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ORIGINAL CONTRIBUTION

Treatments in child and adolescent bipolar disorders

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Abstract The existence of bipolar disorder in adolescents is now clearly established. However, whether bipolarity exists in children is more controversial. We reviewed the literature on acute and prophylactic treatment of bipolar disorder in youths. The guidelines for the treatment of bipolar disorder in children and adolescents are generally similar to those applied in adult practice. But no evidence-based data support the use of mood stabilisers or antipsychotics since we only found two placebo-randomised controlled trials testing the efficacy of lithium in the paediatric literature. Therefore, we support the view that prescriptions should be limited to the most typical cases. In fact, the use of mood stabilisers or antipsychotics in the treatment of bipolar disorder in children and adolescents appears to be of limited use when a comorbid condition, such as attention deficit hyperactivity disorder, occurs unless aggressive behaviour is the target symptom.

Key words bipolar disorder – child – adolescent – acute treatment – prophylactic treatment

Introduction

For a long time, the idea that bipolar disorders (BD) exist in adolescence was an unpopular one. Today, there is a growing interest in the topic [1–3]. Using DSM-IV diagnostic criteria, an epidemiological study reported a prevalence of 1% for all forms of adolescent bipolar disorders [4]. However, if we look only at bipolar I disorder (at least one typical manic episode), the prevalence in adolescence decreases at 0.1%.

A manic episode during adolescence presents certain semiological features that can result in diagnostic difficulties, and consequently, therapeutic ones as well [5]. The mood episodes are more frequently associated with psychotic symptoms (in 30% to 70% of cases, depending on the study) than in adults [2, 6]. Differentiating between a manic episode and an acute delusional schizophrenic episode remains difficult at this stage of life. The frequency of diagnostic errors during the initial evaluation is estimated at approximately 50% of cases [7]. However, experienced clinicians can properly diagnose mania [8].

During a manic episode in adolescence, the classical euphoria is often replaced by a dysphoric mood, and in some cases, irritability or aggressive behaviour [9–11]. Mood is frequently mixed, and mood changes may be characterised by rapid cycles [2]. Behavioural disorders may also occur, including sexual disinhibition, which can lead to reckless sexual behaviours and endanger the adolescent [12]. From a therapeutic point of view, it is essential to give a proper diagnosis at this age in order to treat an acute episode effica-

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ciously. Moreover, an adapted prophylactic treatment can prevent possible relapses, which often entail a significant risk of suicidal acts, substance abuse, and a major dysfunction in social, academic and affective life.

Since the late 1990s, interest has shifted to a paediatric bipolar disorder that tends to be chronic and continuous [2] and is highly comorbid with attention deficit hyperactivity disorder (ADHD) [13], with the occurrence of psychotic symptoms being the exception [14]. In the view of many authors, paediatric bipolar disorder does not represent the same disorder as is found in adults [15–18]. All point out the confusion between the bipolar disorder seen in adults, which has defined episodes of depression and mania with intervals without any symptoms, and the atypical clinical symptomatology of mania in children. Given that having clear euthymic periods is not a diagnostic criterion for BD in the DSM-IV, continuous forms of hypomania, which are frequent in children, may fit the criteria for bipolar disorder as well. In other words, should we interpret euphoria and grandiosity in young children in the same way as we would in adults [14]? Should we ignore the impact of environmental factors or learning difficulties on emotional regulation, since these aspects of psychopathology are often left out of structured diagnostic interviews [14, 16]?

Carlson [14] recently reviewed some research issues raised by the current definition of bipolar disorder in children and adolescents to consider what a broader definition of mania with less clear-cut episodes, more childhood psychopathology and concurrent comorbidity might represent: [1] a developmentally altered condition; this implies that it will change in adulthood; [2] an earlier and more severe condition; this implies adolescent/adult BD to be on the same continuum as paediatric bipolar condition; [3] a subtype or a related condition, such as rapid cycling in adult BD; [4] a temperamental, genetically related construct that is stable and may or may not predict BD in adulthood.

