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A Systematic Chart Review of the Nature of Psychiatric Adverse Events in Children and Adolescents Treated with Selective Serotonin Reuptake Inhibitors

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ABSTRACT

Objective: **Despite a rapidly growing literature on the efficacy of the selective serotonin reuptake inhibitors (SSRI) in the treatment of juvenile psychiatric disorders, relatively little is described about emotional, behavioral, and cognitive adverse effects associated with their use. To this end we completed a retrospective analysis of medical charts to determine the incidence, nature, and clinical correlates of treatment emergent adverse effects in the behavioral, cognitive, and emotional domains.**

Methods: **We systematically evaluated the medical charts of children treated with SSRI for depressive or obsessive-compulsive disorders for a mean (±SD) of 26.9 ± 20.8 months to determine the incidence, nature, and clinical correlates of treatment emergent psychiatric adverse events (PAE). Charts were reviewed for diagnoses, type and dose of SSRI and adjunct medication, specific type of PAE, and time to onset and offset of PAE.**

Results: **In total, 82 charts of children and adolescents (mean age 12.2 ± 3.2 years) were examined. PAE occurred in 22% of children and were most commonly related to disturbances in mood. PAE were not associated with psychiatric diagnosis(es), age, sex, concurrent medications, doses or specific serotonin reuptake inhibitors. The onset of PAE was observed typically 3 months after SSRI exposure (median = 91 days). Although PAE diminished with SSRI discontinuation, those that emerged early in treatment diminished significantly more rapidly than those that emerged later (median offset was 10 and 49 days, respectively). Re-exposure to an SSRI resulted in another PAE in 44% (n = 18) of the group.**

Conclusion: **Based on the retrospective review of medical charts, youth receiving SSRI appear to be at risk for treatment emergent PAE and recurrence with re-exposure to an SSRI. Prospective longer term studies evaluating the course and prognosis of youths manifesting PAE to SSRI are necessary.**

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INTRODUCTION

With the increased use of psychotropic medication for emotional and behavioral disorders in youth, one of the most disturbing adverse outcomes is a worsening of emotional, cognitive, or behavioral symptoms (Ovsiew 1992; Wilens et al. 1998). These psychiatric adverse events (PAE) to medication can be significantly impairing, affecting both the child and family. Unfortunately, little is known about this phenomenon in children and adolescents.

The selective serotonin reuptake inhibitors (SSRI)—including fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram—are among the most commonly used psychotropics in children and adolescents. Large single- and multisite controlled studies of these agents have demonstrated their efficacy for depressive, anxiety, and obsessive-compulsive disorders (OCD) (Emslie et al. 1997, 2000; Geller et al. 2001; Keller et al. 2001; March et al. 1998; Riddle et al. 2001; Wagner 1998; Walkup et al. 2001). In these short-term studies, therapeutic dosing of SSRIs resulted in demonstrable efficacy with a low burden of adverse events. In contrast, naturalistic data indicate a high risk for PAEs (Biswas et al. 2001; Diaferia et al. 1994; Go et al. 1998; Masi et al. 2001; Riddle et al. 1991). Hence, given the limited understanding of the nature, associations, and time course of PAEs, more information is necessary. One manner to examine this issue with the inherent limitations of retrospective reporting is to examine the clinical charts of youth exposed to SSRIs over time to derive hypotheses about PAEs over time in this context.

The delineation of PAE with SSRI is of high clinical and scientific value. Such information would assist clinicians in identifying the nature and subgroup of youth at relatively higher risk for developing PAE. For example, are children with depression at higher risk than those with other disorders such as OCD to develop PAE? How long after exposure to an SSRI do PAE emerge, and what is the duration of the event? Are PAE more linked to a specific SSRI, and are they likely to recur when an individual is re-exposed to an SSRI? Scientifically, the development of PAE may signal an underlying condition or assist in better defining subtypes of children with a similar presentation of a disorder. For instance, data on depressed youth who manifest psychosis, pervasive agitation, irritability, and sleep difficulties in association with an antidepressant suggest that these children and adolescents may be prone to develop mania (Biederman et al. 2000; Geller et al. 1993).

