Activation Adverse Events Induced by the Selective Serotonin Reuptake Inhibitor Fluvoxamine in Children and Adolescents

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Abstract

Objective: The aim of this study was to examine the prevalence of activation cluster adverse events (AC-AEs) in youths treated with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine for anxiety and the relationship of AC-AEs to SSRI blood levels.

Methods: Data from the Research Units on Pediatric Psychopharmacology (RUPP) Anxiety Study were examined for 45 youths (22 active fluvoxamine, 23 placebo) treated for *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV) anxiety disorders at the Johns Hopkins University site with an 8-week forced-flexible titration schedule. As part of the double-blind placebo-controlled trial, AC-AEs were recorded by clinicians at weekly patient visits. AC-AEs were defined as hyperactivity, activation, and disinhibition. Demographic characteristics, daily doses, and week-8 blood levels were examined in relation to the presence of AC-AEs. The prevalence of AC-AE and time to first event were established for those who experienced this side effect.

Results: AC-AEs were found in 10 of 22 participants (45%) receiving fluvoxamine and only 1 of 23 in the placebo group (4%). The onset of AC-AEs occurred from week 1 to week 8, with the majority occurring at or before week 4. The mean fluvoxamine blood level at week 8 in subjects with AC-AEs was higher than in subjects without AC-AEs ($n = 16$, $t = -2.61$, $p = 0.04$). Neither the age of the participants nor family history of bipolar or anxiety disorder differed between those who did and did not develop an AC-AE.

Conclusions: AC-AEs were common side effects of fluvoxamine, often appeared during the first 8 weeks of treatment, and were associated with higher fluvoxamine blood levels. Close monitoring for AC-AEs, not only when initiating SSRI treatment but also throughout dose titration, is recommended for early identification of activation.

Introduction

THE USE OF SELECTIVE SEROTONIN reuptake inhibitors (SSRIs) among children and adolescents has increased steadily over the last decade, accounting for approximately half of all antidepressant use in this population (Zito et al. 2003). Recent safety concerns have focused on the increased risk of suicidal behavior among children and adolescents treated with SSRIs (Hammad 2004; Whittington et al. 2004; Leslie et al. 2005). While suicidal ideation and attempts (SI/SA) are important adverse events, the development of behavioral adverse events from these medications is even more common among children and adolescents (Safer and Zito 2006; Goodman et al. 2007). Although it has been speculated that behavioral adverse events, commonly referred to as "activation," may be related to SI/SA, the evidence remains scant (Teicher et al. 1993; Wong et al. 2004). Behavioral adverse events have been described as activation cluster adverse events (AC-AEs) that may include an increased activity level, impulsivity, insomnia, or disinhibition without manic symptoms (Riddle et al. 1991). AC-AEs should be differentiated from manic symptoms, which encompass a change in mood and behavior with coexisting symptoms of grandiosity and euphoria (Walkup and Labellarte 2001).

It is not clear how many children and adolescents treated with SSRIs develop AC-AEs. The best available estimates of SSRI-related AC-AEs range from a mean of 10.7% in children (2.1% in adolescents) in a review of published pediatric, double-blind, placebo-controlled trials (Safer and Zito 2006), to 22% in a retrospective clinical chart review of 82 children

(Wilens et al. 2003) and 50% in a prospective study of 24 children treated with fluoxetine for obsessive compulsive disorder (Riddle et al. 1991). Activation is up to twice as prevalent in children compared with adolescents and represents a frequent cause for discontinuation from SSRI clinical trials in preadolescents but not adults (Safer and Zito 2006). This suggests that as people age, they may be biologically less vulnerable to this adverse event.

AC-AEs often respond to dose reduction or a slower titration schedule (Riddle et al. 1991; Gualtieri and Johnson 2006) and may mirror the pharmacokinetics of the agent (Walkup and Labellarte 2001). Thus, dose and metabolism may be important factors in the development of AC-AEs among youths treated with SSRIs.