Notwithstanding the controversies regarding paediatric bipolar disorder, a group of experts recently published recommendations in the *Journal of the American Academy of Child and Adolescent Psychiatry* on treatment of bipolar disorder in children and adolescents between 6 and 17-years old [3]. The recommended therapeutic treatment is similar to what is proposed for an adult subject. If there are no psychotic features, acute treatment should be a monotherapy with a mood stabiliser (lithium, divalproate, or carbamazepine) or with an antipsychotic (olanzapine, risperidone, or quetiapine) for 4 to 6 weeks (or 8 for lithium). If the response is low, a second drug can be prescribed; an association of two mood stabilisers is preferred to a combination of an antipsychotic and a mood stabiliser. If there are psychotic features, a treatment combining a mood stabiliser and an antipsychotic is recommended. If there is a partial response, an association of three drugs is then advocated: two mood stabilisers and an antipsychotic. If there is no response or poor tolerance, treatment with electroconvulsive therapy (ECT) (in adolescents only) or clozapine is possible [3]. The Food and Drug Administration (FDA) allows lithium prescriptions for BD only for adolescents older than twelve. Extrapolating from the data from studies conducted on adults, this procedure presents some risks [19, 20]. Mood stabiliser prescriptions during adolescence seem to have increased considerably [21]. Bhangoo et al. [22] reported practitioners' most popular prescriptions for youths with BD in a psychiatric setting: the treatment included on average more than three psychotropic drugs, the most frequently prescribed being valproate, lithium and gabapentine [22]. The choice of gabapentine was based on no rationale since this drug works no better than a placebo in adult BD [23].

In light of the numerous controversies that have arisen from these recommendations [15], we propose in this article to review the available scientific literature on BD treatments in young people. We will pay particular attention to age-specific aspects and diagnosis at inclusion, and we will discuss the possible developments in clinical research and practice, taking our clinical expertise into account.

Methods

We searched the Medline database with the following keywords: *bipolar disorder* and/or *children-adolescents* and/or *pharmacological treatment*. We found 28 publications between 1972 and March 2005. We excluded isolated clinical cases and reports with fewer than 6 patients. For open trials, we found 6 publications concerning mood stabilisers and 2 on antipsychotics with fewer than 10 patients; 5 publications on mood stabilisers and 3 on antipsychotics with more than 10 patients; 3 publications on an association of mood stabilisers and 2 on a combination of mood stabilisers and antipsychotics. We also found 3 retrospective studies including more than 10 patients. Finally, we only found two double-blind controlled and randomised studies evaluating lithium versus a placebo. For prophylactic treatment, we found 4 studies (1 retrospective, 2 open and prospective, and 1 double-blind and controlled). In total, 21 reports were included in our review (Table 1). Since ECT can also be used in bipolar I disorder, a specific review was

