



Review

Adult ADHD and its comorbidities, with a focus on bipolar disorder

Larry J. Klassen ^{a,b,*}, Martin A. Katzman ^{c,d,e,f}, Pratap Chokka ^g^a Department of Psychiatry, Faculty of Medicine, University of Manitoba, Canada^b Eden Mental Health Centre, Manitoba, Canada^c START Clinic for Mood and Anxiety Disorders, Ontario, Canada^d Department of Psychiatry, Faculty of Medicine, University of Toronto, Ontario, Canada^e Northern Ontario School of Medicine, Laurentian and Lakehead University, Ontario, Canada^f Department of Psychology, Lakehead University, Ontario, Canada^g University of Alberta, Alberta, Canada

ARTICLE INFO

Article history:

Received 20 March 2009

Received in revised form 29 June 2009

Accepted 30 June 2009

Available online 15 August 2009

Keywords:

Attention deficit disorder

Attention deficit disorder with hyperactivity

Bipolar disorder

Psychostimulants

Mood stabilizers

Treatment

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a syndrome that most often presents in childhood. However, the condition is also relatively common in adults, with prevalence rates reaching 5% in the general population, with more than half the children affected by ADHD retaining the condition during their adult years. While the disorder in children is most often described as a disorder involving hyperactivity and impulsiveness, ADHD presents with very different characteristics in adulthood, notably with less externalizing symptoms and with a higher rate of psychiatric comorbidities, including major depressive disorder, bipolar disorder (BD), anxiety disorders and substance abuse. This review will focus on the evidence relating to bipolar disorder BD and its potential link with ADHD, looking at epidemiological, familial and neuroimaging studies. The comorbid presentation of people suffering with ADHD and BD (ADHD/BD) is associated with a more severe disease course, more severe mood disorder symptoms, and lower functional scores. Importantly, the co-segregation of these two conditions makes ADHD diagnosis challenging because its symptoms are often mistakenly assumed to be part of BD. As a result, patients with comorbid ADHD/BD are under-diagnosed and under-treated. Optimal diagnosis, understanding and treatment of the comorbid condition are important, as ADHD/BD has been associated with significant functional impairment and suboptimal treatment responses when compared to ADHD or BD populations alone.

© 2009 Elsevier B.V. All rights reserved.

Contents

1. Introduction	2
2. ADHD and psychiatric comorbidity	2
3. Bipolar disorder	3
4. Hypotheses and diagnosis/methodology problems	4
5. Epidemiological studies	4
6. Familial studies	5
7. Neurobiological studies	5
8. Characteristics of ADHD/BD	5
9. Conclusions	6
Role of funding source	7
Conflict of interest	7

* Corresponding author. Eden Mental Health Centre, 1500 Pembina Ave., Winkler, Manitoba, Canada R6W 1T4. Tel.: +1 204 325 4325; fax: +1 204 325 8429.
E-mail address: ljklassen@edenhealth.mb.ca (L.J. Klassen).

Acknowledgement	7
References	7

1. Introduction

Attention deficit hyperactivity disorder (ADHD) characterized by a continuous history of hyperactivity, forgetfulness, distractibility, impulsiveness and/or inattention, depending on the type of ADHD. Consequently, its impact on quality of life is considerable and most patients suffering with ADHD experience substantial functional impairments in their daily activities. Surveys suggest that people with ADHD achieve fewer educational milestones beyond high school, are less likely to be employed full-time, and have significantly lower average household incomes than people without the disorder (Biederman and Faraone, 2006).

Originally described in a pediatric population, it is now also recognized as a condition found in adults. Depending on the study, childhood prevalence of ADHD varies between 3 and 12% (Tamam et al., 2008; Kent and Craddock, 2003; Wingo and Ghaemi, 2007). While adult prevalence is quite similar across studies, usually 4–5% (Tamam et al., 2008; Wingo and Ghaemi, 2007; Sobanski et al., 2007; Fischer et al., 2007). Thus, it can be estimated that up to 50% of children affected by ADHD retain the condition during their adult years (Tamam et al., 2008). Although the condition is now well characterized in adults, it is generally accepted that the onset of ADHD occurs during childhood (Biederman, 2005).

The diagnosis and treatment of adult ADHD can be a challenge, because hyperactive symptoms tend to decrease with age, thus making it more difficult to diagnose adult ADHD (Nierenberg et al., 2005). Furthermore, adults with ADHD tend to present less with externalizing and hyperactive symptoms, compared to ADHD when initially diagnosed in childhood, which further complicates referral and diagnosis (Karam et al., 2008). In addition, adult ADHD is often associated with a number of psychiatric comorbidities such as major depressive disorder (MDD), Generalized Anxiety Disorder (GAD), alcohol and/or substance abuse, bipolar disorder (BD), and a variety of conduct or behavioral disorders. Therefore, many symptoms that are directly attributable to ADHD are often mistakenly associated with other psychiatric conditions and consequently not fully treated (Fischer et al., 2007; Kessler et al., 2006). This review addresses adult-onset ADHD, its etiology and its psychiatric comorbidities. More specifically, it focuses on the co-occurrence of ADHD and bipolar disorder in adults. The Medline (PubMed) database was searched for articles published prior to August 2008 that matched any combination of the following keywords: attention-deficit, hyperactivity disorder, bipolar, mania, adult, comorbidity, diagnosis, and treatment. The resulting articles that were identified through this search were considered for this review, which addresses epidemiological, genetic and neurobiological data linking ADHD and bipolar disorder.

