR = 3.2; 95% CI = 1.1 to 9.4), compared with controls.

Biological Markers

No study on biological markers of comorbid adult ADHD and bipolar disorder has been done.

Treatment

One open, nonrandomized, 6-week trial using bupropion to treat ADHD in 30 adults with comorbid adult ADHD and bipolar disorder addressed treatment response.[23] The subjects (10% bipolar I disorder and 90% bipolar II disorder) were required to be "stable" on their "antimanic agents" (defined as mood stabilizers or antipsychotics or a combination of both) for at least 4 weeks and to continue with their existing mood-stabilizing regimen to be entered into this trial. The definition of *stable mood* at baseline was not given. At endpoint, 82% of the subjects had improvement in ADHD symptoms, which was defined as a reduction in the ADHD symptom checklist scale score of 30% or more, without concurrent mania. One subject dropped out of the study at week 2 due to hypomanic activation. There were also significant reductions in both manic and depressive symptoms at endpoint based on the Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HAM-D-21). The mean ± SD YMRS scores at baseline and endpoint were 8.0 ± 5.9 and 3.4 ± 4.4, respectively, p < .001. The HAM-D-21 scores at baseline and end point were 10.6 ± 7.7 and 4.6 ± 5.7, respectively, p < .001.

DISCUSSION

Comorbid adult ADHD and bipolar disorder has been insufficiently studied, with relatively more emphasis on comorbidity rates and few data on course, neurobiology, heredity, and treatment.

Studies of comorbidity rates of adult ADHD in bipolar disorder patients had relatively large sample sizes, yielding a narrower range of comorbidity rates (9.5%–21.2%). Studies of comorbidity rates of bipolar disorder in adult ADHD patients had relatively small sample sizes and yielded a wider range of rates (5.1%–47.1%). With adult ADHD having its own range of prevalence rates (1.5%–4.4%),[1,3,5] it is not unexpected to have a wide range of comorbidity rates of adult ADHD and bipolar disorder in the adult ADHD samples. Furthermore, these comorbidity rates should be interpreted with caution since the sample population (clinically-referred versus epidemiologic) as well as the diagnostic criteria for adult ADHD varied across studies.

Regarding the issue of symptom overlap, the only study[18] to assess it did not address the redundancy inherent in the diagnostic criteria of ADHD, allowing this diagnosis to be made more easily than bipolar disorder when 3 overlapping criteria were removed. Hence, the possibility of adult ADHD as an artifact of symptom overlap with bipolar disorder cannot be ruled out. Furthermore, it is our conjecture that symptom overlap within the ADHD diagnostic criteria may inflate the prevalence rate of ADHD and thus the rate of coexisting ADHD and bipolar disorder. This matter needs to be addressed in future empirical studies.

Phenomenologically, patients with comorbid adult ADHD and bipolar disorder had bipolar I disorder much more frequently than bipolar II, and high rates of comorbidity with other psychiatric illnesses (Table 4), suggesting a greater severity of illness, which is consistent with a true comorbidity.

Course-of-illness characteristics assessed in 3 studies[13,14,20] also provided evidence of increased illness severity in the adult ADHD/bipolar disorder patients compared with patients with bipolar disorder alone, again supportive of the comorbidity concept. The features of earlier onset of bipolar disorder, greater number of lifetime affective episodes, increased risks of suicide attempts, violence, and legal problems strikingly resemble those of patients with combined bipolar disorder and substance use disorder.[24–27] Furthermore, 90% of adult ADHD/bipolar disorder patients were found to develop substance use disorder in their adolescent years compared with only 33% of bipolar disorder patients, 38% of ADHD patients, and 30% of controls, in the one and only study on this topic.[20] This finding raises the possibility that a subgroup of patients with bipolar disorder have some characteristics that render them susceptible to both ADHD and substance use and a more severe course of illness. Stimulant exposure during teenage years has been speculated to be potentially one of these factors based on 2 studies in the pediatric bipolar population. One study[28] found that bipolar adolescents with a history of stimulant exposure prior to their onset of bipolar disorder had an earlier age at onset of bipolar disorder compared with those without prior stimulant exposure, even after comorbid ADHD was controlled for, and that there was no difference in age at onset of bipolar disorder between bipolar adolescents with and without ADHD. The authors suggested that stimulant exposure and not ADHD may lead to an earlier onset of bipolar disorder. The other study of the pediatric bipolar population[29] found that stimulant-exposed adolescents with bipolar disorder had a more severe hospital course that was not fully explained by ADHD comorbidity. Future studies are needed to compare the course of illness of bipolar disorder patients with stimulant exposure in their youth to that of bipolar disorder patients without stimulant exposure in their youth to clarify the effects of stimulant exposure in bipolar disorder course.

