ELSEVIER

Journal of Affective Disorders 82 (2004) 149–158

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Preliminary communication

Treatment-emergent mania in pediatric bipolar disorder: a retrospective case review

Gianni L. Faedda[a,b,c,*], Ross J. Baldessarini[b,c], Ira P. Glovinsky[a,d], Nancy B. Austin[a]

[a] *'Lucio Bini' Mood Disorders Center, New York, NY 10022, USA*
[b] *Department of Psychiatry and Neuroscience Program, Harvard Medical School, Boston, USA*
[c] *Bipolar and Psychotic Disorders Program and Laboratories for Psychiatric Research, McLean Hospital, Belmont, MA 02478, USA*
[d] *Village Educational Center, Beverley Hills, MI 48301, USA*

Received 31 July 2003; accepted 3 December 2003

Abstract

Background: Pediatric bipolar disorder (BPD) can be misdiagnosed as a depressive, attention, conduct, or anxiety disorder and treatment with antidepressants and stimulants is common. Risk of adverse outcomes related to such treatment remains poorly defined. *Methods*: We analyzed clinical records of 82 children (mean age 10.6 years) meeting modified DSM-IV diagnostic criteria for BPD to evaluate risk and timing of operationally-defined treatment-emergent mania (TEM) or increased mood-cycling following pharmacological treatment. *Results*: Of 82 juvenile BPD patients, 57 (69%) had been given a mood-elevating agent at least once; 33/57 (58%) so-exposed met criteria for TEM, with median latency of 14 days; TEM was observed twice as often with antidepressants as stimulants (44% vs. 18%). TEM led to first-recognition of BPD in 14 cases (17%), and some drug-exposed children (4–9%) had prominent suicidal, homicidal or psychotic behavior. In addition to recent exposure to a mood-elevating agent, TEM was associated with early-onset anxiety and female gender. *Limitations*: Findings are retrospective in clinically diagnosed and treated outpatients, but involved otherwise unselected cases of juvenile BPD. *Conclusions*: TEM was reported in 58% of children with probable juvenile BPD within several weeks of new exposure to a mood-elevating agent.

Keywords: Antidepressants; Bipolar disorder; Children; Mania; Stimulants

1. Introduction

Juvenile bipolar disorder (BPD) was clearly described in the early 20th century by Ziehen (1927), but now is considered rare, and its very existence controversial, especially before puberty (Biederman et al., 2000; Faedda et al., 1995, 2003; Geller et al., 2001; Papolos and Papolos, 2002). Pediatric BPD presents particular diagnostic challenges due to developmental variance in phenomenology and illness-course, as well as frequent symptomatic overlap or comorbidity of pediatric BPD with attention, conduct, depressive, and anxiety disorders (Faedda et al., 1995, 2003; Geller et al., 2001; Wozniak et al., 1995). In contrast to a biphasic, episodic and relatively slow-cycling course in some adults with BPD, pediatric forms usually involve mixed mood-states and a sub-

* Corresponding author. 'Lucio Bini' Mood Disorders Center, 245 East 50th Street, New York, NY 10022, USA. Tel.: +1-212-644-3111.
E-mail address: gianni.faedda@moodcenter.org (G.L. Faedda).

0165-0327/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2003.12.011

chronic, unstable and unremitting course. These forms, do not meet DSM-IV-TR (APA, 2000) episode-*durationduration criteria, but are well within the "spectrum" of BPD described by Akiskal and Pinto (1999).*

Effects of mood-elevating, mood-stabilizing and antipsychotic agents on the onset, course and treatment-response of juvenile BPD also are particularly poorly defined. Antidepressants are especially clinically relevant to managing depressive or dysphoric phases of BPD, as well as anxiety and attention deficit syndromes commonly comorbid with BPD. In adults with BPD, antidepressants appear to precipitate manic or dysphoric-mixed states, increase mood instability or contribute to rapid-cycling, and perhaps limit responsiveness to mood-stabilizing treatments (Altshuler et al., 1995; Dilsaver and Swann, 1995; Ghaemi et al., 2000; Henry et al., 2001; Koukopoulos et al., 1992, 2003; Papolos, 2003; Post et al., 1997; Sachs et al., 2000; Stoll et al., 1994; Tondo et al., 1981; Wehr, 1993; Wehr and Goodwin, 1979; Wehr et al., 1988), although a causal relationship has been questioned (Altshuler et al., 2003). The occurrence of manic-like symptoms during treatment with antidepressants and stimulants is recognized by DSM criteria for substance-induced mood disorder (with manic or mixed features), distinct from BPD.

Children who progress to manifest BPD often present with depressive-dysthymic, anxiety, or attention deficit symptoms long before manic symptoms clarify the diagnosis (Faedda et al., 1995, 2003; Geller et al., 2001; Kovacs, 1989; Kovacs et al., 1994). Such presentations encourage trials of antidepressant or stimulant treatment. Exposure of children and adolescents to mood-elevating agents is common in the US. In 900,000 subjects below age 20 enrolled in two US healthcare systems, "the 1996 prevalence of any psychotropic medication among youths younger than 20 years was remarkably similar (5.9–6.3%) across all three sites, with stimulants and antidepressants consistently ranked first and second" (Zito et al., 2003). Given high rates of comorbidity and misdiagnosis, many juveniles with BPD are exposed to mood-elevating agents (Faedda et al., 1995, 2003; Greenberg et al., 2003; Wozniak et al., 1995), and some may abuse stimulants as well (Woodworth, 2000). The American Academy of Child and Adolescent Psychiatry (McClellan and Werry, 1997) recommended that: "Psychostimulants must be used with caution in patients with BPD and are best avoided during acute manic phases". More recently, the AACAP Practice Parameters for the use of Stimulants (Greenhill et al., 2001) asserted that "Stimulants do not precipitate young adult BPDs in boys comorbid for both attention deficit-hyperactivity disorder (ADHD) and non-psychotic BPD on mood stabilizers, either acutely or later on (Carlson et al., 2000)". These statements imply that stimulant treatment in children with BPD is relatively safe, but this proposition remains controversial and needs to be reconsidered in light of emerging research.