Although adverse events are routinely monitored in clinical trials, there are few data regarding activation in children and adolescents. Findings from a large, multisite, placebo-controlled trial reported increased motor activity in 27% of the treatment group; however, this did not differ significantly from the placebo group (12%; $p = 0.06$) (Research Units for Pediatric Psychopharmacology [RUPP] Anxiety Study Group 2001). However, this only describes increased motor activity, not any of the other accompanying behavioral components of AC-AEs, and therefore may underestimate the occurrence of AC-AEs.

Despite these few studies citing specific behavioral AEs, the frequency of AC-AEs, time-to-onset of activation, dosing, and blood levels in youths treated with SSRIs have not been investigated. The following exploratory study used data collected as part of the RUPP Anxiety Study (Research Units for Pediatric Psychopharmacology Anxiety Study Group 2001) to examine more closely the frequency and timing of AC-AEs in children and adolescents treated with SSRIs and to identify the associations between these AC-AEs and SSRI doses and blood levels. We hypothesized that: (1) AC-AEs are fairly common in fluvoxamine-treated children and adolescents and (2) AC-AEs are positively correlated with fluvoxamine blood levels. Here the term "children" will be used to refer to children and adolescents.

Methods

RUPP Anxiety Study

The RUPP Anxiety Study was a multicenter, placebo-controlled, double-blind, randomized, controlled trial designed to test the efficacy of fluvoxamine among 128 youths aged 6–17 years (mean 10.8 years) with social anxiety, separation anxiety, or generalized anxiety disorders. Participants were randomized to receive either active fluvoxamine treatment or placebo over the 8-week acute phase of the trial. The five sites involved in the study included Duke University, the Johns Hopkins University, Columbia University, New York University and University of California, Los Angeles.

Children and adolescents were included in the study if they met criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) for social phobia, generalized anxiety disorder, or separation anxiety disorder. Additional criteria were: clinically important symptoms according to the Pediatric Anxiety Rating Scale (PARS) (Research Units for Pediatric Psychopharmacology Anxiety Study Group 2002), score under 60 on the Children's Global Assessment Scale (CGAS)

indicating functional impairment (Shaffer et al. 1983), and child and parent agreement to attend clinic assessments. Diagnoses were based on child and parent reports of Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) (Kaufman et al. 1997) interviews obtained by experienced child and adolescent psychiatrists and psychologists, blinded to treatment condition. Criteria for exclusion included: active substance use, mental retardation as assessed by the Kaufman Brief Intelligence test (intelligence quotient [IQ] <70), current suicidal ideation, a history of or a current diagnosis of mania, psychosis, or pervasive developmental disorder, or previous treatment with an SSRI in appropriate doses. Before participating in the study, a complete description was provided and parents signed an informed consent; children aged older than 6 years of age signed assents.

Following a 3-week lead-in supportive psychotherapy phase, nonimproved children were randomized to receive active treatment or placebo. A total of 128 children were randomized to either active treatment with fluvoxamine or placebo. Individuals randomized to the active treatment group followed a forced-flexible titration schedule. Doses of 25 mg daily on the first study day were raised to 50 mg in the first study week for children (aged 12 years or younger) or 75 mg in the first study week for adolescents. The dose could be gradually increased up to a maximum of 250 mg daily in children and 300 mg daily in adolescents at week 8, unless the youths experienced an adverse event or symptoms remitted. The dose was decreased by 25–50 mg/day or the medication was held at the same dose if the youths developed an adverse event that affected their level of functioning and therefore was judged to be clinically significant, justifying a dose change.

