Eur Arch Psychiatry Clin Neurosci (2008) 258:385–393 DOI 10.1007/s00406-008-0807-x

ORIGINAL PAPER

Lut Tamam · Gonca Karakus · Nurgul Ozpoyraz

Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates

Received: 15 June 2007 / Accepted: 16 January 2008 / Published online: 24 April 2008

Abstract The aim of this study was to determine the frequency of adult attention deficit hyperactivity disorder (ADHD) comorbidity with lifetime bipolar disorder, and the influence of this comorbidity on various demographic and clinical variables in patients. Patients (n = 159) with a previous diagnosis of bipolar disorder (79 female, 80 male) were included in this study. All patients were interviewed for the presence of current adult and childhood ADHD diagnosis and other axis I psychiatric disorder comorbidities using the structured clinical interview for DSM-IV (SCID) and the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime Version (K-SADS-PL). The subjects also completed a Wender Utah rating scale (WURS-25) and a Current Symptoms Scale for ADHD symptoms. In particular, patients' clinical characteristics, the age of onset of bipolar disorder, and the number of episodes were noted. Twenty-six of the 159 bipolar patients (16.3%) were diagnosed with adult ADHD, while another subgroup of patients (n = 17, 10.7%) received a diagnosis of childhood ADHD but did not fulfill criteria for adult ADHD. Both of these two subgroups (patients with adult ADHD, and patients with only childhood ADHD) had an earlier age of onset of the disease and a higher number of previous total affective or depressive episodes than those without any lifetime ADHD comorbidity. However only bipolar patients with adult ADHD comorbidity had higher lifetime comorbidity rates for axis I psychiatric disorders, such as panic disorder and alcohol abuse/dependence, compared to patients without lifetime ADHD. Bipolar patients with comorbid adult ADHD did not differ from bipolar patients with comorbid childhood ADHD in terms of any demographic or clinical variables except for adult ADHD scale scores. In conclusion, ADHD is a common comorbidity in bipolar patients, and it adversely affects the course of the disease and disrupts the social adjustment of the patients. Regular monitoring of ADHD will help to prevent problems and complications that could arise in the course of the disease, particularly in patients with early onset bipolar disorder.

Key words attention deficit hyperactivity disorder (ADHD) · bipolar disorder · comorbidity · adult ADHD · childhood ADHD · prevalence

L. Tamam, MD · G. Karakus · N. Ozpoyraz
Department of Psychiatry
Cukurova University Faculty of Medicine
Adana, Turkey

L. Tamam, MD (✉)
Department of Psychiatry
Cukurova University Faculty of Medicine
01330 Adana, Turkey
Tel.: +90-533/630-6006
E-Mail: ltamam@yahoo.com

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders, with prevalence rates ranging from 3 to 9% depending on the sampling group and diagnostic criteria [19, 22]. Prospective studies have shown that an average of 50% of children with ADHD continue to meet criteria for ADHD after reaching adulthood, which corresponds to a 4–5% prevalence rate for adult ADHD in the community [21, 38, 42].

A possible association between ADHD and the manic phase of bipolar disorder has attracted significant interest because the symptoms of both disorders are so similar across all age groups: talkativeness, distractibility, and increased motor activity [33, 39, 43]. Several studies among children and adolescents with bipolar disorder report prevalence rates of comorbid ADHD ranging from 38 to 98% [15, 26, 39, 44]. In patients with bipolar disorder, the rate of

ADHD comorbidity decreases steadily as the studied population grows older [9]. This rate is as high as 98% in a pre-pubertal manic group [44], around 70% in early adolescence [39], and 30% in late adolescence [15]. The rate of ADHD comorbidity in adults is even lower, ranging from 9 to 35% [33]. In a recent review, Wilens and Dodson [42] reported an approximate rate of 15% of ADHD comorbidity in adult bipolar patients, a rate lower than that for younger bipolar patients but much higher than the average (4–5%) estimated for the general population [20].

Bipolar patients with comorbid ADHD are reported to have higher affective dysregulation, earlier onset of the disease, more depressive and mixed periods, shorter inter-episode euthymic periods, and more frequent accompanying disorders, like alcohol and substance abuse, than patients without comorbid ADHD [29, 33, 36]. Moreover, in a recent study [34], investigators report that adult bipolar patients with a history of childhood ADHD demonstrated an attenuated response to pharmacotherapy with mood stabilizers, indicating the possible unfavorable effect of ADHD on the course of bipolar disorder. Some authors have suggested that ADHD and mania may be independent disorders, and that the comorbid condition may represent a distinct clinical phenotype of bipolar disorder featuring earlier age of onset, poorer response to treatment, and poorer prognosis [12, 40]. In particular, the age of onset was proposed to be the critical developmental variable identifying a subtype of bipolar disorder highly comorbid with ADHD [26]. Noting the predominantly chronic course and the irritable mood common to bipolar disorder and childhood ADHD, Masi et al. [26] suggested that this specific phenotype might be indicative of a symptomatological continuity between ADHD and early onset bipolar disorder.

Understanding the relationship between ADHD and bipolar disorder has been made difficult by the use of different diagnostic criteria, such as the Utah and DSM criteria, the lack of a standardized semi-structured interview procedure, and problems in obtaining third-party corroboration for childhood ADHD. It has also been made difficult because of sampling limitations in previous studies, such as the inclusion of too few cases in a cohort, the inclusion of patients in the acute phase of bipolar disorder, or the inclusion of cases of only one gender. More studies that analyze a larger group of bipolar patients and that overcome most of the methodological problems of previous investigations are still required in order to identify the distinguishing clinical and phenomenological features of these comorbid cases. This would clearly help to determine whether there is a relationship between ADHD and bipolar disorder, and to define the nature of that relationship.

