A Pilot Study of Antidepressant-Induced Mania in Pediatric Bipolar Disorder: Characteristics, Risk Factors, and the Serotonin Transporter Gene

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Background: *Antidepressant-induced mania (AIM) has been described in bipolar disorder (BD) and has been associated with the short-allele of the serotonin transporter gene (5-HTT). We wished to investigate the frequency of and risk factors for AIM in pediatric patients with or at high risk for BD.*

Methods: *Fifty-two children and adolescents (30 with BD and 22 with subthreshold manic symptoms, 15.1 ± 3.4 years old), all with a parent with BD, were interviewed with their parents for manic/depressive symptoms occurring before and after past antidepressant treatment. The 47 subjects with serotonin reuptake inhibitor (SSRI) exposure were genotyped for the 5-HTT polymorphism.*

Results: *Fifty percent of subjects were AIM+ and 25.5% had new onset of suicidal ideation. The AIM+ and AIM− groups did not differ significantly in relation to allele ($p = .36$) or genotype ($p = .53$) frequencies of the 5-HTT polymorphism. The AIM+ subjects were more likely to have more comorbidities (3.2 vs. 2.4; $p = .02$) and be BD type I ($p = .04$) than AIM− subjects.*

Conclusions: *Youth with or at high risk for BD may be particularly vulnerable to SSRI AIM and thus should be monitored if given SSRIs. In this preliminary study, we did not find that the 5-HTT polymorphism significantly influenced vulnerability to AIM.*

Key Words: Bipolar disorder, child, adolescent, antidepressant-induced mania, suicide, serotonin transporter gene

Depressive episodes in bipolar disorder (BD) may be the most devastating aspect of the illness (Gijsman et al 2004), and adults with BD typically spend more time in depression than in mania or hypomania (Ghaemi et al 2000). Children and adolescents with BD also commonly have depressive symptoms and often present with coincident manic and depressive symptoms (Geller and Luby 1997). Thus, treating depressive episodes is arguably the most important component of the clinical management of BD; unfortunately, it may also be more challenging than treating mania. Since mood-stabilizing medications are not always effective in suppressing depressive symptoms (Biederman et al 2000), patients with BD are often prescribed antidepressants. Antidepressant therapy, however, carries with it the risk of a quick switch in polarity, known as antidepressant-induced mania (AIM).

Antidepressant-induced mania has been documented in both major depressive disorder (MDD) and BD, but it seems that the risk of AIM is significantly elevated in patients with BD (Angst 1985; Post et al 1997). Though AIM has been primarily studied in adults, the existing pediatric research suggests that children with BD are also particularly susceptible to AIM. In a 4-year follow-up of children with major depressive disorder, AIM was highly predictive of an eventual bipolar outcome (Strober and Carlson 1982). Additionally, retrospective chart studies of children already carrying a bipolar diagnosis have reported high rates of treatment-induced manic symptoms. A study of 82 outpatients with BD reported that 44% of those that received antidepressants experienced AIM and an additional 14% had a stimulant-induced mania (Faedda et al 2004). Biederman et al (2000) made the more specific observation that youths with BD who received selective serotonin reuptake inhibitors (SSRIs) were three times more likely to develop manic symptoms by the next follow-up visit than subjects who did not receive an SSRI; risk of manic relapse was not predicted by other types of antidepressants.

Since switches in polarity are intrinsic to BD, there is controversy in the literature over whether such retrospective chart reviews (Faedda et al 2004; Biederman et al 2000) adequately account for the natural progression of the disorder (Brent 2004). This distinction is especially problematic in pediatric BD, where mixed episodes and rapid cycling are common (Craney and Geller 2003). Indeed, Geller et al (2002), in a prospective follow-up of 89 children with BD, reported that antidepressant use did not predict relapse into mania. Furthermore, some studies of adults with BD indicate that AIM is usually less severe than spontaneous mania and resolves quickly once the antidepressant is discontinued (Stoll et al 1994). Therefore, it is still not clear how common true AIM is in children with BD.

In contrast to research focusing on pediatric BD, studies of children with other psychiatric diagnoses have not reported high rates of AIM. In a study of 259 pediatric psychiatric inpatients, only 2% of who had BD, the rate of drug-induced behavioral disinhibition was 7.5% (Carlson and Mick 2003). Since these data were gathered in the early 1990s, medications commonly prescribed to children today, especially SSRIs and atypical antipsychotics, were not thoroughly studied (i.e., SSRIs were used in only 1.7% of treatment weeks). A more recent study (Wilens et al 2003) investigated adverse responses, primarily related to mood disturbances, in 82 children and adolescents receiving SSRIs for depressive disorders or obsessive-compulsive disorder (OCD). Twenty-two percent of this group had a negative reaction to SSRIs, with only 7% of this population experiencing manic symptoms. While the sample of subjects with BD was fairly small (23%), there was a nonsignificant association between BD and adverse responses to SSRIs ($p = .1$).

Given that children with BD appear to have a higher incidence of AIM than children with other psychiatric diagnoses and that this trend seems to be mirrored in adult psychiatric patients, the subject of AIM in pediatric BD warrants further investigation. Developing a better understanding of the factors that influence

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susceptibility to AIM would be of great clinical relevance, as it would help physicians differentiate between medications that should be immediately discontinued because they aggravate the disorder from those that warrant a longer trial. Reliable demographic and clinical risk factors for AIM have not been consistently identified in adults. Henry et al (2001) found that neither gender, age, nor bipolar disorder type (I vs. II) were associated with AIM. In pediatric BD research, one study reported that female gender combined with early-onset anxiety was associated with AIM (Faedda et al 2004). Additionally, a large-scale study of a health maintenance organization (HMO) database found that age was inversely related to an individual's risk of having a first episode of mania induced by an antidepressant (Martin et al 2004). The study was limited, however, by the fact that the authors classified all manic episodes after antidepressant trials as AIM, rather than assessing whether or not these manias may have been due to the natural progression of the illness (Brent 2004). Despite the limited findings to date, treatment of children with BD would be improved if a biological variable with a more specific and stronger correlation to AIM were to be identified.