In adults with BPD, stimulant-abuse probably contributes to affective and behavioral instability and limits response to mood-stabilizing treatment (Baldessarini and Tarazi, 2001). The potential for specific adverse psychiatric responses among patients with known or latent BPD, particularly during treatment with stimulants or other mood-elevating agents unopposed by mood-stabilizing agents, has been reported (Koehler-Troy et al., 1986). Moreover, adverse psychiatric consequences may include a worse course of BPD long after stimulant treatment in youth (DelBello et al., 2001; Mota-Castillo et al., 2001; Soutullo et al., 2002). Given widespread use of mood-elevating drugs in children, and the plausibility of increased risk of inducing mania with such treatment in those with BPD, this risk is surprisingly poorly documented. A recent issue of the *Journal of Child and Adolescent Psychopharmacology* (vol. 13:2, 2003) was devoted to the topic of switching; the occurrence of antidepressant-induced manic-like syndromes remains, however, controversial. The editor, Dr. Carlson concludes: "The tentative conclusions we can draw from these studies are that, examined carefully, behavioral toxicity (which includes switching, drug-induced behavioral disinhibition, rebound, and psychiatric adverse events) is not as common as case reports and clinical practice would lead one to believe. Second, when behavioral toxicity actually occurs, it may tell us more about the child's ability to tolerate a drug than it does about diagnosis. It may be that the implications of behavioral toxicity include some relation with BPD. However, behavioral toxicity, manic-like responses, actually switching (and developing BPD), and rapid-cycling are not mutually inclusive and need to be defined well and studied separately".

Antidepressant-induced manic-like syndromes have also been reported in a few cases in children or adolescents exposed to either tricyclic (TCA) or serotonin reuptake inhibitor (SRI) antidepressants (Biederman et al., 1999, 2000; Briscoe et al., 1995; Faedda et al., 1995; Go et al., 1998; Venkataraman et al., 1992). In a recent chart review of 82 pediatric patients treated with an SSRI for depressive symptoms and/or obsessive–compulsive disorder (OCD), 7% experienced manic symptoms, and 9.7% became psychotic (Wilens et al., 2003). However, the risks of antidepressant-induced manic and mixed states, cycle acceleration or treatment resistance in pediatric cases of BPD remain poorly defined.

All antidepressants have been associated with such effects, though some may be more risky than others (Himmeloch et al., 1991; Peet, 1994). The US FDA (2003) recently issued a specific warning on potentially increased self-injury and suicidal impulses during treatment of juveniles with paroxetine. Such cases might well include children with unrecognized BPD. Mania-like symptoms in pediatric patients have been considered a manageable side effect of otherwise helpful antidepressant (Venkataraman et al., 1992) or stimulant treatment (Grcevich et al., 2001), or as indicating serious BPD psychopathology (Akiskal and Pinto, 1999; Akiskal et al., 1985, 2003; Baldessarini, 2001; Carlson and Kelly, 1998; Faedda et al., 1995; Strober and Carlson, 1982). Such reactions have encouraged caution in the continued use of stimulants or antidepressants, unless combined with a mood-stabilizing agent and used in moderate doses (Akiskal et al., 1985, 2003; Faedda et al., 1995; Strober and Carlson, 1982).

Based on the preceding evidence of adverse psychiatric effects of mood-elevating agents in adults with BPD, and plausible bases for anticipating similar risks in children, we examined the records for: (a) evidence of treatment-emergent mania (TEM); (b) association with particular agents; (c) predictors of TEM. We also hypothesized that treatment of children with BPD with such drugs would: (1) precipitate or worsen manic symptoms, (2) induce psychotic symptoms (3) increase aggressive tendencies (suicidal or homicidal thoughts or acts), but (4) have limited effects on already relatively rapid mood-fluctuations or cycling. We examined associations of exposure to psychotropic agents in children diagnosed with BPD, and their clinical responses to identify the prevalence, characteristics and predictors of psychiatrically adverse outcomes.

2. Methods

We reviewed the records of all children evaluated and diagnosed with BPD between April, 1998 and April, 2002 at the 'Lucio Bini' Mood Disorders Center in New York City. We used all available medical records and supplemental information provided by referring clinicians and family members, all as detailed elsewhere (Faedda et al., 2003) to estimate ages at: first psychiatric symptoms (affective or behavioral), first psychiatric intervention, first diagnosis of BPD, and family history of affective, psychotic, or substance use disorders. Current psychiatric diagnoses were based on DSM-IV-TR criteria, determined by extensive interviews of parents and examination of each patient by at least two experienced child-psychiatry research clinicians (GLF, IPG, NBA). Most cases were from the clinical practices of the authors.