In an effort to contribute to this controversial issue, we have conducted a study among a relatively large group of bipolar patients who were followed up in a university research hospital. We have tried to avoid several of the methodological limitations of previous studies described above. The aims of the present study were to evaluate the prevalence rate and possible clinical implications of adult ADHD comorbidity on clinical and demographic features of bipolar patients and on the course of bipolar disorder.

Methods

Study setting and subjects

The sample included 159 consecutive adult patients (79 female, 80 male) aged between 18 and 65 years who were recruited from regular attendees of the outpatient clinic of the Bipolar Disorder Unit of the Department of Psychiatry, Cukurova University Medical School. The study was carried out between September 2004 and January 2007. The Hospital of Cukurova University Medical School is a hospital located in Adana, in the south of Turkey, and serves a population of 3 million, including surrounding provinces.

Patients included in the study had already received a diagnosis of bipolar disorder [bipolar I, bipolar II, bipolar NOS (not otherwise specified)] according to DSM-IV-TR [2] and were symptomatically in remission (Young Mania Rating scale score <12, Hamilton Depression Scale score <8) as determined during the last month before the study. Excluded from the study were those potential subjects who showed confusion, agitation, or any cognitive disorder such as delirium or dementia at the time of assessment, who were unable to cooperate for the psychiatric interview and other assessments, or who did not give written consent to participate in the study.

Of 181 patients approached, 12 were excluded from the study as they were not in remission in the last month, and another 10 did not give informed consent to participate in the study, resulting in a sample size of 159. After the approval of the study by the institutional review board, written informed consent was obtained from all participants. All patients included in the study were on mood stabilizer treatment at the time of inclusion, either as monotherapy or as combination therapy. Of 159 patients included in the study, 122 (77%) were on lithium monotherapy or lithium combination therapy: 75 were on lithium monotherapy, 24 on lithium and valproate combined therapy, 12 on lithium and carbamazepine therapy, 7 on triple therapy (lithium, valproate, carbamazepine), and 4 on lithium and lamotrigine therapy. Moreover, 24 (15%) and 13 (8%) of the patients, respectively, were on valproate and carbamazepine monotherapy . In addition to mood stabilizer treatment, 36 patients were taking long-term atypical antipsychotic treatments to augment mood-stabilizing activity: 21 were on olanzapine, eight on risperidone, and seven on quetiapine.

Procedures and assessment instruments

Patient assessment took place in two phases: an initial 1/2 h of testing, followed by 2–2.5 h of diagnostic and clinical interview by a staff psychiatrist. In the initial phase lasting approximately 1/2 h, patients completed two self-report questionnaires: Turkish versions of the current symptoms scale (CSS) [3] and the Wender Utah rating scale (WURS-25) [30], which allowed quantitative evaluation of current and childhood ADHD symptoms, respectively. Following testing, detailed psychiatric, diagnostic, and clinical interviews lasting approximately 2–2.5 h were conducted by a second author (G.K.), who is a certified staff psychiatrist working in our bipolar disorder unit and who was blind to the study hypotheses at the time of the interviews. The results of psychometric tests were provided to the psychiatrist at the time of interview, but used only as supplementary material for making the final diagnosis. In the case of discrepancy between the scales and

the interview findings, the psychiatric interview was repeated by two different physicians (G.K. and L.T.) to reach a consensus on the final diagnosis.

As indicated above, patients were asked before the diagnostic interview to complete the Turkish version of the CSS [3], an adult ADHD screening test serving as an auxiliary test to determine current ADHD symptoms. Originally developed by Barkley and Murphy [4], the CSS is an 18-item self-report screening measure for adult ADHD that provides three scores reflecting DSM-IV [2] diagnostic criteria for (1) ADHD, predominantly hyperactive-impulsive type; (2) ADHD, predominantly inattentive type; and (3) ADHD, combined type. The normative data for the Turkish version of the CSS has been reported by Aycicegi et al. [3]. This version demonstrated acceptable levels of internal consistency (Cronbach's alpha coefficient for total score 0.78) and excellent test-retest reliability (for total score 0.82) [3]. Total CSS and subscale scores were highly correlated with the corresponding number of fulfilled DSM-IV criteria (for total, $r = 0.956$, $P < 0.001$; for hyperactivity-impulsivity, $r = 0.945$, $P < 0.001$; for inattention, $r = 0.903$, $P < 0.001$).

The Turkish version of the WURS-25 [30], a 25-item self-report scale, was also administered to all subjects to evaluate childhood ADHD symptoms retrospectively. WURS-25 is based on the Utah criteria, which were developed to diagnose ADHD in adults [37]. The Turkish version of the WURS has been found to be a reliable and valid scale for assessing childhood symptoms of ADHD in adults. In the Turkish version of WURS, the cut-off point was taken as 36 or more, which could correctly classify 82.5% of adults with ADHD (sensitivity) and 90.8% of controls (specificity) [30]. The total WURS-25 score was taken into account during assessments.