It has been hypothesized that individual differences in the serotonin transporter (5-HTT) may account for varying responses to antidepressants, and therefore these differences could be used as a biological predictor of AIM. A common polymorphism in the serotonin transporter gene (*SLC6A4*) is a 44-base pair (bp) deletion/insertion in the upstream promoter region, known as the 5-HTT-linked polymorphic region (*5-HTTLPR*) (Heils et al 1996). The long (*l*) variant leads to greater transcriptional activity of the 5-HTT gene than the short (*s*) variant (Lesch et al 1996). Theoretically, an *ss* or *ls* individual would have a relatively lower membrane concentration of serotonin transporter protein and thus could have a higher proportion of reuptake proteins blocked by antidepressants than an *ll* individual, leading to a greater concentration of serotonin in the synapse and possibly an exaggerated response to antidepressants (Mundo et al 2001).

The three studies that have investigated this correlation with AIM in adults with BD have had conflicting results. Mundo et al (2001) compared the allele frequencies in a group of 27 bipolar patients (36.3 ± 8.5 years) who had experienced AIM (AIM+ group) with those in a matched population of 29 bipolar patients (36.3 ± 7.7 years) who had never experienced AIM (AIM− group). They reported an excess of the *s* allele and the *ss* genotype in the AIM+ group compared with the AIM− group. The later studies of Rousseva et al (2003) (AIM+ group with 83 subjects, 26.7 ± 11.5 years; AIM− group with 149 subjects, 25 ± 11.7 years) and Serretti et al (2004) (AIM+ group with 169 subjects, 46.68 ± 13.80 years; AIM− group with 247 subjects, 42.93 ± 14.45 years) did not find a significant difference at this polymorphism between subjects with and without AIM. However, the cohort of patients with AIM used by Mundo et al (2001) had a relatively earlier mean age at onset of BD (19.8 years) than those used by Rouseseva et al (2003) (26.7 years) and Seretti et al (2004) (32.0 years). There have been no previous studies examining the association of AIM and the 5-HTT gene in pediatric populations.

Given the paucity of research on AIM in pediatric BD and the inconclusive findings regarding the role of *5-HTTLPR* in adult AIM, we wished to characterize AIM in children with or at high risk for BD and investigate potential risk factors of AIM, including the *s* allele, in this population. Based on the preceding evidence of AIM in children with BD, we hypothesized that there would be a high rate of AIM and also a significant level of suicidal ideation following antidepressant treatment in our sample. Despite the limitations highlighted by Brent (2004), we considered the Martin et al (2004) data and predicted that antidepressant exposure at an earlier age would confer greater risk for AIM. Furthermore, since Mundo et al (2001) had significant results using a relatively early-onset cohort, we hypothesized that in our pediatric population, having the *s* allele would be a risk factor for AIM and that there would be a greater frequency of the *s* allele and the *ss* genotype in subjects with AIM compared with subjects without this adverse response.

Methods and Materials

Sample Population

The subjects for this study were drawn from a larger population of 225 children and adolescents participating in a longitudinal study at the Stanford Pediatric Bipolar Disorders Program. Families were recruited through the Adult and Pediatric Bipolar Disorders Clinics at Stanford and through general referral from clinicians and parents in the community. Written and verbal informed consent was obtained from parents of subjects, and the study was approved by the Stanford Panel on Human Subjects in Medical Research. All patients in this population had at least one parent with bipolar I or II disorder as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al 1995). Each child was evaluated by the affective disorders module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al 1996), as well as the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) (Kaufman et al 1997), during which a thorough history of psychotropic medication exposure was obtained. These interviews were performed by trained masters-level clinicians and/or a board certified psychiatrist, all of whom had established interrater reliability. Based on the WASH-U-KSADS, children were classified as having either: 1) bipolar I or II disorder; 2) subsyndromal BD (significant symptoms of attention-deficit/hyperactivity disorder [ADHD] and mood symptoms as indicated by a minimum Young Mania Rating Scale [YMRS] [Young et al 1978] score of 12 or a Children Depression Rating Scale-Revised [CDRS-R] [Poznanski et al 1984] score of 30); or 3) unaffected. Furthermore, blood samples were being collected from participants and their families for genetic analysis.

Of those already participating in the genetic research, a group of 52 bipolar and subsyndromal subjects (ages 7.6–22.0, 15.1 ± 3.4 years old) who had current or past treatment with at least one antidepressant were identified. Antidepressants included selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, and escitalopram) and atypical antidepressants (bupropion, venlafaxine, trazadone, and serzone).

For all subjects, information about age at antidepressant exposure, duration of exposure, class of antidepressant, and concurrent use of mood stabilizers or antipsychotics was gathered. The following demographic and clinical variables were also collected from the WASH-U-KSADS and SCID-I: gender, ethnicity, bipolar or subsyndromal status, age at BD diagnosis and diagnostic subtype of BD if applicable, comorbid Axis I diagnoses, presence or absence of psychotic symptoms during mood episodes, and family history of mood disorders and ADHD. We obtained family history of mood disorder using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al 1977) and parental history of ADHD using the behavioral disorders supplement from the K-SADS-PL (Kaufman et al 1997).

