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Diagnostic transition towards schizophrenia in adolescents with severe bipolar disorder type I: An 8-year follow-up study

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ABSTRACT

Background: The diagnosis of bipolar disorder-I (BD-I) is currently well-established. However, more studies exploring diagnostic stability and psychosocial adaptation during follow-up in adulthood are needed.
Objectives: We assessed factors at follow-up (FU): (1) the diagnostic stability of manic/mixed episodes from adolescence to adulthood, (2) psychosocial adaptation, and (3) factors associated with psychosocial adaptation.
Methods: A sample of 80 adolescents hospitalized in a university hospital between 1993 and 2004 for a manic or mixed episode were contacted for an FU assessment on average 8 years after the index episode. Assessments included socio-demographic data, mortality, lifetime psychiatric diagnosis, the Social Adaptation Scale, negative life events and insight.
Results: Of the 64 patients with available information, one patient died from a heart attack. Of the 55 patients available for an FU assessment, 35 (63.6%) still presented a diagnosis of BD-I at FU, whereas 20 (36.4%) had changed diagnosis towards a schizophrenia spectrum disorder. Psychosocial adaptation was moderate to poor for most patients, and 91% of the patients had at least one relapse. A low socio-economic status, intellectual disability, negative life events, a history of sexual abuse, and treatment with classical antipsychotics at FU were significantly associated with poorer psychosocial adaptation. In contrast, better insight, a family history of depression and a diagnosis of BD-I at FU were associated with better psychosocial adaptation.
Conclusion: BD-I in adolescent inpatients can lead to important morbidity and mortality during outcome. Diagnostic stability is high, but a high proportion of patients also show a transition towards a schizophrenia spectrum disorder.

1. Introduction

The existence of BD-I in adolescents is now well-established, while bipolar disorder (BD) in prepubescent children remains controversial (Harrington and Myatt, 2003; Carlson, 2005, 2011a,b; Consoli and Cohen, 2013). The NIMH proposed to distinguish three phenotypes in young people with bipolar symptomatology: a narrow phenotype, an intermediate and a large phenotype (BD—not otherwise specified) (Leibenluft et al., 2003; Carlson, 2005, 2009; Masi et al., 2006). To limit heterogeneity, Leibenluft initially proposed the term of Severe Mood Dysregulation (Leibenluft et al., 2003; Leibenluft, 2011). More recently, the Disruptive Mood Dysregulation Disorder has been selected by the DSM 5. In such a context, assessing homogenous samples of BD-I is highly recommended. There are few studies of the outcomes of adolescents with BD-I, and even fewer studies address only the narrow phenotype. The consistency of this diagnostic over time and the psychosocial outcome of these participants are still acute issues (Carlson, 2011a,b). (Carlson (2011a,b), in a recent editorial, wrote that: "we don't know what ultimately became of these teens and if they continued to have BD-I".

The lifetime prevalence rate of BD-I in adolescents is between 0.1% and 1.2% (Lewinsohn et al., 1995; Kim-Cohen et al., 2003; Van Meter et al., 2011). Interest in bipolar disorders in adolescents has increased, with several retrospective studies revealing that 20%–60% of adults with BD had their first symptoms before the age of 20 years (Joyce, 1984; Lish et al., 1994; Perlis et al., 2004). The phenomenology of acute manic or mixed episodes in adolescents can be summarized as follows: a higher frequency of mixed episodes than purely manic ones, more frequent aggression and irritability (McElroy et al., 1997; Patel

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et al., 2006), the presence of psychotic signs in 30%–60% of the cases (which can lead to diagnosis difficulties (Calderoni et al., 2001; Carlson et al., 1994; Kowatch et al., 2005; Soutullo et al., 2005)), high rates of comorbidities and a higher likelihood of a rapid cycling profile (Schurhoff et al., 2000; Birmaher et al., 2006).

Few prospective studies have addressed the course of BD in adolescents and the determinants of BD outcome (Strober et al., 1995; Carlson et al., 2000; Jairam et al., 2004; DelBello et al., 2007; Geller et al., 2008; Birmaher et al., 2009; Stringaris et al., 2010; Escamilla et al., 2011). In the rare studies which have addressed these issues, samples are sometimes heterogeneous, including adolescents as well as prepubescent children, narrow phenotype (BD-I) as well as broad phenotype (BD-nos), and inpatients as well as outpatients. In previous studies, only of adolescents exhibiting BD-I (Strober et al., 1995; Carlson et al., 2000; Jairam et al., 2004; DelBello et al., 2007), all except one showed diagnostic stability at follow-up. In the lone alternative report, 18% of the cases instead showed diagnosis transition towards schizophrenia or pharmacologically induced psychosis at follow-up (Carlson et al., 2000). Frequent relapses were reported, which included depressive, manic or mixed relapses ranging from 17.6% to 64.7% (Geller et al., 2000; Fagiolini et al., 2005; Fleck et al., 2005; Garno et al., 2005). Studies including both the broad and the narrow phenotypes of BD, as well as prepubescent children and adolescents, have also reported a diagnostic stability equal to 100% (Geller et al., 2008; Escamilla et al., 2011). However, studies including only the narrow phenotype remain few, and the duration of follow-up remains short, varying from two to five years. We can summarize the determinants of poor outcome as follows: mixed polarity, low socio-economic status, younger age at onset, previous affective episodes, psychosis and female sex. Measures of poorer outcome included lower likelihood of full recovery or poorer global clinical functioning at follow-up (Geller et al., 2000, 2008; Fagiolini et al., 2005; Garno et al., 2005; Escamilla et al., 2011). Psychosocial impairment was assessed in only a few studies and deserves more attention (Goldstein et al., 2009). Data are also very few concerning suicide attempts, although suicidal risk seems higher in the first ten years of the illness and with earlier bipolar onset (Carter et al., 2003; Slama et al., 2004; Goldstein et al., 2012; Halfon et al., 2013).