To better understand the nature of PAE, we systematically evaluated the effects of exposure to SSRI with attention to PAE. We sought to delineate the prevalence, nature, and duration of PAE and to assess their association with clinical variables. Based on limited literature (Apter et al. 1994; Biederman et al. 2000; Cook et al. 2001; Geller et al. 1993; Riddle et al. 1991; Rosenberg et al. 1999; Tierney et al. 1995; Wilens et al. 1998), we hypothesized that PAE would be frequently identified in children and adolescents receiving SSRI.

METHODS

The sample included all children consecutively referred to our Pediatric Psychopharmacology Clinic between 1993 and 2000. Each child had been evaluated with a structured diagnostic interview confirmed by direct clinical interview with the child and parent. This clinic sample was unselected, as children were referred for a pediatric psychopharmacology evaluation because of severe psychopathology—not for evaluation of any specific disorder. From this pool of subjects, we identified those who were exposed to an SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) during their visits to the clinic for the treatment of depression or OCD. We identified 82 such children and adolescents.

All children were evaluated at referral using the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children, Epidemiological Version (Ambrosini 2000; Orvaschel 1985), for Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (American Psychiatric Association 1987) and DSM-IV (American Psychiatric Association 1994) criteria, administered to the mother by raters trained and supervised by the senior investigator. The

raters were blind to the clinical diagnosis but knew that the child had been referred to a pediatric psychopharmacology clinic. A sign-off committee of experienced, board-certified child and adolescent psychiatrists chaired by the senior investigator reviewed all diagnoses. We evaluated our assessment procedures by computing kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff in our research program. Based on 173 interviews, median kappa was 0.86, with key disorders attaining kappas higher than 0.82 (0.99 for attention deficit hyperactivity disorder, 0.93 for conduct disorder, 0.83 for major depression, and 0.94 for bipolar disorder).

A diagnosis was rated positive only if the committee's consensus was that criteria were met to a clinically meaningful degree. By "clinically meaningful" we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture.

Assessments of adverse events

Using a team of trained and supervised research assistants who were independent from the care of these children, we evaluated the clinical charts of all 82 youths treated naturalistically with SSRI. We queried for clinical demographic data, adjunctive medication regimens with SSRI, and type and dose of SSRI. Individual results of the chart review were subsequently reviewed with a senior psychopharmacologist.

To evaluate the nature and associations of PAEs, we developed a list of potential PAEs within the cognitive, behavioral, and emotional domains (see Table 2). We developed a composite of the mood, behavioral, emotional, and PAE subcategories to delineate a group that experienced side effects consistent with the spectrum of psychiatric disturbance (PAE). We systematically examined all chart notes from clinic visits to determine if an adverse event had occurred, and if so, the nature and time course of the event. We also recorded the occurrence of all treatment emergent PAEs. All adverse events were noted by spontaneous report to the clinician as recorded in the medical chart. We coded an adverse event based on review of the clinical notes in which clear evidence of the event being related adversely to the treatment was available.

Because patients were treated clinically and naturalistically, the intervisit interval and the number of visits varied. This sample of children was treated by six clinicians—all of whom were trained and supervised by a senior psychopharmacologist (J.B.).

After reviewing each clinical note, the review team discussed the most appropriate categorization to be given for that patient, for that visit, based on the recorded information. Although demographic information was collected during the initial visit, information on pharmacotherapy and adverse events were recorded at each visit. The remission from the PAE was determined by both the absence of the continuation of the spontaneous reporting of the specific PAE as well as evidence of improvement in the PAE reflected in the clinical notes. Because clinicians used a wide spectrum of medications, they were grouped by class as follows: (1) SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), (2) mood-stabilizing agents (lithium, carbamazepine, and valproic acid), (3) tricyclic antidepressants and atypical antidepressants (bupropion, venlafaxine, and nefazodone), (4) stimulants (methylphenidate, amphetamine, and pemoline), and (5) antipsychotics (typical and atypicals).

For patients who manifested a PAE, we also examined the time course of the PAE. The time to onset of a PAE was determined by comparing the report of the adverse event relative to the exposure to the SSRI. Offset of the PAE was determined by comparing the remission from the PAE relative to the onset of the PAE.