Assessment of AIM

Interviews about the subjects' experiences on antidepressants were conducted with both the parent and child, if the subject was older than 12 years at the time of antidepressant exposure, or with only the parent, if the subject was younger than 12 years. During these interviews, the subject and/or parent were asked to describe any psychologically adverse reactions that had arisen within 3 months of introducing a new antidepressant or increasing the dose of a currently used one (heretofore referred to as changing antidepressant status). To prevent any reporting bias, the families were only told that we were collecting information about reactions to antidepressants, and the nature and hypotheses of the study were not mentioned.

Subjects who did not report a poor reaction to medication were questioned regarding their earliest exposure to an SSRI or to any other antidepressant if there was no SSRI exposure. If a subject had an adverse reaction to more than one antidepressant, a reaction to an SSRI was evaluated over a reaction to other classes of antidepressants, due to our interest in effects of serotonergic differences on AIM. If further clarification was required, the earliest reaction would be evaluated over later ones. The elapsed time between changing antidepressant status and onset of the poor reaction was noted.

Mood effects of antidepressant exposure were measured using the YMRS. Parents and children were directly interviewed using the YMRS, and a composite score reflecting the interviewer's overall impression of score for each item was used. The YMRS is an 11-item interview which queries the core symptoms of mania in the child, including elevated mood, irritability, psychomotor agitation, hypersexuality, and aggressive behavior. Originally designed for use with bipolar adults, the YMRS has been adapted for use with children and is considered one of the best available instruments for assessing pediatric mania (Carlson et al 2003). The YMRS has been widely used in phenomenological (Rajeev et al 2003) and treatment outcome studies of youth with subsyndromal and syndromal BD (Chang et al 2003; Findling et al 2003). However, the validity of this instrument in retrospective use beyond the previous week has not yet been proven.

Each subject's moods and behaviors were rated with the YMRS for the week before antidepressant status was changed and then again either during the negative reaction or 1 month after change in status if no negative reaction occurred. Onset of suicidal ideation was investigated and was defined as a score of 4 or above on question 13 of the CDRS-R, along with a report that this ideation began only after medication was started. The YMRS and CDRS-R scores were verified with trained masters-level or doctoral-level clinicians or a board certified child psychiatrist, who all achieved interrater reliability on these measures at a kappa of .8.

Subjects were first broadly classified based on whether or not they had a severe negative reaction to antidepressants. Those placed in the reaction positive group (RXN+) reported that their mood became noticeably more elevated, expansive, or irritable, to an extent that disturbed daily function, within the first 3 months of changing antidepressant status; those without such a change were classified as reaction negative (RXN−). Subjects in the RXN+ group were then further assessed to see if they experienced enough additional symptoms to qualify as having mania. Antidepressant-induced mania was defined as an expansive, euphoric, or irritable mood, plus three other cardinal symptoms of mania (four if the mood was only irritable), as delineated by the DSM-IV. In addition, if subjects were found to be manic or hypomanic before a change in antidepressant status, then they were evaluated for worsening of manic symptoms on the antidepressants, as indicated by an increase of at least 4 on the YMRS along with reports from parents and subjects.

This information was discussed with a board certified child psychiatrist blind to type of antidepressant exposure and genotype. The duration used to qualify AIM was at least 1 day and not the 4 to 7 days required by DSM-IV criteria, because many subjects stopped taking antidepressants within 1 to 4 days of onset of manic symptoms. Given this modified time period, we did elicit for possible environmental causes of mood fluctuation (i.e., making the cheerleading squad), which the child psychiatrist took into account in assessing the reactions. If a change in mood was thought to be due to environmental events, it was not considered to be AIM. Patients were classified as positive for induced mania (AIM+) if they had a new manic episode or worsening of a preexisting one after antidepressant status changed and negative for induced mania (AIM−) if this did not occur.

Genotyping

DNA was extracted from 200 μL of frozen blood using the Qiagen DNeasy Kit (Qiagen, Hilden, Germany [Cat. #69506]). Oligonucleotide primers flanking the 5-HTT-linked polymorphic region and corresponding to the nucleotide positions -1416 to -1397 (stpr5, 5'-GGC GTT GCC GCT CTG AAT GC) and -910 to -888 (stpr3, 5'-GAG GGA CTG AGC TGG ACA ACC AC) of the 5-HTT gene 5'-flanking regulatory region were used to generate 484 bp or 528 bp fragments. Polymerase chain reaction (PCR) amplification was carried out in a final volume of 30 μL consisting of 50 ng of genomic DNA, 50 ng each of sense and antisense primers, 15 μL of Taq PCR Master mix (Qiagen, Cat. #201445), 10% dimethyl sulfoxide (DMSO), and 1 mol/L betaine. Annealing was carried out at 61°C for 30 seconds, extension at 71°C for 1 minute, and denaturation at 95°C for 30 seconds for a total of 35 cycles. The PCR products were electrophoresed through 5% polyacrylamide gel (acrylamide/bis-acrylamide ratio 19:1) at 60 V for 60 minutes. A 100-bp marker was used to measure the PCR product size for *l* and *s* allele. Alleles were called by raters blind to clinical status of the participant.

Statistical Analysis

Exploratory analyses were done to compare the AIM+ and AIM− groups across certain demographic and clinical variables. Our primary hypothesis was that a younger age at antidepressant exposure would be associated with AIM; thus, for our two age-related comparisons our alpha was set at .025, using a Bonferroni correction for two tests. Our remaining nongenetic comparisons between the AIM+ and AIM− groups were exploratory to generate further hypotheses, so no correction for multiple testing was used for these tests. The *t* test (two-tailed) for independent samples was used for continuous variables (age at onset and number of comorbid Axis I disorders) and the Pearson χ^2 test was used to compare categorical values (gender, bipolar diagnosis [BD type I, BD type II, or subsyndromal], age group at onset of AIM, and concurrent use of a mood stabilizer or antipsychotic medication).

