Medication use in Adolescents Treated in a French Psychiatric Setting for Acute Manic or Mixed Episode

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ABSTRACT

Objective: In the absence of recommendations from drug regulatory agencies for most medications to treat severe manic or mixed episode in adolescence, this study aims to (i) describe the pharmacological treatment prescribed in an inpatient setting for acute manic or mixed episodes in adolescents; (ii) determine whether type of episode, duration of stay, improvement, and psychotic features were associated with the nature of the given treatment; (iii) compare the results with evidence-based data. **Method**: From 1993 to 2003, we received 80 subjects, aged 12 to 20 years, consecutively hospitalized for a manic or mixed episode. Socio-demographic, clinical and treatment data were extracted by reviewing patients' charts. Treatment data were available for 75 subjects. **Results**: Most patients received a combination treatment including mood stabilizer (82.6%), classical antipsychotic (AP) (86.6%) and atypical AP (24%). Despite prolonged hospitalisation (minimum stay = 17 days), 69 (86.2%) patients were scored very much or much improved at discharge. Secondary therapeutic options occurred in 15 subjects because of poor therapeutic response (N=13), severe adverse effects (N=5) or both. Two patients had electroconvulsive therapy as third therapeutic option. Adolescents with psychotic symptoms were significantly more frequently treated by lithium (Fisher exact test: p=0,0052). No other variable was associated with treatment. **Conclusions**: This study reported on patterns of medication use that mainly followed treatment recommendations and evidence-based data existing in adults. However, the presence of psychotic features appeared to favour the use of lithium in this French sample.

Key words: bipolar disorder, adolescence, pharmacological treatment

RÉSUMÉ

Objectif: Dans un contexte de prescriptions hors AMM (Autorisation de mise sur le marché) dans le traitement des épisodes maniaques ou mixtes aigus à l'adolescence, cette étude se propose 1) de décrire le traitement pharmacologique prescrit chez des adolescents hospitalisés pour un épisode maniaque ou mixte 2) de déterminer si le type d'épisode, la durée de l'hospitalisation, l'amélioration clinique et la présence de signes psychotiques sont associés au type de traitement prescrit 3) de comparer les résultats aux données issues d' «evidence-based medecine». **Méthodologie:** De 1993 à 2003, nous avons hospitalisé 80 sujets, âgés de 12 à 20 ans, pour un épisode maniaque ou mixte. Les données socio-démographiques, cliniques et pharmacologiques ont été extraites des dossiers des patients. Les données sur le traitement étaient disponibles pour 75 patients. **Résultats:** La majorité des patients a reçu une combinaison de traitements associant un stabilisateur de l'humeur (82,6%), un antipsychotique classique (86,6%) et un antipsychotique atypique (24%). Malgré la durée prolongée de l'hospitalisation (17 jours minimum), l'évaluation clinique de 69 patients (86,2%) montre une forte voire très forte amélioration clinique à la sortie. Une deuxième option thérapeutique a concerné 15 sujets en raison d'une mauvaise réponse thérapeutique (n=13), d'effets secondaires sévères (n=5) ou de ces deux raisons. 2 patients ont reçu un traitement par électroconvulsivothérapie en troisième option thérapeutique. Les adolescents présentant des symptômes psychotiques ont été significativement plus fréquemment traités par lithium (fisher exact test: p = 0,0052). Aucune autre variable n'est associée au type de traitement. **Conclusions:** Cette étude rapporte des schémas de traitement principalement en accord avec des recommandations et des données issues d' «evidence-based medecine» existant chez l'adulte. La présence de symptômes psychotiques semble toutefois favoriser la prescription de lithium dans cet échantillon français.

