Brief Communication

Comorbidity With ADHD Decreases Response to Pharmacotherapy in Children and Adolescents With Acute Mania: Evidence From a Metaanalysis

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Objective: To assess whether comorbid attention-deficit hyperactivity disorder (ADHD) influences response to treatment in young patients with acute mania.

Methods: We conducted a metaanalysis of 5 open trials of 100, 35, 41, 60, and 37 children and adolescents. The pooled group included 273 children and adolescents with bipolar disorder (BD), divided into 2 subgroups: those with (n = 132), and those without (n = 141), ADHD comorbidity.

Results: There was a moderate and significant reduction in relative risk (RR) favouring treatment response in children and adolescents with BD but without ADHD comorbidity (RR 0.822; 95%CI, 0.69 to 0.97; P = 0.021). The negative effect of ADHD comorbidity on treatment response was more significant in studies including adolescents only or subjects with BD I only.

Conclusion: These findings suggest that children and adolescents with BD and ADHD tend to be less responsive to drugs used in treatment of acute mania.

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Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- BD in prepubertal children may differ from BD in adolescents.
- Evidence-based data concerning the treatment of children and adolescents with BD are lacking.
- Comorbidity with ADHD may limit pharmacologic treatment response in children and adolescents with BD.

Limitations

- The metaanalysis included open trials only, with no standardized procedure for clinical assessment of BD and (or) ADHD symptomatology and with heterogeneous study design.
- Consequently, the metaanalysis had only 273 subjects, and we could not distinguish between the treatments used in the studies.

Key Words: *bipolar disorder, attention-deficit hyperactivity disorder, child, adolescent, acute treatment, metaanalysis*

Over the last years, there has been a growing interest in BD in children and adolescents. Although epidemiologic data are scarce, the estimated prevalence of all forms of youth BD diagnosed according to DSM-IV criteria is 1%.[1,2] In the 1990s, it was shown that a manic episode during adolescence presents some semiologic particularities that bring about both diagnostic and therapeutic difficulties.[3] From the late 1990s, interest shifted to pediatric BD, which tends to be chronic and continuous[4] and highly comorbid with ADHD,[5] with psychotic symptoms being exceptional.[6] Since these 2 disorders share similar symptoms and since there are no specific clinical criteria for BD in children, the current classifications[6] have the following major methodological problems:

- Periodicity is not considered in pediatric BD.
- The developmental perspective is put aside.
- Genetic studies do not prove the hypothesis of a vulnerability shared by these 2 disorders.
- Follow-up studies do not show a link between the 2 disorders.

Consequently, whether the 2 clinical expressions of bipolarity in children and adolescents are on the same continuum or represent the same disease remains controversial.[1,6] Nevertheless, in the field of psychopharmacology, many treatment studies have been based on weak inclusion criteria in terms of the clinical definition of BD and patient age: for instance, BD I is included with BD II; adolescents are included with children, which implies including clear episodic BD with pediatric chronic BD; BD with comorbid ADHD is included with BD without comorbid ADHD. Two studies showed that comorbidity with ADHD decreased the level of response to lithium in adolescents with BD I.[7,8] However, 2 other studies,[9,10] one including children and subjects with BD II,[9] did not report similar findings. To investigate this crucial issue, the current study provides a metaanalysis of the available data testing the influence of comorbid ADHD on treatment response in juvenile acute manic episodes, whatever the chosen pharmacologic treatment.

Methods

Study Inclusion

We searched the MEDLINE database, using the following key words: bipolar disorder and (or) children–adolescents and (or) pharmalogic treatment. From January 1, 1972, until March 31, 2005, 28 publications were released. We excluded isolated clinical cases, reports involving fewer than 6 patients, and prophylactic treatment studies. We selected the remaining 17 reports for inclusion in the metaanalysis.

To be significant for the metaanalysis, trials had to report treatment response in samples of children and adolescents with BD where comorbidity with ADHD was systematically addressed. Clinical-outcome data had to be available on treatment response according to ADHD comorbidity. When detailed outcome was not available, we asked the authors of the papers to provide us with their data so that we could include their sample in the metaanalysis.

Response Criteria and Hypothesis

Given the heterogeneity of the study designs, it was not possible to use a unique and common response criterion across selected trials for the metaanalysis. Therefore, we used the primary outcome measure of each trial to discriminate between responders and nonresponders (Table 1). We assessed 2 hypotheses. Hypothesis 1 was that existing comorbid ADHD decreases treatment response in children and adolescents with acute mania. Hypothesis 2 was that the negative effect (should there be one) on treatment response is higher in studies including adolescents only or subjects with BD I only. We hypothesized that, in studies including children or subjects with BD II, heterogeneity in diagnosis should contribute to the variability in response rates.