2. ADHD and psychiatric comorbidity

ADHD has been associated with a number of psychiatric comorbidities. In children with ADHD, the most prevalent

comorbid conditions include oppositional defiant disorder (ODD: 40.6%) (Elia et al., 2008), especially in children presenting combined or hyperactive–impulsive ADHD types. While children presenting with uncomplicated classical bipolar disorder is thought to be rare (no cases were reported in an epidemiologic study of 4500 American prepubertal children) (Costello et al., 1996), children presenting with minor depression/dysthymia (MDD: 21.6%) and generalized anxiety disorder (GAD: 15.2%) are also common in this population (Elia et al., 2008). Thus comorbidity is the rule rather than the exception (Masi et al., 2006).

In adults, it has been reported that almost 80% of ADHD patients present at least one lifetime psychiatric comorbidity (Fischer et al., 2007), with major depressive disorder (MDD) as the most common condition (prevalence 24.4% to 31%) (Fischer et al., 2007; Biederman et al., 1993). Anxiety disorders are also a common comorbid condition of patients with ADHD. The odds ratio for the development of an anxiety disorder in adults with ADHD has been reported to be between 1.5 and 5.5, depending on the specific anxiety disorder. In the general population, the prevalence of any anxiety disorder approaches 20%, while this figure increases to 47% in adults with ADHD (Kessler et al., 2006). Moreover, 65% of adult patients diagnosed with co-occurring ADHD and BD present a lifetime history of at least one anxiety disorder (Tamam et al., 2008). Importantly, ADHD combined with other psychiatric conditions, such as MDD, contributes to increased use and costs of mental health services (Fischer et al., 2007).

Substance abuse constitutes another common comorbid disorder seen in ADHD adult patients, who may use alcohol, drugs and nicotine as a form of self-medication (Ohlmeier et al., 2007). In a study investigating 91 alcohol-dependent participants, 23.1% fulfilled the DSM-IV diagnostic criteria for childhood ADHD (Ohlmeier et al., 2007). Moreover, 33.3% of these patients sustained ADHD throughout adulthood. In this alcohol-dependent population, 76.2% of ADHD patients had an “average to high” use of nicotine, compared to 45.7% in the group without ADHD. This research suggests that alcohol and nicotine addictions are more prevalent in ADHD patients than in the general population, showing a potential causative effect of ADHD on the risk of substance abuse as well as a downward prognostic indication for those with both (Ohlmeier et al., 2007). This is particularly so in men, as there is the suggestion that ADHD-suffering females were more likely to develop comorbidities with depressive episodes and eating disorders while more males were likely to be affected by substance abuse disorders (Sobanski et al., 2007). There is emerging evidence that treatment of ADHD in childhood or adolescence might reduce the virulence and trajectory of substance use disorders in adulthood. For example, a recent study by Wilens et al. (2008) showed that treating children with ADHD with stimulants had a highly significant protective effect on later development of substance use disorders and cigarette smoking. Based on this information, we could hypothesize that treatment of ADHD with stimulants in adults with concomitant ADHD and substance abuse could help manage the

comorbid substance abuse disorder. However, to our knowledge, no data examining this hypothesis are available at this time. Thus, pharmacotherapy for ADHD in childhood has the potential to modulate the development and course not only of ADHD, but perhaps also of other psychiatric comorbidities.

Recent attention has focused on the comorbidity between ADHD and bipolar disorder. Studies suggest that children and adults with ADHD have a high prevalence of comorbid BD and are more likely to have a positive family history of BD (Dilsaver et al., 2003; Secnik et al., 2005). Similarly, children with ADHD are at higher risk of developing BD in adulthood (Biederman et al., 1996a).

ADHD alone and, to a greater extent, ADHD associated with other psychiatric disorders, has considerable impact on patient quality of life. Compared to the general population, adults with ADHD are twice as likely to be arrested, have a two-fold increased risk of being divorced, and a 78% greater risk of being unemployed (Faraone and Biederman, 2004). Moreover, ADHD is associated with driving impairments, receiving more speeding tickets and license suspensions compared to controls (Barkley et al., 2002). At least one study suggests that adults with ADHD have a significantly lower household income compared to their peers (Biederman and Faraone, 2006). Finally, teens with ADHD also exhibit riskier sexual behaviours, are less likely to use contraception and are more at risk of unwanted pregnancies and sexually transmitted diseases (Barkley et al., 2002). Thus, ADHD clearly affects the patient's life at an educational, professional, and personal level.

Despite the relatively high prevalence of adult ADHD, only 11% of adult patients are treated due to multiple factors, including failure to seek medical advice, misdiagnosis and/or treatment of the comorbid condition instead of ADHD (Stephen and Kevin, 2008). Some of these issues are likely related to physicians' lack of awareness of adult ADHD. It is regrettable that the DSM-IV-TR diagnostic criteria for adult-onset ADHD still require that impairment in at least two domains be described before the age of 7. Awareness of the diagnostic option of ADHD NOS (not otherwise specified) and the administration of a short screen for adult ADHD would positively impact on diagnosis and treatment of this population. In general, ADHD therapies used in children are also effective in adults. Approved pharmacological agents include stimulants (e.g., mixed amphetamine salts, dexamethylphenidate, methylphenidate) and non-stimulants (e.g., atomoxetine). Long acting agents can be more convenient for adults (Stein, 2007). Limited information is available on psychosocial therapies, particularly in adults with ADHD, but preliminary data are encouraging. In a group of 31 adults, cognitive-behavioural therapy combined with medication was more effective in reducing ADHD, anxiety and depression symptoms than pharmacotherapy alone (Safren et al., 2005).

Still, given the limitations of our current knowledge base, it becomes imperative to follow the general principle of treatment whereby the recognition of all the comorbidities in any patient is key and where we treat the most destabilizing illness (for example the bipolar illness) first and then continue in a step-wise fashion to manage all the comorbidities (mood and anxiety disorders, ADHD and substance abuse). Treating ADHD has been shown to decrease the severity of comorbid substance abuse, although in severe

cases, treating substance abuse first might be necessary to ensure treatment compliance (Newcorn et al., 2007). Considering the current lack of empirical data on treatment of ADHD and comorbidities, patients should be managed on a case-by-case basis, with the most severe condition given treatment priority.