In cases considered to represent new manic symptoms closely associated with treatment with a mood-elevating agent, diagnoses of both BPD and organic mood disorder were given. For descriptive purposes the rate of symptomatic recurrence before and after treatment was recorded, and described as ultra–ultra-rapid-cycling (UURC, >365 phases per year), ultra-rapid-cycling (URC, 5–365 phases per year), rapid-cycling (RC, ≥ 4 episodes or phases per year). A detailed record of all past treatment trials was constructed for each case, including medication type, dose, duration, benefits and adverse responses and their timing in days from initiation of treatment.

TEM was diagnosed if *all* four of the following criteria were met: (1) a disabling manic or mixed syndrome, with or without psychotic features, associated with use of a mood-elevating drug; (2) emergence within 30 days of either new administration or increased dosage of an antidepressant, stimulant, or both; (3) ≥ 4 of the following 13 symptoms rated as *newly present* or *substantially worse*: sleep disturbances 3.1 early or middle insomnia; 3.2 decreased sleep; major mood change 3.3 euphoria; 3.4 irritability; 3.5 anger; 3.6 lability; 3.7 anxiety; major behavioral change 3.8 hyperactive; 3.9 impulsive 3.10 hypersexual; 3.11

aggressive; 3.12 self-injurious behavior; 3.13 substantial change in speech (rapid, pressured, intrusive, loud, vulgar or abusive); (4) discontinuation of the suspected agent and/or additional treatment with antimanic drugs as clinically indicated.

These criteria ensured that transient mild side effects or a mild variation of mood or behavior would not be counted as TEM. Required simultaneous mood and sleep symptoms selected for *syndromal* changes (rather than a side effect or isolated symptom). Furthermore, disability and a clinical need to treat selected for the more serious cases of adverse reaction to these agents.

Records were rated for quality and completeness of information as: (0) minimal, (1) satisfactory, (2) substantial, and (3) extensive; only records with scores of ≥ 1 were included for study. Data analyses used SPSS® statistical software (version 11.0; Chicago, IL), including ANOVA methods (F) for continuous data (averages are mean ± standard deviation [S.D.]), and contingency tables (χ^2or Fisher exact-p) for categorical variables; statistical significance required two-tailed $P < 0.05$. Stepwise logistic-regression was used to identify variables predictive of adverse outcomes, with their contributions rated as odds ratios (OR) with 95% confidence intervals (CI).

Table 1
Characteristics of pediatric subjects with BPD

Measure	Boys ($N=54$)	Girls ($N=28$)	All ($N=82$)
Age at first symptoms*	3.2 ± 3.5	2.2 ± 3.8	2.8 ± 3.9
Age at first treatment*	6.6 ± 3.4	7.3 ± 3.9	6.8 ± 3.6
Age at BPD diagnosis*	9.2 ± 3.4	10.4 ± 3.7	9.6 ± 3.6
Age at clinic assessment*	10.1 ± 3.5	11.5 ± 3.7	10.6 ± 3.6
BPD subtype			
Mania	57.4	39.2	52.4
Hypomania	37.0	46.4	40.2
Cyclothymia	3.7	14.3	7.3
DSM duration criteria met	51.8	53.5	52.4
Comorbid diagnoses			
Psychosis	31.4	32.1	31.7
OCD	29.6	21.3	26.8
Anxiety	20.4	28.6	23.2
LD	18.5	10.7	15.9
ADHD	13.0	7.1	11.0
ODD/CD	7.4	10.7	8.5
Eating	1.9	0.7	4.9
Substance use	1.9	7.1	3.7

Data are % of all subjects with BPD, or mean ± S.D. age (years). No sex difference was statistically significant (χ^2 or Fisher exact p). Abbreviations: ADHD, attention deficit-hyperactivity disorder; BPD, bipolar disorder; CD, conduct disorder; DSM, DSM-IV; LD, learning disability; OCD, obsessive–compulsive disorder; ODD, oppositional-defiant disorder.

*See Section 2.

3. Results

DSM-IV criteria for BPD were met by 82 children. Age at inclusion averaged 10.6 ± 3.6 years (range, 3–17 years; 73.2% were prepubertal) and clinical characteristics are detailed elsewhere (Faedda et al., 2003). Quality of records was rated at 2.6 ± 0.5 (range, 2–3), indicating that extensive information was available. Age at first psychiatric symptoms averaged 2.8 ± 3.9 years, with first treatment at 6.8 ± 3.6 years. The *diagnosis* of BPD occurred at age 9.6 ± 3.6 years (Table 1).

Prior to diagnosis of BPD, 93% of our patients received one *or more* of the following psychiatric diagnoses: attention deficit (59.8%), anxiety or obsessive–compulsive (39.1%), depressive (36.6%), or oppositional-defiant or conduct disorder (20.7%, Faedda et al., 2003).

At the initial evaluation over 50% had been diagnosed with mania, 40% with hypomania, and 7% with cyclothymia, but only 52% met DSM-IV *duration* criteria for a manic or hypomanic episode. Comorbid diagnoses included psychosis (31.7%), OCD (26.8%), other anxiety disorders (23.2%), learning disabilities (15.9%), ADHD (11%) and oppositional-defiant or conduct disorder (8.5%, Faedda et al., 2003).

Of the 82 BPD patients, 84% had been exposed to at least one trial of a psychotropic drug and 69.5% received a mood-elevating agent. Only 29% had no known exposure to a mood-elevating agent and 16% was never exposed to a psychotropic agent. Of the 57 patients treated with a mood-elevating agent, 28% had been given at least an antidepressant but no stimulant, 18% had been given stimulants but no antidepressants, and 23% were exposed to both. Several of the 82 BPD patients, were exposed to multiple agents, including mood-stabilizing agents, atypical antipsychotics, and others.