For the genetic analysis, the 47 subjects who had exposure to proserotonergic compounds were included, while the 5 subjects who only had exposure to the dopaminergic antidepressant buproprion were excluded. The allele and genotype frequencies at the *5-HTTLPR* were compared between the AIM+ and AIM− groups using the Pearson χ^2 test, as well as the Armitage trend test (due to non-Hardy-Weinberg equilibrium [HWE] of allele

frequencies/genotypes). The time from change in antidepressant status to onset of AIM was compared across the genotypes using the Pearson χ^2 test. An analysis of covariance (ANCOVA) was used to covary for exposure to mood stabilizers and/or antipsychotic medications during the antidepressant trial. To determine age effects on AIM, a binary logistic regression was used to test if AIM could be predicted based on age at antidepressant exposure along with either genotype or presence of the *s* allele.

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, Illinois). The level of significance was set at .05 unless otherwise noted.

Results

In this sample, 64.4% of subjects reported a negative reaction to antidepressants (RXN+). Fifty percent of subjects were AIM+, with 20 (38.5%) having a new manic episode and 6 (11.5%) having worsening of a preexisting episode. Of the 47 subjects informative on suicide, 12 (25.5%) had onset of suicidal ideation within the first 3 months of antidepressant use.

To thoroughly characterize antidepressant response, subjects were classified broadly (as RXN+ or RXN−) and specifically (as AIM+ or AIM−). Most subjects who were RXN+ but not AIM+ experienced extreme irritability after antidepressant exposure but not additional symptoms of mania. The main demographic and clinical variables of the RXN+/RXN− and AIM+/AIM− groups are summarized in Table 1. Neither age at onset of mania nor age at time of AIM was associated with the presence of AIM (Table 1). In our exploratory analyses, only two comparisons were significant: the subjects in the AIM+ group had more comorbidities (3.2 ± 1.2) than those in the AIM− group (2.4 ± 1.2) ($t = 2.39$, $df = 50$, $p = .02$), and more AIM+ subjects were BD type I than subsyndromal BD or BD type II (Pearson $\chi^2 = 6.44$, $df = 2$, $p = .04$). Data collected on the period of antidepressant exposure are presented in Table 2. There were no significant differences between groups in the frequency of concurrent use of mood stabilizers (lithium, carbamazepine, valproate, or oxcarbazepine) and/or antipsychotics (risperidone, olanzapine, and quetiapine) during the period of antidepressant exposure, but information about doses and plasma levels was not available.

Only the 47 subjects who had taken proserotonergic compounds were used for the allelic comparisons, because it was hypothesized that the polymorphism at the *5-HTTLPR* influenced AIM by modulating serotonergic pathways. Five subjects who had only been exposed to buproprion were excluded. Two subjects considered RXN+ due to poor reactions to buproprion were considered AIM− in the genetic analysis, because they later had uneventful exposure to SSRIs. Furthermore, since it was hypothesized that the interaction between antidepressants and the *s* allele would lead to mania, the genetic data were only compared between the AIM+ and AIM− groups. The demographic and clinical data on medication exposure were similar to that in the larger group.

As shown in Table 3, there was no significant difference between the allele (Pearson $\chi^2 = .84$, $df = 1$, $p = .36$) or genotype (Pearson $\chi^2 = 1.29$, $df = 2$, $p = .53$) frequencies across the AIM+ and AIM− groups. An Armitrage trend test similarly

Table 1. Demographic and Clinical Variables in Subjects with and without Negative Reactions to Antidepressants and with and without Antidepressant-Induced Mania

	Reaction		AIM		
	Yes ($n = 34$)	No ($n = 18$)	Yes ($n = 26$)	No ($n = 26$)	Two-Sided *p*
Sex, M/F	26:8	10:8	19:7	17:9	.55
Age at Participation, Mean (SD)	14.7 (3.6)	16.2 (3.0)	15.0 (3.4)	15.4 (3.6)	
Ethnicity, No. (%)					
Caucasian	30 (88.2)	12 (66.7)	25 (96.2)	17 (65.4)	
Hispanic	2 (5.9)	2 (11.1)	1 (3.8)	3 (11.5)	
Multiracial	2 (5.9)	4 (22.2)	0	6 (23.1)	
Bipolar Diagnosis, No. (%)					
Subsyndromal	12 (35.3)	10 (55.6)	8 (30.8)	14 (53.8)	
Bipolar I	18 (52.9)	5 (27.8)	16 (61.5)	7 (26.9)	.04
Bipolar II	4 (11.8)	3 (16.7)	2 (7.7)	5 (19.2)	
Age at Bipolar Onset[a], Mean (SD)	11.6 (3.4)	12.8 (4.2)	11.5 (3.2)	12.5 (4.2)	.47
Axis I Disorders, Mean (SD)	2.88 (1.25)	2.61 (1.34)	3.2 (1.23)	2.4 (1.20)	.02
Axis I Disorders, No. (%)					
None	0	1 (5.6)	0	1 (3.8)	
Bipolar Disorder	22 (64.7)	8 (44.4)	18 (69.3)	12 (46.2)	
Major Depressive Disorders[b]	11 (32.4)	7 (38.9)	10 (38.5)	8 (30.8)	
Anxiety Disorders	15 (44.1)	7 (38.9)	13 (50.0)	9 (34.6)	
Attention-Deficit/Hyperactivity Disorder	28 (82.4)	15 (83.3)	22 (84.6)	21 (80.8)	
Oppositional Defiant Disorder	19 (36.5)	6 (33.3)	17 (65.4)	8 (30.8)	
Obsessive-Compulsive Disorder	1 (55.9)	2 (11.1)	1 (3.8)	1 (3.8)	
Posttraumatic Stress Disorder	1 (2.9)	2 (11.1)	1 (3.8)	2 (7.7)	
Eating Disorders	0	1 (5.6)	0	1 (3.8)	
Psychosis, No. (%)	9 (26.5)	5 (27.8)	9 (34.6)	5 (19.2)	
Family History, Mean (SD)[c]	.52 (.2)	.54 (.2)	.53 (.2)	.52 (.2)	

AIM, antidepressant-induced mania.
[a]Age of onset of bipolar disorder only. The 30 subjects with bipolar disorder, but not the 22 subjects who are subsyndromal, were counted.
[b]Since having bipolar disorder precludes having major depressive disorder, this category only applies to the 22 subsyndromal subjects.
[c]Data was unavailable for two subjects.