Table 1 Main studies on bipolar disorder treatment in children and adolescents

Authors (year)	N, *Age* (duration)	Drug	Study design	Inclusion criteria	Scales and measurements	Improvement %*
1A—Lithium salts						
Geller et al. (1998a)	25, *12–18 years* (6 weeks)	Lithium vs. PBO	Controlled randomised Wash-out (2 weeks)	BD I, BD II + addiction	**CGAS**; K-SADS mood	46% vs. 8% *P*=0.046 (NS with K-SADS)
Kafantaris et al. (2004)	40, *12–18 years* (2 weeks)	Lithium vs. PBO	Controlled randomised in responding patients	BD I Patients responding to lithium (4 weeks)	**YMRS**; CGI	52.6% vs. 61.9% (NS) of Σ exacerbation
Kafantaris et al. (2003)	100, *12–18 years* (4 weeks)	Lithium	Open	BD I ADHD comorbidity Excluded: substance abuse	**YMRS**; CGI	63%
Strober et al. (1988)	50, *13–18 year* (6 weeks)	Lithium	Open	BD I	**CGI**	68%
Kowatch et al. (2000)	42, *6–18 years* (6 weeks)	Lithium vs. divalproate vs. carbamazepine	Open	BD I, BD II	**YMRS**	38% vs. 53% vs. 38% (NS)
Findling et al. (2003)	99, *5–17 years* (20 weeks)	Lithium + sodium divalproate	Open	BD I, BD II Excluded: substance abuse	**YMRS**; CDRS-R; CGAS	42%
Kowatch et al. (2003)	35, *7–18 years* (24 weeks)	Lithium or carbamazepine or divalproate ± another drug after 8 weeks	Open	BD I, BD II ADHD comorbidity	**YMRS**; CGAS; CGI-BP	80%
State et al. (2004)	42, *12–19 years*	Lithium or divalproate	Retrospective controlled	BD I ADHD comorbidity	**CGI**	92% (ADHD=0) vs. 57% (+ADHD) (*P*=0.007)
Strober et al. (1998a)	30, *13–17 years* (4 weeks)	Lithium	Controlled open trial	BD I vs. BD I + ADHD	**BRMS**	80.6% vs. 57.7% (*P*=0.005)
1B—Anticonvulsants						
Deltito et al. (1998)	36, *13–18 years* (12 months)	Divalproate	Open	BD (N=4), mixed states (N=16), depressions, others	**CGI-S**	67% (manic Σ)
Wagner et al. (2002)	40, *7–19 years* (8 weeks)	Divalproate	Open	BD I, BD II ADHD comorbidity Excluded: substance abuse	**MRS**	61%
1C—Atypical neuroleptics						
Frazier et al. (1999)	28, *4–17 years* (24 weeks)	Risperidone	Retrospective	BD I, BD II ADHD comorbidity (85%)	CGI-I	82% (manic Σ) 69% (psychotic Σ)
Frazier et al. (2001)	23, *5–14 years* (8 weeks)	Olanzapine	Open	BD I, BD II Excluded: substance abuse	**YMRS**, CGI	50%
Masi et al. (2002)	10, *12–17 years*	Clozapine	Open	BD I Resistant to other psychotropes	**CGI-S**, MRS, CGAS, BPRS	100%
Delbello et al. (2002)	30, *12–18 years* (6 weeks)	Divalproate + quetiapine vs. divalproate + placebo	Controlled randomised	BD I treated with divalproate	YMRS	87% vs. 53% (*P*=0.05)
Barzman et al. (2004)	30, *5–19 years* (1–9 months)	Aripiprazole	Retrospective	BD I, BD II, others ADHD comorbidity (53%)	**CGI-S**	67%
Pavuluri et al. (2004)	37, *5–18 years* (24 weeks)	Risperidone + lithium vs. risperidone + divalproate	Open	BD I ADHD comorbidity	**YMRS**, CGI-BP, CDRS-R	82.4% vs. 80% (NS)
1D—Relapse prevention studies						
Strober et al. (1990, 1995)	37, *13–17 years* (18 months)	Lithium	Open prospective	BD I	Relapse	More relapse if treatment ending (92% vs. 37%, *P*=0.05)
Henry et al. (2003)	15, *4–18 years* 1.4 ± 1.5 years	Divalproate	Retrospective	BD I, BD II, depression, disruptive disorders	**CGI**	53% respond to treatment after 1.5 years
Findling et al. (2005)	60, *5–17 years* (18 months)	Lithium vs. divalproate	Double-blind controlled	BD I, BD II ADHD comorbidity Excluded: substance abuse	YMRS, CGAS, CDRS-R	No difference for relapse or treatment ending between the two drugs
Dailey et al. (2005)	31, *14–18 years* (12 months)	Lithium or carbamazepine or divalproate (±AD)	Open prospective	BD I + severe delinquent behaviour	Number of delinquent acts	Fewer delinquent acts in compliant subjects (*P*<0.001)

*according to the scale in bold; AD: antidepressant; BD: Bipolar Disorder; BPRS: Brief Psychiatric Rating Scale; BRMS: Bech-Rafaelsen Mania Scale; CDRS-R: Children's Depression Rating Scale–Revised; CGAS: Children's Global Assessment Scale; CGI: Clinical Global Impression; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children; MRS: Mania Rating Scale; NS: Not significant; Σ: symptoms; YMRS: Young Mania Rating Scale

conducted with the keywords *ECT* and *Children-Adolescents* for the 1990–2005 period.

Results

Acute treatment (Table 1)

Lithium salts (Table 1A)

In the literature, we found 5 open trials including a small number of subjects [24–28].

Interestingly, all studies conducted with lithium in monotherapy-included adolescents only (Table 1). Two open studies reported data from a substantial sample of subjects [29, 30]. Strober et al. explored lithium's efficacy during a manic episode in 50 adolescents from 13 to 17 years old (6 weeks of treatment) and found a therapeutic response in approximately 68% of the cases (Clinical Global Impression, or CGI, evaluation). It also seemed that the younger the subject, the lower the response to lithium therapy. The study conducted by Kafantaris et al. evaluated lithium's efficacy during an adolescent manic episode treatment with a sample of 100 adolescents aged 12 to 18-years old. After four weeks of treatment, positive therapeutic responses were reported in 63% of the cases according to measurements done with the Young Mania Rating Scale (YMRS) and the CGI. Finally, two controlled studies, one retrospective [31] and the other open [18], showed that comorbidity with ADHD significantly decreased lithium's efficacy in bipolar adolescents.