Operationally-defined TEM was diagnosed in 35 of 69 patients exposed to any psychoactive agent (50.7% risk). In 33 of these 35 cases, (58% of 57 children exposed, Table 2) TEM was associated with use of an antidepressant (75.7%), or a stimulant (24.2%; Table 3). One case was associated with carbamazepine treatment, and a corticosteroid was implicated in another. No other TEM was associated with mood stabilizers, antipsychotic, or other psychotropic agents. In our analysis of TEM symptoms we refer to all the 35 events observed, as there was no difference between events by causative agent. Among the 33 instances of TEM associated with antidepressants and stimulants, 10 involved new manic or mixed syndromes, and 23 were acute exacerbations of a previously diagnosable BPD. In 14 children, BPD was first diagnosed following TEM in 14 children.

Initial symptoms of emerging mania included marked mood change (100% of cases; especially irritability or anger), sleep disturbances (86%), increased activity (restlessness, agitation; 91%), impulsive or aggressive behavior. Hypersexuality and pressure-of-speech were common, and self-injury (20%), suicidal ideation (14%) and suicidal acts (6%) also were noted (Table 2). These symptoms resolved rapidly (typically within 2 weeks) when the suspect mood-elevating agent was discontinued, supporting the conclusion that these outcomes were treatment-related. Mood-elevating medication was stopped in 94% of cases. Symptoms of TEM were severe enough to warrant additional treatment with mood-stabilizing or antipsychotic agents in 83% of cases. New onset of psychosis (12%) or homicidal ideation (6%) contributed to hospitalization of four patients (12%); in three other cases hospitalization was refused, suggesting that inpatient treatment may be needed in at least 20% (7/33) of children with BPD with TEM.

The agents most often associated with TEM were SRI antidepressants (60.6% of cases), followed by atypical antidepressants (bupropion or trazodone, 9.1%), and then TCAs (6.1%). However, this ranking

Table 2
Incidence (%) of TEM symptoms in children with BPD

Symptoms	Boys ($N=20$)	Girls ($N=15$)	All cases ($N=35$)
Major mood change	100.0	100.0	100.0
Lability	100.0	100.0	100.0
Irritability	95.0	100.0	97.1
Anger	80.0	100.0	88.6
Anxiety	50.0	60.0	54.3
Euphoria	50.0	40.0	45.7
Major behavioral change	100.0	100.0	100.0
Hyperactive	100.0	80.0	91.4
Impulsive	85.0	73.3	91.4
Aggressive	75.0	80.0	77.1
Change in speech pattern	50.0	33.3	42.8
Hypersexual	30.0	13.3	22.8
Self-injurious behavior	20.0	20.0	20.0
Suicidal ideation	10.0	20.0	14.3
New psychosis	20.0	0.0	11.4
Suicide attempts	5.0	6.7	5.7
Homicidal ideation	10.0	0.0	5.7
Sleep disturbances	85.0	86.6	85.7
Early/middle insomnia	65.0	73.3	68.6
Decreased sleep	20.0	13.3	17.1
Intervention required	100.0	100.0	100.0
Agent discontinued	95.0	93.3	94.3
Antimanic treatment	80.0	86.7	82.8
Hospitalized	15.0	6.7	11.4

All cases met a priori criteria for TEM, associated with treatment with a mood-elevating agent. Some categories overlap and new mania includes psychotic episodes.

Table 3
Incidence (%) of TEM in children with BPD by mood-elevating agent, and latency to event

Treatment type	Boys	Girls	All cases
All agents[a]	45.0 (18/40)	88.2 (15/17)	57.9 (33/57)
Antidepressants[b]	35.0 (14/40)	64.7 (11/17)	43.8 (25/57)[c]
SRIs	42.8 (12/28)	63.6 (7/11)	48.7 (19/39)
Tricyclic	0.0 (0/3)	100 (2/2)[d]	40.0 (2/5)
Bupropion or trazodone	22.2 (2/9)	50.0 (2/4)	30.7 (4/13)
Stimulants[e]	11.4 (4/35)	40.0 (4/10)	17.8 (8/45)[c]
Methylphenidate	15.0 (3/20)	37.5 (3/8)	21.4 (6/28)
Amphetamines	10.0 (1/10)	50.0 (1/2)	16.7 (2/12)
Antidepressant + stimulant	6.3 (1/16)[f]	0.0 (0/5)	4.8 (1/21)
Days from start of mood-elevating treatment to onset of mania			
Mean ± S.D.	10.5 ± 8.0	14.9 ± 0.0	12.5 ± 7.4
Median (range)	8.5 (1–28)	14.0 (7–30)	14.0 (1–30)

Percentages (and proportions) of pediatric BPD patients exposed to mood-elevating agents, who developed TEM.
[a] Girls>boys (χ^2[1 df] = 9.15, $P=0.0025$).
[b] For antidepressants: girls>boys (χ^2[1 df] = 4.28, $P=0.039$).
[c] Antidepressants>stimulants (Fisher exact $P=0.006$).
[d] Both cases also received a SRI.
[e] For stimulants: girls>boys (Fisher exact $P=0.059$).
[f] SRI + methylphenidate.

reflects relative *exposure rates* and not agent-specific risk. More appropriately, proportions of patients with TEM, among those exposed to specific types of agents, ranked: SRIs (48.7%), TCAs (40.0%), other antidepressants (30.7%), methylphenidate (21.4%), or amphetamines (16.7%). Risk of TEM in children exposed to a mood-elevating agent was twice-greater among girls than boys (88.2% vs. 45.0%; χ^2[1 df] = 9.15, $P = 0.0025$), and this sex difference tended to be sustained with both antidepressants and stimulants (Table 3). Overall, the latency from onset of TEM averaged 12.5 ± 7.4 days, with a median of 14 days (Table 3).

