

# Treatment-Emergent Adverse Events from Selective Serotonin Reuptake Inhibitors by Age Group: Children versus Adolescents

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## ABSTRACT

**Objective:** The aim of this study was to report the frequency of common treatment-emergent adverse events (AEs) from selective serotonin reuptake inhibitors (SSRIs) in children, adolescents, and adults.

**Method:** AE data were obtained from all published double-blind, placebo-controlled SSRI studies of children and adolescents that separated AE findings by age group. The AE findings were pooled for purposes of age-group comparisons. Double-blind, placebo-controlled SSRI studies of adolescents ( $n = 2$ ) and of adults identified in systematically identified trials ( $n = 22$ ) were assessed to compare patterns and rates across the age span. Other reports, primarily from the published SSRI literature, were added to clarify the findings presented.

**Results:** Activation and vomiting SSRI AEs were 2- to 3-fold more prevalent in children than in adolescents, and their rate was lowest in adults. Somnolence as a SSRI AE was uncommon in children; its rate increased with advancing age. Insomnia and nausea were common SSRI AEs across the age span. Activation AEs were a frequent reason for discontinuation from SSRI clinical trials in preadolescents, whereas somnolence, nausea, and insomnia AEs were the most common reasons for trial discontinuations in adults.

**Conclusions:** Children are particularly vulnerable to specific AEs from certain medications, such as SSRIs. It is likely that the level of children's biological immaturity explains part of this phenomenon.

## INTRODUCTION

ADVERSE EVENTS (AE) associated with selective serotonin reuptake inhibitor (SSRI) treatment of youths are a particularly pertinent issue at this time, as major concerns about suicidal behavior accentuated by these drugs have been highlighted in the scientific literature, the media, within the U.S. Food and Drug Administration (FDA) (Leslie et al. 2005; Whitt-

ington et al. 2004), and in the European Medicines Agency (2005). But SSRIs result in other, more common AEs in youths that merit appraisal. The most prominent of these are: Activation, insomnia, somnolence, and gastrointestinal symptoms, and there are data to indicate that some of these are particularly common in younger-aged youths.

To determine if children are particularly vulnerable to specific AEs in association with SSRI

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treatment, it is appropriate that their rates be compared to older youths. As an example, risperidone and olanzapine induce different degrees of weight gain per baseline body weight in the preschool years (Biederman et al. 2005), in primary school age, and in adolescence (Safer 2004).

Unfortunately, most placebo-controlled trials of SSRIs for youths have either combined all of the findings from preadolescent and adolescent youths (e.g., Emslie et al. 1997, 2002; Geller et al. 2001; Liebowitz et al. 2002a; March et al. 1998; Pediatric OCD Treatment Study 2004; Rynn et al. 2001; Wagner et al. 2004a) or limited the research population only to adolescents (e.g., Keller et al. 2001; Simeon et al. 1990; TADS 2004). No placebo-controlled trials of SSRIs include only children. However, four large placebo-controlled clinical trials of SSRIs in youths—which separately analyzed their AE findings by age group (preadolescent versus adolescent)—were located after a thorough search of the medical literature. The findings from these studies were pooled. Additionally, the AE findings from the only two published, exclusively adolescent-age, double-blind, placebo-controlled studies of SSRI treatment were included to supplement the available adolescent data.

The primary focus of this paper will, therefore, be to compare pooled rates of common SSRI AE rates for preadolescents with those of adolescents. Pooled rates are feasible because—although there are some differences between individual SSRIs in their rate of AEs—large meta-analyses of adult trials reveal these to be few (Brambilla et al. 2005; Edwards and Anderson 1999; Kroenke et al. 2001).

## METHOD

The Medline was searched for SSRI placebo-controlled clinical trials covering the period from 1984 through mid-2005 that *separately* identified the AE rates for youths by age group: Children (ages, 6–11 or 12 years) and adolescents (ages, 12 or 13 to 17 or 18 years), according to the age grouping in each study. Four such studies were located, which included one presented only at a scientific meeting. To broaden the age-based analysis, two placebo-controlled SSRI studies ex-

clusively covering adolescents were located and appraised for AE frequency. The SSRI AE data on adults were obtained from a *consecutive* trial literature search of placebo-controlled SSRI reports in the *Journal of Clinical Psychiatry*, where most such studies have been published. Twenty-two such reports were located, covering the period from 1985 to mid-2005.

The major AE patterns in SSRI trial reports were organized into 5 categories: (1) Activation (including restlessness, hyperkinesia and hyperactivity, and agitation); (2) somnolence (including sedation and drowsiness); (3) insomnia; (4) nausea; and (5) vomiting. In a separate analysis, the rate of discontinuation from SSRI studies associated with AEs is presented for youths and adults, and in fixed-dose studies.