Statistical Analysis

The statistical analysis was performed with EasyMA software (Cucherat et al, Lyon, FR, 2001). We used the RR as a parameter of efficacy, with a fixed-effect model that assumed a constant treatment effect between trials. For each study, we calculated the pooled estimate of the overall RR, using the inversed variance-weighted RR. A chi-square association and chi-square heterogeneity tests were performed, and the *P* value for significance was set at 0.05. The RRs with the corresponding 95%CI are presented in the analysis. The same analysis was used to subgroup studies with adolescents only in comparison with others and to subgroup studies of subjects with BD I only in comparison with others.

Results

Selected Trial Characteristics (Table 1)

Among the 17 trials selected from the MEDLINE database search, only 8 included children or adolescents with BD and comorbid ADHD. Four reports offered sufficiently detailed data for the metaanalysis.[7–10] One team sent us unpublished detailed data for inclusion in the study.[11] One no longer had available raw data.[12] Finally, 2 teams did not answer our request or refused to participate in the metaanalysis.[13,14] In sum, the current analysis included 5 open trials of 100, 35, 41,

Abbreviations used in this article

ADHD	attention-deficit hyperactivity disorder
BD	bipolar disorder
CI	confidence interval
RR	relative risk

Table 1 Characteristics and study designs of the trials included in the metaanalysis

Authors	*n* (Age in years)	Drug treatment	Study design	Inclusion criteria	Response criteria	Trial weight, %
Strober et al[8]	60 (13–17)	Lithium	Open 4 weeks	BD I ADHD comorbidity	CGI	22
Kafantaris et al[10]	100 (12–18)	Lithium	Open 4 weeks	BD I ADHD comorbidity No substance abuse	↘33%YMRS; CGI	37
Kowatch et al[9]	35 (7–18)	Lithium or carbamazepine or divalproate	Open 24 weeks	BD I, BD II ADHD comorbidity	↘50%YMRS	13
State et al[7]	42 (12–19)	Lithium or divalproate	Retrospective study	BD I ADHD comorbidity	CGI-BD	15
Pavuluri et al[11]	37 (5–18)	Risperidone + lithium compared with risperidone + divalproate	Open 24 weeks	BD I ADHD comorbidity	↘50%YMRS	13

CGI = Clinical Global Impression; YMRS = Young Mania Rating Scale

60, and 37 children and adolescents. The pooled group included 273 children and adolescents with BD, divided into 2 subgroups: those with (n = 132), and those without (n = 141), ADHD comorbidity.

The Effect of ADHD Comorbidity on Response to Treatment in Youth With Acute Mania

There was no significant heterogeneity (P = 0.56) among trials. In only 2 trials was there a significant decrease in treatment response related to ADHD comorbidity.[7,8] However, when the 5 trials were combined, there was a moderate and significant reduction in RR that favoured treatment response in acute episodes among children and adolescents with BD but without comorbid ADHD (Figure 1 shows a pooled RR of 0.822; 95%CI, 0.69 to 0.97; P = 0.021).

Secondary analyses were performed after we subgrouped studies with adolescents only,[7,8,10] in comparison with others,[9,11] and studies with subjects having BD I only,[7,8,10,11] in comparison with others.[9] As hypothesized, the effect of existing comorbid ADHD on treatment response was higher in studies including adolescents only. There was, first, a clear and significant reduction in RR that favoured treatment response in acute episodes among adolescents having BD without comorbid ADHD (Figure 2a: adolescents RR 0.77; 95%CI, 0.63 to 0.95; P = 0.013) and, second, no evidence of heterogeneity (P = 0.30) between subgroups. Moreover, the effect of existing comorbid ADHD on treatment response was higher in studies including subjects with BD I only. There was a moderate and significant reduction in RR that favoured treatment response in children and adolescents having BD 1 only without comorbid ADHD (Figure 2B: adolescents RR 0.810; 95%CI, 0.68 to 0.96; P = 0.015); as well, there was no evidence of heterogeneity (P = 0.36) among subgroups. However, this analysis should be viewed with caution because one subgroup (subjects with either BD I or BD II) was limited to a single trial only[9] that included 35 individuals.