3. Bipolar disorder

Bipolar disorder (BD) is a considerable public health concern, with lifetime prevalence around 1% for bipolar I disorder and up to 5% when including all bipolar spectrum disorders (Kent and Craddock, 2003; Wingo and Ghaemi, 2007; Akiskal et al., 2000). This disorder is recognized to have a considerable negative impact on patient functioning and quality of life (Nierenberg et al., 2005; Sentissi et al., 2008; Biederman et al., 1997; Brown, 2006). Bipolar disorder patients are commonly affected by comorbid psychiatric conditions, including anxiety, depression and substance use disorders (Fischer et al., 2007; Biederman et al., 1993; Ohlmeier et al., 2007). ADHD has been recognized as a prevalent comorbidity in both adult (Tamam et al., 2008; Sentissi et al., 2008; Tamam et al., 2006) and juvenile (Tamam et al., 2008; Sachs et al., 2000) patients with BD, however this comorbidity is less well understood. Epidemiological, neuroimaging and family studies have highlighted a potential association between BD and ADHD, however, this relationship is still equivocal and its exact nature remains to be characterized.

Traditionally, BD has been described as a condition that is episodic in its nature. The term bipolar suggests two phases: a down or depressive phase and an elevated (manic or hypomanic) phase. The elevated or manic phase is characterized by affective lability, whereby the person appears overly talkative, distractible, and exhibits increased activity, physical restlessness and loss of normal social inhibitions, all of which are similar in ADHD. Nevertheless, patients suffering with BD may also experience a decreased need for sleep, psychotic symptoms, hallucinations and inflated self-esteem, which are not characteristic of people suffering with ADHD (Wingo and Ghaemi, 2007).

In children, BD remains a controversial issue, with some investigators reporting that it is extremely rare, and others suggesting that the condition is under-diagnosed or misdiagnosed in this population (Kent and Craddock, 2003; Costello et al., 1996). Separating BD from ADHD in adults is often understood by looking for the periodic nature of BD as opposed to the rather consistent symptomatic representation seen in ADHD. One of the main challenges to this diagnostic strategy relates to the fact that juvenile BD follows a different developmental course than in adults. In children, BD is often described as a continuous, non-episodic irritable mood, which contrasts from the clinical presentation seen in adult BD. When these symptoms are accepted as signs of bipolar disorder in children and teenagers, the prevalence reaches 0.3% (Kent and Craddock, 2003). Although other psychiatric disorders, such as anxiety and depression, have been described differently for adults and children, this is not yet the case for bipolar disorder; in fact, some have proposed that childhood and adult BD might in fact represent two distinct disorders (Kent and Craddock, 2003).

4. Hypotheses and diagnosis/methodology problems

In the past decade, the potential relationship between ADHD and BD in both children and adults has been increasingly discussed in the literature. This has been at least partly in response to reports of high rates of comorbidity between the two disorders. *Sachs et al. (2000)* proposed four hypotheses that could help explain the high rate of co-segregation of mania and ADHD symptoms:

- 1- Comorbidity is a chance phenomenon;
- 2- Comorbidity is an artifact of overlapping criteria;
- 3- Comorbidity is due to a common diathesis that leaves patients vulnerable to separate illnesses;
- 4- Symptoms of ADHD that precede the onset of BD represent a prepubertal expression of illness antecedent to the development of a full affective episode.

Several symptoms for ADHD and BD overlap in the DSM-IV, which might complicate diagnosis in patients presenting both disorders (*Table 1*) (*Kent and Craddock, 2003; Wingo and Ghaemi, 2007*). Only one study has assessed whether the high rate of comorbidity was due to symptom overlap. *Milberger et al. (1995)* used two different methods, subtraction and proportion, to investigate the rates of ADHD and BD comorbidity when taking into account the overlapping diagnostic criteria. The subtraction method removed all symptoms that were common to both conditions. Using this new tool, 79% and 64% of ADHD/BD subjects retain their ADHD and bipolar disorder, respectively. The proportion method was less conservative and respectively 86% and 93% of patients retained a diagnosis of ADHD and bipolar disorder, respectively. These data support the argument that overlapping symptoms within the DSM-IV is not responsible for the high comorbidity rates described in several studies. *Table 1* provides a way to compare and contrast between the two illnesses.

Several methodological issues arise when investigating the literature concerning a possible relationship between ADHD and BD. Firstly, only a handful of studies have examined both conditions concurrently. Moreover, in these studies, ADHD diagnostic tools vary widely, some relying on self-report, others diagnosing childhood ADHD in adults retrospectively. Secondly, diagnostic criteria for ADHD are based on childhood symptoms while BD is mostly understood in adulthood. It is challenging to establish a link between two conditions that are described at different developmental stages. Thirdly, most studies looking at ADHD and BD comorbidities have done so in a clinical population. Consequently, there is a possibility of Berkson bias, i.e., that treatment-seeking patients tend to present more comorbidities than the general affected population (*Nierenberg et al., 2005; Berkson, 1946*). Nonetheless, there appears to be a variety of studies that point to associations between ADHD and BD.

5. Epidemiological studies

The first suggestion of a possible link between ADHD and BD came from epidemiological studies that reported an unusually high rate of BD in ADHD patients and/or increased rates of ADHD in BD populations. These epidemiologic studies suggested that children and teenagers with ADHD have up to a 10-fold increased risk for bipolar disorder (*Biederman et al.,*

Table 1

Overlapping and non-overlapping symptoms in ADHD and bipolar disorder.