However, we only found two controlled double-blind studies evaluating the efficacy of lithium during a manic, mixed or hypomanic episode (bipolar I or II disorder) during adolescence. The first is a 6-week double-blind controlled trial versus placebo [32], which showed lithium to be significantly more efficacious than the placebo, in 25 adolescents presenting with both bipolar I or II disorder and substance abuse, according to the Children's Global Assessment Scale (CGAS). But no significant statistical difference appeared between the two groups when the evaluation of the mood symptoms' persistence was used as a criterion (Schedule for Affective Disorders and Schizophrenia for School-Age Children, or K-SADS). The second study evaluated the exacerbation of symptoms under lithium or a placebo in a group of 40 adolescents who had responded in a 4-week open phase to lithium treatment [33]. After this first step, subjects were randomised and received either a lithium treatment or a placebo for two weeks. The exacerbation of manic symptoms, according to the YMRS, was greater in the adolescent group-taking placebo than in those taking lithium. However, there was no significant statistical difference between the two groups.

We found very few studies of lithium tolerance in young subjects. Lithium half-life elimination is lower in children and total renal clearance is higher [34]. Some authors have suggested that a curative or prophylactic treatment with lithium can be given to adolescents and children with the same medical precautions as with adults [2]. One study, however, showed significant side effects such as enuresis, asthenia and ataxia in children younger than 13 treated for aggressive behaviours with low doses of lithium [35]. Side effects of neurological origin appear to be more frequent in young children [36]. Weight gain and acne are side effects that subjects perceive to be particularly shameful during adolescence. Finally, since lithium is teratogenic, its prescription is not recommended during pregnancy. Consequently, patients should be cautious about taking lithium when there is a sexual disinhibition.

Anticonvulsants (Table 1B)

As shown in Table 1B, there are many methodological issues affecting the studies on the use of anticonvulsants in youth BD: open trials, including adolescents only or children and adolescents, and studies with combination therapy, which makes caution imperative in interpreting the results.

Two studies investigated valproate or sodium divalproate in adolescents. The first was an open report of a sample of six adolescents [37]. Another open study was conducted in 36 adolescents between 13 and 18 years old who were treated with sodium divalproate in monotherapy or in association [38]. A clinical improvement (manic features, psychotic features, agitation, emotional instability, aggressivity and anxiety) occurred in two-thirds of manic or mixed subjects ($N = 20$).

Other open trials included children and adolescents. The main open clinical study explored the therapeutic efficacy of sodium valproate in 40 children and adolescents (between 7 and 19-years old) with a manic, mixed or hypomanic episode [39]. The results showed a clinical improvement in 61% of subjects according to the Mania Rating Scale (MRS).

The Kowatch et al. [40] study compared the therapeutic effects of three mood stabilisers in a group of 42 bipolar children and adolescents aged 8 to 18 years old who had had a bipolar I or II disorder episode [40]. This open trial looked at acute, and not prophylactic, effects of lithium, sodium divalproate and carbamazepine. The study lasted six weeks. The therapeutic response, evaluated with the YMRS (score decreased by more than 50%) was 53% for sodium divalproate, 38% for lithium, and 38% for carbamazepine. The authors

found good tolerance, without any major side effects, whichever treatment was used. However, 31% of the subjects were non-compliant. An open trial studied the therapeutic efficacy of an association of lithium and sodium divalproate in 99 children and adolescents between 5 and 17 years old and presenting bipolar I or II disorders according to the DSM-IV diagnostic criteria [41]. Only 42% showed a clinical recovery from their symptoms at the end of the 20-week study.

Finally, another open trial including 35 children and adolescents showed that an association of a mood stabiliser with another psychotropic drug was superior to monotherapy with a mood stabiliser [42]. After 8 weeks with a mood stabiliser (lithium, carbamazepine or divalproate), a second psychotropic treatment was added based on response: either another mood stabiliser or a psychostimulant or an antidepressant or an antipsychotic. Over the 6 month duration of the study, 60% of the subjects received a second treatment. The therapeutic response rate was 80% according to the YMRS. Most patients (80%) had comorbid ADHD.

Regarding carbamazepine and its indication in bipolar disorders in young subjects, we found only one open trial comparing carbamazepine, lithium and divalproate but the preliminary results were weak [43].