Statistical analysis

To evaluate graphically and statistically the onset and offset data of PAEs and their relation to SSRI administration, we used Kaplan-Meier curves. The Kaplan-Meier product-limit method was used to estimate survival

curves—to graphically represent separately the (1) onset of PAEs after SSRIs and (2) the offset of PAEs after the discontinuation of an SSRI. To eliminate outliers (patients who had extreme times to onset or offset of their PAEs with SSRIs) we used boxplots, which examine datapoint outliers; values greater than 2 SD from the mean were dropped. To determine statistical significance between Kaplan-Meier survival curves, we applied the log-rank test. To determine the significance of potential risk factors for the occurrence of PAEs, the Cox proportional hazards regression model was used. The statistical significance of each covariate in these regression models was determined by Wald's test, and significance was set at $p < 0.05$. Analyses were performed with STATA, version 7.0 (Stata Corporation, College Station, TX). Data are expressed as mean ± SD unless otherwise reported.

RESULTS

Eighty-two subjects cared for by six child psychiatrists met our criterion of having received an SSRI during their visits to the clinic (Table 1). Children's ages ranged from 3 to 18 years (mean age was 12 years). A preponderance of the sample was male. The mean follow-up spanned over 2 years (26.9 ± 20.8 months; range 0.2–72 months); patients were seen a mean of 12.3 ± 9.8 study visits (range 2–51 study visits).

Patients were being treated with an SSRI for depressive (major depression, dysthymia, or mood disorder not otherwise specified) and/or OCD (Table 2). The sample was highly comorbid, with attention deficit hyperactivity disorder ($n = 62$, 76%) and oppositional defiant disorder ($n = 26$, 32%) most frequently cooccurring. Sertraline, paroxetine, and fluoxetine were the most commonly used SSRIs. Concomitant medications with SSRIs included stimulants ($n = 48$, 59%), antipsychotics ($n = 18$, 22%), antihypertensives ($n = 25$, 30%), mood stabilizers ($n = 27$, 33%), and anxiolytics ($n = 11$, 13%).

SSRI treatment emergent adverse events are reported in Table 2. Overall, 74% ($n = 61$) of children and adolescents experienced an adverse event to an SSRI over the course of their therapy. Combining adverse events in the behavioral, emotional, and psychosis domains, 18 (22%) subjects in our sample had experienced at least one SSRI treatment emergent PAE. Disturbances in mood were the most common PAE reported.

We failed to find any associations with age groups (child, adolescent: hazard ratio [HR] = 0.4, 95% confidence interval [CI] = 0.1–1.7, $p = 0.2$) or sex (HR = 2.8, 95% CI = 0.7–10.6, $p = 0.1$) and the development of a PAE. We further evaluated the associations of the current diagnosis of depression or OCD and did not find any significant relation with the development of a PAE (major depression: HR = 1.1, 95% CI = 0.3–4.2, $p = 0.9$; OCD: HR = 0.6, 95% CI = 0.1–4.6, $p = 0.6$). Nonsignificant associations for the development of PAEs were also found for bipolar disorder (HR = 0.2, 95% CI = 0.02–1.4, $p = 0.10$), disruptive behavior disorders (HR = 0.93, 95% CI = 0.3–3.2, $p = 0.9$), anxiety disorders (HR = 0.9, 95% CI = 0.2–3.4, $p = 0.9$), and other psychiatric disorders (HR = 2.4, 95% CI = 0.5–12.7, $p = 0.3$).

There was no effect of the presence of concurrent medication or medication class and the development or course of PAEs (stimulants: HR = 2.9, 95% CI = 0.6–13.3, $p = 0.2$; mood stabilizers: HR = 0.2, 95% CI = 0.02–1.4, $p = 0.1$). Similarly, there was no association between type of SSRI and the development of a PAE (Fisher's exact test, $p = 0.9$).

The time course for the development and resolution of a PAE after exposure to an SSRI is shown in Fig. 1. In the 18 children and adolescents in whom PAEs developed, all had their SSRI discontinued. PAEs did not onset immediately after exposure to an SSRI. The median time to onset (i.e., half of cases of PAEs) was 91 days. One quarter of the sample had the onset of their PAE within 35 days of treatment. PAEs appeared to remit rapidly with discontinuation of the SSRI (Fig. 1B). Half of the PAEs were resolved within 28 days, and three quarters of PAEs had resolved by 49 days (Fig. 2).