ADHD	Bipolar disorder
<i>Overlapping symptoms</i>	
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 uninformed	4. Loss of normal social inhibitions
11. Blurts out answers before questions have been completed	
12. Difficulty awaiting turns	
<i>Non-overlapping symptoms</i>	
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 for potential adverse consequences.
18. Difficulty following through on instructions/fails to finish work	

Comparison of DSM-IV Diagnostic criteria for ADHD and BD. Adapted with permission from *Kent and Craddock (2003)* and from *Wingo and Ghaemi (2007)*.

1996b). In this particular study, bipolar disorder was diagnosed in 11% of ADHD subjects at baseline and in another 12% at a 4-year follow-up. In comparison, bipolar disorder in age- and sex-matched healthy control subjects approached 0%. Similarly, *Faraone et al. (1997a)* found that bipolar disorder prevalence in children with ADHD ranged from 11% in an outpatient population to 22% in hospitalized patients. These rates are much higher than would be expected in the general population, where the juvenile BD rate is around 0.3% (*Kent and Craddock, 2003*).

Considerably more data are available on the rates of ADHD in adults affected with bipolar disorder. It has been proposed that the rate of ADHD comorbidity in BD patients is as high as 38–98% in children and adolescents (*Tamam et al., 2008; Sachs et al., 2000*) but that it decreases with age, reaching 9–35% in adult populations (*Tamam et al., 2008; Nierenberg et al., 2005; Sentissi et al., 2008; Tamam et al., 2006*). Only one study involving 73 subjects with childhood-onset BD found a lower rate of ADHD: three (4%) of the participants were diagnosed with ADHD (*Jaideep et al., 2006*). The limited number of subjects could explain the discrepancy between this study and the others. Nonetheless, these rates are significantly higher than the prevalence of BD in the general population, usually estimated at about 1% (*Kent and Craddock, 2003; Wingo and Ghaemi, 2007; Tamam et al., 2006*).

Most of the reported comorbidity rates estimated the concurrent presence of ADHD and BD in adult participants. However, some studies have also investigated the rate of BD in

adults who were diagnosed with childhood ADHD but who did not retain the condition during their adulthood. In these cases, the comorbidity prevalence increased to 21.3% (Winokur et al., 1993) and 34.1% (Tamam et al., 2006).

The prevalence of ADHD and BD comorbidity varies depending on the subtype of ADHD and BD involved. For example, Millstein et al. (1997) reported higher rates of bipolar disorder in patients presenting the combined type of ADHD compared to patients with either the inattentive or the hyperactive-impulsive subtypes of ADHD. Notably, bipolar disorder patients with comorbid ADHD are more likely to be diagnosed with type 1 bipolar disorder (Nierenberg et al., 2005). Notably, little information is available regarding the comorbidity between ADHD and bipolar II disorder. Clearly, more studies are needed to establish this potentially clinically-relevant relationship.

Significantly lower rates of comorbid ADHD and BD have been reported in studies outside of North America (Masi et al., 2006; Vershulst et al., 1997). For instance, in a study conducted in 50 Indian children and teenagers affected by bipolar disorder, none of the participants were diagnosed with ADHD (Srinath et al., 1998). It has been hypothesized that the wide use of stimulants in North America to treat children with ADHD might favour an earlier onset of bipolar disorder, therefore contributing to the high comorbidity rates previously discussed. Indeed, DelBello et al. (2001) found that prior stimulant therapy significantly lowered the age of mania onset in adolescent patients with BD; this effect was stronger in those patients who had been treated with two stimulants compared to those treated with only one. Interestingly, this effect was independent of the presence of ADHD. This raises the question whether the high comorbidity rate between ADHD and BD is due to a biological effect or whether it is an effect of exposure to stimulants. Alternatively, it could be argued that more severe or treatment resistant ADHD patients (requiring more than one psychostimulant), may have a higher likelihood of developing BD.

6. Familial studies

Both ADHD and bipolar disorder individually are known to have strong familial links. Only a handful of studies have investigated the genetic contribution of comorbid ADHD and BD. In one study, Faraone et al. (1997b) investigated 140 boys with ADHD, 120 controls and their 822 first-degree relatives. As expected, relatives from ADHD patients with and without BD were more likely to have ADHD. No significant differences were found in ADHD risk between the ADHD and ADHD/BD groups. Interestingly, relatives of ADHD/BD patients had a five-fold elevated risk for BD. This relationship was not present in the ADHD only group. The same research group also replicated their original study using a similar number of girls and reported comparable results (Faraone et al., 2001). Based on these findings, the authors suggest that ADHD/BD could be a distinct condition, arguing that the atypical clinical presentation of childhood BD in ADHD/BD patients constitutes additional evidence to support their claim (Faraone et al., 1997a,b).

If we accept the hypothesis of ADHD/BD as a separate condition in children, then we should expect BD and ADHD to co-segregate in families of ADHD/BD patients. This effect was demonstrated in two studies (Faraone et al., 1997b; Wozniak

et al., 1995) in which relatives of ADHD/BD patients presented increased risks for the comorbid conditions themselves, suggesting that the two conditions are transmitted together and not independently. In a study of 12 ADHD relatives of comorbid patients, 42% also met the criteria for BD as opposed to only 3% in the non-ADHD relatives ($p < 0.01$) (Wozniak et al., 1995). Finally, the authors suggest that the comorbid condition could represent a separate entity and could be linked to what other authors have called “childhood-onset BD”. Clearly, more work is necessary to investigate the clinical course, outcome and therapy options of this potential new subtype of BD.

7. Neurobiological studies

In recent years, neuroimaging studies have highlighted the importance of prefrontal, basal ganglia and anterior cingulate dysfunction in ADHD patients (Rubia et al., 1999; Bush et al., 1999; Teicher et al., 2000). Similarly, BD patients have shown differences in frontal, temporal, corpus callosum and basal ganglia (Videbech, 1997). Thus, similar areas of the brain are involved in both conditions with only the temporal lobe seeming to play a role in BD alone. Although similar brain area dysfunction could suggest a relationship between BD and ADHD, it is important to recognize that these brain areas are not restricted to BD and ADHD pathologies. In fact, the same areas appear to be activated differentially in a number of psychiatric conditions including the anxiety disorders (Brambilla et al., 2002) and depression (Brambilla et al., 2002; Drevets, 2000). Importantly, most of the ADHD neuroimaging research has been conducted in children whereas BD studies have been conducted mostly in adults. To our knowledge, no neuroimaging studies have been conducted with ADHD, BD and ADHD/BD patients concurrently.