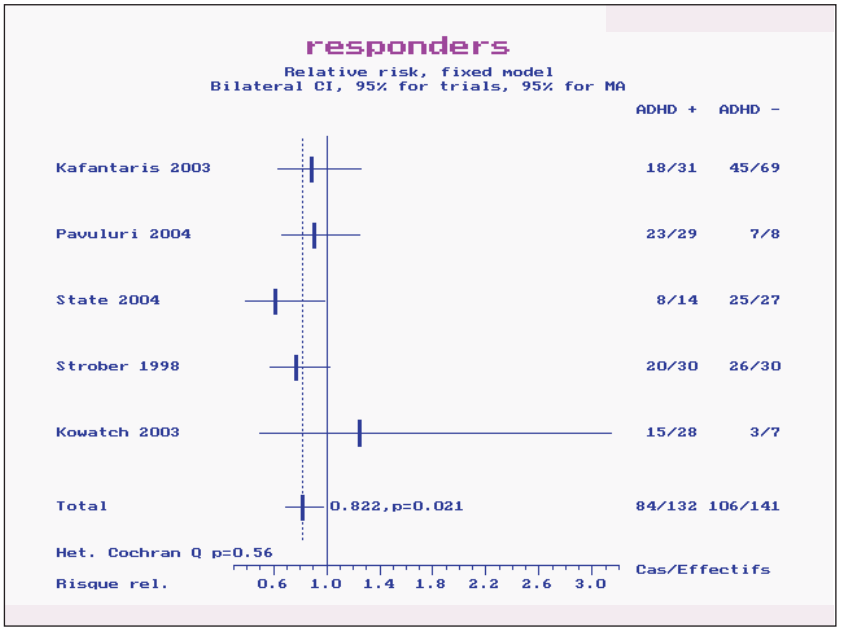
Discussion

Limitations

Before we discuss the results, several limitations should be kept in mind:

- Although the study achieved its objectives, the metaanalysis was relatively modest in size, including 5 trials with a total of only 273 subjects.
- All studies were open trials.
- Clinical diagnoses of ADHD and (or) BD were obtained by different and varying methods and, in most cases, were not standardized.
- Given the heterogeneous study designs, we could not use the same measuring instrument for treatment response.

Figure 1 RRs of individual trials and the combined analysis for response to pharmacotherapy in youths with BD, according to ADHD comorbidity



- Similarly, we could not distinguish among the different treatments used in the studies (for example, mood stabilizers or atypical neuroleptics) because most studies accepted polyprescriptions and were, as noted, open trials.
- One study[7] was a retrospective chart review and had the largest difference in response rates (Figure 1). However, the study only had a 15% weight in the metaanalysis.

Variability of the Therapeutic Response in Youth BD According to ADHD Comorbidity

The current metaanalysis confirms the principal hypothesis showing a moderate but significant reduction ($P = 0.021$) of the RR favouring treatment response in children and adolescents with acute mania without comorbid ADHD. The secondary hypotheses were also supported by the metaanalysis: the negative effect of ADHD comorbidity on treatment response was more significant in studies including only adolescents and (or) subjects with BD I. Compared with the children's response, the adolescents' response to treatment was increased. In a similar way, subjects with BD I, whatever their age, responded to treatment better than subjects with either BD I or BD II. Although diverse medications were used in the trials, adolescents with BD I are expected to respond to treatment better, whatever the antimanic treatment received. However, an alternative explanation of the poorer response in children with BD comorbid with ADHD may be an increased severity and a poorer prognosis, despite a clinical continuum.[15]

Clinical Implications for Research and Psychopharmacology

At present, studies on the treatment of children and adolescents with BDs remain scarce and difficult to interpret. So far, they have reported an improvement rate between 38% and 80%.[1] This variability might be due to the heterogeneous inclusion criteria, particularly regarding the age range (adolescents only, compared with children and adolescents), diagnosis (BD I only, compared with either BD I or BD II), and associated comorbid conditions (ADHD or substance abuse).

In the future, using reliable data in our clinical practice concerning acute mania in youth will be of paramount importance. Data should be provided by controlled studies performed within the same age range and higher sample sizes, using more homogeneous inclusion and outcome criteria. The current data suggest that acute mania comorbid with ADHD in young patients should be distinguished and needs to be addressed. With respect to the Robins and Guze[16] criterion of response to treatment, BD and BD comorbid with ADHD seem to follow different pathways. Typical BD should be differentiated from other BD in pharmacologic trials, as suggested by the metaanalysis: despite the disappointing results of the available studies, BD I in adolescents might respond better to pharmacologic treatments.