Table 2. Antidepressant Exposure Information in Subjects with and without Negative Reactions to Antidepressants and with and without Antidepressant-Induced Mania

	AIM		
	Yes ($n = 26$)	No ($n = 26$)	Two-Sided p
Age at Antidepressant Exposure, No. (%)			
5.0–9.9 years old	11 (42.3)	9 (34.6)	
10.0–14.9 years old	13 (50.0)	10 (38.5)	.19
15.0–20.0 years old	2 (7.7)	7 (26.9)	
Type of Antidepressant, No. (%)			
SSRI	20 (76.9)	21 (80.8)	
Atypical Antidepressant	6 (33.3)	5 (19.2)	
Duration of Antidepressant Trial (years), Mean (SD)	.71 (1.4)	1.7 (1.4)	
Change in YMRS Score, Mean (SD)	15.3 (7.0)	.9 (7.2)	
Concurrent Mood Stabilizer and/or Antipsychotic,[a] No. (%)			
Yes	9 (34.6)	8 (30.8)	.55
No	15 (57.7)	18 (69.3)	

AIM, antidepressant-induced mania; SSRI, selective serotonin reuptake inhibitor; YMRS, Young Mania Rating Scale.
[a]Data was unavailable for two subjects.

revealed no significant differences ($\chi^2 = .84$, $p = .36$; $\chi^2 = 2.20$, $p = .33$, respectively). However, all three subjects with the *ss* genotype responded negatively to antidepressants, and two were in the AIM+ group.

Within the AIM+ group, the time from change in antidepressant status to onset of AIM was divided into three groups: onset within 1 week ($n = 12$), onset between 1 week and 1 month ($n = 5$), and onset between 1 month and 3 months ($n = 5$). Time to onset was not affected by presence of the *s* allele (Pearson $\chi^2 = 1.12$, $df = 2$, $p = .57$) or genotype (Pearson $\chi^2 = 2.75$, $df = 4$, $p = .60$).

Concomitant use of mood stabilizers or antipsychotics did not limit antidepressant-induced mood destabilization in regard to presence of the *s* allele (Pearson $\chi^2 = .52$, $df = 2$, $p = .77$) or genotype (Pearson $\chi^2 = .87$, $df = 3$, $p = .83$).

The age at antidepressant exposure did not significantly change the risk of AIM. Moreover, the interaction between age at antidepressant exposure and either the presence of the *s* allele ($\chi^2 = 3.746$, $df = 2$, $p = .154$) or the interaction between age at exposure and genotype ($\chi^2 = 3.828$, $df = 2$, $p = .147$) could predict AIM.

Discussion

This is the first study of which we are aware to assess AIM in children with and at high risk for BD by direct interview and the first study to investigate the relationship between the 5-HTT gene and AIM in a pediatric sample. In our sample of children with either subthreshold or fully diagnosable BD and a family history of the disorder, most subjects had a poor response to antidepressant treatment, with AIM and new suicidal ideation frequently occurring within 1 month of treatment. Subjects who experienced AIM were more likely to be BD type I than BD type II or subsyndromal and tended to have a greater number of Axis I diagnoses than patients who did not experience AIM, though these findings should be considered preliminary, as we did not correct for multiple comparisons in our exploratory analyses. Neither gender nor age at onset of mania was associated with AIM. Exploratory analyses also did not find use of concurrent antipsychotic or mood stabilizer to decrease the incidence of AIM. Regarding our genetic findings, neither the presence of the 5-HTT *s* allele nor the *ss* genotype was a risk factor for AIM. There was no association between age at antidepressant exposure and incidence of AIM, and age at exposure combined with genotype at the *5-HTTLPR* did not predict AIM.

These naturalistic data suggest that in children with a family history of BD, those who have a diagnosis of BD or have subthreshold manic symptoms frequently develop AIM at some point in their treatment. The high incidence of treatment-emergent problems in this sample is much greater than the 22% reported by Wilens et al (2003) among children with depressive disorders or OCD and on par with the 44% in children with BD reported by Faedda et al (2004). These results are also in concordance with the literature on adults, which consistently demonstrates a higher incidence of AIM in patients with bipolar type I disorder than those with major depressive disorder (Papolos 2003). However, most studies have reported lower overall rates of AIM in adults with BD, ranging from approximately 20% to 40% (Goldberg and Truman 2003).

Unfortunately, these studies (including ours) are all retrospective, as prospective data on AIM in pediatric BD does not currently exist. Geller et al (2002) did publish prospective data on natural relapse rates in childhood BD and reported that antidepressant use did not predict recovery from or relapse into mania. This study did not specifically elicit AIM events, however, but instead considered only manic symptoms that lasted for at least 2 weeks. Any cases of AIM that led to termination of the antidepressant trial and subsequent resolution of manic symptoms within that 2-week window would not be counted. Therefore, the rate of antidepressant-related problems may be underreported in this study.