Pharmacologic treatments for both ADHD and BD act on the dopaminergic, noradrenergic and serotonergic systems. ADHD is usually treated with stimulants whereas BD treatment involves either mood stabilizers, including anticonvulsants, antipsychotics, lithium, and at times, antidepressants. The fact that similar classes of medications can treat both conditions suggests that ADHD and BD could involve dysfunctions of the same neurotransmitters. However, this finding is not specific to these two conditions as dopamine and serotonin systems are also involved in several other psychiatric disorders (Kent and Craddock, 2003).

In conclusion, on the basis of neurobiological evidence alone, it is not possible to conclude that ADHD and BD are related disorders. However, the preliminary imaging information supports other evidences highlighted by epidemiological and familial studies. Taken together, all these evidences, strongly suggest that ADHD and BD are correlated, and even that ADHD/BD might constitute a separate condition. Surely, chance alone cannot explain these findings in a satisfactory manner. However, additional research with powerful imaging tools would be necessary to determine whether the link between ADHD and BD resides at the clinical or at the biological level.

8. Characteristics of ADHD/BD

In the light of these studies, researchers have highlighted specifically different disease characteristics found in the

comorbid ADHD/BD condition. For instance, most (Kent and Craddock, 2003; Wingo and Ghaemi, 2007; Nierenberg et al., 2005; Masi et al., 2006; Sachs et al., 2000; Jaideep et al., 2006) but not all (Tamam et al., 2006) studies support the fact that comorbid patients present at an earlier age for first onset mania symptoms as compared to the BD patients, without the ADHD comorbidity. In fact, on average, comorbid ADHD/BD patients experience mania symptoms 3–5 years earlier than BD patients (Nierenberg et al., 2005; Masi et al., 2006). As such, it has also been argued that the earlier age of onset is the critical variable to differentiate ADHD/BD from BD.

As well, the comorbid condition is associated with a more severe course of the mood disorder (Wingo and Ghaemi, 2007; Nierenberg et al., 2005; Tamam et al., 2006) and a higher probability of being diagnosed with type 1 bipolar disorder (Nierenberg et al., 2005). In addition, comorbid patients' first BD episode is more likely to be of depressive nature (71% in a ADHD/BD population vs. 22% in a BD-only group) (Nierenberg et al., 2005; Tamam et al., 2006). Subsequently, these patients experience depressive episodes more frequently than BD patients (Tamam et al., 2006) with shorter duration of wellness (Nierenberg et al., 2005). For instance, 40.7% of patients with ADHD/BD reported more than 20 lifetime manic episodes whereas this proportion decreased to 29.6% in BD patients without comorbid ADHD (Nierenberg et al., 2005). On the other hand, patients with ADHD/BD are generally less compliant to treatment (Tamam et al., 2006), which could partly explain why they present more serious and recalcitrant symptoms. The nature of ADHD symptoms (i.e., inattention, lack of organization and forgetfulness) may account for the additional difficulty of ADHD/BD patients to adhere to treatment. As such, prioritizing therapies, as discussed earlier, may be essential to reach maximal benefits.

Finally, compared to BD patients, ADHD/BD patients have lower functional scores, lower education, fewer partnerships, more suicide attempts and more legal problems (Nierenberg et al., 2005; Sentissi et al., 2008). A recent study in euthymic BD outpatients reported that comorbid ADHD predicts significantly lower social functioning and adaptation compared to patients with BD without ADHD (Sentissi et al., 2008). Furthermore, BD patients with comorbid ADHD have lower attentional resources (Biederman et al., 1997), working memory and executive functions (Brown, 2006). Taken together, these findings suggest that the comorbid condition has considerable negative impact on patients' quality of life and overall functioning and may thereby prevent patients from reaching their full potential.

Currently, only a handful of studies have investigated the response to treatment of comorbid ADHD/BD patients. State et al. (2004) reviewed the medical records of 42 adolescent BD patients who were treated with either lithium ($n = 29$) or divalproex sodium ($n = 13$). Out of these patients, 14 (34.1%) also had a diagnosis of ADHD. ADHD/BD patients had significantly lower response rates to both treatments compared to BD patients (57.1% vs. 80.9%, respectively, $p = 0.007$). In contrast, Scheffer et al. (2005) found that, in 40 children with ADHD/BD whose mania symptoms were stabilized by divalproex sodium, mixed amphetamine salts was a safe and effective treatment to improve ADHD symptoms. For ADHD alone, long-acting stimulants are recommended as first-line

therapy for children, which can be complemented by atomoxetine in the event of a suboptimal response or intolerable side effects (Banachewski et al., 2006; Gibson et al., 2006). To our knowledge, no studies have compared the efficacy and safety of stimulants versus atomoxetine in adults with ADHD. However, one systematic review of the literature supports the use of stimulants (Peterson et al., 2008). Atomoxetine might be particularly useful in adults with ADHD concomitant with substance abuse or depression (Faraone & Antshel, 2008). Importantly, in contrast with the hypothesis stating that stimulant use could precipitate manic symptoms in ADHD/BD patients, two studies reported that treatment with psychostimulants was not associated with worsening of mania symptoms (Scheffer et al., 2005; Biederman et al., 1998). To our knowledge, the association between atomoxetine and mania symptoms has not yet been systematically evaluated. Based on the efficacy of stimulants in managing ADHD symptoms and considering that no strong evidence supports an association between stimulants and mania, stimulants should remain the first-line therapy to treat ADHD symptoms in ADHD/BD patients, while bupropion and atomoxetine could be considered for some patients.