We then examined the relation between time to offset and time to onset. Patients with a relatively more rapid time to onset (less than median) had a more rapid resolution of their PAEs (Fig. 3). In contrast, patients with de-

TABLE 1. CLINICAL CHARACTERISTICS AND DEMOGRAPHICS OF THE SAMPLE (*N* = 82)

Characteristics	*Mean ± SD*	n *(%)*
Age (years)		
Baseline	12.2 ± 3.2	
Follow-up	14.3 ± 3.4	
Mean follow-up visits (*n*)	12.3 ± 9.8	
Duration of follow-up (months)	26.9 ± 20.8	
Sex (male)		50 (61)
Psychiatric disorders[a]		
Mood disorders		
Major depressive disorder		62 (76)
Dysthymia		10 (12)
Bipolar disorder		19 (23)
Mood disorder NOS		20 (24)
Disruptive behavior disorders		
Attention deficit hyperactivity disorder		68 (83)
Oppositional defiant disorder		26 (32)
Conduct disorder		8 (10)
Anxiety disorders		
Multiple anxiety disorders (≥2)		11 (13)
Obsessive-compulsive disorder		17 (21)
Separation anxiety disorder		9 (11)
Overanxious disorder		9 (11)
Panic disorder		8 (10)
Generalized anxiety disorder		6 (7)
Anxiety disorder NOS		13 (16)
Pervasive developmental disorder		6 (7)
Other disorders		4 (5)
Psychosis		
Learning disorders		6 (7)
Tourette's disorder		4 (5)
Posttraumatic stress disorder		4 (5)
Encopresis		4 (5)
Enuresis		4 (5)
SSRI medications[a,b]		
Sertraline	108.8 ± 67.4	56 (68)
Paroxetine	19.3 ± 11.5	27 (33)
Fluoxetine	32.8 ± 15.0	18 (22)
Fluvoxamine	83.6 ± 23.4	6 (7)
Citalopram	23.3 ± 22.4	3 (4)
Concomitant medications[a]		
Other antidepressants		
Tricyclics		23 (28)
Bupropion		8 (10)
Other non-SSRI antidepressants		19 (23)
Stimulants		48 (59)
Methylphenidate		35 (43)
Amphetamines		21 (27)
Mood stabilizers		27 (33)
Antihypertensives		25 (30)
Antipsychotics		18 (22)
Anxiolytics		11 (13)

NOS = not otherwise specified; SSRI = selective serotonin reuptake inhibitor.

[a]Not mutually exclusive; refer to lifetime rates of psychopathology at intake and during the course of the study period.

[b]Data in the "mean ± SD" column show daily dose (in mg); data in the "*n* (%)" column show the number of subjects on a particular medication.

layed onset (greater than median) had significantly longer offset (median = 49 days). By log rank test, $\chi^2(1) = 8.74$, $p = 0.003$.

We further examined the risk of developing subsequent PAEs to another SSRI exposure. Of the 18 patients who experienced a PAE on an

TABLE 2. ADVERSE EVENTS IN CHILDREN AND ADOLESCENTS TREATED WITH SSRIs (N = 82)

Nature of adverse event	n (%)[a]	*Nature of adverse event*	n (%)[a]
Any mood	17 (21)	Any Sleep (con't)	
Irritable	12 (15)	Other	2 (2)
Anxiety	8 (10)	Nightmares	0
Depressed	7 (9)	Any gastrointestinal	24 (29)
Manic	5 (6)	Dececreased appettite	9 (11)
Angry	1 (1)	Nausea	7 (9)
Other	1 (1)	Weight gain	7 (9)
Dysphoric	0	Thirsty	3 (4)
Labile	0	Increased appetite	3 (4)
Obsessions	0	Diarrhea	2 (2)
Compulsions	0	Constipation	2 (2)
Any behavior	4 (5)	Weight loss	1 (1)
Other	3 (4)	Other	1 (1)
Aggressive	1(1)	Encopresis	0
Impulsive	0	Any physical	16 (20)
Withdrawn	0	Headache	8 (10)
Oppositional	0	Other	6 (7)
Any psychotic	8 (10)	Stomach ache	4 (5)
Other	1 (1)	Dizzy	2 (2)
Auditory hallucinations	0	Sweating	0
Visual hallucinations	0	Rash	0
Delusions	0	Chest pain	0
Paranoia	0	Cramps	0
Any cognitive (blunted)	0	Palpitations	0
Any extrapyramidal	2 (2)	Any cardiovascular	0
Tremors	1 (1)	Any miscellaneous	7 (9)
Other	1 (1)	Tics	4 (5)
Drooling	0	Enuresis	2 (2)
Slurred speech	0	Other	1 (1)
Any sleep	29 (35)	Picking	0
Drowsy	19 (23)	Any PAE	18 (22)
Insomnia	14 (17)	Any adverse event	61 (74)

PAE = psychiatric adverse event (includes mood, behavioral, and psychotic domains); SSRI = selective serotonin reuptake inhibitor.