A bipolar diagnosis also seems to be associated with an increased risk of antidepressant-emergent suicidality. The incidence of postantidepressant increases in suicidal thoughts or gestures in our sample (25.5%) was higher than the rate previously reported in a retrospective study of children with BD (14%) (Faedda et al 2004) and considerably higher than the 4%

Table 3. Allele and Genotype Frequencies in the Subjects with and without Antidepressant-Induced Mania

Polymorphisms	Total Sample ($n = 47$)	AIM+ ($n = 22$)	AIM− ($n = 25$)	$\chi^2(df)$	Two-Sided p
Alleles, No (%)					
s	36 (38.3)	19 (43.2)	17 (34.0)		
l	58 (61.7)	25 (56.8)	33 (66.0)	.835 (1)	.36
Genotypes, No (%)					
ss	3 (6.4)	2 (9.1)	1 (4.0)		
ls	30 (61.7)	15 (68.2)	15 (60.0)	1.29 (2)	.53
ll	14 (31.9)	5 (22.7)	9 (36.0)		

AIM+, experience antidepressant-induced mania; AIM−, did not experienced antidepressant-induced mania.

frequency reported by the U.S. Food and Drug Administration (FDA) for depressed children and adolescents (U.S. Food and Drug Administration 2004). Therefore, children with BD or with subsyndromal symptoms may have a significantly higher probability of developing suicidal ideation on antidepressants than children who suffer from MDD.

In reviewing the demographic data, several observations indicated that the likelihood of experiencing AIM might be directly correlated with the severity of BD. First, the AIM+ group tended to have more comorbid Axis I diagnoses than the AIM− group, an indirect indication of severity of illness (McElroy et al 2001). Second, there was a higher frequency of AIM in subjects with BD type I than subjects who were subsyndromal or had BD type II. If clinical severity does modulate antidepressant response, it might explain why certain subjects tolerated antidepressants at younger ages but then developed a negative response at later exposures, once the disease had progressed. This hypothesis, however, would need to be investigated more thoroughly in a study carefully defining clinical severity.

Our hypothesis that the *s* allele and *ss* genotype would be genetic risk factors for AIM was not supported. In our sample, the frequency of the *s* allele was not significantly elevated in the AIM+ group (Pearson $\chi^2 = .835$, $df = 1$, $p = .361$). The effect size was extremely small ($R^2 = .021$); to have 80% power to detect a difference between *s* allele frequencies of .43 (AIM+) versus .34 (AIM−), we would need a sample of 240 cases and the same number of control subjects.

Moreover, there were a similar percentage of *ls* individuals in the AIM+ and AIM− groups, suggesting that there was no relationship between the heterozygous genotype and AIM. Though we found no correlation between the *ss* genotype and AIM, this negative finding was limited by only having three subjects with the *ss* genotype. Perlis et al (2003) reported that only the *ss* genotype was associated with treatment-emergent physical adverse effects. In our sample, all three of our *ss* subjects did have negative reactions to antidepressants, with two experiencing AIM. It is possible that in a larger sample, a significant correlation between AIM and the *ss* genotype would be found, but with an effect size for genotype as small as .027, it is difficult to predict that from these results.

Our results are in concordance with two studies of AIM in adults with BD (Serretti et al 2004; Rousseva et al 2003) and discordant with the findings of Mundo et al (2001). We originally predicted that our results would be more similar to those of Mundo et al (2001), because our sample also had an early age of BD onset. Nonetheless, we did find a higher rate of the *s* allele in AIM+, and we only had a 65% chance to replicate the finding by Mundo et al (2001), assuming the risk increase found in that study. One problem is that the genotypes are not in Hardy-Weinberg equilibrium, as we would have expected a total of six to seven subjects with an *ss* genotype but found only three. However, we still did not find significant differences between groups when using the Armitage trend test, which is valid if genotypes are not in HWE, whereas the standard chi-square is not. Thus, it is also possible that other genetic factors that contribute to this earlier, familial form of the disorder or the environmental stressors associated with having a parent with BD could strongly modulate the reaction to antidepressants and thereby overwhelm the more subtle influence of the serotonin transporter polymorphism.

Furthermore, we were not able to fully support our hypotheses that there would be a higher incidence of AIM in younger patients and that an interaction between age at antidepressant exposure and the *s* allele could predict AIM. Our results resembled those published by Martin et al (2004), which showed the highest risk of AIM in peripubertal patients between the ages of 10 and 14. In our sample, there was a trend toward higher incidence of AIM among patients with younger age at antidepressant exposure. Of those in our group who had AIM, 50% experienced it for the first time between the ages of 10 and 14; an additional 42.3% switched between the ages of 5 and 9. Only two of the nine subjects first exposed to antidepressants in later adolescence (15–20 years old) had AIM. However, it has been noted that Martin et al (2004) may have overestimated AIM, especially in the younger age groups, because they did not account for the natural course of BD and therefore some of the switches attributed to antidepressants could have occurred regardless (Brent 2004). In contrast, the study could have underestimated the incidence of AIM in older children, because it defined AIM as a new diagnosis of BD, thereby excluding any child who experienced AIM after receiving a bipolar diagnosis. Lastly, though genotype combined with age could not predict AIM, the two *ss* individuals with AIM were in the youngest age category (6–9 years old) at the time of switching. The small sample size in each age group as well as the small number of *ss* subjects may have obscured a true interaction between the two variables. Therefore, while the data are inconclusive, it still might behoove clinicians to be especially vigilant when prescribing antidepressants to younger children.