Mots-clés: trouble bipolaire, adolescence, traitement pharmacologique

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Introduction

Today, a growing interest is developing on the topic of bipolar disorder in adolescents (Carlson et al. 1994; Geller and Luby 1997; Pavuluri et al. 2005). Epidemiological data reported a prevalence of 1% in all forms of adolescent bipolar disorders (Kim-Cohen et al. 2003; Lewinsohn et al. 1995). However, if we only look at bipolar I disorder (at least one typical manic or mixed episode), prevalence in adolescence decreased to 0.1% (Kim-Cohen et al. 2003; Lewinsohn et al. 1995). Even if bipolar disorders are actually better recognized, there are too few studies about this pathology in adolescence and especially in the most severe forms like BD type I. On the other hand, controversies exist about bipolar disorder in prepubertal children in Europe and in USA (Carlson 2005; Harrington and Myatt 2003).

Regarding pharmacological treatment in adolescents with BD-I, the Food and Drug Administration allows lithium prescription for adolescents older than twelve and recently approved aripiprazole for acute and maintenance treatment in manic and mixed episodes associated with BD-I with or without psychotic features in paediatric patients aged 10-17 years (Zhang 2008). In addition, risperidone has an indication for acute treatment in manic and mixed episodes (DelBello 2007). Although not published yet, an FDA summary of the registration study, a 4-week double-blind placebo-controlled trial including 296 children and adolescents aged 10-17 years, showed that aripiprazole (10 or 30 mg/day) was superior to placebo in reducing bipolar symptoms. Similarly, a synopsis of the registration study, a 3-week double-blind placebo-controlled trial including 169 children and adolescents aged 10-17 years, showed that risperidone (0.5-2.5 or 3-6 mg/day) was superior to placebo in reducing bipolar symptoms. However, most of the treatment studies published in the field are open-label, not controlled, and the subject samples are very often small and heterogeneous (Consoli et al. 2007; Pavuluri et al. 2005). Only two placebo-controlled double-blind studies with lithium are reported in the literature with no significant statistical difference as well (Geller et al. 1998; Kafantaris et al. 2004). There is also a double-blind, randomized, placebo-controlled trial with oxcarbamazepine with no significant statistical difference between the two groups (Wagner et al. 2006). Another recent study examined topiramate in youths with BD using a placebo-controlled design. But again results were inconclusive (Delbello et al. 2005). A single-blind trial of quetiapine for the treatment of mood symptoms in adolescent at high risk for developing bipolar I disorder reported good therapeutic response but adolescents recruited did not meet DSM IV criteria for BD (DelBello et al. 2007). There is no published controlled study versus placebo for the other mood stabilizers (carbamazepine, valproate or sodium divalproate), yet a study compared divalproate, with quetiapine adjunction, versus placebo (Delbello et al. 2002). Only a recent placebo-controlled study with olanzapine showed a significant clinical improvement in the patients exposed to the active compound (Tohen et al. 2007). For this last olanzapine study, the sample was homogeneous, as recommended by several authors, regarding age (only adolescents) and diagnosis (only BD type I) (Carlson et al. 2003; McClellan 2005). Furthermore, there are two controlled studies concerning ECT but both of them are retrospective (Bloch et al. 2001; Kutcher and Robertson 1995). Finally, there is no controlled study evaluating prophylactic treatment against placebo, but at least two naturalistic prospective studies support the use of lithium in this indication for BD I adolescents (Dailey et al. 2005; Strober et al. 1995).