The side effects of anticonvulsant treatments have been studied more in young subjects because they are prescribed for epileptic disorders. The side effects induced by carbamazepine most often seen in children are drowsiness, lack of coordination and dizziness. More severe side effects exist, which are also observed in adults, such as hepatic and blood toxicities. For young, fertile women, hormonal contraception is not adequate since carbamazepine is an enzymatic inductor. The FDA does not authorise carbamazepine prescriptions for psychiatric disorders, no matter what the subject's age may be [20, 44]. Side effects induced by sodium valproate in young subjects include nausea, vomiting, ataxia, tremors, alopecia, hunger with weight gain, and potentially lethal hepatic toxicity. A metabolic syndrome associated with obesity, hyperinsulinism, polycystic ovaries and hyperandrogenism has been described in young women [45]. Studies done on bipolar women who were treated with valproate have produced controversial results [46–48]. As we await data from other clinical studies, no conclusion can yet be drawn [3]. During pregnancy, close monitoring is necessary, since there is a risk of abnormal neural tube development, particularly during the first trimester.

Antipsychotics (Table 1C)

Antipsychotics are also used in the acute treatment of manic or mixed episodes. They are efficacious against psychotic symptoms and psychomotor agitation. However, we found no controlled placebo studies done on a sample of young people, although a follow-up study of adolescents with bipolar disorder showed that 17% of them were under an antipsychotic treatment [49]. The literature review showed that few clinical trials existed in this area, and that most of them were open trials, with a rather small number of children and adolescents [50, 51].

Two studies included adolescents only. The first, an open trial, evaluated clozapine efficacy in 10 adolescents between 12 and 17-years old who presented with a mixed or manic episode, that was severe and resistant to mood stabilisers and antipsychotics other than clozapine [52]. The ten subjects of this study showed a clinical improvement according to the CGI evaluation. The second, a double-blind controlled study, compared sodium divalproate with quetiapine to sodium divalproate with a placebo [53]. Thirty adolescents between 12 and 18 years old and presenting with bipolar I disorder participated in the trial. The therapeutic response, according to the YMRS, was significantly superior (87% versus 53%, $P = 0.05$) for subjects treated with the combination treatment.

Four other studies included children and adolescents. A retrospective study done on 28 children and adolescents with a bipolar disorder who were treated with risperidone alone showed a clinical improvement of 82% for manic symptoms and 69% for psychotic symptoms (CGI evaluation) [54]. An open trial examined olanzapine efficacy in monotherapy for manic, mixed or hypomanic episodes in 23 children and adolescents between 5 and 14-years old (55). The treatment lasted eight weeks. A clinical improvement occurred in 50% of subjects according to the YMRS. Recently, a naturalistic retrospective study examined the effectiveness and tolerability of aripiprazole for paediatric BD (56). Thirty children and adolescents were examined and two-thirds were considered as responders to 10 mg/day of aripiprazole on average. However, the results should be regarded with caution as the subjects' clinical status was heterogeneous and only 4 responders were taking aripiprazole in monotherapy. Finally, an open trial compared the therapeutic efficacy of an association of a mood stabiliser (lithium or sodium divalproate) and risperidone for six months in 37 children and adolescents aged 5 to 18 years who had bipolar I disorder according to the DSM-IV [57]. The evaluation included the YMRS, CGI-BP and CDRS-R scales, and showed a symptomatic improvement in 80% of the subjects whatever the therapeutic regimen.

Nowadays, the side effects of psychotropic treatments in children and adolescents are poorly studied except for antipsychotics. Neurological effects are less

Table 2 Meta-analysis (1993–2003) of studies of the use of electroconvulsive therapy in children and adolescents including 10 patients and more

Author Year Location	Number of patients (age in years)	Duration design	Evaluation of the response to ECT
2A—Main characteristics of the studies included in the meta-analysis			
Schneekloth et al. 1993 Rochester, USA	20 (13–18)	8 years Retrospective	CI
Kutcher and Robertson 1995 Toronto, Canada	16 (16–22)	8 years Retrospective controlled	CI, BPRS
Ghaziuddin et al. 1996 Ann Arbor, USA	11 (13–18)	3 years Retrospective	CI, CDRS-R, GAF
Moise et Petrides. 1996 New York, USA	13 (16–18)	10 years Retrospective	CI
Cohen et al. 1997 Paris, France	21 (13–19)	11 years Retrospective	CI
Walter et Rey. 1997–2003 Sydney, Australia	72 (14–18) (84 series)	9 years Retrospective	CI, GAF
Strober et al. 1998 Los Angeles, USA	10 (13–17)	18 years Retrospective	CI, HAM-D, LIFE
Duffett et al. 1999 London, UK	12 (12–18)	1 year Retrospective	CI
Bloch et al. 2001 Tel Aviv, Israel	24 (13–19)	5 years Retrospective controlled	CI
Diagnosis	Number of diagnoses**	% of improved cases according to studies	Total number of improved cases (%)
*2B—Efficacy of ECT according to diagnosis**			
MDE without psychotic features	36	64%–100%	26 (72%)
MDE with psychotic features	65	50%–100%	57 (89%)
Manic episode	25	75%–100%	23 (92%)
SCZ and schizophreniform disorder	44	24%–60%	20 (40%)
Schizo-affective disorder	19	24%–100%	7 (37%)
Catatonic episode***	11	80%–100%	9 (82%)
Other diagnosis	11	0%–100%	6 (54%)
TOTAL	211	50%–100%	142 (71%)