The AE data for the SSRI and placebo populations were pooled for the major symptom categories, and these rates were then compared by age group. Suicidal ideation and behavior in relation to SSRI treatment of youths are only briefly discussed because of limited published information by age group.

Most studies identified only AEs that were noted twice during the research period and which affected 5% or more of the subjects. For those AE features with a less than 5% rate, a midpoint estimate of 2% was arbitrarily used in comparisons of pooled data, rather than assuming that no subjects had that particular AE.

Data from analyses of both published and unpublished literature on youths treated with SSRIs are included in this paper to add relevant information on the rate and patterns of the AEs described. Published information on dose, duration, and diagnoses in relation to SSRI AEs was also added.

## RESULTS

### *Activation frequency*

Table 1A lists the rate (%) of activation for children and adolescents who received SSRIs or placebos in placebo-controlled trials that separated the findings by age group. Activation in these SSRI trials ranged from 8% to 17% for children, averaging 10.7% (32 of 298) for the active drug and 3.4% (10 of 294) for

TABLE 1A. RATE OF ACTIVATION ADVERSE EVENTS FROM SSRIs: CHILDREN VERSUS ADOLESCENTS

Investigators and diagnoses	SSRI and duration	Preadolescents		Adolescents		Preadolescents (mg/kg)	Adolescents (mg/kg)
		SSRI	Placebo	SSRI	Placebo		
Wagner et al. 2002 Depression (3 studies) OCD (1 study)	Paroxetine 8–12 weeks	10% (11/108)	4% (4/104)	2% <sup>a</sup> < 5%/362	2% < 5%/283	20.6 mg	24.2 mg
Wagner et al. 2003 Depression	Sertraline 10 weeks	8% (7/86)	2% (2/88)	2% < 5%/103	2% < 5%/ 96	102 mg 2.6 mg/kg	134 mg 2.2 mg/kg
Wagner et al. 2004 Social Anxiety Disorder	Paroxetine 16 weeks	9% (4/46)	0% (0/45)	2% (2/117)	0% (0/111)	22 mg 0.57 mg/kg	26 mg 0.42 mg/kg
Geller et al. 2004 OCD	Paroxetine 10 weeks <b>Totals</b>	17% (10/58) <b>10.7%</b> <b>(32/298)</b>	7% (4/57) <b>3.4%</b> <b>(10/294)</b>	5% (2/40) <b>2.1%</b> <b>(13/622)</b>	4% (2/48) <b>1.9%</b> <b>(10/538)</b>	20 mg	27.0 mg

SSRIs = selective serotonin reuptake inhibitors; OCD = obsessive-compulsive disorder.

<sup>a</sup>The midpoint of 2% was arbitrarily selected for purposes of comparison.

placebo (Geller et al. 2004; Wagner et al. 2002; Wagner et al. 2003; Wagner et al. 2004b). By contrast, the average activation rates for adolescents in these trials were 2.1% (13 of 622) for SSRIs and 1.9% (10 of 538) for placebo. In the two placebo-controlled trials of SSRIs that included only adolescents (Keller et al. 2001; TADS 2004), the average rates of activation were 3.2% (10 of 309) for the drug and 1.0% (2 of 199) for placebo (Table 1B). Thus, the activation rate for adolescents receiving SSRIs in placebo-controlled trials is consistently far below that of children.

Activation/hyperactivity is almost never mentioned as a side effect in placebo-controlled trials of adults. (In the one exception, the placebo rate for hyperkinesia in adults exceeded that for fluoxetine [Mendels et al 1987]). Clearly, the pooled age-grouped evidence across the age span indicates that activation/restlessness as an AE from SSRIs decreases with advanced age. Agitation was, however, mentioned as a side effect in 4 of the 22 adult placebo-controlled trials, and the combined rate for agitation in these studies was 5.9% (87 of 1469) for SSRIs and 4.5% (37 of 821) for placebo (Cohn and Wilcox 1992; Keller et al. 2000; Mendels 1987; Reimherr et al. 1990).

Anxiety/nervousness was mentioned as a SSRI AE in 10 of the 22 adult studies, with a rate of 10.1% (399 of 3962) for the SSRI and 6.8% (163 of 2399) for placebo. It is quite possible that anxiety/nervousness reflects an adult equivalent of activation, but the evidence, at present, is insufficient to make this case.

#### *Temporal onset of activation*

In youths, it is consistently reported that activation can occur at any time during treatment

with an SSRI (Jain et al. 1992; McConville et al. 1996; Riddle et al. 2001; Tierney et al. 1995; Wilens et al. 2003). Nevertheless, there is a tendency for activation to be more prominent during the first 2 or 3 weeks of treatment (Apter et al. 1994; Braconnier et al. 2003; Geller et al. 2004; Riddle et al. 1990; Tierney et al. 1995).