The limited amount of data regarding pharmacological treatment of BD I in adolescents implies that practitioners may extrapolate data coming from studies conducted in adults, despite the risks arising from this procedure as it has been shown in adolescent depression (Cohen 2007; Cohen et al. 2008; Mueller and Orvaschel 1997; Ryan et al. 1999). Indeed, the use of mood stabilizers and antipsychotics in adolescents seem to have increased in the US, UK and Canada in the past decade (Kowatch and DelBello 2003) although it does not seem to be the case in France (Sevilla-Dedieu and Kovess-Masfety 2008). Bhangoo et al reported practitioners' most popular prescriptions for youths BD in a US community setting: the treatment in youths included on average more than three psychotropic drugs, the most frequently prescribed being valproate, lithium and gabapentine (Bhangoo et al. 2003). The choice of gabapentine was based on no rationality since this drug was not superior to placebo in adult BD (Pande et al. 2000). Furthermore, except for lithium and aripiprazole, medications more prescribed in this study are not approved for adolescents by the FDA, and medication patterns, for example the sizeable portion of children (15%) with a trial of topiramate and/or lamotrigine without ever having had a trial of lithium, is again based on no rationality (Kowatch et al. 2005). We did not find other studies than Banghoo's one describing treatment of bipolar adolescents in a naturalistic psychiatric setting. However, even in clinical practice with adults, it is admitted that treatment of bipolar disorder is complex and often requires medication combination mainly due to the clinical heterogeneity of acute mania (Fountoulakis et al. 2007). To better understand this heterogeneity and help prescription in clinical practice, observational studies are essential whereas, due to inclusion and exclusion criteria, results of randomised controlled trials cannot be always generalized to all clinical situations (Reed et al. 2009).

Regarding response to treatment and therapeutic decision making, some clinical characteristics must be considered: (i) the type of episode (manic or mixed) as adults studies suggest that mixed episodes are more resistant to treatment (Bowden 2001); (ii) presence or absence of psychotic features as we could hypothesize that more antipsychotics would be used to treat a manic or mixed episode with psychotic features than without psychotic features (Bowden 2001); (iii) duration of hospitalisation as we can expect concurrent effect of milieu therapy (Bowden 2001).

The current study aimed to describe psychotropic medication use in adolescents hospitalised for an acute manic or mixed episode in a French clinical setting. Using

a retrospective design, we aimed (i) to describe the pharmacological treatment of acute manic or mixed episodes in a sample of eighty adolescents hospitalized in a French university department of child and adolescent psychiatry; (ii) determine whether associations between duration of stay, type of episode, presence psychotic features and improvement during inpatient stay and the nature of the treatment given were similar in adolescents than those described in adult samples (Bowden, 2001); (iii) to compare the results with evidence-based data.

Methods

Participants

By reviewing patient charts and staff reports, we systematically looked for all children and adolescents consecutively hospitalized for an acute manic or mixed episode between 1993 and 2003 at the Pitié-Salpêtrière Hospital, a university teaching hospital in Paris area that realizes 30%-50% of all inpatients stay in child and adolescent psychiatry. During the study period, out of 4165 inpatients, 120 subjects were hospitalized with a discharge diagnosis of BD, schizoaffective or schizophreniform disorder, brief psychotic episode, manic episode, mixed episode and BD NOS**.** Two experienced child and adolescent psychiatrists of the department who had been the treating clinicians for some of the subjects but not all, reviewed the charts and selected all cases (n=80) meeting a DSM IV discharge diagnosis of BD-I (manic or mixed episode). No a priori exclusion criteria such as mental retardation were used. This report was a preliminary study of a follow up one. Thirty two subjects (40%) of the preselected participants could have been traced and evaluated at this point of the study. They were administered the Diagnostic Interview for Genetic Studies (DIGS), a life-time semi-structured interview (Nurnberger et al. 1994) (French translation Claudine Laurent). The DIGS confirmed that the index episode diagnosis was manic or mixed in all of them. The study was conducted according to the hospital ethics committee regulation.