[a]Frequency counts were tabulated if a patient ever experienced an adverse effect related to an SSRI.

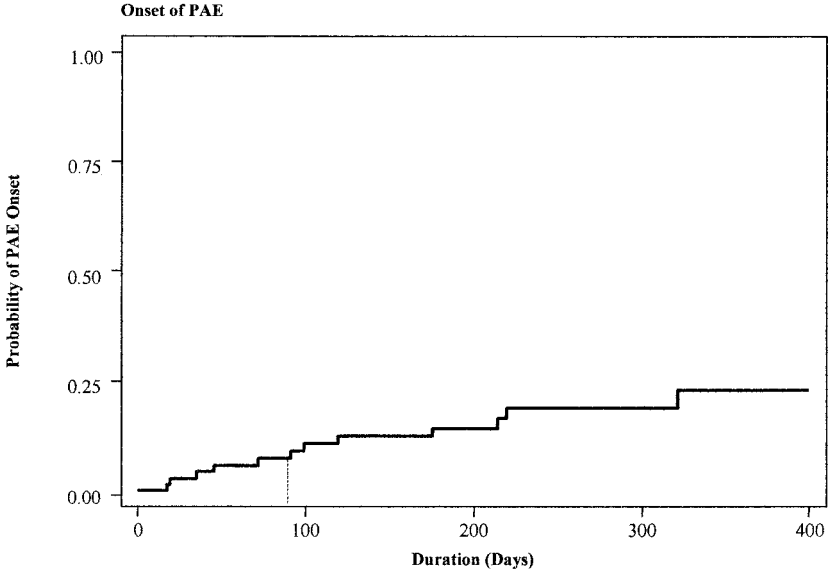

FIG. 1. Time to onset of SSRI-related PAE. This figure shows the proportion of subjects with a PAE over time. Median time to onset among subjects who developed a PAE was 91 days (dotted line). PAE = psychiatric adverse effect; SSRI = selective serotonin reuptake inhibitor.

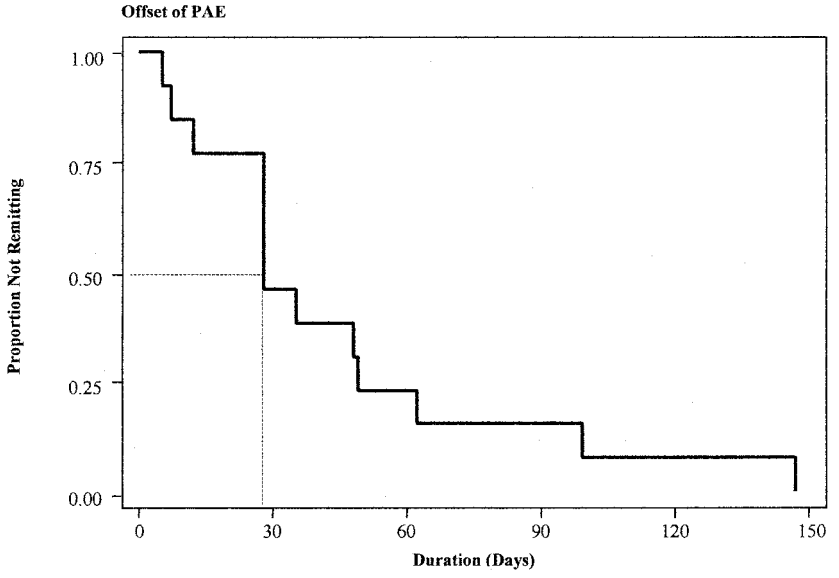

FIG. 2. Time to offset of SSRI-related PAE. This figure depicts the proportion of subjects with a PAE who had not remitted over time. Median time to offset was 28 days (dotted line). PAE = psychiatric adverse effect; SSRI = selective serotonin reuptake inhibitor.

SSRI, 8 (44%) subsequently developed another SSRI-induced PAE on re-exposure to an SSRI.