In this study, we contacted a sample of 80 adolescents who experienced a manic or mixed episode leading to hospitalization for a follow-up (FU) assessment. By selecting a very severe group of adolescents with only BD-I (narrow phenotype) during a long period of admission, we hypothesized a more homogeneous group of patients, a long duration of FU and a better life-time diagnosis since the longer the disease duration the better differential diagnosis between BD-I, schizophrenia and schizo-affective disorder is. The aims were to assess the following factors at FU: (1) the diagnostic stability of severe manic/mixed episodes from adolescence to young adulthood, (2) psychosocial adaptation (including morbidity, suicidal behaviors and mortality), and (3) factors associated with psychosocial adaptation.

2. Methods

2.1. Participants

The sample was identified by retrospective chart review as follows. For the years 1993–2003, we examined the discharge diagnoses of all children and adolescents who had been admitted to our in-patient services (the Pitié-Salpêtrière Hospital, a university teaching hospital in Paris) which include separate units for ages 8–12, ages 12–15, ages 15–18, and an "acute" unit for more severely agitated or functionally impaired patients. We identified 120 patients with DSM-III-R discharge diagnoses of bipolar disorder (manic episode, mixed episode and BD not-otherwise specified), schizoaffective disorder, brief psychotic disorder or psychotic disorder not otherwise specified. Discharge diagnoses were given by the senior clinician in charge of the patient but were rarely based on research procedure. In our experience, these are the diagnoses that have been assigned to patients who, on further evaluation, proved to have experienced a manic episode. Patients with prominent affective features do not receive schizophrenia diagnoses in our department. We undoubtedly missed some bipolar cases who, for example, were treated for depression and then developed mania without being re-admitted to our service during this time period, but it is likely that we captured all or almost all of the manic episodes observed on our services during this period.

The 120 charts that met these discharge diagnoses were then reviewed in detail by D.C. and by one other faculty or staff psychiatrist in each case. This was accomplished in meetings of the two diagnosticians to review each case, rather than by a blind rating procedure, so that discussion and resolution of clinical issues could be accomplished efficiently. We completed the Young Mania Rating Scale, Hamilton Depression Scale, Montgomery-Asberg Depression Rating Scale and Brief Psychiatric Rating Scale for each patient based on the entire hospital record (which included detailed physician's and nursing notes almost daily), and used those ratings to complete a DSM-III-R checklist for diagnostic criteria for manic episode. Of the 120 screened cases, 80 met criteria for mania (including 73 with discharge diagnoses of bipolar disorder, 3 of schizoaffective, 2 of brief psychotic disorder, and 2 of psychotic disorder NOS) and were selected for the follow-up study. Clinical characteristics and pharmacological treatment received at index episode were described in detail in previous reports (Brunelle et al., 2009; Consoli et al., 2009).

Between 2005 and 2006, patients were contacted for a follow-up assessment (on average, 8 years after index episode). Extensive efforts were made to contact these individuals and their families, under a protocol approved by the relevant ethics committee that included first a posted letter describing the study and announcing a telephone contact to carry a direct interview in the following days. Help from treating psychiatrists was also requested unless explicit refusal from the patient. We were able to contact and interview 33 patients in person and 22 by telephone; follow-up information was obtained for 34 patients from physicians. It was possible to interview a family member for 22 patients (10 personally-interviewed and 12 of telephone-interviewed). Five patients refused to participate and twenty were lost for clinical assessment. Finally, 55 patients (69%), 32 females and 23 males, were included in the follow-up analysis. No significant differences were found between lost patients and patients assessed at follow up with regard to sex ($p = 0.667$) and the following variables at intake: age, socio economic status (SES), intellectual disability, psychotic features and polarity ($p = 0.363$, $p = 0.45$, $p = 0.556$, $p = 0.668$, and $p = 0.684$, respectively). The diagram flow is presented in Fig. 1.

In-person interviews were carried out by A.C. and J.B. using the French version of the Diagnostic Interview for Genetic Studies DIGS 2.0 (French translation LeBoyer/Poirier modified by C Laurent) (Nurnberger et al., 1994). Telephone interviews with the patients focused on the main objectives of the study and followed the same procedure that the direct interview, but were limited to social adjustment, life events, number of relapses and re-hospitalization, and psychotropic treatment. Telephone interviews were repeated when needed according to patient's agreement. Interviews with clinicians and family informants aimed at confirming and completing patients' data. With psychiatrists, a specific focus was made on life time diagnosis. Information about mortality was obtained during the year 2007 by contacting legal administration for information on mortality status for all participants born in France. Mortality was therefore available for 64 patients.