Results from the first family study[21] suggest that ADHD/bipolar disorder is an ADHD subtype, since there was no elevated risk of bipolar disorder in relatives. However, a closer look at the 95% confidence interval of the relative risk of having relatives with bipolar disorder in probands versus controls (RR = 2.1; 95% CI = 0.6 to 8.1) reveals a moderate to high likelihood of an elevated risk in probands, making the results from the first study also likely consistent with a comorbidity. Elevated risks of having relatives with ADHD/bipolar disorder, with ADHD, and with bipolar disorder in probands compared with controls in the second study[22] also suggested the comorbidity concept. Neither study specified whether ADHD diagnosis in the relatives meant childhood or adult ADHD or both.

In the treatment trial,[23] the subjects were required to have "stable" mood for at least 4 weeks before they could enter the trial. However, the definition of *stable mood* was not provided. The simultaneous improvement of manic symptoms (reflected by the reduction in the YMRS score) and ADHD symptoms in response to bupropion may have been the result of improvement of symptoms that overlap between mania and ADHD. The reduction in the HAM-D score reflects the antidepressant effect of bupropion on subsyndromal depression. The main problem with interpreting this study is that the subjects' response to bupropion treatment as a function of baseline mood severity was not addressed. If mood symptoms had remained unchanged but ADHD symptoms improved, then the study might have been interpretable as suggestive of the concept of ADHD and bipolar disorder comorbidity (i.e., ADHD symptoms would be independent of bipolar disorder symptoms.) However, the results reflect improvement of both manic and depressive mood symptoms, along with ADHD symptoms, thus not directly supporting the comorbidity concept any more than the possibility of a bipolar disorder or ADHD subtype. Results of this treatment trial should be viewed in light of its methodological limitations as an open, non-randomized study, with inclusion of milder cases of bipolar disorder (90% of subjects had bipolar II disorder), and relatively short treatment duration.

With regard to treatment strategy, a systematic chart review of the pediatric patients with comorbid ADHD and bipolar disorder suggested that mood stabilization is a prerequisite for successful pharmacologic treatment of ADHD in children with both ADHD and manic symptoms.[30] In the only treatment trial of adult ADHD/bipolar disorder patients,[23] patients were required to have stable mood for at least 4 weeks and to continue with their mood stabilizing regimen before they were treated with bupropion for ADHD symptoms.

Finally, it is generally agreed that association should not be interpreted as causation, which requires a con-

Table 5. Summary of Diagnostic Validation of Coexisting Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder

Diagnostic Concept	Phenomenology (4 studies)	Course of Illness (3 studies)	Heredity (2 studies)	Biological Markers (no studies)	Treatment Response (1 study)[a]
Comorbidity	Equivocal (1 study)[b]; yes (3 studies)[c]	Yes (3 studies)[d]	Yes (1 study)[e]; likely (1 study)[f]	No data	Equivocal
ADHD subtype	No	No	Yes (1 study)[g]	No data	Equivocal
Bipolar disorder subtype	No	No	No	No data	Equivocal
A new disease entity	No	No	No	No data	Equivocal

[a]Treatment study[23] showing improvement of ADHD and mood symptoms.
[b]Study on symptom overlap.[19]
[c]Phenomenology studies[13–15] suggesting increased disease severity, manifested by a predominance of bipolar I disorder and high rates of comorbidity with other psychiatric illnesses.
[d]Course-of-illness studies[13,14,20] showing increased disease severity, as reflected by higher rates of suicide attempts, legal problems, and violence; more lifetime affective episodes; and higher risks of having substance addiction in adolescent years.
[e]Faraone et al. 2001 family study[22] showing probands having elevated risks of relatives with ADHD/bipolar disorder or ADHD or bipolar disorder compared with controls.
[f]Faraone et al. 1997 family study[21] showing probands having elevated risks of relatives with ADHD/bipolar disorder or ADHD, or bipolar disorder (likely when examining 95% confidence interval) compared with controls.
[g]Farone et al. 1997 family study[21] showing probands having elevated risks of relatives with ADHD/bipolar disorder or ADHD, but not with bipolar disorder, compared with controls.

fluence of different lines of evidence, as explained in Hill's classic epidemiologic paper.[31] The facets of an association examined by Hill included strength, consistency (i.e., whether it has been repeatedly observed by different persons in different places, circumstances, and time), and specificity, among others. Although the strength of the association of adult ADHD and bipolar disorder comorbidity based on comorbidity rate studies is at least moderate, other aspects of this literature poorly meet Hill's criteria for causality. The genetic studies have not been replicated by other research groups, nor has the single treatment study. The phenomenology data do not establish specificity since the question of symptom overlap has not been resolved. As seen in the summary table (Table 5), with such insufficient and relatively equivocal data, it is presently unclear whether coexisting adult ADHD and bipolar disorder is a true comorbidity or a broad manifestation of emotional and cognitive symptoms that could be a subtype of bipolar disorder or a subtype of ADHD. More research is greatly needed to clarify the diagnostic validity and treatment approach to this proposed comorbid syndrome.

Drug name: bupropion (Wellbutrin and others).

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