Clinical characteristics

For the description of all prescriptions and their potential prognostic impact, we retrospectively reviewed charts (clinician and nurse notes) from the hospitalization period. All information pertaining to the identity of the subjects was removed. Procedures and clinical description of the sample are detailed elsewhere (Brunelle et al. 2009). Selected data included sociodemographic data (gender, age at admission, parental origins, socio-economic status) and other variables extracted for descriptive purposes and/or as potential correlates: (i) the type of episode (manic vs. mixed) and the type of onset (acute [<10 days] or not); (ii) the presence or absence of psychotic feature; (iii) duration of hospitalization; (iv) the Clinical Global Impression Scale-Severity of illness (CGI-S) (Guy 1970) and the Global Assessment of Functioning Scale (GAF) (Endicott et al. 1976) that are both systematically scored at admission and discharge, to assess clinical improvement (ΔGAF) during inpatient stay; (v) the Young Mania Rating Scale (YMRS) (Young et al. 1978) (inter-rater reliability intraclass correlations = 0.83). Mental retardation was also recorded and defined by global IQ, verbal IQ or performance IQ < 70 (WISC III and WISC IV) and when no cognitive evaluation was done during the stay because of clinical impairment, subjects were identified as having mental retardation according to the following definition of the American Association on Intellectual and Developemental Disabilities: *Intellectual disability is a disability characterized by significant limitation both in intellectual functioning and in adaptative behaviour as expressed in conceptual, social and practical adaptive skills. This disability originates before the age of 18* (Luckasson et al. 2002).

Treatment variable

For every adolescent, data about pharmacological treatment and ECT during the stay were also retrospectively collected in charts (clinician and nurse notes, leaf of prescription). Only treatments lasting more than one week only were kept. Therapeutic classes were defined on the basis of the EphMRA classification (European pharmaceutical Market Research Association): antipsychotics (AP), normothymics, also called mood stabilizers, antidepressants, anxiolytics. Treatment variables selected were (i) mood stabilizers divided into lithium, carbamazepine, valproate (sodium valproate, divalproate, valpromid); (ii) classical AP; (iii) atypical AP; (iv) combination A: mood stabilizer + classical AP; (v) Combination B: mood stabilizer + atypical AP; and (vi) others. We also collected data regarding ECT. These pharmacological treatments have been prescribed by several clinicians (5 seniors and 12 residents), during the ten year corresponding period of the study. Course of treatment and reasons for change (no therapeutic response and/or major adverse event) were also recorded.

Statistical analysis

Statistical analyses were performed using the R software version 2.7 (The R Foundation for statistical computing). First, for treatment description, we used classic descriptive statistics. Second, the distribution of the continuous variables was assessed using the Shapiro-Wilk test and the F-test test with regard to the assumption of normality and the assumption of equal variances respec-

Table 1: Clinical and socio-demographic characteristics of youths hospitalized from 1993 to 2003 for bipolar type 1 disorder in a University hospital (N=80)

Socio-demographic characteristics	
Sex	45 F, 35 M
Age (mean ± SD) [range]	15.67 ± 1.89 [12-20]
Socio-economic status: N (%) good and middle	50 (63.3)
Paternal origin: N (%) migrants	34 (44.2)
Maternal origin N (%) migrants	33 (43.4)
Clinical characteristics	
Current episode	49 Manic, 31 Mixed
Acute onset (≤ 10 days): N (%)	30 (37.5)
Psychotic features: N (%)	50 (63.8)
Catatonic features: N (%)	4 (5)
Mental retardation: N (%)	17 (21.3)
Duration of stay, days, (mean ± SD) [range]	80.4 ± 50.7 [17-245]
Scores at admission	
GAF (mean ± SD) [range]	23 ± 7.9 [10-40]
CGI-S: N (%) severely and extremely ill	61 (76.3)
YMRS (mean ± SD) [range]	22.2 ± 6.5 [12-36]
Scores at discharge	
GAF (mean ± SD) [range]	64 ± 14.4 [30-90]
CGI-I: very much improved N (%)	18 (22.4)
much improved N (%)	51 (63.8)
minimally improved N (%)	11 (13.8)

[a] N=31; [b] N=42; [c] N=42; IQ= Intellectual Quotient; GAF=Global Assessment of Functioning scale; CGI-S=Clinical Global Impressions-Severity of Illness scale; BPRS=Brief Psychiatric Rating Scale; YMRS=Young Mania Rating Scale; CGI-I=Clinical Global Impressions- Improvement

tively. To test the association between the selected quantitative variables (duration of stay, ΔGAF) and treatment variables (mood stabilizers lithium, carbamazepine, valproate, classical AP, atypical AP, combination A and B) we used ANOVA test. For qualitative variables (type of episode, presence or absence of psychotic feature), Fisher exact test was used. Two-tailed values of $p < 0.05$ were considered statistically significant.