2.2. Patient' assessment

The variables assessed at index episode included sex, age at index episode, origin, socio-economic status, age at onset, polarity of index episode (manic or mixed), presence of psychotic signs and/or catatonic signs, intellectual disability, family history, duration of stay and scales

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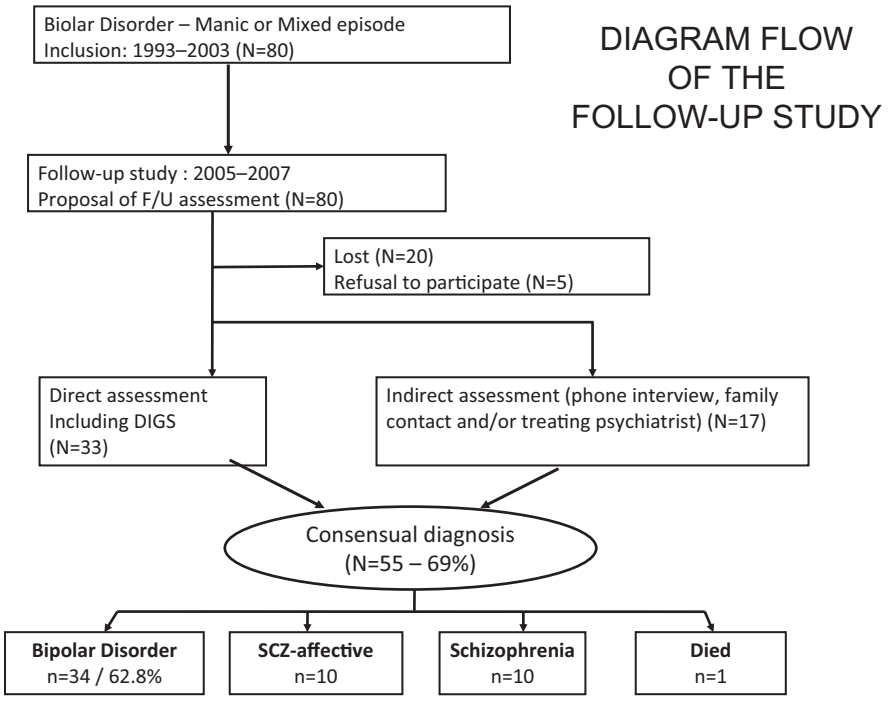

Fig. 1.

assessing clinical severity (the Brief Psychiatric Rating Scale or BPRS (Overoll and Gorham, 1962), the Clinical Global Impression or CGI (Guy, 1976), the Global Assessment Functioning or GAF (Endicott et al., 1976), the Young Mania Rating Scale or YMRS (Young et al., 1978), and the Montgomery and Asberg Depression Rating Scale or MADRS (Montgomery and Asberg, 1979)) (Brunelle et al., 2009). Psychological assessment was made at index episode for 40 adolescents. Assessments included a cognitive evaluation (WISC III-R) and psychodynamically oriented projective psychological testing (Rorschach and TAT) for those without intellectual disability (ID) (Chabert, 1997). Excluding patients with ID, two scores regarding psychosocial risk and schizophrenia risk were computed using the Clinical Global Impression (CGI) method with a 4-point Likert scale based on an overall subjective rating given by a panel of expert psychologists who received all protocols. The two scores were CGI-psychosocial risk and CGI-schizophrenia risk. This methodology has been previously described in detail, and it demonstrates a moderate to good inter-rater reliability (kappa = 0.54 and 0.75, respectively) (Louet et al., 2010).

At follow-up, life-time diagnosis was made through a consensus based on all available data: patient's charts, the DIGS [34] (French translation by Claudine Laurent), and information from the family and the treating psychiatrist. The DIGS elicits information necessary to diagnose psychotic, mood, anxiety, substance abuse, and eating disorders by DSM-IV criteria, as well as suicidal behaviors and current treatment. Current clinical state was assessed using the following instruments: the Montgomery-Asberg Depressive Rating Scale (MADRS) to evaluate depressive symptoms (Montgomery and Asberg, 1979), the Young Mania Rating Scale (YMRS) for manic symptoms (Young et al., 1978), and the Brief Psychiatric Rating Scale (BPRS) to index global psychopathology (Overoll and Gorham, 1962). The work/school, leisure, and peer relationships sections of the Social Adjustment Scale (SAS self report or hetero-questionnaire when clinical status did not permit the use of the self report) were administered to evaluate the quality of recent social functioning (Weissman and Bothwell, 1976). This information was used to rate a global adaptation score (CGI-SAS), which was computed using the Clinical Global Impression (CGI) method with a 5-point Likert scale, ranging from one (highly adapted) to 5 (poorly adapted). This score took into account current work or school achievement, leisure activities, peer relationships, and autonomy from family (according to age as described in Taieb et al. (2002).