Families and their children met with a psychiatrist weekly for the first 6 weeks, and then at the end of study at week 8. During each visit, the clinician provided supportive psychotherapy, assessed anxiety symptoms using the PARS, and documented adverse events using open-ended questions. The pharmacotherapist clinician used the paper-based Adverse Event questionnaire form to document AEs. Clinicians would ask both parents and youths open-ended questions regarding AEs prior to documenting them weekly on the Adverse Event form. These clinicians would use COSTART terminology (Coding Symbols for a Thesaurus of Adverse Reaction Terms) to document AEs, including behavioral AEs. This practice was standard in clinical trials at that time, prior to the advent of more systematic AE reporting tools. For all youths in the active treatment group, plasma blood levels were assessed at week 8, and daily doses were recorded weekly. Clinicians and participants were blind to group assignment and the identical capsules were administered to both treatment arms. Full details of this trial have been described elsewhere (Research Units for Pediatric Psychopharmacology Anxiety Study Group 2001).

Laboratory procedures

The method used to obtain the fluvoxamine blood levels was a liquid-liquid extraction followed by high-pressure liquid chromatography with ultraviolet detection. Clovoxamine was used as an internal standard. Standard curves were linear and the lower limit of detection was 10 ng/mL (1 mL analyzed).

Study sample

The focus of this paper is the data from all 45 youths who were enrolled in the RUPP Anxiety Study at the Johns Hopkins University (JHU) site. In this sample of 45 youths, 23 were randomized to placebo and 22 were randomized to active treatment with fluvoxamine. At the JHU site, AC-AEs were rated by the two pharmacotherapist clinicians and documented on the Adverse Event form.

Study measures

The current analysis uses the AC-AEs that were recorded at weekly assessments conducted by two psychiatrists at the JHU site. Daily dose and plasma blood levels were obtained for the youths. Daily doses were recorded from baseline (i.e., study entry) through week 8. Plasma blood levels were obtained at week 8, i.e., the end of the study for all participants. Demographic information on the participants and families was abstracted from the child's study chart. Child-specific information included age, gender, race, and type of anxiety diagnosis. In addition, family psychiatric history of anxiety disorder, bipolar disorder, and major depressive disorder was collected.

The rationale to use solely the JHU site data for this study was based on several logistical and methodological reasons. First, 42% (16/38) of the available blood levels were obtained at JHU. The remaining blood levels were distributed across four geographically distinct sites. Second, behavioral adverse event monitoring was not an objective of the original study, and so individual research charts needed to be reviewed to obtain the AC-AE information. Consequently, it was not practical to travel to each site to review one or two charts per site, and we did not want to introduce interrater variation in chart abstraction by having different individuals abstract the data from the other sites.

The RUPP charts for the JHU site were reviewed on the basis of consensus criteria between the authors and a review of the literature. The following terms were used to identify AC-AEs:

1. Activation: Activated, disruptive, activation, animated;
2. Disinhibition: Disinhibited, doing things they wouldn't normally do, disinhibition, aggression or outburst;
3. Hyperactivity: Hyper, hyperactivity, increased energy.

As noted above, AC-AEs were defined as hyperactivity, activation, or disinhibition. An event was rated as: (1) mild if there was no impairment (meaning that the child still functioned at their baseline level, and the event was judged to be within the normal range for other similarly-aged children) and required no dose decrease; (2) moderate if there was minimal functional impairment (meaning that the child had mild deficits in their daily level of function beyond the range of other similarly aged children), and the medication dose was either held or reduced; or (3) severe if there was major functional impairment (meaning that there was severe impairment in the daily level of function, including for example developing important new psychiatric or medical symptoms or requiring a different level of care), and the treatment was then stopped. This AC-AE description was used to attempt to capture AC-AEs that would impact prescribing practice.

The first author verified all AC-AEs according to the previously described terms, which were rated as moderate or severe by blinded chart review. Only events rated as moderate or severe were included in the present analysis, as these were the AC-AEs that affected the prescribed dose of fluvoxamine. The results were later cross-referenced to the larger multisite RUPP database to ensure all cases had been reviewed. Timing of activation was categorized as early onset (i.e., occurring within weeks 1–4) or late onset (i.e., occurring between weeks 4 and 8).