Results

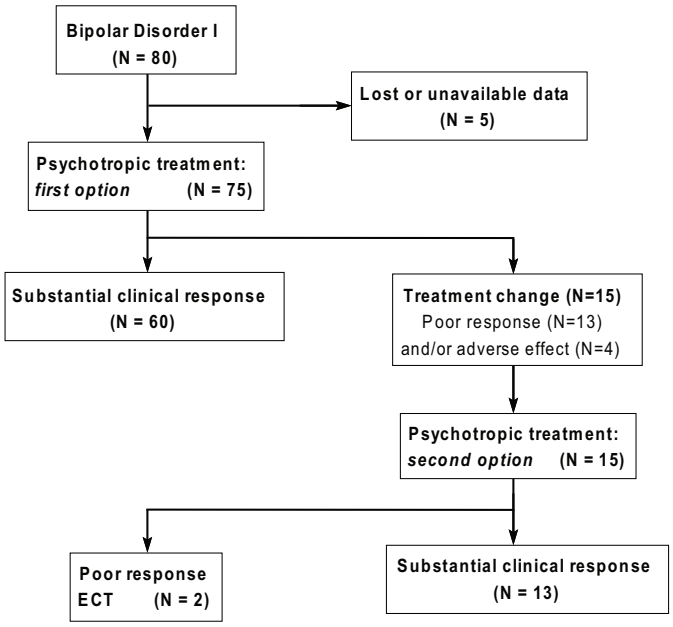
Socio-demographic and clinical characteristics of the sample

The sample was composed of 45 females and 35 males with a mean age of 15.67 (±1.89) years [range: 12-19]. The socio-demographic and clinical characteristics of the sample are summarized in table 1 and detailed elsewhere (Brunelle et al. 2009). Forty nine adolescents presented with a manic episode and 31 with a mixed episode. Thirty subjects (37.5%) reported an acute onset of the episode (≤ 10 days). Psychotic features were found in 50 patients (63.8%). Mean IQ was in the low range of normality [mean IQ = 83.4 (±23.4)] and 17 subjects (21.3%) had mental retardation. Clinical severity scores, as assessed on the different scales at admission, confirmed that the sample was composed of severely impaired patients representing one end of the BD spectrum. Despite prolonged hospitalization in many cases

Table 2. Pharmacological treatment for adolescent inpatients with acute manic or mixed episode in a university setting

Medication use: first option	**Subjects** N (%)
Treatment received by class	
Normothymics :	**62** (82.6)
– carbamazepine	28 (37.3)
– valproate, valpromid, divalproate	20 (26.6)
– lithium	14 (18.6)
Classical antipsychotic	**65** (86.6)
Atypical antipsychotic (AP)	**18** (24)
Others (anxiolytics, antidepressants)	**18** (24)
Combination of treatment	
Normothymic + classical AP	**50** (66.6)
Normothymic+ atypical AP	**15** (20)
Classical AP + atypical AP	**6** (8)

Figure 1. Diagram flow of treatment options in adolescents with bipolar disorder I hospitalized in a French University setting



(minimum stay = 17 days), it should be highlighted that 69 (86.2%) patients were scored very much or much improved during their stay.

Description of the pharmacological treatment (Table 2)

Treatment data were lost or unavailable for five subjects among the 80 subjects hospitalized and treated for an acute manic or mixed episode. Among the 75 adolescents remaining, 62 (82.6%) received normothymics or mood stabilizers. Twenty eight received carbamazepine, 20 received valproate (valpromid, divalproate, sodium valproate) and 14 received lithium.