Despite our negative genetic findings, the high rate of AIM in our sample has important implications for the management of children and adolescents with BD or subsyndromal BD. Clinicians might first consider alternate agents to treat symptoms of depression and/or anxiety in this population. Though there have been few studies of agents for the treatment of bipolar depression in children and adolescents, lamotrigine (Kusumaker and Yatham 1997; Chang et al 2006) or lithium (Patel et al 2006) may eventually prove effective in this population. The high rate of antidepressant-emergent suicidality in our cohort is also important, given the current concern that antidepressant use may increase suicidality in children in general; it is possible that onset of suicidality following SSRI treatment is more of a concern for young patients with BD than for those with MDD. Finally, antidepressants have also been reported to cause "behavioral activation" in children with MDD or BD (Bhangoo et al 2003; Guile 1996), a phenomenon presumably falling short of full mania. Thus, all children, particularly those with BD, should be carefully assessed after beginning antidepressant treatment for emergence of mania and/or suicidal symptoms, and these symptoms should be carefully differentiated from uncomplicated behavioral activation.

Future research should work to isolate other predictors of AIM. It may be valuable to determine if AIM represents an exaggeration of normal antidepressant response or if it is biologically related to spontaneous mania. If the latter is true, AIM could be a valuable model for studying the origins of mania.

Limitations

Several limitations in the study design must be considered. Foremost, this study was retrospective and therefore confounded by issues such as the quality of subjects' memory and limited data. The objectivity of our informants may have been compromised by the widespread, negative media coverage of antidepressant use in children going on at the time of these interviews. Though the subjects were not told our hypotheses, they may have been more likely to report problems with the antidepres-

sants, especially in relation to increased suicidal ideation. Despite the limitations of our study regarding retrospective recall and reporting, our study has an advantage over past retrospective chart and database reviews (Biederman et al 2000; Carlson and Mick 2003; Faedda et al 2004; Wilens et al 2003) in that we were able to gather additional information and clarify data directly with the subjects and their families.

Additionally, if the child was younger than 12 when they experienced AIM or first received antidepressants, we chose to interview only their parents, even though Tillman et al (2004) found poor agreement between parent and child reports for symptoms of prepubertal mania. Our justification for this choice in informants was that it would be difficult for young children to remember accurately the details of a sudden-onset switch that happened in the past, especially if it resolved quickly. Also, the Tillman et al (2004) study showed that children report more of the symptoms that differentiate BD from ADHD (such as elation and grandiosity); so in speaking only with the parents, we reasoned our data would be a more conservative estimate of AIM.

As the design of our study was naturalistic and not case-controlled, AIM+ and AIM− groups differed significantly across some clinical variables. Also, since treatment occurred in the community, doses and duration of antidepressants were not controlled and trials were not necessarily stopped upon the appearance of manic symptoms. Therefore, as seen in Table 2, the duration of antidepressant trials was highly variable and fairly long, even for the subjects who had adverse reactions. The naturalistic nature of the data, along with the fact that there was not a control group of subjects with BD without antidepressant exposure, make it impossible to say definitively that the reported manic or suicidal symptoms were caused by the antidepressants and not a natural part of the disease. It seems probable that most of these manic reactions were correlated with medication treatment, however, as half the instances of AIM occurred within the first week of antidepressant use and the majority occurred within 1 month.

The methodology is also limited by the fact that the YMRS has not been validated for use in this retrospective manner. However, there are no prospective, controlled studies of AIM in children that we are aware of, probably due to the ethical problems and logistic difficulties in conducting such an investigation. Furthermore, as there is not a universally accepted set of criteria for AIM, our study used the YMRS to elicit information in a nonbiased yet methodologically rigorous manner to increase the validity of the data. For example, we began the interview with open-ended questions regarding response to antidepressants, and when no exposure was more problematic than another, we assessed reaction to the first SSRI the child was prescribed. We specifically assessed for symptoms of mania by DSM-IV criteria and used a well-established qualitative measure of pediatric mania (the YMRS) to back up our categorical decisions. When possible, we also interviewed both the parent and child.

A possible limitation in our genetic data was that subjects from a variety of ethnic backgrounds were included in this study. The prevalence of the *s* allele can vary widely across ethnicities and even across different groups of Europeans (Gelernter et al 1999). Though our sample was predominantly Caucasian, the allele and genotype frequencies could still have been heavily influenced by ethnic stratification and therefore not been as informative regarding AIM. Also, given that AIM is a complex behavioral outcome, it is unlikely that only one gene would be responsible for this outcome. However, given the past literature, it remains possible that singe-gene polymorphisms may be determined to confer a small but measurable risk for AIM.

The next logical study would utilize a prospective design, in which antidepressant doses and exposure to mood stabilizing agents would be carefully controlled and include a control group matched for all demographic and clinical variables. In such a study, the sample size for the genetic analysis would also be expanded considerably beyond the current 47 subjects. However, given that our data had such a small effect size for the presence of the *s* allele on AIM (R^2 = .021), it is unlikely that controlling for these limitations would change the results significantly. The effect size of genotype on AIM (R^2 = .027) is also small, but given the paucity of *ss* subjects, it could be valuable to replicate this study with a larger sample size to test for genotypic effects.

Finally, a theoretical limitation to this study is that the hypothesized relationship between the *s* allele and AIM was not based on strong cellular evidence but rather on inferences made in hopes of finding a useful clinical predictor of AIM. Currently not enough knowledge exists regarding the specifics of serotonin neurotransmission or the way in which antidepressants bring about mood elevation to outline a strong molecular mechanism by which antidepressants interact with the *5-HTTLPR* to initiate AIM. Therefore, more complex genetic, cellular, or environmental interactions may be responsible for induced mania.

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Andreasen NC, Endicott J, Spitzer RL, Winokur G (1977): The family history method using diagnostic criteria. Reliability and validity. *Arch Gen Psychiatry* 34:1229–1235.