CI: Clinician's Impression; BPRS: Brief Psychiatric Rating Scale; CDRS-R: Children's Depression Rating Scale–Revised; GAF: Global Assessment of Functioning Scale; HAM-D: Hamilton Depression scale; LIFE: Longitudinal Interval Follow-up Evaluation; MDE: major depressive episode; SCZ: schizophrenia

* In Bloch et al. study, efficacy per patient and diagnosis is not given. We have attributed an equal response rate for all diagnoses: 58%

** The total number of diagnoses (211) is greater than the number of patients (199) since some patients from Walter and Rey's studies received several ECT treatments

*** SCZ or MDE with catatonic features

pronounced with antipsychotics than with classical medications. Paradoxically, tardive dyskinesia is more frequent in children and adolescents than in adults [58–60]. Drowsiness during the day and transitory asthenia are frequently reported [60]. However, neurological tolerance seems to be greater than endocrinal tolerance. Weight gain is greater in young subjects than in adult subjects: on average 5 to 7 kg, according to some studies [52, 55, 60]. Other side effects resemble those seen in adults.

Electroconvulsive therapy (Table 2)

The number of studies of ECT during adolescence is low and there are only three controlled studies. Even though the use of ECT in youths continues to be controversial, there is a growing interest nowadays. Caution is recommended, but its efficacy is observable in the treatment of severe and resistant mood disorders and catatonic syndromes [61]. Long-term side effects have not been sufficiently studied.

In France, there are no specific recommendations concerning ECT in adolescence. In the United States, the American Academy of Child and Adolescent Psychiatry (AACAP) recently issued recommendations [62]. They reminded readers that its use is illegal for patients under a certain age (14- or 16-years old) in some states. The opinion of an outside psychiatrist is recommended, with a memory evaluation before, at the end, and 3 to 6 months after the last session of the treatment. Three parameters were cited in the guidelines for ECT decision making: the nosographic diagnosis, the severity of symptoms and the resistance to psychotropic treatment.

A literature review from the first use in 1942 to 1996 showed that 396 children and adolescents under 18 years old were treated with ECT, but most of these studies reported only single cases or very small series

[63]. According to this review, the reason for ECT treatment was mood disorders in 72% of cases. A significant improvement or complete disappearance of symptoms was seen in 53% of subjects, and in 70% of mood disorder cases. Since 1993, nine retrospective studies including ten patients or more have been published (Table 2A). Two of them were controlled trials [64, 65]. These more recent studies agreed with the results obtained in Rey and Walter's (1997) review. In particular, 23 of 25 patients (92%) treated with ECT for a manic episode saw their condition improve (Table 2B).

ECT's side effects are rarely studied. No deaths have been reported in adolescents [62]. The theoretic risk is similar to the risk from brief general anaesthesia. ECT side effects described in adolescents include transient memory impairments, prolonged epilepsy fits (more frequent in adolescents than in adults) and tardive seizures, and other benign and transitory effects (headaches, confusional states, nausea, muscular pains) [66–68]. Eleven bipolar adolescents treated for a severe mood episode were evaluated in terms of their cognition four years later and compared with ten matched adolescents not treated with ECT. No objective significant difference was found in long-term anterograde memory, even though subjective memory problems were reported by two subjects from the ECT group [69]. Two groups studied patients' and parents' experiences and opinions concerning ECT in young people [70, 71]. In general, the two studies showed that patients and their parents had a positive attitude toward ECT, even though the treatment frightened the adolescents and their parents initially.

Prophylactic treatments

A prophylactic treatment prevents disease development in general. In bipolar I disorder, it prevents relapses of manic, mixed or depressive episodes. We found no double-blind placebo controlled study on the prophylactic efficacy of mood stabiliser treatment during adolescence, whether the treatment was lithium salts, carbamazepine or sodium valproate. However, four studies have explored this issue (Table 1D).