At follow-up, we also collected data regarding substance use, suicide attempts (DIGS), presence of insight, negative life events (loss, history of physical and/or sexual abuse) and family history (history of unipolar or bipolar disorder or other). Presence of insight was assessed with clinical assessment, parental information and the following scales: the Scale of Unawareness of Mental Disorder (SUMD-R) (Amador et al., 1993; Paillot et al., 2010) and the Visual Analogic Scale, which explore observance (Fleck et al., 2005). The presence of insight was determined based upon available data as a binary variable (0 = low insight; 1 = good insight). This procedure was assessed calculating the inter-rater reliability for 20 patients (kappa = 0.6). The data regarding substance use, the presence of suicide attempts, family history and current pharmacological treatment were collected from specific sections of the Diagnostic Interview for Genetics Study (DIGS). Life events were assessed using the Amiel–Lebigre life events scale (Amiel-Lebigre et al., 1984). We then distinguished two types of life events known to be associated with BD in the medical literature in adults: life events concerning loss (loss of a parent, separation) and life events concerning maltreatment. We also added to this scale an item concerning a history of sexual abuse, directly asking the participant if he or she had previously suffered from sexual abuse. To improve reporting, when direct information from clinical interview was not possible, the same data were probed through phone interview, parental assessment and psychiatrist information. Variables and measurement tools are summarized in Table 1.

2.3. Assessment of mortality

To assess mortality, we used the Standardized Mortality Ratio (SMR) ([number of observed deaths/number of expected death] x 100) and the 95% Confidence interval (CI), calculated using the method of Harris and Barraclough (Harris and Barraclough, 1998). Using the mortality rates for boys and girls aged 15–20 years in Ile-de–France (Paris area) per

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Table 1
Variables and measurement tools.

Variables [measurement tools]	
Index episode (IE)	Follow-up (FU)
Sex, age, origin, SES	Life time psychiatric diagnosis [DIGS]
Age at onset	Current clinical state:
Polarity of IE	Mania [YMRS]
Psychotic/catatonic signs	Depression [MADRS]
ID	Global clinical functioning [BPRS, CGI, GAF]
Family history	Psychosocial adaptation: work/school, leisure, peer relationships [SAS]
Duration of stay	Substance use [DIGS]
Global clinical functioning [BPRS, CGI, GAF]	Suicide attempts [DIGS]
Current clinical state:	Family history [DIGS]
Mania [YMRS]	Negative life events [Amiel–Lebigre]
Depression [MADRS]	Insight [SUMD-R, Visual Analogic Scale]
Cognitive and projective psychological testing [WISC III-R, Rorschach, TAT]	

CGI: Clinical Global Impression; SES: socio-economic status; SAS: Social Adaptation Scale; BPRS: Brief Psychiatric Rating Scale; MADRS: Montgomery–Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale; ID: intellectual deficiency; GAF: Global Assessment Functioning; DIGS: Diagnostic Interview for Genetic Studies; SUMD: Scale of Unawareness of Mental Disorder; WISC: Wechsler Intelligence Scale for Children; TAT: Thematic Apperception Test.

100,000 people (47 and 21, respectively), we could estimate the number of expected deaths in our sample for all causes (natural and suicide), including the number of expected completed suicides, given that in this age group suicide accounts for 7% and 10% of deaths in boys and girls, respectively. SMR related to all causes was calculated. The difference between the observed and expected numbers of the deceased was tested using the z test variable: $z = [OD - ED]/(\sqrt{ED})$, where OD denotes number of observed dead and ED denotes expected number of dead (Engqvist and Rydelius, 2006). The SMR, which gives the risk of death compared with the general population of similar age and gender, is significantly increased when the lower CI is more than 100, and it is significantly reduced when the upper CI is less than 100.

2.4. Statistical analysis

All statistical analyses were performed using the R statistical package, version 2.12.2. The significance level α was set to 0.05, and all statistical tests were two-tailed. Qualitative variables were compared using Fisher's exact test, and group comparisons were conducted using either Mann–Whitney's test (if there were 2 groups) or the Kruskal–Wallis test (if there were more than 2 groups). Finally, relationships between quantitative variables were assessed by Spearman's rank correlation.

3. Results

3.1. Socio-demographic characteristics and diagnosis at follow-up

Mean duration of follow up (FU) was 8 years [range 2–12]. At follow-up, twenty participants were lost and five refused to participate. Therefore, the final sample at follow-up included 55 participants, but SMR was calculated on the basis of 64 participants with valuable information regarding mortality. Mean age at FU evaluation was 24 years (±3.89) [range 16–30]. The sex ratio was 32 females to 23 males. At follow-up, 35 participants (63.6%) still presented with a diagnosis of BD-I, while 20 (36.4%) participants had changed lifetime diagnosis (schizophrenia: $N = 10$, 18.2%, and schizo-affective disorder: $N = 10$, 18.2%). Participants presented with the following comorbidities at follow-up: 7 participants presented substance abuse (13%), 3 presented anxiety disorders (6%) (1 panic and 2 phobic disorders), 1 had borderline personality disorder (2%) and 1 exhibited an eating disorder (2%). None presented OCD or ADHD. Socio-demographic and clinical data are presented in Table 2.

Table 2
Socio-demographic and clinical characteristics at index episode and at follow-up of the sample of 55 adolescents with bipolar disorder type I (BD-I).