Data analyses

Descriptive analyses were conducted to compare the presence of activation at any time during the 8-week trial (any versus none) as well as early or late onset between the 23 youths in the placebo group and the 22 youths in the active fluvoxamine treatment group. Using the subgroup of 22 youths who received active treatment with fluvoxamine, bivariate associations between activation (anytime during the study and early versus late onset) and demographic characteristics, weekly milligram doses (mg) and week-8 blood levels (ng/mL) were examined. Differences in demographic characteristics between those who did and did not develop AC-AEs during the study were examined using chi-squared tests with Fisher exact test correction for small cell sizes. Two-sample t-tests were used to examine group differences in blood levels and daily doses. Eight-week blood levels were compared between participants who were activated and those who were not activated at week 8. Daily doses at the time activation was first noted and at week 8 were compared among those who developed activation during the study. Time to onset of activation was displayed using Kaplan—Meier curves. Cox proportional hazard regression models were used to estimate the risk of developing AC-AEs as a function of dose and blood level, adjusting for age and gender. Statistical significance was set at the 5% level, and all analyses were performed using STATA (version 8).

Results

Characteristics of the sample

The baseline characteristics of the sample did not differ by treatment assignment in terms of age, gender, or race (Table 1) There were no significant differences by type of anxiety diagnosis (generalized anxiety disorder, separation anxiety disorder, or social anxiety disorder) in either the fluvoxamine or placebo treatment groups.

Comparing characteristics within the 22 participants treated with fluvoxamine (Table 2), those participants who developed AC-AEs did not significantly differ from those who did not develop AC-AEs with respect to age ($p = 0.70$) or gender ($p = 0.39$). Family history of bipolar affective disorder ($p = 0.65$), anxiety disorders ($p = 0.22$), or major depressive disorders ($p = 0.57$) did not differ significantly between youths who experienced AC-AEs and those youths who did not experience AC-AEs. No study participants demonstrated emergence of suicidal behavior or ideation during this acute phase of the trial.

In terms of other co-occurring adverse events with the AC-AEs, insomnia was a presenting symptom in 2 of the 10 participants with AC-AEs (20%). However, AC-AEs did not

Table 1. Baseline Characteristics of the Sample by Treatment Group

	Fluvoxamine n = 22	Placebo n = 23	p
Child demographics			
Age in years, mean (SD)	10.0 (2.4)	9.7 (2.6)	0.73
Female, n (%)	10 (48)	11 (50)	0.88
Caucasian, n (%)	21 (95)	22 (96)	1.00[a]
Anxiety diagnoses			
General anxiety disorder, n (%)	7 (31)	7 (35)	0.92
Separation anxiety disorder, n (%)	12 (55)	9 (45)	0.30
Social phobia, n (%)	3 (14)	4 (20)	1.00[a]
Family psychiatric history			
Bipolar affective disorder, n (%)	3 (14)	2 (9)	0.66[a]
Major depressive disorder, n (%)	8 (36)	5 (22)	0.28
Anxiety disorder, n (%)	7 (32)	4 (17)	0.31[a]

[a]Fisher exact test.

present concurrently with insomnia. Two participants with AC-AEs presented with concurrent panic attack symptoms. No participants developed manic symptoms consisting of decreased need for sleep, grandiosity or other related symptoms.

Prevalence of AC-AEs

As shown in Table 3, 45% (10/22) of participants treated with fluvoxamine developed activation during the 8-week study. Of these 10, 7 had an onset at or before week 4 and 3 had an onset after week 4. In contrast, only 1 individual in the placebo group developed AC-AEs, and this occurred at week 5.

Association between daily dose and AC-AEs

Table 3 shows the fluvoxamine dose at the first occurrence of activation and the dose at the end of the study (week 8). Data were not available for the two participants who did not complete the 8-week study; 1 participant was a 6-year-old girl who terminated the study after week 5 and the other participant was an 11-year-old boy who terminated the study at

Table 2. Comparison of Activation Cluster–Adverse Events (AC-AEs) among Children in the Active Treatment Group (n = 22)

	AC-AE n = 10	No AC-AE n = 12	p
Age			
6–9 years	5	5	0.70
10–16 years	5	7	
Gender			
Male	6	5	0.67[a]
Female	4	7	
Family history			
Bipolar affective disorder	1	2	1.00[a]
Anxiety disorder	4	2	0.35[a]
Major depressive disorder	3	5	0.68[a]

[a]Fisher exact test.