Sixty five subjects (86.6 %) received a classical AP and 18 (24%) received atypical AP. Finally, 18 patients received others medications including anxiolytics (n=9), antidepressants (n=7), or others (n=3). Two needed to be treated with ECT. A majority of these adolescents were treated with a combination of medications associating either a mood stabilizer and a classical AP (66.6%), a mood stabilizer and an atypical AP (20%) or a combination of atypical and classical AP (8%).

Treatment option and decision algorithm (Figure 1)

Figure 1 details the diagram flow of treatment options according to response and major adverse effects. Of note, 15 patients (20%) needed a second treatment option. The reasons for changing treatment were a poor therapeutic response and/or serious adverse events. Thirteen subjects needed a second treatment option because of poor therapeutic response (13/15 = 86.6%). Five subjects presented severe adverse effects (5/15 = 33.3%). Three subjects presented at the same time adverse effects and poor therapeutic response. The serious adverse effects observed were: hepatic toxicity (n=2) and agranulocytosis (n=1) with carbamazepine, thrombopenia with divalproate (n=1), and severe nausea/vomiting with valpromid (n=1). Two out of the 15 subjects who received a second treatment option received ECT (bilateral electrod position using Thymatron-IV device; 9 and 10 sessions, respectively) as a third therapeutic option.

Treatment variables associated with type of episode, psychotic features, duration of stay and ΔGAF

Using ANOVA for continuous variable and Fisher exact test for dichotomous ones, we determined whether type of episode, presence or absence of psychotic features, duration of stay and ΔGAF were associated with the type of treatment received during inpatient stay. We found no association between therapeutic variables and duration of stay, the type of episode and the clinical improvement as assessed by ΔGAF=GAF at discharge – GAF at admission. However, we found a significant association between therapeutic class and the presence of psychotic symptoms. Adolescents with psychotic symptoms received significantly more frequently lithium than adolescents without psychotic symptoms (Fisher exact test: p= 0.0052). In this sample, psychotic features were found in 50 patients (62.5 %) (Brunelle et al. 2009).

Discussion

Limitations, strengths and context

Before any comments on the current study, one should keep in mind the limitations and strengths of the study, and the French context as well. The major limitation of this study is its retrospective design, addressing the question of intake diagnosis accuracy and of data quality control (e.g. 5 patients' charts were lost or were not exploitable). Other limitations include the fact that: (i) adverse effects could not be listed in details, so we only reported the most severe ones that is those being a reason for therapeutic change; (ii) the sample size by therapeutic class and the use of pharmacological treatment in combination limited the statistical power and the number of analyses.

The strengths of the study are: (i) the prolonged duration of hospitalizations providing us precise and numerous nurse and medical notes; (ii) the homogeneity of the sample in terms of clinical characteristics (typical and severe forms of bipolar BD type 1; only adolescents); (iii) the European context of free access to care; (iv) the little knowledge on pharmacological treatment and/or use of

medication in clinical setting (Consoli et al. 2007).

Regarding French context, it has to be noted that to date (so during the study period) no medication, either mood stabilizers or antipsychotics, are allowed for bipolar disorder in children and adolescents. Therefore, most psychotropic treatments are prescribed without recommendations of the French Drug Agency. Furthermore, despite the relative low number of comparative pharmacoepidemiological studies, it seems that psychotropic use for minors in France and other European countries is in average twice to third times lower than in the US (Marcelli and Cohen 2009).

Pharmacological treatment options

The high ratio of medication combinations is consistent with the literature data reporting high rates of polypharmacy in youths with BD (Bhangoo et al. 2003; Kowatch and DelBello 2005). In this study, it can be explained also by the clinical severity of the episodes according to CGI-S and GAF scores at admission and duration of stay. Most of the adolescents received a mood stabilizer associated with an AP. A large majority received a classical AP and a minority received atypical ones. This can be explained by the fact that most studies regarding the use of atypical AP in youth with BD are recent and that all positive double-blind placebo-controlled trials with atypical AP were published after our period of recruitment (Tohen et al. 2007; Zhang 2008). In this study, cost of treatment didn't influence the prescriptions because of French sanitary context (free care).