Index episode (IE): n = 55	
Sex	32 F, 23 M
Age: mean ± SD, [range]	15.82 ± 1.89 [12–20]
SES: *n* (%) good and middle	37 (67)
Paternal origin: *n* (%) migrants	24 (43)
Maternal origin: *n* (%) migrants	24 (43)
Family history[a] of depression: *n* (%)	28 (51)
Family history[a] of bipolarity: *n* (%)	7 (13)
Manic/Mixed episodes: *n* (%)	35 (64)/20 (36)
Total IQ: mean ± SD	83.4 ± 23.4
CGI-Severity: mean ± SD	6.05 ± 0.73
GAF-Admission: mean ± SD	22.6 ± 7.83
GAF-Discharge: mean ± SD	63.8 ± 13.45
BPRS: mean ± SD	64.2 ± 13.3
MADRS: mean ± SD	20.56 ± 9.54
YMRS: mean ± SD	22.62 ± 5.7
Follow up (FU): n = 55	
Age: mean ± SD, [range]	24 ± 3.89 [16–30]
Diagnosis at FU	
Bipolar disorder type I: *n* (%)	35 (63.6)
Schizo-affective disorder: *n* (%)	10 (18.2)
Schizophrenia: *n* (%)	10 (18.2)
Current clinical state and clinical severity	
GAF ($n = 34$): mean ± SD	59.27 ± 21.04
BPRS ($n = 34$): mean ± SD	32.4 ± 12.66
MADRS ($n = 34$): mean ± SD	4.7 ± 3.76
YMRS ($n = 34$): mean ± SD	4.1 ± 5.5
Mortality	
Died ($n = 64$): *n* (%)	1 (1.6)
Psychosocial adaptation and suicidality	
CGI-SAS: mean ± SD	3.69 ± 1.5
CGI-S ($n = 34$): mean ± SD	3.61 ± 1.67
Suicide attempts ($n = 34$): *n* (%)	13 (38.2)
Negative life events	
Loss experience ($n = 40$): *n* (%)	36 (94), Subj. impact: 66.4 ± 22.5
Maltreatment ($n = 38$): *n* (%)	2 (5.26), Subj. impact: 80 ± 0.0
Sexual Abuse ($n = 38$): *n* (%)	4 (10.51), Subj. impact: 82.5 ± 17.1
Relapses	
No relapse and no chronic course: *n* (%)	5 (9.1)
Number of relapses ($n = 37$): mean ± SD	2.6 ± 2.1
Insight ($n = 39$): yes, *n* (%)	26 (66.67)
Treatment ($n = 48$)	
Mood stabilizer: *n* (%) Lithium/Valproate/CBZ	29 (60.4): $n = 15/n = 11/n = 2$
First generation antipsychotics: *n* (%)	15 (31.25)
Atypical antipsychotics: *n* (%)	20 (41.67)

[a] First degree; CGI: Clinical Global Impression; SES: socio-economic status; IQ: intellectual quotient; CGI-SAS: CGI-Social Adaptation Scale; BPRS: Brief Psychiatric Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale. Subj. impact: subjective impact on the basis of auto-assessment using an anagogic scale from 0 (no impact) to 100 (maximum impact).

3.2. Mortality, morbidity and suicidality

At FU, one male died from cardiac failure. He had autism and BD-I, and he was given several antipsychotic medications. The all-causes standardized mortality ratio (SMR) was calculated in the sample of all participants known to be either alive or deceased ($n = 64$: 38 women and 27 men) and was equal to 970 [IC = 0.39–3806], which is rather

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high compared to other psychiatric disorders (Harris and Barraclough, 1998).

Furthermore, morbidity was severe with: (a) 50 (91%) participants having at least one relapse (manic, mixed or depressive episode); (b) a moderate to severe impact on global functioning at follow-up (mean GAF score = 59.27 ± 21, SAS-CGI mean score = 3.7 ± 1.5); and (c) 13 (38%) participants out of 34 participants with detailed data presenting at least one suicidal attempt during follow up (see Table 2). Of the 13 participants with suicidal behaviors, a majority made one suicidal attempt (60%), but two reported six suicidal attempts at FU. Further, 9 had a diagnosis of BD-I and 4 had a diagnosis of schizo-affective disorder at FU.

Table 3
Variables associated with CGI-psychosocial adaptation score at follow up of the sample of 55 adolescents with bipolar disorder type I.

Variables	CGI-psychosocial adaptation rho	Univariate analysis *p* value
Quantitative variables (index episode)		
Age at episode index	−0.16	0.25
Age onset illness	−0.17	0.41
Duration index episode	0.14	0.34
BPRS	0.08	0.55
MADRS	−0.23	0.1
YMRS	−0.03	0.85
CGI	0.03	0.86
EGF admission	−0.09	0.52
EGF discharge	−0.24	0.08
Family history		
Depression	−0.32	**0.02**
BD	−0.24	0.08
Other	0.11	0.45