Table 3. Fluvoxamine dose at Time of First Activation and Dose at Week 8 among the 10 Subjects Who Developed Activation[a]

Subject	Week	Dose at time of first activation	End of study week	Dose at the end of the study (mg)
1	4	50	8	75
3	6	150	8	100
4	8	200	8	200
5	7	200	8	150
6	4	125	8	100
7	1	75	8	100
9	2	75	8	75
10	4	125	8	125

[a]Two individuals (subjects 2 and 8) were omitted because they terminated the study before week 8.

week 4, both due to symptoms of hyperactivity and fidgetiness. Of the 8 children who completed the study and developed AC-AEs, the dose at week 8 was either the same or within 50 mg of the dose, at the time AC-AEs were first noted.

Decreasing or holding the fluvoxamine dose resolved AC-AEs in all participants with one exception. This one child could not tolerate more than 75 mg of fluvoxamine despite more than 3 weeks of dose adjustments. For the remaining 7 children, the time to resolution of AC-AEs after dose adjustment ranged from 1 to 3 weeks as follows: 1 week for 3 participants, 2 weeks for 2 participants, and 3 weeks for 2 participants. However, 75% of children who developed AC-AEs before week 8 also experienced later symptoms at week 8 of the study following retitration of the medication dose.

In terms of mean fluvoxamine doses, there was no significant difference ($p = 0.63$) in the mean dose of fluvoxamine at week-8 between the AC-AE group (134 ± 22 mg) and the non-AC-AE group (150 ± 22 mg). Children who developed an AC-AE were not reported to be taking any concurrent medications that would interact with fluvoxamine through metabolic pathways, such as the cytochrome P 450.

Association between blood levels and AC-AEs

Of the 22 subjects in the fluvoxamine group, 8-week blood levels were available for 16 participants. Eight of these participants had AC-AEs and 8 did not have AC-AEs. Of the 6 participants who did not have fluvoxamine blood levels at week 8, 2 did not complete the study (they discontinued treatment at weeks 4 and 5 due to AC-AEs as previously described), 2 were noncompliant with the treatment, and 2 were unaccounted for. As shown in Fig. 1, the mean blood level in subjects with an AC-AE (381.7 ± 232.0 ng/mL) was significantly higher than in subjects without an AC-AE (127.5 ± 68.5 ng/mL; $p = 0.04$). The highest fluvoxamine blood level in the group without AC-AEs was 238 ng/mL; 50% of fluvoxamine participants with AC-AEs had higher blood levels than 238 ng/mL. Moreover, the participant with the highest blood level (677 ng/mL) presented with AC-AEs rated at the highest level (severe).

Onset of AC-AEs

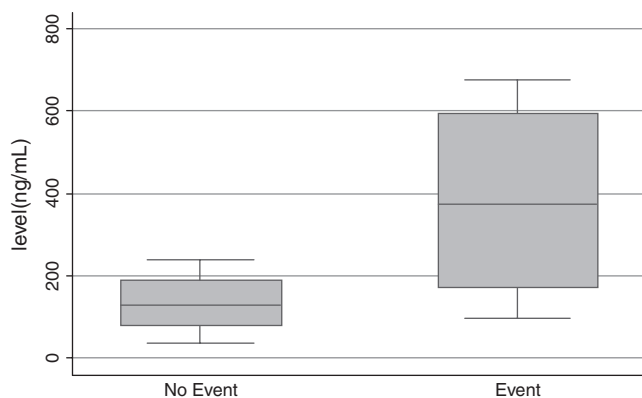The onset of AC-AEs occurred as early as week 1. By week 4, 30% had developed an AC-AE and by week 8 48% had

FIG. 1. Eight-week fluvoxamine blood levels (ng/mL) in the children who did not develop AC-AEs (no event) and those who did develop AC-AEs (event) ($n = 16$). Event = AC-AE and includes two dropouts who had AC-AE. The middle line in each box plot represents the median blood level. The whiskers (extending vertical bars) represent the lines drawn to the smallest and largest observations within the distribution that do not include the outliers. AC-AEs = Activation cluster–adverse events.

developed an AC-AE (Fig. 2). Six of 8 patients who presented with the onset of AC-AEs prior to week 8 remained activated at week 8.