Figure 2a RRs of trials with adolescents only with BD and with children and adolescents with BD for response to pharmacotherapy, according to ADHD comorbidity

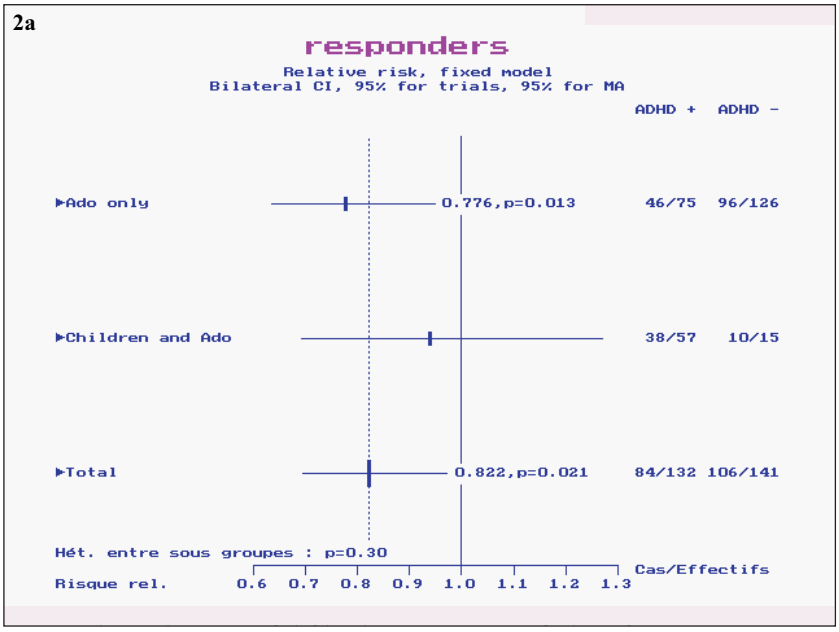
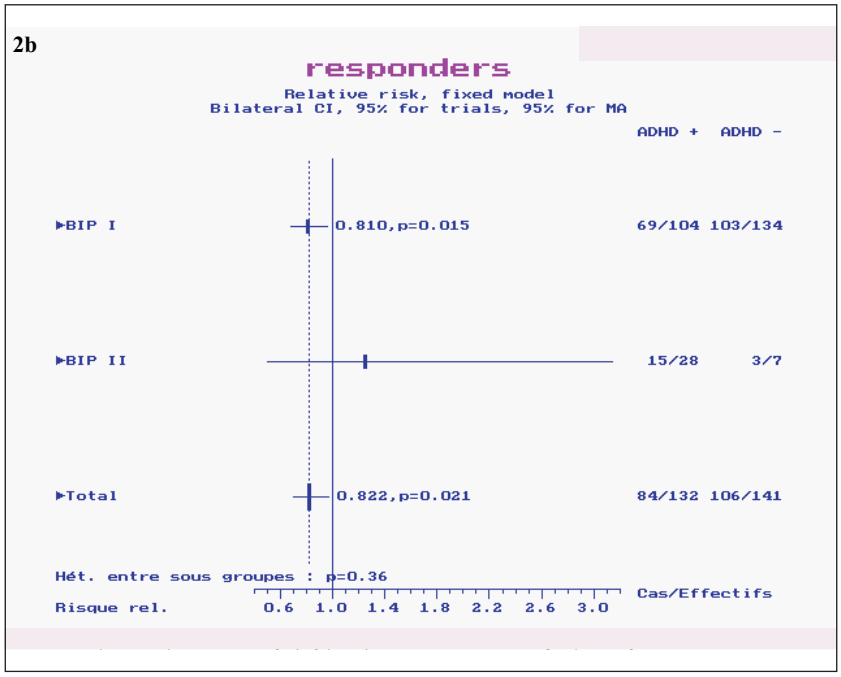


Figure 2b RRs of trials in youths with BD I only and BD I and II for response to pharmacotherapy, according to ADHD comorbidity



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Résumé : La comorbidité du THADA diminue la réponse à la pharmacothérapie chez les enfants et adolescents souffrant de manie aiguë : données probantes d'une méta-analyse

Objectif : Évaluer si le trouble d'hyperactivité avec déficit de l'attention (THADA) comorbide influence la réponse au traitement chez les jeunes patients souffrant de manie aiguë.

Méthodes : Nous avons mené une méta-analyse de 5 essais ouverts de 100, 35, 41, 60, et 37 enfants et adolescents, respectivement. Le groupe comprenait en tout 273 enfants et adolescents souffrant de trouble bipolaire (TB), divisés en 2 sous-groupes : ceux qui avaient (n = 132) et ceux qui n'avaient pas (n = 141) de THADA comorbide.

Résultats : Il y avait une réduction modérée et significative du risque relatif (RR) favorisant une réponse au traitement chez les enfants et les adolescents souffrant de TB mais sans THADA comorbide (RR 0,822; 95 % IC, 0,69 à 0,97; P = 0,021). L'effet négatif de la comorbidité du THADA sur la réponse au traitement était plus significatif dans les études incluant les adolescents seulement ou les sujets souffrant de TB I seulement.

Conclusion : Ces résultats suggèrent que les enfants et les adolescents souffrant de TB et de THADA tendent à répondre moins bien aux médicaments utilisés dans le traitement de la manie aiguë.