Binary variables (index episode IE and follow-up UP)	CGI-psychosocial adaptation score		
	No	Yes	
Psychotic signs (IE)	3.9 ± 1.5	3.55 ± 1.5	0.35
Catatonic signs (IE)	3.67 ± 1.5	5[a]	0.36
Intellectual disability	3.24 ± 1.6	4.79 ± 0.4	**0.001**
Insight (FU)	4.77 ± 0.4	3.04 ± 1.5	**0.001**
Presence of negative life events	1.33 ± 0.6	3.81 ± 1.4	**0.013**
Life events-loss	2.25 ± 1.9	3.77 ± 1.4	0.09
Life events-maltreatment	3.47 ± 1.5	5[a]	0.30
Life events-sexual abuse	3.28 ± 1.5	4.8 ± 0.4	**0.03**
Substance use	3.66 ± 1.6	3.79 ± 1.4	0.78
Transition risk (PA)	4.27 ± 1.1	3.15 ± 1.7	0.1
Psychosocial evolution (PA)	4.29 ± 1.1	2.71 ± 1.7	**0.031**
Mood stabilizer (FU)	3.83 ± 1.5	3.38 ± 1.5	0.33
APA (FU)	3.21 ± 1.6	4.05 ± 1.3	0.09
Classical AP (FU)	3.06 ± 1.5	4.6 ± 0.9	**0.001**
	Female	**Male**	
Sex	3.58 ± 1.6	3.86 ± 1.4	0.52
	Manic	**Mixed**	
Type of index episode	3.88 ± 1.4	3.37 ± 1.7	0.29
Variables	**CGI-psychosocial adaptation score**		
SES: good/middle/low	3.7 ± 1.4/3.05 ± 1.5/ 4.35 ± 1.4		**0.02**
Mother origin[b]	3.38 ± 1.5/1/ 4.36 ± 0.9/3.12 ± 2		0.21
Father origin[b]	3.33 ± 1.4/2.33 ± 2.3/ 4.3 ± 1.1/3.38 ± 2		0.16
Diagnosis at FU: BD/SCZ/SCZ-AFF	3.2 ± 1.5/4.8 ± 0.4/ 4.3 ± 1.3		**0.008**

IE: index episode; FU: follow-up; ID: intellectual disability; CGI: Clinical Global Impression; SES: Socio Economic Status; GAF: Global Assessment of Functioning; SAS: Social Assessment Scale; BPRS: Brief Psychiatric Rating Scale; YMRS: Young Mania Rating Scale; MADRS: Montgomery and Asberg Depression Rating Scale; PA: Psychological Assessement; SCZ: schizophrenia; BD: bipolar disorder; SCZ-AFF: schizo-affective disorder; SES: Socio-economic status.

[a] Only 1 subject.

[b] Africa/French Antilles/Europe/France.

3.3. Variables associated with CGI-psychosocial adaptation score at follow-up

Bivariate analyses were performed in order to determine variables assessed at index episode (IE) and at follow-up (FU) associated with CGI-psychosocial adaptation score at follow-up. All analyses are summarized in Table 3. At index episode, a poor family SES was significantly associated with a poorer psychosocial adaptation at FU ($p = 0.02$). Additionally, intellectual disability was significantly associated with a poorer psychosocial adaptation score compared to participants without ID (mean CGI-SAS score = 4.74 ± 0.4 versus 3.24 ± 1.6, $p = 0.01$). In a subsample ($N = 25$), a high psychosocial risk, as determined using psychological assessment at index episode, was significantly associated with a poorer psychosocial adaptation at follow-up ($p = 0.031$).

A personal history of negative life events ($p = 0.013$) and/or a history of sexual abuse ($p = 0.032$) were associated with a poorer psychosocial adaptation at FU, compared to participants without negative life events or sexual abuse. Current use of classical antipsychotics (AP) at FU was also associated with poorer psychosocial adaptation compared to participants not receiving classical AP ($p = 0.001$).

On the other hand, a family history of depressive episodes was significantly associated with a better psychosocial adaptation (rho = −0.32, $p = 0.02$). The participants exhibiting a capacity for insight presented with a better psychosocial adaptation compared to those without such capacity ($p = 0.001$). In addition, participants who still had a diagnosis of BD-I at FU had a better psychosocial adaptation than those with a diagnosis of schizophrenia or schizo-affective disorder at FU ($p = 0.008$). Notably, gender, index episode polarity (manic versus mixed), and the presence of psychotic symptoms at index episode did not impact the quality of psychosocial adaptation at FU in our sample.

4. Discussion

4.1. Summary of the main findings

This follow-up study assessed the outcome of 55 adolescents with BD-I, on average 8 years after an index episode of manic or mixed presentation leading to inpatient care. Increasing knowledge about the outcome of adolescents with BD-I is crucial to improve medical care and functional impact in adulthood, and to reduce suicidal risk especially as it is the highest the first ten years of the course of the illness. The first major finding was that the diagnostic stability of BD-I was not near 100%. One-third of the participants had a diagnostic transition towards schizophrenia or schizo-affective disorder at follow-up. Second, morbidity was severe in most cases, with a high prevalence of relapse and high severity scores on scales measuring psychosocial adaptation and clinical global functioning. Mortality was also high, and it was estimated to be 9 times higher than for adolescents of the same age and sex living in the same area. It was also three times higher compared to the estimated SMR in adolescent inpatients (Harris and Barraclough, 1998). Although none of the patients had successfully committed suicide at FU, 38% of the participants with available detailed data ($N = 34$) reported at least one suicide attempt over the FU period. Third, several variables assessed at index episode or FU were significantly associated with psychosocial adaptation in young adulthood: a low socio-economic status at index episode (despite free access to care in the French mental health care system), intellectual disability, the presence of negative life events including a history of sexual abuse, and treatment with classical antipsychotics at FU were all significantly associated with poorer psychosocial adaptation. In a subsample without ID, CGI-psychosocial risk determined using psychological assessment at index episode was also a predictor of psychosocial adaptation at follow-up. On the other hand, some protective factors were apparent as well: better insight, a family history of depressive episodes and a

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diagnosis of BD-I at FU were associated with a better psychosocial adaptation.