Discussion

The results of this study suggest that AC-AEs are a relatively common side effect of fluvoxamine in this sample of children with an anxiety disorder. The frequency of SSRI-related activation side effects in this study (48%) is consistent with the 50% reported in a small prospective study (Riddle et al. 1991). One third of AC-AEs occurred in the first month of treatment. Other investigators also have noted that activation occurs early in the course of treatment or after dose changes (Walkup and Labellarte 2001). In addition, 75% of children in the current study who developed AC-AEs before week 8 also experienced symptoms at week 8 of the study

once the medication dose had been retitrated. This suggests that AC-AEs either recurred or persisted with subsequent dose increases.

The relatively lower fluvoxamine doses and significantly higher mean blood levels among children who developed AC-AEs raise the question of a correlation between metabolism and SSRI tolerance. Fluvoxamine is metabolized mainly via the CYP 2D6 isoenzyme and inhibits several other cytochrome P450 enzymes. Genetic polymorphism could influence the variability of these metabolic enzymes and affect SSRI metabolism. Individual metabolic differences or younger age may potentially influence fluvoxamine blood levels (Labellarte et al. 2004). A recent study reported that activation was two- to three-fold more prevalent in children than adolescents (Safer and Zito 2006), suggesting a possible underlying biological vulnerability for developing activation with SSRIs. A pharmacokinetic study suggests that younger children may have a higher exposure to fluvoxamine than adolescents or adults (Labellarte et al. 2004). In this study, although females and younger children had higher blood levels than males and older children respectively, these differences did not reach statistical significance ($p > 0.05$).

The comparatively low rate of AC-AEs in the placebo group of our study, and the resolution of symptoms following dose maintenance or lowering, suggest that AC-AEs are most likely related to fluvoxamine as a pharmacological agent rather than a placebo effect. These findings highlight the importance of remaining vigilant to this side effect, even after initial acute dosing changes, and the need for continued close monitoring. Future studies are needed to assess the influence of cytochrome P450 and individual polymorphisms as this might inform more thoughtful dosing and lessen the likelihood of developing AC-AEs.

AC-AEs often subsided with a dose reduction, which mirrors previously reported findings (King et al. 1991; Riddle et al. 1991). This activation symptom resolution may parallel the agent's pharmacokinetic profile (Walkup and Labellarte 2001), such that AC-AEs would resolve more quickly with agents that have a shorter half-life compared to those with a longer half-life. Fluvoxamine may exhibit nonlinear kinetics,
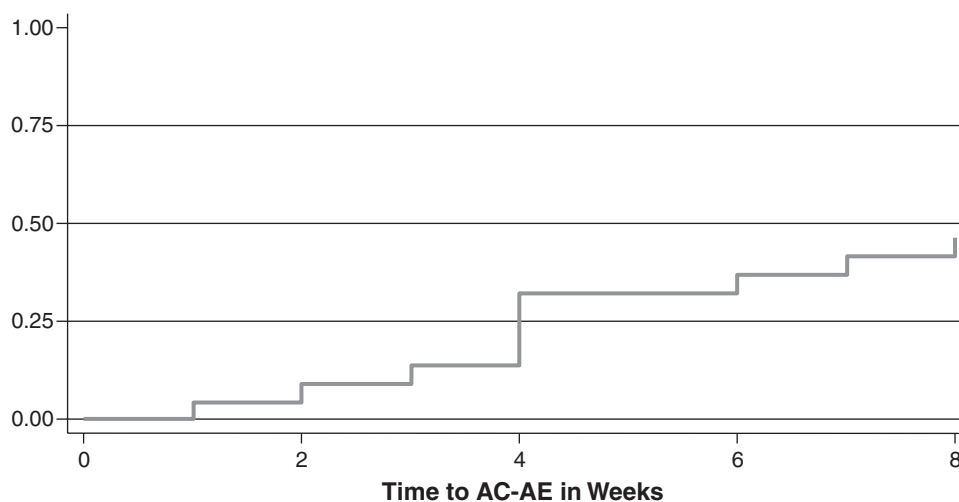