We also contrasted juvenile BPD patients exposed to a mood-elevating treatment who did ($N = 33$) or did not ($N = 24$) develop TEM or new psychosis. Those who reacted adversely in this way were younger (6.16 ± 2.8 vs. 7.89 ± 4 years; F[1; 56 df] = 6.51, $P = 0.013$). In addition, early symptoms, including *sleep disturbances*, *inattention* and *separation anxiety*, all tended to be more frequent among drug-exposed patients who later developed TEM (data not shown).

Assessment of possibly increased cycling rates among the drug-exposed patients was confounded by high prevalence of rapid-cycling, and short exposures to mood-elevating agents. Overall, 85% of the sample experienced ≥4 episodes or major shifts in mood during a 1-year period, and most of these (75%) followed URC or UURC courses, without differing significantly by sex, exposure to mood-elevating agents, or occurrence of TEM (data not shown). Moreover, emergence of TEM on exposure to mood-elevating agents usually led to prompt termination of the exposure, precluding assessment of long-term effects of mood-elevating agents on course-patterns. Nine additional patients experienced exacerbations of manic symptoms that were relatively mild or emerged >30 days after starting an antidepressant or stimulant.

Stepwise multivariate logistic-regression supported a risk-model with three variables, in the following order of estimated risk for TEM: (1) severe early-onset anxiety before drug-exposure (OR = 8.8 [95% CI: 1.1–69.2]); (2) exposure to a mood-elevating drug (OR = 7.0 [CI: 1.3–8.3]); and (3) female sex (OR = 5.2 [CI: 1.2–22.8]). Overall, this model is accurately in predicting TEM was highly significantly (χ^2[2 df] = 15.9, $P < 0.0001$). Risk of TEM was not associated with family-history, adoption or educational status, age-at-onset, or current age (data not shown).

4. Discussion

4.1. Exposure to mood-elevating agents

This retrospective clinical study of 82 children diagnosed with BPD found that 70% were treated with a mood-elevating agent, most often an antidepressant. This high rate of exposure to mood-elevating agents in children with BPD is consistent with the symptomatically complex and diagnostically confusing presentation of this illness in children (Faedda et al., 1995; Faedda et al., 2003; Geller et al., 1995; Geller et al., 2001; Papolos and Papolos, 2002; Wozniak et al., 1995). Most subjects (90.2%) were initially diagnosed with an attentional, conduct, depressive, or anxiety disorder before BPD (bipolar I, II, or cyclothymia) was recognized. Diagnosis of BPD was delayed for 2.8 years from initial psychiatric assessments (age 6.8 years), and almost 7 years from the onset of the first symptoms; indeed, a diagnosis of BPD was made only after appearance of TEM in 17.1% of the cases (Table 1). This experience is consistent with high, and possibly excessive, rates of utilization of antidepressants, stimulants, and other psychotropic agents in contemporary pediatric and child psychiatric clinical practice (Zito et al., 2003), and illicit abuse of stimulants in particular, by juveniles (Soutullo et al., 2002; Woodworth, 2000). Similarly high rates of exposure to antidepressants (69%, Papolos et al., 2003) and stimulants (63%, Greenberg et al., 2003) in children suffering with BPD have been reported. These data are consistent with our findings, and support the observation that mood-elevating agents are commonly used in this population.

4.2. Risk of TEM

An alarmingly high proportion (58%) of children with BPD, when exposed to a mood-elevating agent, experienced operationally-defined TEM. A much higher risk with antidepressants (76%) than stimulants (24%) was observed. These rates are remarkably consistent with other new findings of increased

affective morbidity in BPD cases following exposure to antidepressants (75%, Papolos et al., 2003), or to stimulants (37%, Greenberg et al., 2003). Median latency from initiation of the suspected drug treatment and onset of symptoms of TEM was 14 days. Most cases resolved rapidly with discontinuation of the suspected agent, and/or adding mood-stabilizing treatment. Of the present cases, 8 (24%) experienced a second episode of TEM when exposed to another mood-elevating agent (not included in the present analyses).

Wilens et al. (2003) found a 22.0% incidence of ''psychiatric adverse events'' among 82 juveniles exposed to an SRI for depression or OCD, and a median onset after 91 days of treatment. Carlson and Mick (2003) found mood-elevating drug-associated ''behavioral disinhibition'' in 7.5% of 263 pediatric inpatients, particularly on exposure to an SRI. These findings are hard to compare to the present study based on syndromal criteria used and a cohort with BPD, but we also found a strong association of TEM with use of either SRI or TCA antidepressants more than with stimulants. This association may reflect intrinsic pharmacodynamic risk-differences between antidepressants and stimulants (such as effects on serotonin or norepinephrine versus dopamine neurotransmission). Alternatively there may be clinically important differences in vulnerability to TEM between children with BPD and comorbid anxiety or depressive illnesses versus attentional dysfunctions.