4.2. Diagnostic stability

Since 2000, several prospective studies have been conducted on the diagnostic stability and the course of BD in adolescents (Geller et al., 2000, 2008; Fagiolini et al., 2005; Fleck et al., 2005; Garno et al., 2005; Escamilla et al., 2011; Goldstein et al., 2012). The results are variable, which is unsurprising given the heterogeneity of the samples and of the inclusion criteria. A study with patients with psychosis initially (aged 15 to 60) and with at least one diagnosis of BD over 10 years reported a diagnostic shift in non-bipolar disorder in 49% of the cases (Ruggero et al.). Only one study regarding adolescents (the study by Carlson et al., 2000) had reported a diagnostic transition towards schizophrenia or schizo-affective disorders at outcome. Among a sample of adolescents all hospitalized for an acute manic episode, 18% had a diagnosis of schizophrenia or pharmacologically induced psychosis at 2-year follow-up in that study. Carlson's sample and our sample were rather similar because they both included severe inpatient adolescents with BD-I (manic and/or mixed episodes). At least two hypotheses can be made: (1) It remains difficult to differentiate between severe manic/mixed episodes with psychotic characteristics and schizophrenia (Carlson et al., 1994). Sometimes, only the course of the illness and the outcome in adulthood affords a proper diagnosis. As shown in our study, psychotic features at index were not associated with psychosocial adaptation at FU. (2) In adolescence, severe manic/mixed episode can be, in few cases, the first episode of a schizophrenia spectrum disorder and can lead to poorer psychosocial functioning. The presence of a family history of depressive disorder was significantly associated with a life time diagnosis of BD-I, recalling the well-established genetic vulnerability of BD, although, in some families, associations with SCZ spectrum disorder have also been described.

4.3. Psychosocial adaptation

A substantial number of relapses have been reported in previous studies (Geller et al., 2000, 2008; Fagiolini et al., 2005; Fleck et al., 2005; Garno et al., 2005; Escamilla et al., 2011; Goldstein et al., 2012), but the number of relapses at outcome in our study was the highest rate ever reported. Fully 91% of the participants had at least one relapse or a chronic course. Compared to other follow-up studies, our duration of follow-up was also among the longest. This could be an explanation for this result. Our initial sample included adolescents with particularly severe BD-I, which could also account for our particularly high relapse rate. The global clinical functioning score at follow-up, as well as the psychosocial adaptation score, highlighted an important morbidity. Few studies have assessed psychosocial functioning in youth, whereas in adults, functional impairment has been described in several studies and is not limited to symptomatic periods (Fagiolini et al., 2005). Functional impairment appears to persist in both children and adults during periods of illness remission (Morriss, 2002). In youth, substantial impairment was reported in previous studies of social, familial and academic functioning (Lewinsohn et al., 1995; Geller et al., 2000; Goldstein et al., 2009), e.g., adolescents with BD-I scored below national norms in nearly all quality-of-life domains (Rademacher et al., 2007).

In Fig. 2, we summarized the variables associated with psychosocial outcome. As expected given the little literature available, the presence of negative life events and a history of sexual abuse were associated with poorer psychosocial adaptation at outcome. A history of maltreatment and sexual abuse in patients with BD was previously reported as pejorative on the evolution of the illness, with increased risk for suicide attempts, substance use and rapid cycling (Leverich et al., 2002; Garno et al., 2005). Additionally, a low socio-economic family status was also a pejorative factor on psychosocial outcome, as has been previously reported (Birmaher et al., 2009). Although the sample size did not permit multivariate analysis, this result is unlikely to be due to poor access to care. The French mental health care system is free and does not limit the duration of inpatient stay. Intellectual disability was also associated with poorer psychosocial outcome. Unfortunately, interest relating to BD and ID in adolescence remains very sparse and limited to case reports. Interestingly – and unlike in many previous studies – we did not find that gender, polarity and psychotic symptoms at the index episode were associated with psychosocial functioning at outcome.