After the testing, all patients were subjected to the Turkish version of the structured clinical interview for DSM-IV (SCID-I) [31] to confirm the diagnosis of bipolar disorder and to diagnose other comorbid axis I disorders. The SCID-I examines both current and lifetime axis I psychiatric disorders according to DSM-IV [14]. In the current study, we presented both the lifetime and current prevalence rates for axis I disorders according to SCID-I. For diagnosis of bipolar disorder (BD), patients must have had at least one full manic, hypomanic, or mixed episode not attributable exclusively to substance abuse, medical disorders, or other psychiatric illness. To prevent confounding factors that arise during the active phase of BD, such as the inability to cooperate with the interviewer, increased deficits in cognitive functioning or memory recall due to illness or use of antipsychotics, only patients in remission during the last month were included. Along with the SCID-I interview, a detailed psychiatric interview was conducted to obtain further information regarding course of the illness, sociodemographic features, and familial and medical history. Clinical data collected included age of onset of the disorder, frequency and type of affective episodes, number of hospitalizations, type of the first episode, and the presence of seasonal and psychotic patterns in the affective episodes. Patient hospital records, containing such information as hospital admissions, life charts, and follow-up notes, were examined to establish the time of past affective episodes and to search for a seasonal pattern in the episodes.

Patients were also assessed for the presence of childhood/adolescence or adulthood ADHD according to DSM-IV diagnostic criteria [2]. To reach a full diagnosis of adult ADHD, the following diagnostic criteria were used: (1) presence of at least six attention deficit diagnostic criteria in the DSM-IV, presence of at least six hyperactivity/impulsivity diagnostic criteria during the last six-month period, or presence of both of these sets of criteria; (2) full DSM-IV diagnosis of childhood ADHD by the age of seven; (3) chronic course of ADHD symptomatology from childhood into adulthood not due to manic episodes; (4) some level of impairment in various functionality areas due to ADHD symptoms, such as at school, work, home and with family and friends; (5) manifestation of all symptoms of ADHD independently of any bipolar episode within the last month. The presence of current DSM diagnostic criteria for ADHD in the patients was determined by interrogating each criterion one by one. The number of diagnostic criteria fulfilled by the patients who met adult ADHD diagnosis and the subgroup they fit in were also evaluated.

The Turkish version of the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime Version (K-SADS-PL) [16], together with questions in the supplemental module on behavioral disorders, were used to confirm the diagnosis of childhood ADHD in the subjects. The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria [18]. The validity and reliability study of the Turkish version of this interview has been conducted by Gokler et al. [16]. The presence of childhood ADHD was investigated in these patients by using screening questions included in the second part of this form (section entitled "diagnostic screening interview"), as well as questions in the supplemental module on behavioral disorders. The evaluation of childhood ADHD diagnosis, which is a prerequisite for adult ADHD, was based on the history and information given by the patients and confirmed by the Turkish version of the KSADS-PL behavioral disorders module. In addition, a total score on the Turkish version of the WURS-25 of 36 or higher was used as an aid to confirm the diagnosis of childhood ADHD. Throughout the study, information supplied by the patients was checked with other accessible sources, such as living parents or siblings, spouses, and medical files. It was not possible to access the school records of the patients diagnosed with adult ADHD, so we were unable to use this to verify prior diagnoses and case histories.

Statistical analysis

Descriptive statistical analyses were carried out for the evaluation of demographic and clinical characteristics of the entire group. The sample was divided into three independent groups in the statistical analyses. The first group contained patients without any diagnosis of lifetime ADHD (BD). The other two groups included either patients with comorbid diagnosis of adult ADHD (ADHD-BD), or patients who received a diagnosis of childhood ADHD but did not meet the diagnosis of adult ADHD (cADHD-BD). Mixed, hypomanic, and manic episodes were considered together as manic episodes in comparison analyses, because of the small number of cases in each group. The similarly small number of patients with bipolar II and bipolar NOS cases prevented us from comparing these subgroup results with the larger number of bipolar I cases. Statistical evaluation of the age of onset of bipolar disorder was performed after defining those patients with disease onset before 18 years of age as "early onset," and those with disease onset at or after 18 as "late onset."

For all binary comparisons of categorical variables, either the chi square test or Fisher's exact test was used; the latter was employed when the number of cells with an expected value exceeded 25% of all cells. Comparisons of categories with three or more levels were performed using χ^2 analyses, and 2×2 categorical comparisons for follow-up testing of significant effects was done by chi square tests or Fisher's exact test when necessary. Because the numbers of cases included in the groups were unequal, and the assumptions for parametric testing (normal distribution of values, homogeneity of variances) were violated, Kruskal Wallis non-parametric one-way ANOVAs with a Bonferroni-corrected nominal significance level ($P < 0.017$) were performed for comparing continuous variables in the three independent groups. When the three-group comparison was significant, Mann–Whitney U tests with a Bonferroni-corrected significance level were applied to pairwise comparisons between groups in order to identify the source of the significance.

Logistic regression analyses adjusted for gender and age of onset were conducted separately for comorbid axis I psychiatric disorders that showed significance in univariate analyses. In logistic regression analyses, adult ADHD was taken to be the dependent variable and comorbid disorders as independent variables. For these analyses, the odds ratio (OR) and 95% confidence intervals (CI) are given. All p values were two-tailed, and statistical significance was set as $P < 0.05$. As indicated above, Bonferroni corrections for statistical significance were applied where necessary.

Results

Demographic and diagnostic features

Mean age of the 159 patients (79 female, 80 male) included in the study at the time of evaluation was 33.7 (±10.3) years (range: 18–65 years). The proportion of patients in the whole group diagnosed as bipolar I, bipolar II, and bipolar NOS were 92% (n = 146), 6% (n = 10), and 2% (n = 3), respectively. For the entire group, the mean age of onset of bipolar disorder was 24.5 (±8.4) years, and 27% of cases (n = 44) had early onset bipolar disorder, while the rest of the group (n = 115; 73%) had late onset bipolar disorder. The first affective episode was mania in 59% of the entire group, depression in 34%, hypomania in 4%, and a mixed episode in 3%. The dominant affective episode type was manic or depressive, respectively, in 111 (70%) and 24 (15%) of bipolar patients. The number of depressive and manic episodes was equal among the remaining patients.