Data on treatment responses in ADHD/BD in adults appear to be even more limited. As discussed earlier, this could be due to one or more of the following: under-referral, under-diagnosis and under-treatment of ADHD in comorbid adult populations. In clinical practice, it is then probable that only BD is treated in patients presenting the comorbid condition. This can be an adequate treatment when BD symptoms are more severe than ADHD symptoms, however, it will likely yield suboptimal responses in patients where ADHD is the dominant condition. In an open-label study, adults with ADHD/BD who were taking BD medication (i.e., antipsychotics or mood stabilizers) were given bupropion to control ADHD symptoms. Compared to baseline, bupropion treatment significantly reduced ADHD symptoms, with no evidence of mania activation (Wilens et al., 2003). In all cases, physicians must make conscious decisions about how to time and sequence therapies to get the best risk-benefit profile (Stein, 2007).

In clinical practice, ADHD/BD patients are likely to be treated for BD only. Due to the similar neurobiological etiology of the two conditions, comorbid patients experience some improvements in their condition, both for BD- and ADHD-related symptoms, when treated with traditional BD therapies (Kent and Craddock, 2003). Following BD treatment, some ADHD/BD patients might not fulfill the DSM-IV criteria for ADHD anymore. However, these patients may complain about residual symptoms even with successful treatment of BD. Residual symptoms would be mostly linked to ADHD, and could include difficulty with focus, concentration and/or memory (Kent and Craddock, 2003). This could partially explain the lower functional abilities reported by BD patients, even during periods of euthymia (Malhi et al., 2007). Psychopharmacologic treatment with psychostimulants, in this population, would be generally safe and likely help patients achieve remission and wellness (Scheffer et al., 2005).

9. Conclusions

In conclusion, ADHD and BD are two psychiatric conditions that present similar clinical characteristics and diagnostic

criteria. Moreover, there exists a strong comorbidity rate that could suggest a more complex relationship between these two disorders. Taken together, evidence from epidemiological, familial and neuroimaging studies support this hypothesis, but the exact nature of the association remains to be elucidated. The ADHD/BD condition could constitute a separate disorder, especially in children, where BD symptoms are different than the classical adult BD clinical presentation. Several methodological limitations make studies on comorbid ADHD/BD difficult to interpret. For instance, ADHD and BD have been described at different developmental stages, i.e. in childhood for ADHD and in adulthood for BD. Moreover, symptoms overlap between the two disorders making the differential diagnosis process a challenge.

ADHD patients who are diagnosed with a comorbid condition, either BD or other psychiatric disorders, experience considerably more personal and professional difficulties in their lives and are likely to require mental health services more frequently. Consequently, the consideration and treatment of ADHD and all its associated comorbidities is essential to ensure the best possible patient outcomes. However, very few studies have investigated treatment of patients with comorbid ADHD/BD and, to our knowledge, none of them have involved an adult population. Clearly, more research is needed in this field to better understand the biological mechanisms of the comorbid condition as well as to provide practitioners with better tools to optimally manage their patients.

Role of funding source

Funding for this study was provided by an unrestricted educational grant from Shire Canada; Shire has not received a copy of the article and not had any input in the analysis and interpretation of data or in the writing of the report and in the decision to submit the paper for publication.

Conflict of interest

Dr. Klassen has acted as a speaker, sat on advisory boards and was a consultant for AstraZeneca, Biovail, Eli Lilly, Lundbeck, Shire, Janssen Ortho (JOI), Wyeth, and Boehringer Ingelheim. Dr. Klassen has conducted research with Lundbeck, AstraZeneca, Eli Lilly and Brain Cells Inc. (BCI).

Dr. Chokka has been on the Speakers Bureaus for AstraZeneca, Biovail, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen Ortho (JOI), Lundbeck, Pfizer, Shire, Wyeth Ayerst. Dr. Chokka has received research funding from AstraZeneca and Lundbeck.

Dr. Katzman has received research funding from AstraZeneca, Eli Lilly, GlaxoSmithKline, Solve, Lundbeck, Pfizer, Wyeth, Janssen Ortho, Shire, Solve, Genuine Health, Yakult USA. He has sat on advisory boards for AstraZeneca, Eli Lilly, Bristol Myers Squibb, GlaxoSmithKline, Lundbeck, Pfizer, Wyeth, Janssen Ortho (JOI), Shire, Solve and sat on the speakers bureau for AstraZeneca, Eli Lilly, Bristol Myers Squibb, GlaxoSmithKline, Lundbeck, Pfizer, Wyeth, Janssen Ortho, Shire, Solve, Prothera Inc.

Acknowledgement

We thank Elizabeth Pawluk, who kindly provided support in the submission of this paper and Ms. Christina Clark with the preparation and proof-reading of the manuscript.

References

Akiskal, H.S., Bourgeois, M.L., Angst, J., Post, R., Möller, H., Hirschfeld, R., 2000. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J. Affect. Disord.* 59, S5–S30.

Banachewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., Danckaerts, M., Döpfner, M., Faraone, S.V., Rothenberg, A., Sergeant, J., Steinhausen, H., Sonuga-Barke, E.J.S., Taylor, E., 2006. Long-acting medications for the hyperkinetic disorders. A systematic review of

European treatment guidelines. *Eur. Child Adolesc. Psychiatry* 15, 476–495.

Barkley, R.A., Murphy, K.R., Dupaul, G.I., Bush, T., 2002. Driving in young adults with attention-deficit/hyperactivity disorder: knowledge, performance, adverse outcomes, and the role of executive functioning. *J. Int. Neuropsychol. Soc.* 8 (5), 655–672.

Berkson, S., 1946. Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bull.* 2, 47–53.