Some protective factors – good capacity for insight, a life time diagnosis of BD-I and a family history of depressive episodes – also emerged as variables associated with a better psychosocial outcome. The latter finding may disappear in multivariate analysis, as family history of depression is highly prevalent in patients with BD-I. The former, however, has important clinical relevance. Poor insight into treatment appears to

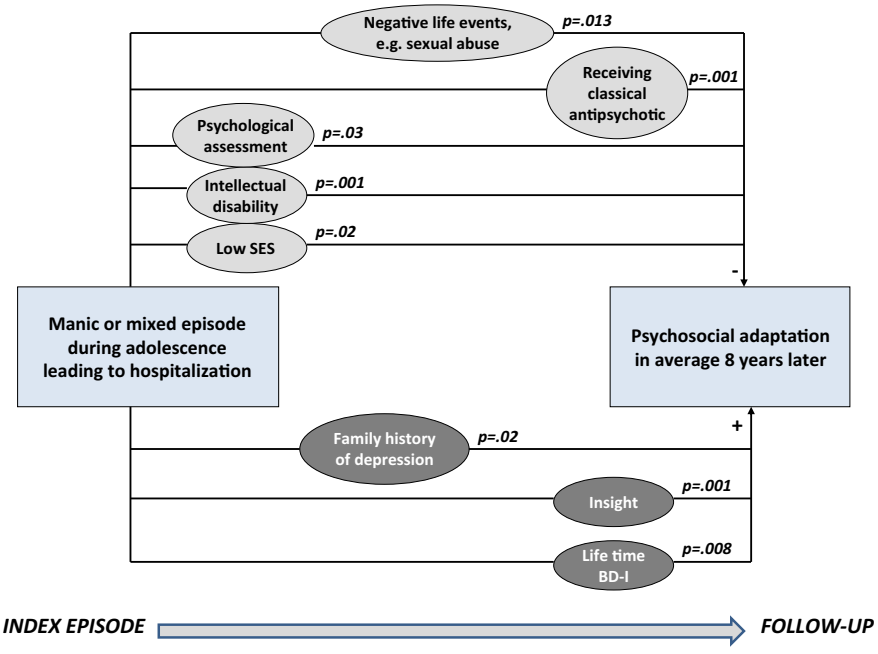

Fig. 2. Variables associated with psychosocial adaptation.

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be a predictor of adverse clinical outcomes (re-hospitalizations, violent and suicidal behaviors) most likely mediated by adherence to treatment (Yen et al., 2008). Therefore, developing psychoeducational interventions targeting insight in young patients with BD may help to improve their outcomes.

Out of 34 participants for whom detailed data on suicidal behaviors were available, 13 (38%) had at least one suicidal attempt during follow-up. Among these, 9 still had a diagnosis of BD at follow-up. This highlighted the substantial suicidal risk in adolescents and young adults presenting with BD: the prevalence rate of BD in adolescents who committed suicide may be as high as 20% (Brent et al., 1993). Adolescents with BD exhibited twice as many suicide attempts as adolescents with major depressive episodes (Lewinsohn et al., 1995), and in Strober et al.' (1995) study of BD-I adolescents, suicide attempts had occurred in 20% of the participants by the five-year follow up. Studies of the risk factors of suicidal behaviors in adolescents with BD remain scarce, even if some risk factors have been previously described (long duration of illness, early-onset BD, severity of clinical state, comorbid panic disorder and substance abuse (Patel et al., 2006). Further studies are therefore needed as suicidality in youth is a crucial issue.

4.4. Limitations and strengths

The results of the current study should be interpreted in the context of its limitations. (1) The low prevalence of BD-I in adolescent inpatients (Carlson, 2005, 2009, 2011a,b) explains the sample size of the study at index episode. (2) At follow up, to collect the maximum amount of data, we choose to take into account direct clinical assessment data as well as indirect data (information from treating psychiatrists and family, patient's charts) and to determine a consensual diagnosis at follow-up. (3) The assessment at follow-up was not blind to index diagnosis. (4) We conducted a retrospective recruitment of the sample and of some data from the index episode. (5) The sample size did not allow for multivariate analysis, so most of the predictions should be considered to be exploratory (6). The retrospective design and the quality of the data extracted from patient charts and staff reports at the index episode can be questioned. Nevertheless, prolonged durations of hospitalizations provided us precise and numerous clinical notes. (7) Despite an average FU duration of 8 years, we also had a large range of duration between initial episode and FU (from 2–20 years) that may have been a source of bias.

The strengths of this study included the following: (1) the homogeneity of the sample, which included only severe BD-I adolescent inpatients; (2) the recruitment in a mental health care system that does not select inpatients based upon family income or SES (as the system is universal and affords free access); (3) the long duration of the follow up (on average 8 years), which enabled us to observe diagnostic transition and relapses; (4) the lack of demographic or diagnosis differences between participants who dropped out and those who were assessed at FU; and (5) the confirmation by interview, in all patients who had DIGS at FU, of diagnosis at index episode.

5. Conclusion

BD-I in adolescent inpatients can lead to important morbidity and mortality. Diagnostic stability is high, but a high proportion of patients show a transition towards schizophrenia spectrum disorder. A better psychosocial prognosis seems to be associated with a lifetime diagnosis of BD-I, a high or medium SES, a better insight and the absence of negative life events and comorbid intellectual disability.

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Contributors

Study concept and design: Cohen, Consoli, Brunelle, Laurent
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Interpretation of data: All authors
Drafting the manuscript: Consoli, Brunelle, Cohen
Critical revision of the manuscript for important intellectual content: Laurent, Cohen
Final draft: All authors

Conflict of interest

Dr. Cohen reported past consultation for or the receipt of honoraria from Schering-Plough, Bristol-Myers-Squibb, Otsuka, Shire, Lundbeck, Janssen, Sanofi-Aventis and IntegraGen. Dr Consoli reported receiving travel support from BMS. No other authors reported financial disclosure or conflict of interest.

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