Twenty-six of 159 patients with bipolar disorder (16.3%; 95% CI: 10.5–22%) included in the present study met the diagnostic criteria for full current adult ADHD. Of the 26 bipolar patients with adult ADHD (15 female, 11 male), seven fulfilled the DSM-IV criteria for attention deficit subtype; 13, the criteria for hyperactive subtype; and six, for mixed subtype . Apart from these 26 patients, 17 patients (6 female, 11 male) (10.7%; 95% CI: 5.7–15.7%) received a diagnosis of childhood ADHD, although they did not meet adult ADHD criteria. Among all patients, 43 (27%; 95% CI: 20.1–33.9%) met the criteria for lifetime ADHD diagnosis. As stated in the Methods section, the sample was divided into three independent subgroups: the ADHD-BD group (n = 26) included bipolar patients with comorbid adult ADHD, the cADHD-BD group (n = 17) included bipolar patients who had a diagnosis of childhood ADHD but did not meet the full criteria of adult ADHD, and the BD group (n = 116) included those as patients without any lifetime ADHD diagnosis. All subsequent analyses were based on these three subgroups.

The three subgroups in the sample did not show any significant differences with regard to the main demographic features of gender, current age, marital status, and duration of education (Table 1). Moreover, these three subgroups did not differ in terms of BD subtype, as the majority of them were composed of bipolar patients: 93% (n = 24) for ADHD-BD, 94% (n = 16) for cADHD-BD, and 91% (n = 106) for BD subgroups.

Clinical features

As presented in Table 1, the ADHD-BD and cADHD-BD groups were more likely to have an earlier age of onset and a higher number of early-onset cases (age of onset <18 years) than the BD group. The ADHD-BD group had a slightly higher number of early-onset cases than the c-ADHD group, though this difference did not reach statistical significance. Compared with the BD group, both the ADHD-BD and cADHD-BD subgroups had a statistically higher number of past

Table 1 Clinical and sociodemographic characteristics of BD with and without adult ADHD comorbidity

	ADHD-BD (n = 26)	cADHD-BD (n = 17)	BD (n = 116)	χ^2	P	Post-hoc pairwise comparison
Gender, n (%)						
Male	11 (42)	11 (65)	58 (50)	2.08	0.353	NS
Female	15 (58)	6 (35)	58 (50)			
Marital status (single), n (%)	16 (62)	8 (47)	62 (53)	0.939	0.625	NS
Duration of education (years), mean (SD)	11.7 (4.4)	12.8 (2.8)	12.7 (3.6)	2.26[a]	0.322	NS
Current age (years), mean (SD)	31.5 (7.5)	37.2 (10.2)	33.8 (10.5)	1.12[a]	0.571	NS
Age at onset of BD (years), (mean (SD))	17.6 (3.2)	19.8 (5.8)	25.7 (8.9)	32.7[a]	$P < 0.0001$	1 > 3, 2 > 3
Early onset BD (<18), n (%)	17 (65)	9 (53)	18 (15)	32.46	$P < 0.0001$	1 > 3, 2 > 3
Late onset BD (≥18), n (%)	9 (35)	8 (47)	98 (85)			
Number of hospitalizations, mean (SD)	2.6 (2.2)	3.2 (2.9)	1.9 (1.7)	3.12 [a]	0.211	NS
Total number of episodes, mean (SD)	6.7 (3.1)	6.0 (3.5)	3.9 (3.2)	28.9	$P < 0.0001$	1 > 3, 2 > 3
Manic episode	2.8 (2.1)	2.7 (2.3)	2.3 (1.8)	1.29	0.524	NS
Depressive episode	2.9 (2.1)	2.5 (2.6)	1.2 (1.8)	38.8[a]	$P < 0.0001$	1 > 3, 2 > 3[b]
Hypomanic episode	0.7 (0.9)	0.5 (0.9)	0.3 (0.8)	7.44[a]	0.024[c]	NS[c]
Mixed episode	0.3 (0.6)	0.3 (0.7)	0.1 (0.4)	2.78[a]	0.249	NS
Type of first affective episode, n (%)						
Manic episode	16 (62)	11 (65)	78 (67)	0.323	0.851	NS
Depressive episode	10 (38)	6 (35)	38 (33)			
Suicidal attempt n (%)	7 (27)	6 (35)	22 (19)	2.74	0.254	NS
Seasonality n (%)	20 (77)	12 (71)	65 (56)	4.63	0.099	NS
Psychotic features n (%)	16 (62)	11 (65)	75 (65)	0.092	0.955	NS

cADHD childhood attention deficit hyperactivity disorder, *ADHD* attention deficit hyperactivity disorder, *BD* bipolar disorder, *SD* standard deviation; *NS* non significant
[a]Kruskal Wallis test
[b]Mann Whitney U test
[c]Nonsignificant after Bonferroni correction

total affective and depressive episodes ($P < 0.001$). The difference in the number of other prior episode types (i.e. mania, hypomania, mixed) was not significant. There was a significant trend for the frequency of hypomanic episodes in a three-group comparison ($P = 0.024$), but this trend disappeared after imposing a Bonferroni correction of the P value to 0.017 in order to avoid statistical error. Nevertheless, pairwise comparison of the ADHD-BD and BD groups showed that ADHD-BD had a higher number of past hypomanic episodes than BD. ADHD-BD had a slightly higher mean number of episodes than cADHD-BD for all episode types, although this difference in mean number did not reach statistical significance for any episode type.