4.3. Cycling and switch rates

High rates of rapid-cycling in this pediatric BPD sample were expected (Geller et al., 1995, 2001, Papolos et al., 2003), and found (85%). Spontaneous rapid-cycling, and early discontinuation of mood-elevating agents following TEM precluded assessment of potential increases in cycling-rates with sustained exposure to a mood-elevating agent, as has been observed in adults with slower-cycling BPD exposed to antidepressants (Ghaemi et al., 2000; Henry et al., 2001; Koukopoulos et al., 1992; Papolos et al., 1998; Tondo et al., 1981). Although we did not score new ultradian mood shifts, such a response has been observed in BPD children exposed to antidepressants or stimulants (Greenberg et al., 2003; Papolos et al., 2003).

4.4. Diagnostic significance of TEM

Currently, official international diagnostic systems of ICD-10 (WHO, 1992) and DSM-IV (APA, 2000) require that TEM be classified as a ''substance-induced'' mood disorder, and not a manifestation of primary BPD. Nevertheless, the present cases of TEM in children were very similar to spontaneous episodes of BPD in symptomatic presentation, illness-course, family-history, and treatment-response. Furthermore, 83% of the pediatric BPD cases reported were diagnosed as such *before* the occurrence of TEM. Mania emerging with mood-elevating treatments in adults may be somewhat milder, but otherwise very similar to mania arising spontaneously in primary BPD (Akiskal et al., 2003; Stoll et al., 1994). For the 17% of the present cases in whom TEM led to a diagnosis of BPD, we found premorbid features consistent with early-onset BPD. In all cases continued treatment with mood stabilizers was needed and beneficial. TEM was more likely among children diagnosed with BPD type I (52%) or type II (40%), than those diagnosed with cyclothymia (7%; Table 1). The occurrence of TEM among all BPD subtypes suggests a degree of vulnerability for TEM even in BPD children without a past history of mania.

Our findings are subject to several sources of bias or artifact potentially relevant to the hypothesis that new or worsening manic symptoms (TEM) were causally linked to treatment with a mood-elevating agent. These include referral, assessment, and reporting biases. In particular, cases referred to specialists in the diagnosis and treatment of pediatric mood disorders are likely to over-represent cases of primary BPD compared to broader clinical samples. Such referrals might also bias toward more severe or highly psychiatrically comorbid cases, that may add to risk of the adverse outcomes encountered (Carlson and Mick, 2003). However, such bias is less likely to distort *relative* risks with particular treatments, such as the observed excess with antidepressants over stimulants. Also, the high prevalence of apparently spontaneous rapid-cycling in childhood BPD complicates the distinction between drug-associated versus spontaneous mood-switching in children. It is possible that all of the observed TEM events could have occurred spontaneously, and were only coincidental to mood-elevating treatment. However, this view does not account

for the rapid improvement of TEM symptoms after discontinuing the suspect agent. Also, in several cases, re-challenge with a mood-elevating agent again resulted in rapidly emerging TEM.

It is also possible that the information on which this study was based was unreliable. In most cases, extensive information was provided by parents or guardians as well as other mental health professionals who had known the patients before referral to our Center. Moreover, given the typical caution used in medicating children, it is not surprising if details of past treatment trials were well documented, including side effects and adverse responses. Most TEM events reported were unexpected, dramatically disruptive, and memorable to family members and clinicians. The reported findings support the clinically prudent, if tentative, proposal that most TEM events were not merely spontaneous or coincidental, but instead, drug-induced phases or an exacerbation of mania in patients at high risk of developing mania.

5. Conclusions

Treatment with mood-elevating agents in children diagnosed with BPD led to new manic, and often psychotic or aggressive, behavioral changes in half of cases exposed and almost half of those given an antidepressant, but not selectively by drug type. Risk of such responses was nearly twice as high in girls as in boys, and was predicted by exposure to a mood-elevating agent and by early-onset anxiety symptoms. The median latency was 14 days, and recovery usually followed shortly after discontinuing antidepressants or stimulants, or adding an antimanic agent.

These findings strongly support our conclusion that additional assessments of the safety and efficacy of antidepressants and stimulants in children with probable, and relatively broadly defined BPD (even without meeting strict DSM-IV duration criteria) are urgently required. Prospective studies involving blinded, randomized assignment to an antidepressant or stimulant versus a placebo in children at risk for BPD would be desirable to test a possible causal relationship between new mood-elevating treatment and TEM. However, such studies would be ethically questionable, given the potential dangers involved. Plausible alternative study designs include prospective comparisons of the course of illness and outcome in children (exposed to antidepressants) with versus without TEM responses, or comparing risk of TEM among children diagnosed with BPD who are treated with a mood-stabilizer plus placebo versus mood-stabilizer plus an antidepressant.

Pending results of further scientific investigation, and review of databases on past use of mood-elevating agents in pediatric samples, we recommend extra caution in the use of antidepressants, stimulants, and steroids for children or adolescents diagnosed with or at risk for BPD, including syndromes not meeting full criteria for DSM-IV adult mania. Use of such drugs should be especially carefully weighed, and patients closely monitored, given: (1) familial predisposition for recurrent mood disorders; (2) early onset of anxiety and mood symptoms, and (3) other clinical features (such as prominent or rapid mood-fluctuations, psychomotor-retarded depression, or depression with psychotic features) consistent with BPD.

Acknowledgments

Supported in part by awards from the Bruce J. Anderson Foundation and the McLean Private Donors Neuropsychopharmacology Research Fund (to R.J.B.). Preliminary results of this study were presented at the Fifth International Conference on Bipolar Disorder, Pittsburgh, PA, June 2003 (Faedda et al., 2003).

References

Akiskal, H.S., Pinto, O., 1999. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr. Clin. North Am. 22, 517–534.