The only significant result about the choice of a therapeutic class concerned lithium. When subjects presented with psychotic symptoms, the more frequently prescribed mood stabilizer is lithium rather than valproate or carbamazepine. This treatment choice may have been influenced by published studies in adults, in which lithium appears to be the gold standard for treatment of acute manic or depressive episodes, and for prevention of manic or depressive relapses in BD (Bauer and Mitchner 2004). Perhaps the presence of psychotic features is considered as a sign of gravity and may lead French doctors to prescribe a more classical treatment used in bipolar disorder in adults. Also, treatments in BD are usually prescribed for a long duration (several years) and lithium long term side effects such as thyroid dysfunction and renal failure may limit its use unless symptoms are particular severe, such as seen with psychotic symptoms. Regarding other variables, there is no association between duration of stay, type of episode and improvement during inpatient stay and the nature of the treatment given.

Regarding treatment changes, they occurred in 20% of the cases, with poor response being the most frequent reason (figure 1). Serious secondary effects accounted for 5 of the cases for which a second treatment option had been decided. This result has to be interpreted with caution because, as mentioned in the methodological limitations of the study, we only reported the most serious adverse effects causing a stop of treatment. Therefore, one cannot conclude that pharmacological treatment was well tolerated in this sample. Actually, it is likely the opposite is true, since most of the psychotropic medications have age-specific side effects, with higher frequency and greater severity in youths than in adults (Hagino et al. 1995; Woods et al. 2002).

Regarding ECT, 2 subjects received this treatment as a third option. Although the number of studies is limited on the use of ECT in adolescents with BD, age ranges and diagnosis are quite homogenous in those studies (Cohen et al. 1997; Consoli et al. 2007). ECT is rarely proposed for a manic episode but rather for psychotic depression with or without catatonic features. Response rate in resistant manic episode is high and similar to that of other mood disorder ranging from 75 % to 100 % (Consoli et al. 2007). Overall, these descriptive results are important because less is known about bipolar I disorder in adolescents, about pharmacological treatments used, and about adverse effects.

Response to treatment

In this study, the therapeutic response was in the higher range of what is reported in the literature (Consoli et al. 2007). Sixty subjects out of 75 (80%) had a positive therapeutic response with the first therapeutic proposal and kept the same treatment at discharge. Changing for a second option helped 9 more patients. Several speculations can be made to explain this result. First, the sample is very homogeneous regarding age range, type of BD and clinical severity. Studies on mediator of treatment response in youths with BD are very limited. However, it appears that the therapeutic response is lower when inclusion criteria such as age, type of BD, severity and comorbidity are heterogeneous (Geller et al. 1998; Kafantaris et al. 2004; Wagner et al. 2006) compared to homogeneous (Dailey et al. 2005; Strober et al. 1995; Tohen et al. 2007). As an example, using a meta-analysis method, Consoli suggested that comorbid ADHD predicted poorer response to pharmacological treatment of BD in young people (Consoli et al. 2007). Second, it is possible that the hospitalization per se contributed to the high response rate in this study. Currently, mean duration of inpatient stay for bipolar children and adolescent in the USA is 5.6 days which is far below what we have in this sample (mean=80 days) (Case et al. 2007).

Conclusion

In a sample of French adolescent inpatients with severe bipolar I disorder, manic or mixed episode, the study indicates that: (i) combination of drugs is required in most cases and usually includes a mood stabilizer and an AP; (ii) serious adverse effects can occur and deserve attention by clinicians; (iii) patterns of medication mainly followed treatment recommendations and evidence-based data; (iv) there is an association between the presence of psychotic features and the nature of the treatment given (lithium).

Acknowledgements/Conflict of Interest

The authors have no financial relationships or conflicts to disclose.

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