The three subgroups did not show any significant differences in the type of first affective episode, frequency of hospitalization, suicidality, seasonal or psychotic features ($P > 0.05$). Sociodemographic and clinical characteristics of the ADHD-BD and BD groups are presented in Table 1.

Axis I psychiatric comorbidities and scales

There were no differences in prevalence rates for lifetime and current axis I psychiatric comorbidities in pairwise comparisons between the ADHD-BD and cADHD-BD groups, or between the cADHD-BD and BD groups. There were also no significant differences in current prevalence of comorbid axis I disorders between the ADHD-BD and BD groups. The only significant difference in axis I psychiatric comorbidities between groups was lifetime prevalence between the ADHD-BD and BD groups. The ADHD-BD group had a higher number of patients with lifetime axis I psychiatric disorders than the BD group, as determined by SCID-I (81, 42% respectively, $\chi^2 = 12.61$, $P < 0.0001$). In addition, pairwise comparison showed that the ADHD-BD group had a significantly higher proportion of patients with at least one lifetime anxiety disorder than the BD group (65 vs. 41%, $\chi^2 = 12.61$ $P = 0.021$); no such difference was observed in the ANOVA three-group comparison ($P = 0.059$, Table 2).

No significant difference between the ADHD-BD and BD groups ($P > 0.05$) in the lifetime and current prevalence rates of various disorders was found. The disorders examined were generalized anxiety disorder, social phobia, specific phobia, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), somatoform disorder, eating disorder, panic disorder, and alcohol dependence/abuse. In univariate analyses, however, the ADHD-BD group showed significantly higher prevalence rates for lifetime panic disorder (35 vs. 10%, $P = 0.003$) and alcohol dependence/abuse (27 vs. 7%, $P = 0.009$) than the BD group. Logistic regression analyses, completed separately for these significant comorbid conditions and adjusted for age of onset, revealed that the lifetime prevalence rates for these two disorders were still significantly higher (for panic disorder adjusted OR: 5.9, 95% CI:1.85–19.04; for alcohol dependence/abuse, adjusted OR: 6.11, 95% CI: 1.6–22.3).

As expected, the mean number of fulfilled ADHD diagnostic criteria and the CSS scores were significantly higher in the ADHD-BD group than in the other two groups. Furthermore, the CSS scores and the mean number of fulfilled ADHD criteria were significantly higher in the cADHD-BD group than in the BD group ($P < 0.0001$). WURS-25 scores, which are indicative of childhood ADHD, were significantly higher in the ADHD-BD and cADHD-BD groups than in the BD group, though the ADHD-BD and cADHD-BD scores were not significantly different from each other.

Lifetime axis I psychiatric disorder comorbidities, the mean total scale scores, and the mean number of diagnostic criteria fulfilled for all groups are shown in Table 2.

Discussion

Our findings showed that 27% of patients with bipolar disorder included in this study had a lifetime diagnosis of ADHD, whereas 16% met the full criteria for current adult ADHD. Patients with current adult ADHD diagnosis (ADHD-BD) and patients with a prior childhood ADHD comorbidity (cADHD-BD) showed an earlier age of onset for bipolar disorder and a higher number of total and depressive episodes than the BD group. These two groups (ADHD-BD and cADHD-BD) did not differ from each other with regards to sociodemographic or clinical variables, as shown in Table 1. There was no difference between cADHD-BD and other groups in terms of psychiatric comorbidity. The ADHD-BD group, however, had significantly higher lifetime (but not current) prevalence rates for axis I disorders, anxiety disorders, panic disorder, and alcohol abuse/dependence than patients without adult ADHD.

The adult ADHD prevalence rate of 16% in the current study was much higher than the rates previously reported for the general population (1–6%) [20]. On the other hand, this rate of adult ADHD comorbidity among bipolar patients is quite consistent with the rate of 15% reported more recently [36, 42]. Though the lifetime ADHD rate of 27% in the current study is higher than the rate of 9.5% reported in a recent large study [29], it is quite comparable to rates reported in a pioneering study by Winokur et al. (21.3%) [43], and in a recent study conducted on clinically referred bipolar adults (22.5%) [17]. All of these findings support the idea that childhood and adult ADHD prevalence rates are higher in patients with bipolar disorder than in the general population.

The results of this study corroborate prior findings documenting a strong association between age of

Table 2 Psychiatric comorbid axis I disorders and scale scores of BD patients with and without adult ADHD comorbidity