Akiskal, H.S., Downs, J., Jordan, P., Watson, S., Daugherty, D., Pruitt, D.B., 1985. Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. Arch. Gen. Psychiatry 42, 996–1003.

Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., Sechter, D., Bourgeois, M.L., Azorin, J.M., Chatenet-Duchene, L., Lancrenon, S., 2003. Validating antidepressant-associated hypomania (bipolar III): systematic comparison with spontaneous hypomania (bipolar II). J. Affect. Disord. 73, 65–74.

Altshuler, L., Post, R., Leverich, G., Mikalauskas, K., Rosoff, A., Ackerman, L., 1995. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am. J. Psychiatry 152, 1130–1138.

Altshuler, L., Suppes, T., Black, D., Nolen, W.A., Keck Jr., P.E., Frye, M.A., McElroy, S., Kupka, R., Grunze, H., Walden, J., Leverich, G., Denicoff, Luckenbaugh, D., Post, R. 2003. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am. J. Psychiatry 160, 1252–1262.

American Psychiatric Association (APA) Committee on Nomenclature and Statistics, 2000. Diagnostic and Statistic Manual of Mental Disorders, Fourth edition American Psychiatric Press, Washington, DC, p. 2000. Text Revision.

Baldessarini, R.J., 2001. Drugs and the treatment of psychiatric disorders: antidepressant and antianxiety agents. In: Hardman, J.G., Limbird, L.E., Gilman, A.G. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, tenth edition McGraw-Hill Press, New York, pp. 447–484. Chapter 19.

Baldessarini, R.J., Tarazi, F.I., 2001. Drugs and the treatment of psychiatric disorders: antipsychotic and antimanic agents. In: Hardman, J.G., Limbird, L.E., Gilman, A.G. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, tenth edition McGraw-Hill Press, New York, pp. 485–520. Chapter 20.

Biederman, J., Mick, E., Prince, J., Bostic, J.Q., Wilens, T.E., Spencer, T., Wozniak, J., Faraone, S.V., 1999. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. J. Child Adolesc. Psychopharmacol. 9, 247–256.

Biederman, J., Mick, E., Spencer, T.J., Wilens, T.E., Faraone, S.V., 2000. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. J. Child Adolesc. Psychopharmacol. 10, 185–192.

Briscoe, J.J., Harrington, R.C., Prendergast, M., 1995. Development of mania in close association with tricyclic antidepressant treatment in children: a report of two cases. Eur. J. Child Adolesc. Psychiatry 4, 280–283.

Carlson, G.A., Kelly, K.L., 1998. Manic symptoms in psychiatrically hospitalized children: what do they mean? J. Affect. Disord. 51, 123–135.

Carlson, G.A., Mick, E., 2003. Drug-induced disinhibition in psychiatrically hospitalized children. J. Child Adolesc. Psychopharmacol. 13, 153–163.

Carlson, G.A., Loney, J., Salisbury, H., Kramer, J.R., Arthur, C., 2000. Stimulant treatment in young boys with symptoms suggesting childhood mania: a report from a longitudinal study. J. Child Adolesc. Psychopharmacol. 10 (3), 175–184.

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

Dilsaver, S.C., Swann, A.C., 1995. Mixed mania: apparent induction by tricyclic antidepressant in five consecutively treated patients with bipolar depression. Biol. Psychiatry 1, 37-60-62.

Faedda, G.L., Baldessarini, R.J., Suppes, T., Tondo, L., Becker, I., Lipschitz, D.S., 1995. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. Harv. Rev. Psychiatry 3, 171–195.

Faedda, G.L., Glovinsky, I.P., Austin, N.B., Aristitzabal, N., Baldessarini, R.J., 2003. Phenomenology and course of pediatric bipolar disorder (Abstract 60). Bipolar Disord. 5 (Suppl. 1), 46.

Food and Drug Administration of the United States (FDA), June 19, 2003 statement (accessed 6/26/03: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01230.html).

Geller, B., Sun, K., Zimerman, B., Luby, J., Frazier, J., Williams, M., 1995. Complex and rapid cycling in bipolar children and adolescents: preliminary study. J. Affect. Disord. 34, 259–268.

Geller, B., Zimerman, B., Williams, M., Bolhofner, K., Craney, J.L., 2001. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. Am. J. Psychiatry 158, 125–127.

Ghaemi, S.N., Boiman, E.E., Goodwin, F.K., 2000. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J. Clin. Psychiatry 61, 804–808.

Go, F.S., Malley, E.E., Birmaher, B., Rosenberg, D.R., 1998. Manic behaviors associated with fluoxetine in three 12- to 18-year-olds with obsessive–compulsive disorder. J. Child Adolesc. Psychopharmacol. 8, 73–80.

Grcevich, S., Rowane, W.A., Marcellino, B., Sullivan-Hurst, S., 2001. Retrospective comparison of adderall and methylphenidate in the treatment of attention deficit hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 11, 35–41.

Greenberg, R., Papolos, D.F., Tresker, S., 2003. Psychostimulant-Induced Adverse Effects in Juvenile-onset Bipolar Disorder. Presented at Fifth International Conference on Bipolar Disorder, Pittsburgh, PA, USA.

Greenhill, L.L., Pliszka, S., Dulcan, M.K., 2001. Practice parameters for the use of stimulant medications in the treatment of children, adolescents, and adults. J. Am. Acad. Child Adolesc. Psychiatry 41 (S), 26–49.