DISCUSSION

The results of this retrospective review of PAEs are limited by the retrospective nature and limited data available in the medical chart. The chart review data suggest that treatment emergent PAE is not uncommon, as it was observed in 22% of youth exposed to an SSRI. SSRI-related PAEs typically occurred 3 months into treatment. In contrast, PAEs remitted rapidly with discontinuation of an SSRI, particularly if it began soon after SSRI exposure. Children with a treatment emergent PAE commonly manifest another PAE with re-exposure to an SSRI. Contrary to our hypothesis, PAEs were not associated with the primary psychiatric disorder being treated (depression or OCD) or with additional psychiatric comorbidity.

Our finding that 22% of children and adolescents of both sexes manifest a PAE with SSRI treatment is reminiscent of findings from short-term clinical trials. For example, sertra-

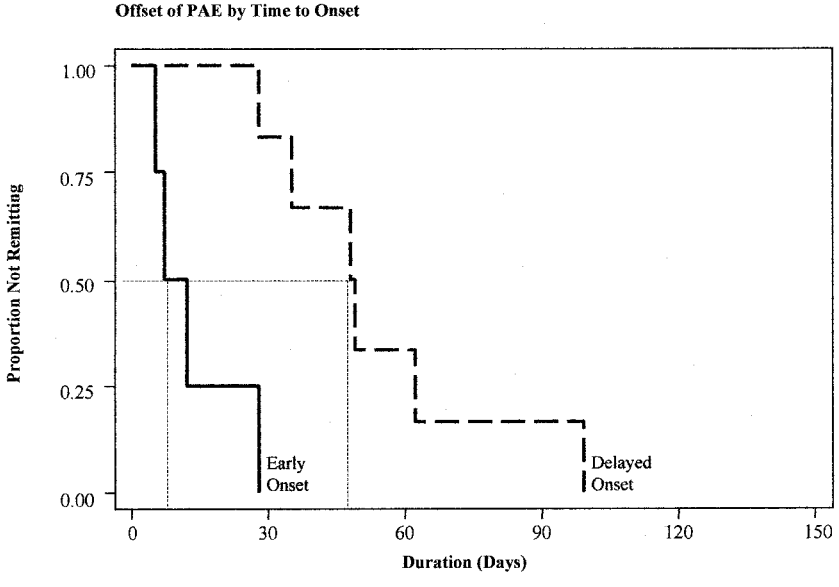

FIG. 3. Time to offset of SSRI-related PAE by time to onset. Subjects were stratified by their PAE onset time: Early onset denotes subjects with time to onset of PAE less than the median of 91 days (see Fig. 1); delayed onset refers to subjects with PAE onset times greater than the median. Median offset times were 10 and 49 days, respectively, for the early onset and delayed onset groups (dotted lines). PAE = psychiatric adverse effect; SSRI = selective serotonin reuptake inhibitor.

line has been reported to result in behavioral adverse events in 21% of children being treated for major depressive disorder (Tierney et al. 1995). Likewise, Riddle and colleagues reported that 50% of children treated with 20–40 mg of fluoxetine for OCD or depressive symptoms manifest a "behavioral side effect" and that these adverse effects resolve rapidly with SSRI discontinuation (Riddle et al. 1991). In reports of larger controlled trials, PAEs were reported in 17% (Keller et al. 2001) to 37% (March et al. 1998) of children receiving an SSRI. It is of interest that our rate of PAEs in this unselected, naturalistic sample of highly comorbid youths mirrors that reported in carefully screened youths entering clinical trials of SSRIs for OCD as well as depressive and anxiety disorders (Emslie et al. 1997; March et al. 1998; Riddle et al. 2001; Walkup et al. 2001).

Youths with SSRI-associated PAEs appear to manifest symptoms equally in all of the behavioral, emotional, and cognitive domains. This distribution of PAEs appears to be consistent with the literature in which activation (Tierney et al. 1995), agitation (March et al. 1998), and sleep disturbance (March et al. 1998; Riddle et al. 1991; Walkup et al. 2001) have been observed. For example, placebo-controlled data from Walkup et al. (2001) showed increased motor activity to be significantly greater in the fluvoxamine-treated group, and March et al. (1998) reported significantly higher rates of insomnia ($p < 0.001$) and agitation ($p = 0.005$) in sertraline-treated patients. A comparison of fluvoxamine versus placebo (Riddle et al. 2001) revealed a trend toward greater agitation ($p = 0.06$) and a significantly higher rate of insomnia ($p = 0.004$) among treated patients. Our data combined with the literature suggest that sleep disturbance and agitation are among the most common PAEs associated with SSRIs. Behavioral activation, although less common than other PAEs, tends to be a more serious PAE, often necessitating discontinuation from clinical trials (Emslie et al. 1997; Tierney et al. 1995).