Two studies included adolescents with BD I only. A prospective study by Strober's group explored the link between the duration of treatment and the occurrence of a relapse [72, 73]. Using an open naturalistic prospective design for a term of 18 months, this study evaluated 37 adolescents who received a prophylactic chemotherapy with lithium for bipolar I disorder. The results showed that an early end to treatment significantly increased the rate of relapse. This rate could reach 92% in the group of adolescents who ended their treatment, while those who continued lithium had a relapse rate of 37% ($P = 0.05$). The authors advocated continuous prophylactic lithium treatment for BD I throughout adolescence and the first years of adulthood [73]. A second naturalistic study explored the effect of mood stabiliser treatment on the number of delinquent acts committed by 31 adolescents between 14 and 18-years old with BD I associated with severe delinquency [74]. The follow-up duration was one year. These adolescents were treated with lithium, divalproate, or carbamazepine. The treatment could be associated with other psychotropic drugs, mainly antidepressants. The number of delinquent acts after treatment decreased significantly in compliant subjects compared to non-compliant ones.

The other studies included children and adolescents with BD I and II. A retrospective study conducted on 15 children and adolescents between 4- and 18-years old explored the prophylactic effect of sodium divalproate for bipolar I and II disorders. The study showed positive therapeutic responses in 53% of the cases (either a moderate or strong response according to the CGI) after a year and a half of treatment on average [75]. Finally, another study compared the prophylactic therapeutic efficacy of lithium and sodium divalproate, in monotherapy, for 18 months [76]. This study included 139 children and adolescents between 5- and 17-years old who had bipolar I or II disorders, according to the DSM-IV. They were initially treated with an association of lithium and divalproate. After four consecutive weeks of clinical remission, there were only 60 subjects left who were being given one of the two mood stabilisers in a randomised and double-blind trial. There was no significant difference between the two groups (lithium versus divalproate) in terms of the duration preceding a clinical relapse or the end of treatment. But, by the end of this study, only two subjects had not relapsed.

Discussion

The literature review shows that evidence-based data regarding the treatment of children and adolescents with BD are very limited. Most of the studies in the field are open and non-controlled, and the subject samples are very often small and heterogeneous. We could only find two controlled double-blind studies for lithium. There was no controlled study against a placebo for the other mood stabilisers (carbamazepine, valproate or sodium divalproate) or antipsychotics. One study compared the adjunction of an antipsychotic, quetapine, to divalproate versus a placebo. Also, even though there were two controlled studies of ECT, all the studies were retrospective. Fi-

nally, there was no controlled study evaluating prophylactic treatment against a placebo, but at least two naturalistic prospective studies are available.

Drug efficacy in bipolar disorder in children and adolescents

In adults, lithium is a treatment renowned for its efficacy as a mood stabiliser in BD. It is effective in the treatment of a manic or depressive episode, and it can prevent the occurrence of a relapse into a manic or depressive state [77]. The results of the two controlled studies of lithium's efficacy in the acute treatment of a manic or hypomanic episode in young people are not conclusive. The two studies showed major weaknesses, as they were characterized by a small number of subjects and diagnostic heterogeneity. Similarly, open studies reported an improvement rate of between 38% and 80% (Table 1A). Many methodological issues may explain these poor results in children and adolescents. For one thing, the clinical criteria appeared very heterogeneous in the different studies, particularly the age range and the diagnoses at inclusion. Most of the studies had a very large age range in their subject groups, including both adolescents and pre-pubescent children. However, two naturalistic follow-up studies gave more encouraging results concerning lithium for relapse prevention in young subjects with bipolar disorder. It is noteworthy that both studies included only bipolar I adolescents [73, 74].

As for the other mood stabilising treatments, the methodological limitations on the studies are similar. First, we found fewer studies. Second, they were not controlled. Third, most of them included a small sample of subjects with a large age range. Fourth, the diagnoses were heterogeneous. Studies of antipsychotic treatments for bipolar disorders are scarce. All studies included poorly defined clinical groups, with both young children and adolescents. Thus, it is difficult to ascertain the efficacy of antipsychotics against mood and/or psychotic symptoms. The same problem exists for other symptoms such as aggressive behaviours and emotional dysregulation which are present in some atypical clinical cases of young subjects. Antipsychotics and mood stabilisers can be efficacious for these latter symptoms [78]. Finally, studies of drugs evaluated in monotherapy were quite rare. However, a few recent studies explored the association of different treatments, either two mood stabilisers or an antipsychotic with a mood stabiliser (Table 1). This is quite surprising since there is a lack of studies on the efficacy of these treatments in monotherapy against a placebo, and on compliance in young subjects. It is legitimate to be worried about recommendations of aggressive treatments. Even though they have proven to be efficacious in adults, this is not the case in adolescents, and even less so in children. Should we advocate clozapine and ECT for atypical cases, as AACAP's expert panel does?