FIG. 2. The Kaplan–Meier estimate of the incidence of AC-AEs by week of fluvoxamine treatment. AC-AEs = Activation cluster–adverse events.

and children 11 years old and younger may show higher mean peak plasma concentration compared with adolescents (Labellarte et al. 2004). These age-related influences on fluvoxamine metabolism might have influenced our findings, with regard to AC-AEs and blood levels, because the average age in this study was 10 years of age.

Our findings are consistent with earlier research showing that AC-AEs are distinct from typical DSM-IV–defined manic symptoms. For one, AC-AE symptoms are discrete from the symptoms of bipolar disorder except for the increased motor activity (Walkup and Labellarte 2001). The lack of euphoria and absence of decreased need for sleep associated with AC-AEs in this study were distinguishable from symptoms of typical mania; this paralleled features previously reported by other investigators (Riddle et al. 1991). Second, 20% of participants ($n = 2$) with AC-AEs experienced insomnia but not concurrently with AC-AE, nor a decreased need for sleep. Although this is lower than previous findings that suggested up to 46% of youths had sleep disturbance as a behavioral side effect when treated with fluoxetine (Riddle et al. 1991), the small number of participants limits our ability to draw any definitive conclusions regarding this association. Third, 30% of children developed AC-AEs within the first 4 weeks of treatment; however, it is possible that some children may develop these symptoms much later in the course of treatment. This is in contrast to the onset of manic symptoms whereby decreased need for sleep, euphoria, or grandiosity generally present earlier in the course of treatment (Walkup and Labellarte 2001). Last, the presence of a family history of bipolar disorder did not appear to predispose children to develop AC-AEs, which corroborates observations suggesting that AC-AEs are different from manic symptoms (Walkup and Labellarte 2001). Neither age, gender, nor a family history of psychiatric disorders was associated with the development of AC-AEs.

This study defined AC-AEs beyond just increased motor activity, which makes comparison to other studies difficult. Findings from the RUPP multicenter study (Research Units for Pediatric Psychopharmacology Anxiety Study Group 2001) showed across all sites a nonsignificant trend toward increased motor activity in 20% of children who received active treatment ($p = 0.06$). However, this only describes motor activity, not the other behavioral components of AC-AEs, and therefore may be an underestimate this side effect. In addition, the frequency of AC-AEs reported in the current study is higher than that found with adult patients treated with fluoxetine (10–25%) (Lipinski et al. 1989). It is not clear what factor is responsible for this difference, but perhaps age, neurodevelopmental differences, or specific SSRI-related metabolic differences could influence the prevalence of AC-AEs in the younger participants in our study.

Although not much is known about the pathophysiology of AC-AEs, several possible mechanisms for the activation syndrome have been proposed. An increase in energy or a movement disorder, similar to akathisia (Gerber and Lynd 1998), may lead to an increased expression of aggressive, impulsive, or self-injurious behavior, particularly if mood has not yet improved synchronously with improved energy level. It is also possible that patients actually switched to a variant of a manic or mixed state (Walkup and Labellarte 2001). It is unclear if AC-AEs are related to akathisia, which may have a similar clinical presentation. Moreover, it is hypothesized

in one case report that activation is related to self-injurious behavior via serotonergic-mediated effects that could compromise a patient's ability to self-regulate their behavior (King et al. 1991). The disinhibition related to activation also could lead to impulse control problems (Wilens et al. 1998; Wilens et al. 2003).