It has been suggested that children with prior or ongoing emotional or behavioral difficulties may be particularly prone to manifest PAEs (Rende 1993). Although we found that 22% of our sample receiving SSRIs had PAEs, further analyses of the data do not support a differential risk for PAEs in youth versus those without comorbid disruptive disorders or labile mood.

In discussing the onset and offset of PAEs, an important methodological issue arises: Our data may have been confounded by the variability in the time at which the actual event occurred. In other words, practitioner reporting in the chart reflects PAEs that emerged anytime prior to the office visit at which the PAE data were recorded. We found that PAEs were slow to onset after SSRI initiation. In fact, half of our children developed SSRI-related PAEs 3 months into treatment. Our data are consistent with Tierney et al.'s (1995), who reported a minority of PAEs initially but the development of activation and other PAEs months after sertraline initiation. Although our data appear to differ with observations by others who observed that the onset of PAEs occurred soon after exposure to an SSRI (Keller et al. 2001; Riddle et al. 1991), we found that in the group of youths who developed a PAE relatively rapidly (median less than 3 months), the bulk of PAEs emerged within the first 3 weeks of treatment (Fig. 1). Clearly a better understanding of the onset of PAEs relative to SSRI administration is necessary. Until such data are available, our results coupled with the literature suggest that children receiving SSRIs should be monitored for the onset of PAEs within the first few months after exposure.

We observed a more rapid offset of PAEs with discontinuation of the SSRI similar to that reported by others (Riddle et al. 1991; Tierney et al. 1995). The complete and rapid remission of the PAEs upon SSRI discontinuation further supports the notion that the PAEs were probably related to the SSRI. Our additional finding that PAE remission was related to onset is noteworthy. In youths with a relatively shorter onset to SSRI-related PAEs, a more rapid recovery from the PAEs was observed, generally within 1 month. In contrast, children with a delayed onset of a PAE had a more belated remission from the adverse event. Further studies evaluating the children with early versus delayed onset SSRI-related PAEs as predictors of later psychopathologic states are necessary.

The results from the current study need to be tempered against their methodological lim-

itations. Our sample size was relatively small, limiting the statistical power. In our review, we only evaluated patients with SSRI exposure; hence, it is unclear if PAEs were related to an SSRI, any medication, or the natural course of the disorder. Moreover, we did not have "baseline" rates of PAEs with which to compare our final results. Similarly, we do not have a placebo comparator with which to derive the incidence of "true" PAEs. The review was done openly and hence may have introduced bias in the study. Variability in the reporting of PAEs may have existed among the six child psychiatrists caring for the children and adolescents included in the chart review. Because no instruments were available to review charts retrospectively for PAEs, we developed a list of potential PAEs and physical adverse events that remains to be validated.

By the nature of chart review methodology, which is limited to documentation in the clinical notes, we may have underestimated the outcome. For example, spontaneous reporting of adverse events in general is likely to underestimate their occurrence. Furthermore, some patients may have experienced PAEs but chose not to return to the clinic. PAEs (e.g., mood disturbance) that were ascribed to SSRIs may have occurred independently of the exposure to an SSRI. The time course of a PAE was an estimate based on reports derived from the next clinic visit and may not accurately reflect the actual day of the onset and offset. Because many of our children and adolescents were receiving combined pharmacotherapy, PAEs that were ascribed to SSRIs may in fact be more reflective of the adjunct medication or combination of medications (including SSRI). Of interest, analyses of our data by presence or absence of additional medications had no effect on our outcomes.

Despite these limitations, PAEs in children receiving SSRIs are relatively common, appear largely idiosyncratic, and remit with SSRI discontinuation. Prompt attention to the symptoms will help disentangle the nature of the reaction. Discussion with families about PAEs as potential adverse events when using SSRIs in youths appears warranted and may enhance recognition and dampen the deleterious impact of this idiosyncratic reaction. Further placebo-controlled, longer term, prospective studies using PAE checklists establishing the "true" incidence and correlates of PAEs are necessary. Further prospective investigation into the longitudinal correlates of children and adolescents with iatrogenically induced PAEs is warranted.

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