N (%)	ADHD-BD (*n* = 26)	cADHD-BD (*n* = 17)	BD (*n* = 116)	χ^2	*P*	Post-hoc pairwise comparison
At least one axis I disorder						
Current	16 (62)	7 (41)	44 (38)	4.86	0.088	NS
Lifetime	21 (81)	10 (59)	49 (42)	13.1	<0.001	1 > 3[a]
At least one anxiety disorder						
Current	13 (50)	6 (36)	43 (37)	1.60	0.449	NS
Lifetime	17 (65)	9 (53)	47 (41)	5.67	0.059	1 > 3[a]
GAD						
Current	1 (4)	0 (0)	6 (5)	0.965	0.617	NS
Lifetime	4 (15)	2 (12)	14 (12)	0.224	0.894	NS
Panic disorder						
Current	5 (20)	2 (12)	9 (8)	3.14	0.207	NS
Lifetime	9 (35)	4 (24)	11 (10)	11.5	0.003	1 > 3[a]
Social phobia						
Current	5 (20)	0 (0)	15 (10)	3.50	0.148	NS
Lifetime	7 (27)	1 (6)	23 (20)	5.14	0.077	NS
Specific phobia						
Current	4 (15)	1 (6)	8 (7)	2.17	0.337	NS
Lifetime	5 (20)	3 (18)	9 (8)	3.89	0.143	NS
OCD						
Current	7 (27)	3 (18)	23 (20)	0.76	0.683	NS
Lifetime	8 (31)	3 (18)	26 (22)	1.16	0.558	NS
PTSD						
Current	1 (4)	0 (0)	1 (1)	1.77	0.414	NS
Lifetime	3 (12)	2 (12)	5 (4)	2.85	0.240	NS
Somatoform disorder						
Current	2 (8)	1 (6)	5 (4)	0.54	0.764	NS
Lifetime	4 (15)	3 (18)	7 (6)	4.17	0.125	NS
Eating disorder						
Current	0 (0)	0 (0)	1 (1)	0.37	0.830	NS
Lifetime	0 (0)	0 (0)	2 (2)	0.75	0.687	NS
Alcohol abuse/dependence						
Current	4 (23)	1 (6)	6 (5)	3.75	0.152	NS
Lifetime	7 (27)	2 (12)	8 (7)	8.94	0.011	1 > 3[a]
Substance abuse/dependence						
Current	3 (12)	1 (6)	9 (8)	0.54	0.764	NS
Lifetime	3 (12)	2 (12)	12 (10)	0.55	0.973	NS
Mean (SD)						
WURS-25	47.8 (12.3)	44.2 (10.6)	10.9 (8.5)	93.9[b]	*P* < 0.0001	1 > 2, 1 > 3 [c]
CSS—total	10.4 (1.9)	3.3 (2.3)	1.5 (1.9)	77.0	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[d]
CSS—attention deficit	4.5 (2.1)	1.8 (1.6)	0.7 (1.2)	60.9[b]	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[c]
CSS—hyperactivity	5.9 (1.7)	1.5 (1.1)	0.7 (1.1)	74.1[b]	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[c]
Total ADHD diagnostic criteria	10.6 (2.0)	3.5 (2.1)	1.3 (1.9)	81.5[b]	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[d]
ADHD-attention deficit	4.6 (2.1)	1.8 (1.5)	0.8 (1.3)	60.7[b]	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[c]
ADHD-hyperactivity/impulsivity	5.9 (1.8)	1.7 (1.3)	0.6 (0.9)	83.1[b]	*P* < 0.0001	1 > 2, 1 > 3, 2 > 3[c]

cADHD childhood attention deficit hyperactivity disorder, *ADHD* attention deficit hyperactivity disorder, *BD* bipolar disorder, *GAD* generalized anxiety disorder, *OCD* obsessive compulsive disorder, *PTSD* posttraumatic stress disorder, *WURS* Wender Utah rating scale, *CSS* current symptoms scale, *SD* standard deviation

[a] χ^2 test (or Fisher exact test) used for pairwise comparison

[b] Kruskall Wallis test

[c] Mann Whitney U test used for post-hoc pairwise comparison

onset of the disorder and ADHD comorbidity [13, 33]. In the current sample, 65% of the ADHD-BD group and 53% of the cADHD-BD group had early onset of the disorder (<18 years of age), while this rate was only 20% in the BD group. In a previous study, Sachs et al. [33] suggested that co-occurring ADHD may be a marker for early onset (juvenile-onset) bipolar disorder based on their finding that ADHD comorbidity was associated with earlier onset of bipolar disorder by an average of eight years. After citing the earlier onset of the disorder in families with high loading for affective illness, the same authors suggested that early onset bipolar disorder could be a subtype with higher genetic loading and therefore increased vulnerability to the development of both early affective and non-affective psychopathology [33]. Other studies reporting similar findings have led to widespread acceptance of the idea that lifetime ADHD comorbidity is associated with early onset bipolar disorder [5, 10, 29, 41].

The ADHD-BD group, but not the cADHD group, had higher lifetime prevalence rates for axis I disorders, anxiety disorders, and alcohol abuse/dependence than patients without adult ADHD. Among all axis I comorbidities, lifetime panic disorder and alcohol abuse/dependence were significantly higher in

the ADHD-BD group than in the BD group, even after controlling for age of onset. The higher number of lifetime episodes and presence of other axis I comorbidities in patients with both BD and ADHD compared with patients suffering from BD only, suggest that the course of bipolar disorder is more severe and disabling in patients with persistent ADHD. Both ADHD and bipolar disorder are closely associated with increased morbidity and disability [25]. Therefore, the comorbidity of these two disorders is expected to aggravate the clinical picture and lead to more important problems. Adding to this picture other axis I disorders like anxiety and alcohol use disorders, which are known to lead to poorer prognosis in bipolar disorder patients, make it clear that comorbidity is an important consideration in treating BD [35]. Furthermore, core ADHD symptoms like attention deficit, hyperactivity, and impulsivity can prevent bipolar disorder patients from following their treatment regime, thereby increasing the tendency to develop new affective episodes [32, 36]. Indeed, Nierenberg et al. [29] have reported that ADHD comorbidity is associated with a greater frequency of other comorbid conditions, including several anxiety disorders and alcohol abuse and/or dependence. Such patients experience more episodes of mania and depression, a greater number of irritable days, more suicide attempts, and a more severe disease course.