Biederman, J., 2005. Attention-deficit/hyperactivity disorder: a selective overview. *Biol. Psychiatry* 57, 1215–1220 Electronic publication 2004 Dec 18.

Biederman, J., Faraone, S.V., 2006. The effects of attention-deficit/hyperactivity disorder on employment and household income. *MedGenMed* 8, 12.

Biederman, J., Faraone, S.V., Spencer, T., Wilens, T., Norman, D., Lapey, K.A., Mick, E., Lehman, B.K., Doyle, A., 1993. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am. J. Psychiatry* 150, 1792–1798.

Biederman, J., Faraone, S., Milberger, S., Gershon, J., Tsuang, M.T., 1996a. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Arch. Gen. Psychiatry* 53, 437–446.

Biederman, J., Faraone, S.V., Mick, E., Wozniak, J., Chen, L., Ouellette, C., Marrs, A., Moore, P., Garcia, J., Mennin, D., Lelon, E., 1996b. Attention deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J. Am. Acad. Child Adolesc. Psych.* 35, 997–1008.

Biederman, J., Wilens, T., Mick, E., Faraone, S.V., Weber, W., Curtis, S., Thornell, A., Pfister, K., Jetton, J.G., Soriano, J., 1997. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 21–29.

Biederman, J., Mick, E., Bostic, J.Q., Prince, J., Daly, J., Wilens, T.E., Spencer, T., Garcia-Jetton, J., Russell, R., Wozniak, J., Faraone, S.V., 1998. The naturalistic course of pharmacologic treatment of children with maniclike symptoms: a systematic chart review. *J. Clin. Psychiatry* 59, 628–637.

Brambilla, P., Barale, F., Caverzasi, E., Soares, J.C., 2002. Anatomical MRI findings in mood and anxiety disorders. *Epidemiol. Psychiatr. Soc.* 11, 88–99.

Brown, T.E., 2006. Executive functions and attention deficit hyperactivity disorder: implications of two conflicting views. *Int. J. Disability* 53, 35–46.

Bush, G., Frazier, J.A., Rauch, S.L., Seidman, L.J., Whalen, P.J., Jenike, M.A., Rosen, B.R., Biederman, J., 1999. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting stroop. *Biol. Psychiatry* 45, 1542–1552.

Costello, E.J., Angold, A., Burns, B.J., Stangl, D.K., Tweed, D.L., Erkanli, A., Worthman, C.M., 1996. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch. Gen. Psychiatry* 53, 1129–1136.

DeBello, M., Soutullo, C., Hendricks, W., Niemeier, R.T., McElroy, S.L., Strakowski, S.M., 2001. Prior stimulant treatment in adolescents with bipolar disorder: association with age and onset. *Bipolar Disord.* 3, 53–57.

Dilsaver, S.C., Henderson-Fuller, S.M., Akiskal, H.S., 2003. Occult mood disorders in 104 consecutively presenting children referred for the treatment of attention-deficit/hyperactivity disorder in a community mental health clinic. *J. Clin. Psychiatry* 64, 1170–1176.

Drevets, W.C., 2000. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog. Brain Res.* 126, 413–431.

Elia, J., Ambrosini, P., Berrettini, W., 2008. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child Adolesc. Psychiatry Ment. Health* 2, 15–23.

Faraone, S.V., Biederman, J., 2004. A controlled study of functional impairments in 500 ADHD adults. Paper presented at the 157th annual APA meeting; May 6, 2004, New York, NY.

Faraone, S.V., Antshel, K.M., 2008. Diagnosing and treating adults with attention-deficit/hyperactivity disorder. *World Psychiatry* 7, 131–136.

Faraone, S.V., Biederman, J., Wozniak, J., Mundy, E., Mennin, D., O'Donnell, D., 1997a. Is comorbidity with ADHD a marker for juvenile-onset mania? *J. Am. Acad. Child Adolesc. Psych.* 36, 1046–1055.

Faraone, S.V., Biederman, J., Mennin, D., Wozniak, J., Spencer, T., 1997b. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J. Am. Acad. Child Adolesc. Psych.* 36, 1378–1390.

Faraone, S.V., Biederman, J., Monuteaux, M.C., 2001. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? *J. Affect. Disord.* 64, 19–26.

Fischer, A.G., Bau, C.H.D., Grevet, E.H., Salgado, C.A., Victor, M.M., Kalil, K.L., Sousa, N.O., Garcia, C.R., Belmonte-de-Abreu, P., 2007. The role of comorbid major depressive disorder in the clinical presentation of adult ADHD. *J. Psychiatric Res.* 41, 991–996.

Gibson, A.P., Bettinger, T.L., Patel, N.C., Crismon, M.L., 2006. Atomoxetine versus stimulants for treatment of attention-deficit /hyperactivity disorder. *Ann Pharmacother.* 40 (6), 1134–1142.

Jaideep, T., Reddy, Y.C.J., Srinath, S., 2006. Comorbidity of attention deficit hyperactivity disorder in juvenile bipolar disorder. *Bipolar Disord.* 8, 182–187.