Henry, C., Sorbara, F., Lacoste, J., Gindre, C., Leboyer, M., 2001. Antidepressant-induced mania in bipolar patients: identification of risk factors. J. Clin. Psychiatry 62, 249–255.

Koehler-Troy, C., Strober, M., Malenbaum, R., 1986. Methylphenidate-induced mania in a prepubertal child. J. Clin. Psychiatry 47, 566–567.

Koukopoulos, A., Faedda, G.L., Proietti, R., D'Amico, S., De Pisa, E., Simonetto, C., 1992. Un Syndrome depressif Mixte. L'Encephale 18, 19–21.

Koukopoulos, A., Sani, G., Koukopoulos, A.E., Minnai, G.P., Girardi, P., Pani, L., Albert, M.J., Reginaldi, D., 2003. Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients. J. Affect. Disord. 73, 75–85.

Kovacs, M., 1989. Affective disorders in children and adolescents. Am. Psychologist 44, 209–215.

Kovacs, M., Akiskal, H.S., Gatsonis, C., Parrone, P.L., 1994. Childhood-onset dysthymic disorder: clinical features and prospective naturalistic outcome. Arch. Gen. Psychiatry 51, 365–374.

McClellan, J., Werry, J., 1997. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. American Academy of Child and Adolescent Psychiatry. J. Am. Acad. Child Adolesc. Psychiatry 36 (5), 157–176.

Mota-Castillo, M., Torruella, A., Engels, B., Perez, J., Dedrick, C., Gluckman, M., 2001. Valproate in very young children: open case series with brief follow-up. J. Affect. Disord. 67, 193–197.

Papolos, D.F., 2003. Switching, cycling, and antidepressant-induced effects on cycle frequency and course of illness in adult bipolar disorder: a brief review and commentary. J. Child Adolesc. Psychopharmacol. 13, 165–171.

Papolos, D.F., Papolos, J., 2002. The Bipolar Child, second edition Broadway Books, New York, NY.

Papolos, D.F., Veit, S., Faedda, G.L., Saito, T., Lachman, H.M., 1998. Ultra-ultra rapid cycling Bipolar Disorder is associated with the low activity catecholamine-O-methyltransferase allele. Mol. Psychiatry 3, 346–349.

Papolos, D.F., Greenberg, R., Tresker, S., Freeman, K., 2003. Antidepressant-induced adverse effects in juvenile-onset bipolar disorder (Abstr P150). Bipolar Disord. 5 (Suppl. 1), 73.

Post, R.M., Denicoff, K.D., Leverich, G.S., Frye, M.A., 1997. Drug-induced switching in bipolar disorder; epidemiology and therapeutic implications. CNS Drugs 8, 351–365.

Sachs, G.S., Koslow, C.L., Ghaemi, S.N., 2000. Teatment of bipolar depression. Bipolar Disord. 2, 256–260.

Soutullo, C.A., DelBello, M.P., Ochsner, J.E., McElroy, S.L., Taylor, S.A., Strakowski, S.M., Keck Jr., P.E. 2002. Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. J. Affect. Disord. 70, 323–327.

Stoll, A.L., Mayer, P.V., Kolbrener, M., Goldstein, E., Suplit, B., Lucier, J., Cohen, B.M., Tohen, M., 1994. Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am. J. Psychiatry 151, 1642–1645.

Strober, M., Carlson, G.A., 1982. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch. Gen. Psychiatry 39, 549–555.

Tondo, L., Laddomada, P., Serra, G., Minnai, G., Kukopulos, A., 1981. Rapid cyclers and antidepressants. Int. Pharmacopsychiatry 16, 119–123.

Venkataraman, S., Naylor, M.W., King, C.A., 1992. Mania associated with fluoxetine treatment in adolescents. J. Am. Acad. Child Adolesc. Psychiatry 31, 276–281.

Wehr, T.A., 1993. Can antidepressants induce rapid cycling? Arch. Gen. Psychiatry 50 (6), 495–496.

Wehr, T.A., Goodwin, F.K., 1979. Rapid cycling between mania and depression caused by maintenance tricyclics. Psychopharmacol. Bull. 15, 17–19.

Wehr, T.A., Sack, D.A., Rosenthal, N.E., Cowdry, R.W., 1988. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am. J. Psychiatry 145, 179–184.

Wilens, T.E., Biederman, J., Kwon, A., Chase, R., Greenberg, L., Mick, E., Spencer, T.J., 2003. A systematic chart review of the nature of psychiatric adverse effects in children and adolescents treated with selective serotonin reuptake inhibitors. J. Child Adolesc. Psychopharmacol. 13, 143–152.

World Health Organization (WHO), 1992. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, tenth revision (ICD-10) World Health Organization (WHO), Geneva.

Woodworth, T., 2000. Statement by deputy director, Office of Diversion Control, to US Drug Enforcement Administration. Congress Rec, May 16.

Wozniak, J., Biederman, J., Kiely, K., Ablon, S., Faraone, S., Mundy, E., Mennin, D., 1995. Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. J. Am. Acad. Child Adolesc. Psychiatry 34, 1577–1583.

Ziehen, T., 1927. Die Geistkrankheiten im Kindesalter [Mental Illnesses in Children], second edition. von Reuther and Reichard Verlag, Berlin.

Zito, J.M., Safer, D.J., DosReis, S., Gardner, J.F., Magder, L., Soeken, K., Boles, M., Lynch, F., Riddle, M.A., 2003. Psychotropic practice patterns for youth: 10-year perspective. Arch. Pediatr. Adolesc. Med. 157, 17–25.