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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Received November 3, 2005; revised May 2, 2006; accepted June 8, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.06.010

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).