Karam, R.G., Bau, C.H., Salgado, C.A., Kalil, K.L., Victor, M.M., Sousa, N.O., Vitola, E.S., Picon, F.A., Zeni, G.D., Rohde, L.A., Belmonte-de-Abreu, P.,

- Grevet, E.H., 2008. Late-onset ADHD in adults: milder, but still dysfunctional. *J. Psychiatr. Res.* (Epublication 2008 Nov 12).
- Kent, L., Craddock, N., 2003. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? *J. Affect. Disord.* 73, 211–221.
- Kessler, R.C., Adler, L., Barkley, R., Biederman, J., Conners, C.K., Demler, O., Faraone, S.V., Greenhill, L.L., Howes, M.J., Secnik, K., Spencer, T., Ustun, T.B., Walters, E.E., Zaslavsky, A.M., 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.
- Malhi, G.S., Ivanovski, B., Hadzi-Pavlovic, D., Mitchell, P.B., Vieta, E., Sachdev, P., 2007. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disord.* 9, 114–125.
- 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.
- Milberger, S., Biederman, J., Faraone, S.V., Murphy, J., Tsuang, M.T., 1995. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. *Am. J. Psychiatry* 152, 1793–1799.
- Millstein, R.B., Wilens, T.E., Biederman, J., Spencer, T.J., 1997. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *J. Atten. Disord.* 2, 159–166.
- Newcorn, J.H., Weiss, M., Stein, M.A., 2007. The complexity of ADHD: diagnosis and treatment of the adult patient with comorbidities. *CNS Spectr.* 12 (8 Suppl 12), 1–14.
- Nierenberg, A.A., Miyahara, S., Spencer, T., Wisniewski, S.R., Otto, M.W., Simon, N., Pollack, M.H., Ostacher, M.J., Yan, L., Siegel, R., Sachs, G.S., STEP-BD Investigators, 2005. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol. Psychiatry* 57, 1467–1473.
- Ohlmeier, M.D., Peters, K., Kordon, A., Seifert, J., Wildt, B.T., Wiese, B., Ziegenbein, M., Emrich, H.M., Schneider, U., 2007. Nicotine and alcohol dependence in patients with comorbid attention-deficit/hyperactivity disorder (ADHD). *Alcohol Alcohol.* 42, 539–543 Electronic publication 2007 Aug 31.
- Peterson, K., McDonagh, M.S., Fu, R., 2008. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. *Psychopharmacology (Berl)* 197 (1), 1–11.
- Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., Bullmore, E.T., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am. J. Psychiatry* 156, 891–896.
- Sachs, G.S., Baldassano, C.F., Truman, C.J., Guille, C., 2000. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. *Am. J. Psychiatry* 157, 466–468.
- Safren, S.A., Otto, M.W., Sprich, S., Winett, C.L., Wilens, T.E., Biederman, J., 2005. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behav. Res. Ther.* 43, 831–842.
- Scheffer, R.E., Kowatch, R.A., Carmody, T., Rush, A.J., 2005. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am. J. Psychiatry* 162, 58–64.
- Secnik, K., Swensen, A., Lage, M.J., 2005. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. *Pharmacoeconomics* 23, 93–102.
- Sentissi, O., Navarro, J.C., Oliveira, H.D., Gourion, D., Bourdel, M.C., Baylé, F.J., Olié, J.P., Poirier, M.F., 2008. Bipolar disorders and quality of life: the impact of attention deficit/hyperactivity disorder and substance abuse in euthymic patients. *Psychiatry Res.* (Epublication 2008 Sept 10).
- Sobanski, E., Brüggemann, D., Alm, B., Kern, S., Philipsen, A., Schmalzried, H., Hessler, B., Waschkowski, H., Rietschel, M., 2007. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). *Eur. Arch. Psychiatry Clin. Neurosci.* 257, 371–377.
- Srinath, S., Reddy, Y.C.J., Girimaji, S.C., Seshadri, S.P., Subbakrishna, D.K., 1998. A prospective study of bipolar disorder in children and adolescents from India. *Acta Psychiatr. Scand.* 98, 437–442.
- State, R.C., Frye, M.A., Altshuler, L.L., 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.
- Stein, M.A., 2007. The complexity of ADHD: diagnosis and treatment of the adult patient with comorbidities. *CNS Spectr.* 12 (8 Suppl 12), 1–16.
- Stephen, V.F., Kevin, M.A., 2008. Diagnosing and treating attention-deficit/hyperactivity disorder in adults. *World Psychiatry* 7, 131–136.
- Tamam, L., Tuğlu, C., Karatas, G., Ozcan, S., 2006. Adult attention-deficit hyperactivity disorder in patients with bipolar I disorder in remission: preliminary study. *Psychiatry Clin. Neurosci.* 60, 480–485.
- Tamam, L., Karaku, G., Ozpoyraz, N., 2008. Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. *Eur. Arch. Psychiatry. Clin. Neurosci.* 258, 385–393 Electronic publication 2008 Apr 24.
- Teicher, M.H., Anderson, C.M., Polcari, A., Glod, C.A., Maas, L.C., Renshaw, P.F., 2000. Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nat. Med.* 6, 470–473.
- Vershulst, F.C., van der Ende, J., Ferdinand, R.F., Kasius, M.C., 1997. The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. *Arch. Gen. Psychiatry* 54, 329–336.
- Videbech, P., 1997. MRI findings in patients with affective disorder: a meta-analysis. *Acta Psychiatr. Scand.* 96, 157–168.
- Wilens, T.E., Prince, J.B., Spencer, T., Van Patten, S.L., Doyle, R., Girard, K., Hammer, P., Goldman, S., Brown, S., Biederman, J., 2003. An open trial of bupropion for the treatment of adults with attention-deficit/hyperactivity disorder and bipolar disorder. *Biol. Psychiatry* 54, 9–16.
- Wilens, T.E., Adamson, J., Monuteaux, M.C., Faraone, S.V., Schilling, M., Westerberg, D., Biederman, J., 2008. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. *Arch. Pediatr. Adolesc. Med.* 162, 916–921.
- Wingo, A.P., Ghaemi, S.N., 2007. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. *J. Clin. Psychiatry* 68, 1776–1784.
- Winokur, G., Coryell, W., Endicott, J., Akiskal, H., 1993. Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). *Am. J. Psychiatry* 150, 1176–1181.
- Wozniak, J., Biederman, J., Mundy, E., Mennin, D., Faraone, S.V., 1995. A pilot family study of childhood-onset mania. *J. Am. Acad. Child Adolesc. Psychiatry* 34, 1577–1583.