SSRIs may increase the serotonin-related inhibition of dopaminergic cells in the ventral tegmental area of the midbrain, which may lead to activation (Lipinski et al. 1989). The role of the frontal lobe in SSRI-induced behavioral activation, disinhibition, and SSRI-induced amotivational syndrome or apathy is not known, although the frontal lobe may mediate different adverse events (Hoehn-Saric et al. 1991; Garland and Baerg 2001; Reinblatt and Riddle 2006). A better understanding of the mechanisms of activation could potentially improve monitoring and the clinical management of children treated with SSRIs.

Limitations

These findings should be interpreted with an appreciation for several methodological limitations. First, the study was a retrospective review of existing data and does not allow for long-term follow up to determine the persistence or recurrence of AC-AEs. This approach does not provide definitive answers to primary research questions; however, the authors thought this was an important first step in the field, given the significance of the subject matter and the limited information available. Because the AC-AE ratings were subjective measures, there is the potential for under- or over-reporting AC-AEs. In an attempt to minimize this potential bias, the first author examined the research charts to verify the severity of the event; however, this potentially might have inadvertently introduced misclassification error. Without systematic inquiry for adverse events, AC-AEs may have been underreported; the method of eliciting AC-AEs spontaneously by clinicians after open-ended questions and using COSTART terms was the standard in clinical trials at that time.

The dose titration schedule used in this clinical trial reflected a rapid dose escalation to minimize placebo exposure. As is common in many other pediatric psychopharmacology studies, the dose escalation is not typical of titration schedules used in clinical practice; this would impact the generalizability of these results to clinical practice because it possibly may overestimate the frequency of AC-AEs resulting from rapid dose increases. These data describe only moderate-to-severe activation effects that were sufficient to cause clinicians to reduce dosage in the context of a research study; thus, they may not represent the full prevalence of all activation adverse events. The lower mean dose of fluvoxamine among those who developed AC-AEs relative to those who did not may have been related to protocol guidelines, such as dose reduction in the "activated" children over the course of the study. Unfortunately, data were not available to permit examination of the effect of very large body mass differences independent of age. The study included younger children, which may have limited the ability to detect an association between the development of AC-AEs and age.

The sample in this study may not be generalizable to some patients because the child sample was predominantly Caucasian and did not have psychiatric co-morbidities. Data were not collected on the P450 genotype of the participants; because

genotype variants may affect fluvoxamine metabolism, plasma blood level differences may have been related to genotype variation in metabolism. Although parents did not report any other co-prescribed psychotropic medications, which may have affected fluvoxamine blood levels, it is possible that they did not recall such information accurately. The results also are limited by a small sample size. Examining only one site might be a potential source of bias because there might be site-specific differences; thus, not replicating findings at the other RUPP sites limits the power of this report. Even though most of the blood level samples were obtained at the JHU site, the study protocol was strictly enforced across all sites to reduce site-specific variation, and so it is unlikely that this compromised the integrity of the data. However, because there are no other data that have examined this phenomenon, this exploratory work is important for future research in this field.

Clinical implications

Several potentially important clinical findings emerged from this investigation. First, AC-AEs are relatively common side effects of fluvoxamine in children and may appear at any point within the first 8 weeks of treatment, suggesting the need for close monitoring in the first month after initiating treatment because this is when many adverse events occur. There also is a risk of recurrence of AC-AEs that highlights the utility for careful SSRI dose titration and continued monitoring for AC-AEs reoccurrence. AC-AEs may not only impact daily functioning, but they may also compromise medication compliance. It appears that these adverse effects resolve with dose reduction. This work provides some preliminary evidence of increased fluvoxamine blood levels associated with increased AC-AEs. These preliminary data require further study to determine whether the AC-AEs associated with increased blood levels are related to metabolic variability and to help identify clinical strategies that would minimize this relatively frequent adverse event among children treated with SSRIs.

Disclosures

Acknowledgments

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