Another significant finding in the present study consistent with other reports is the observation of more frequent episodes of depression in patients in the ADHD-BD and cADHD-BD groups than in the BD group [29, 36, 41]. A close relationship between depression and ADHD has previously been reported, and the risk of developing lifetime unipolar or bipolar depression is increased in those with an ADHD diagnosis [5, 32]. ADHD and major depression (MD) have been found to co-occur in 9–38% of cases in both epidemiologic and clinical studies of children and adolescents [32]. Similar patterns are thought to exist in adults. MD was present in 31% of referred adults with ADHD, and in 17% of nonreferred ADHD adults [8]. Along the same lines, Alpert et al. [1] have found that 16% of adult outpatients with an MD diagnosis fulfill the diagnostic criteria of childhood ADHD, and ADHD symptoms have persisted into adulthood in 75% of these patients. Based on these findings and on family studies implicating a familial link between ADHD and depression, some authors have proposed that ADHD and depression may represent different expressions (i.e. phenotypes) of a common etiology (i.e. genotype) [25]. Faraone and Biederman [11] hypothesized that ADHD and depression probably share several familial risk factors, either environmental or genetic, and that the difference between depressed and nondepressed ADHD patients can be attributed to other environmental factors. Molecular genetic analysis has implicated the gene for the dopamine D2 receptor as playing a role in both ADHD and depression, and psychosocial studies have suggested that the two disorders share such risk factors as maternal depression, dysfunctional family environment, and parental conflict [6, 11]. However, as Marks states, if the "phenotypes" hypothesis were true, one would expect to encounter high rates of depression in prospective studies of ADHD at follow-up, which has not been observed in several different investigations [25]. These contradictory reports show the necessity of further research into this issue.

This study has several limitations that should be mentioned. First, this study has been carried out on a sample composed of highly educated patients undergoing follow-up at a specialized psychiatry unit. Therefore, it is not possible to generalize our findings to all bipolar disorder patients or to community-based sampling. Secondly, because of the cross-sectional phenomenological nature of the study, we could not assess the effects of some variables likely to affect the course of the disorder (i.e. treatment compliance and response to treatment). Third, the relatively small number of ADHD-BD and cADHD-BD cases might limit the power of this study because of an increased risk of type II error. However, our calculations showed that most of our statistical evaluations had a power of more than 80%-an acceptable rate for most statistical studies–and a medium effect size. Another limitation of the study is retrospective collection of childhood symptoms by adult subjects to make a diagnosis of childhood ADHD. Some research indicates that in such retrospective evaluations, adults can minimize and underreport their childhood ADHD symptoms [23]. However several other studies show that adults with ADHD are acceptable reporters of their childhood, and that self-reporting of ADHD symptoms is a reliable and valid method of assessing ADHD in adults [24, 28]. In the present study we tried to minimize this limitation by analyzing childhood experiences with a semi-structured interview scale like K-SADS, conducting detailed interviews supplemented by self-reported scales like CSS, reviewing old medical files where available, and trying to corroborate the information from the patient by interviewing close relatives. Another problem in BD and ADHD studies could be bidirectional symptom overlap between these two disorders, which could result in unintentional over-diagnosis of both disorders [27, 29]. However, several studies addressing this issue in the literature showed that even after correction for overlapping symptoms, the majority of patients maintained their original diagnosis of ADHD and comorbid disorders, including bipolar disorder [7, 27].

Conclusion

Adult ADHD is a common comorbidity in bipolar disorder patients that adversely affects patient prog-

nosis and is associated with a greater number of affective episodes and more frequent axis I psychiatric disorders, such as panic disorder and alcohol use disorders. Large symptom overlap between these two disorders and the occurrence of other axis I comorbidities could obscure the correct diagnosis of BD and ADHD comorbidity, and could affect the treatment options considered. Considering the diagnosis of ADHD as an option in BD patients, particularly early-onset BD patients, together with close follow-up and screening using appropriate scales, could help prevent possible problems and complications in the disease course. To allow for more definitive conclusions, the exact relationships between BD and ADHD and the symptom profiles of comorbid patients in different age groups should be studied.