Regarding the use of ECT in bipolar adolescents, although the number of studies was more limited, the age ranges and diagnoses were more homogeneous. ECT is rarely proposed for manic episodes but rather for psychotic depression with or without catatonic features (Table 2). The response rate in resistant manic episodes is high and similar to that of other mood disorders, ranging from 75% to 100%.

Current and future methodological problems

In a commentary on the recommendations published in the AACAP review [3], McClellan (2005) pointed out the confusion between bipolar disorder in adults, which has defined episodes of depression and mania with intervals without any symptoms, and the atypical clinical symptomatology of mania in children. In the opinion of many authors, and in ours, these different clinical cases do not represent the same disorder [15–18]. According to these authors, the DSM-IV diagnostic criteria for adults should not be applied to children without taking into consideration certain specific developmental aspects, which do not have the same psychopathological significance in adults. For one thing, given that having clear euthymic periods is not a diagnostic criterion for BD in the DSM-IV, continuous forms of hypomania, which are frequent in children, as first described by psychoanalyst Melanie Klein, may fit the criteria for BD as well. Consequently, the diagnostic criteria for inclusion in the studies selected heterogeneous samples even when they referred to the DSM-IV. For some studies, only youths with bipolar I disorder were included, while in others, subjects with both bipolar I and II disorders were included. Similarly, comorbid conditions were not systematically excluded (Table 1). Finally, some subjects with more typical bipolar I disorder were excluded from the studies, because of a need for hospitalisation or a suicidal risk [32]. These facts may explain why the results are heterogeneous and poor.

Moreover, in some studies, comorbid disorders like ADHD were associated with bipolar disorders. Inevitably, an adapted treatment for these comorbid disorders, such as psychostimulants, was included. Two studies by Strober's team showed that comorbidity with ADHD decreased the response level for lithium in adolescents with BD I [18, 31]. Knowing that the link between BD and ADHD in children is highly controversial [15–17, 79, 80], we wonder why studies evaluating the antimanic properties of a drug

include young subjects based on broad and poorly defined clinical criteria. For example, in the study by Findling et al. [76], up to 60% of the subjects had comobidity with ADHD. Many isolated cases and clinical series showing an association between bipolarity and ADHD have been described in the literature. However, the hypothesis that these two disorders are related is rather weak. Since the two disorders have similar symptoms and there is no specific clinical criterion for BD in children, there are major methodological problems in the current classification criteria [81]. The fact that the two disorders share some symptoms results in diagnostic problems that are difficult to resolve. In addition, periodicity is not taken into account in child BD while the episodic nature of the disease with baseline mood periods is well known in adolescents and adults. As a matter of fact, many authors describe paediatric 'bipolar disorder' as a chronic and continuous disorder [2]. The association hypothesis is strongly supported by the works of Biederman's team at Harvard, but the developmental perspective is completely set aside. It is possible that some of the children described by this team have a diagnosis of bipolar II disorder exclusively [80]. Genetic studies do not prove the hypothesis that these two disorders share a vulnerability and follow-up studies show no link between the two disorders [82, 83]. However, the existence of manic symptoms in hyperactive children affects their functional prognosis [79].

Finally, the small number of studies means that there are few data concerning long- and short-term side effects of the pharmacological treatments of BD in young people. However, these treatments can cause side effects similar to those seen in adults, in addition to age-specific side effects. In these cases, the younger the subject, the more severe the side effects. This is true of some side effects due to lithium in children such as neurological ones [36], and of antipsychotics, such as weight gain and tardive dyskinesia [60].

Two years before the publication of the recommendations concerning the therapeutic approach to BD, the American Academy of Child and Adolescent Psychiatry, in collaboration with Best Practice, brought together another group of experts to examine the methodological issues regarding treatment studies in BD in young people [84]. These experts said that it was necessary to apply a rigorous methodology in clinical trials and to include a large number of subjects in order to be able to evaluate the efficacy and compliance of mood stabilising treatments in young patients. In light of what we have said previously concerning the numerous methodological problems, it will be essential in the future to be able to use reliable data in our clinical practice concerning bipolar disorders during adolescence. These data should come from controlled studies done on the same age range, with a large number of subjects and with a clinically homogeneous sample. More specifically, we think it is absolutely necessary to distinguish between bipolarity and ADHD in young patients, since there still are unresolved nosographic issues concerning the definition of bipolarity. We also suggest that a period of euthymia should be added to the inclusion criteria for BD.

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