Angst J (1985): Switch from depression to mania: A record survey over decades between 1920 and 1982. *Psychopathology* 18:140–154.

Bhangoo RK, Lowe CH, Myers FS, Treland J, Curran J, Towbin KE, et al (2003): Medication use in children and adolescents treated in the community for bipolar disorder. *J Child Adolesc Psychopharmacol* 13:515–522.

Biederman J, Eric M, Spencer TJ, Wilens TE, Faraone SV (2000): Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol* 10:185–192.

Brent DA (2004): The rewards of reducing risk. *Arch Pediatr Adolesc Med* 158:824–825.

Carlson GA, Jensen PS, Findling RL, Meyer RE, Calabrese J, DelBello MP, et al (2003): Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: Report of a consensus conference. *J Child Adolesc Psychopharmacol* 13:13–27.

Carlson GA, Mick E (2003): Drug-induced disinhibition in psychiatrically hospitalized children. *J Child Adolesc Psychopharmacol* 13:153–163.

Chang K, Saxena K, Howe MG (2006): An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry* 45:298–304.

Chang KD, Dienes K, Blasey C, Adleman N, Ketter T, Steiner H (2003): Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J Clin Psychiatry* 64:936–942.

Craney J, Geller B (2003): Commentary: Clinical implications of antidepressant and stimulant use on switching from depression to mania in children. *J Child Adolesc Psychopharmacol* 13:201–204.

Faedda GL, Baldessarini RJ, Glovinskya IP, Austina NB (2004): Treatment-emergent mania in pediatric bipolar disorder: A retrospective case review. *J Affect Disord* 82:149–158.

Findling RL, McNamara NK, Gracious BL, Youngstrom EA, Stansbrey RJ, Reed MD, et al (2003): Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry* 42:895–901.

First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0)*. New York: Biometric Research, New York State Psychiatric Institute.

Gelernter J, Cubells JF, Kidd JR, Pakstis AJ, Kidd KK (1999): Population studies of polymorphisms of the serotonin transporter protein gene. *Am J Med Genet* 88:61–66.

Geller B, Craney JL, Bolhofner K, Nickelsburgh MJ, Williams M, Zimerman B (2002): Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 159: 927–933.

Geller B, Luby J (1997): Child and adolescent bipolar disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 36:1168–1176.

Geller BG, Warner K, William M, Zimmerman B (1996): *WASH-U-KSADS (Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia)*. St. Louis: Washington University.

Ghaemi SN, Boiman EE, Goodwin FK (2000): Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *J Clin Psychiatry* 61: 804–808.

Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM (2004): Antidepressants for bipolar depression: A systematic review of randomized, controlled trials. *Am J Psychiatry* 161:1537–1547.

Goldberg J, Truman C (2003): Antidepressant-induced mania: An overview of current controversies. *Bipolar Disord* 5:407–420.

Guile JM (1996): Sertraline-induced behavioral activation during the treatment of an adolescent with major depression. *J Child Adolesc Psychopharmacol* 6:281–285.

Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al (1996): Allelic variation of human serotonin transporter expression. *J Neurochem* 66: 1–4.

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.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al (1997): Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988.

Kusumakar V, Yatham LN (1997): An open study of lamotrigine in refractory bipolar depression. *Psychiatry Res* 72:145–148.

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al (1996): Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274:1527–1530.

Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D (2004): Age effects on antidepressant-induced manic conversion. *Arch Pediatr Adolesc Med* 158:773–780.

McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, et al (2001): Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry* 158:420–426.

Mundo E, Walker M, Cate T, Macciardi F, Kennedy JL (2001): The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: Preliminary findings. *Arch Gen Psychiatry* 58:539–544.

Papolos DF (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.

Patel NC, DelBello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, et al (2006): Open-label lithium for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry* 45:289–297.

Perlis RH, Mischoulon D, Smoller JW, Was YJ, Lamon-Fava S, Lin KM, et al (2003): Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. *Biol Psychiatry* 54:879–883.

Post RM, Denicoff KD, Leverich GS, Frye MA (1997): Drug-induced switching in bipolar disorder; epidemiology and therapeutic implications. *CNS Drugs* 8:351–365.

Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R (1984): Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. *J Am Acad Child Adolesc Psychiatry* 23: 191–197.

Rajeev J, Srinath S, Reddy YC, Shashikiran MG, Girimaji SC, Seshadri SP, et al (2003): The index manic episode in juvenile-onset bipolar disorder: The pattern of recovery. *Can J Psychiatry* 48:52–55.

Rousseva A, Henry C, van den Bulke D, Fournier G, Laplanche JL, Leboyer M, et al (2003): Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. *Pharmacogenomics J* 3:101–104.

Serretti A, Artioli P, Zanardi R, Lorenzi C, Rossini D, Cusin C, et al (2004): Genetic features of antidepressant induced mania and hypo-mania in bipolar disorder. *Psychopharmacology (Berl)* 174:504–511.

Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, et al (1994): Antidepressant-associated mania: A controlled comparison with spontaneous mania. *Am J Psychiatry* 151:1642–1645.

Strober M, Carlson G (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.

Tillman R, Geller B, Craney JL, Bolhofner K, Williams M, Zimerman B (2004): Relationship of parent and child informants to prevalence of mania symptoms in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 161:1278–1284.

U.S. Food and Drug Administration (2004): FDA proposed medication guide: About using antidepressants in children or teenagers. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIMedicationGuide.htm.

Wilens TE, Biederman J, Kwon A, Chase R, Greenberg L, Mick E, et al (2003): A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with SSRIs. *J Child Adolesc Psychopharmacol* 13:143–152.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978): A rating scale for mania: Reliability, validity and sensitivity. *Br J Psychiatry* 133:429–435.