References

1. Alpert JE, Maddocks A, Nierenberg AA, O'Sullivan R, Pava JA, Worthington JJ, Biederman J, Rosenbaum JF, Fava M (1996) Attention deficit hyperactivity disorder in children among adults with major depression. Psychiatry Res 62:213–219
2. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders (DSM-IV-TR) 4th edition, text revision, American Psychiatric Association, Washington D.C.
3. Aycicegi A, Dinn WM, Harris CL (2003) Assessing adult attention deficit/hyperactivity disorder: a Turkish version of the current symptoms scale. Psychopathology 36:160–167
4. Barkley RA, Murphy KA (1998) Attention-deficit hyperactivity disorder: a clinical workbook, 2nd edn. Guilford Press, New York
5. Biederman J (2004) Impact of comorbidity in adults with attention deficit/hyperactivity disorder. J Clin Psychiatry 65(suppl 3):3–7
6. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT (1990) Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. J Am Acad Child Adolesc Psychiatry 29:526–533
7. Biederman J, Faraone SV, Mick E, Wozniak J, Chen L, Ouellette C, Marrs A, Moore P, Garcia J, Mennin D, Lelon E (1996) Attention deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? J Am Acad Child Adolesc Psychiatry 35:997–1008
8. Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle A (1993) Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 150:1792–1798
9. Biederman J, Mick E, Faraone SV (2000) Age-dependent decline of symptoms of attention deficit disorder: impact of remission definition and symptom type. Am J Psychiatry 157:816–818
10. Biederman J, Mick E, Faraone SV, Van patent S, Burback M, Wozniak J (2004) A prospective follow-up study of pediatric bipolar disorder in boys with attention-deficit/hyperactivity disorder. J Affect Disord 82S:S17–S23
11. Faraone SV, Biederman (1997) Do attention deficit hyperactivity disorder and major depression share familial risk factors? J Nerv Ment Dis 185:533–541
12. Faraone SV, Biederman J, Monuteaux MC (2001) Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype. J Affect Disord 64:19–26
13. Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D (1997) Is comorbidity with ADHD a marker for juvenile-onset mania? J Am Acad Child Adolesc Psychiatry 36:1046–1055
14. First M, Spitzer R, Gibbon M, Williams JB (1997) Structured clinical interview for DSM-IV axis I disorders. American Psychiatric Press, Washington
15. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL (1998) Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultrarapid or ultradian cycling. J Affect Disord 51:81–91
16. Gokler B, Unal F, Pehlivanturk B, Kultur EC, Akdemir D, Taner Y (2004) Okul Çağı Çocukları İçin Duygulanım Bozuklukları ve Şizofreni Görüsme Çizelgesi-Şimdi ve Yasam Boyu Şekli-Türkçe Uyarlamasının Geçerlik ve Güvenirliği. Cocuk ve Genclik Ruh Sagligi Dergisi 11:109–116
17. Henin A, Biederman J, Mick E, Hirshfeld-Becker DR, Sachs GS, Wu Y, Yan L, Ogutha J, Nierenberg AA (2007) Childhood antecedent disorders to bipolar disorder in adults: a controlled study. J Affect Disord 99:51–57
18. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988
19. Kent L, Craddock N (2003) Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord 73:211–221
20. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM (2006) The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication. Am J Psychiatry 163:716–723
21. Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM (2005) Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry 57:1442–1451
22. Mancini C, Van Ameringen M, Oakman JM, Figueiredo D (1999) Childhood attention deficit/hyperactivity disorder in adults with anxiety disorders. Psychol Med 29:515–525
23. Mannuzza S, Klein RG, Besler A, Malloy P, LaPadula M (1998) Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry 155: 493–498
24. Manuzza S, Klein RG, Klein DF, Besler A, Shrout P (2002) Accuracy of adult recall of childhood attention deficit hyperactivity disorder. Am J Psychiatry 159:1882–1888
25. Marks DJ, Newcorn JH, Halperin JM (2001) Comorbidity in adults with attention-deficit/hyperactivity disorder. Ann NY Acad Sci 931:216–238
26. Masi G, Perugi G, Toni C, Millepiedi S, Mucci M, Bertini N, Pfanner C (2006) Attention-deficit hyperactivity disorder—bipolar comorbidity in children and adolescents. Bipolar Disord 8:373–381
27. Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT (1995) Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. Am J Psychiatry 152:1793–1799
28. Murphy P, Schachar R (2000) Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults. Am J Psychiatry 157:1156–1159
29. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, Pollack MH, Ostacher MJ, Yan L, Siegel R, Sachs G (2005) Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1,000 STEP-BD participants. Biol Psychiatry 57:1467–1473
30. Oncü B, Günay Ş, Şentürk V (2005) Wender-Utah Derecelendirme Ölçeği Türkçe Formunun Eriskin Dikkat Eksikliği ve Hiperaktivite Bozukluğu'nda Geçerlik ve Güvenilirlik Çalısması. Turk Psikiyatri Derg 16:252–259
31. Ozkürkcügil A, Aydemir Ö, Yıldız M, Esen Danacı A, Köroglu E (1999) DSM-IV eksen I bozuklukları için yapılandırılmıs klinik görüsmenin (SCID-I) Türkçeye uyarlanması ve güvenilirlik calismasi. Ilac ve Tedavi Dergisi 12:233–236
32. Pliszka SR (1998) Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: an overview. J Clin Psychiatry 59(suppl 7):50–58

33. Sachs GS, Baldassano CF, Truman CJ, Guille C (2000) Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. Am J Psychiatry 157:466–468
34. State RC, Frye MA, Altshuler LL, Strober M, DeAntonio M, Hwang S, Mintz J (2004) Chart review of the impact of attention-deficit/hyperactivity disorder comorbidity on response to lithium or divalproex sodium in adolescent mania. J Clin Psychiatry 65:1057–1063
35. Tamam L, Özpoyraz N (2002) Comorbidity of anxiety disorders in patients with bipolar-I disorder. Psychopathology 35:203–209
36. Tamam L, Tuğlu C, Karatas G, Özcan S (2006) Adult attention hyperactivity disorder in patients with bipolar I disorder in remission: preliminary study. Psychiatr Clin Neurosci 60:480–485
37. Ward MF, Wender PH, Reimherr FW (1993) The Wender Utah rating scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150:885–890
38. Wender PH, Wolf LE, Wasserstein WS (2001) Adults with ADHD: an overview. Ann NY Acad Sci 931:1–16
39. West SA, McElroy SL, Strakowski SM, Keck PE, McConville BJ (1995) Attention deficit hyperactivity disorder in adolescent mania. Am J Psychiatry 152:271–273
40. Wilens T, Biederman J, Spencer T (2002) Pharmacotherapy for ADHD in adults: a review of the literature. J Atten Disord 4:189–202
41. Wilens TE, Biederman J, Wozniak J, Gunawardene S, Wong J, Monuteaux M (2003) Can adults with attention-deficit/hyperactivity disorder be distinguished from those with comorbid bipolar disorder? Findings form a sample of clinically referred adults. Biol Psychiatry 54:1–8
42. Wilens TE, Dodson W (2004) A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry 65:1301–1313
43. Winokur G, Coryell W, Endicott J, Akiskal H (1993) Further distinction between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). Am J Psychiatry 150:1176–1181
44. Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, Mennin D (1995) Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 34:867–876