#### *Is SSRI-induced activation linked to insomnia?*

Generally, insomnia in youths as a SSRI AE was approximately twice as commonly reported as was activation (e.g., Keller et al. 2001; March et al. 1998; Riddle et al. 2001). Consequently, these AEs do not necessarily coexist. For example, in the study by Riddle et al. (1992), only 3 of the 6 children who developed insomnia had concomitant activation. In other studies, SSRI-induced insomnia was present in the absence of SSRI-induced activation (e.g., Birmaher et al. 1994; Simeon et al. 1990).

#### *Is SSRI-induced activation linked to suicidality?*

The rate of SSRI-induced activation in youths who participated in placebo-controlled, clinical trials was assessed in relation to suicidality as part of a recent FDA review (Hammad 2004, pp. 96–98). Hammad reported that youths who experienced SSRI-induced agitation or hostility were two to three times more likely to experience suicidal ideation or behavior than youths not experiencing these AEs.

#### *Vulnerabilities in relation to activation with SSRIs*

Youths with mental retardation, autism, Tourette's Disorder, panic disorder, and perva-

**TABLE 1B. RATE OF ACTIVATION ADVERSE EVENTS FROM SSRIs: EXCLUSIVELY ADOLESCENTS**

<i>Investigators and diagnoses</i>	<i>SSRI and duration</i>	<i>Rate of SSRI activation ADEs</i>	
		<i>SSRI</i>	<i>Placebo</i>
Keller et al. 2001 Depression	Paroxetine 8 weeks	8% (7/93)	0% (0/87)
TADS 2004 Depression	Fluoxetine 12 weeks	1% (3/216)	2% (2/112)
	<b>Totals</b>	<b>3.2% (10/309)</b>	<b>1.0% (2/199)</b>

SSRIs = selective serotonin reuptake inhibitors.

sive developmental disorder have moderately high rates (over 20%) of SSRI-induced activation, as reported in open-label and case series studies (Awad 1996; Cook et al. 1992; Martin et al. 2003; Masi et al. 2001; Scahill et al. 1997). Preschool and very young school-aged youths similarly appear to represent an unusually vulnerable population for SSRI-induced activation (Raches et al. 2002).

*Is activation dependent upon the dose of the drug?*

Keller et al. (2001), Birmaher et al. (2003), and March et al. (1998) reported that raising the dose of an SSRI increased activation AEs and that reducing the dose had a salutary effect, but King et al. (1991) and Martin et al. (2003) reported that the SSRI dose was unrelated to activation, and Geller et al. (1995) reported that a somewhat lower SSRI dose was associated with more behavioral activation. Nonetheless, the weight of evidence suggests that an increased dose of a SSRI in children increases the rate of activation and also that certain youth populations are particularly sensitive to this AE.

*Somnolence*

Table 2A lists the rate of somnolence for children and adolescents who received SSRIs or placebos in double-blind, placebo-controlled trials that separated their findings by age group. Somnolence rates in SSRI trials in children averaged 3.0% (9 of 298) for SSRIs and 3.4% (10 of 294) for placebos. The average somnolence rate for adolescents was 11.3% (70 of 622) for SSRIs and 5.0% (27 of 538) for placebo. In the two placebo-controlled trials of SSRIs that included only adolescents, the average rate for somnolence was 5.8% (18 of 309) for the active drug and 2.0% (4 of 199) for placebo (Table 2B). The evidence that somnolence as an AE associated with SSRIs is age related is further supported by adult data. In the 22 adult placebo-controlled trials of SSRIs, the rate of somnolence ranged from 11% to 29% and averaged 16.5% (1213 of 7303) for the active drug versus 7.6% (167 of 2209) for placebo. Thus, the average SSRI-placebo difference in reports of somno-

lence increased from -0.4% in preadolescents to 6.3% in adolescents to 8.9% in adults. In effect, somnolence is rare as a SSRI AE in children and common in adults.

*Insomnia, nausea, and vomiting AEs*

Insomnia reported in SSRI double-blind, clinical trials was quite variable from study to study. For children, it averaged 12% for the active drug and 3% for placebo. For adults, the rate of insomnia averaged 17% for the active drug and 7% for placebo (data not shown). Rates of nausea as a SSRI AE were also variable in youths and more commonly reported for adults (data not shown).

In the four placebo-controlled studies of SSRIs for youths that separately recorded AEs by age group, vomiting was reported to range in children from 7% to 9%, averaging 8.1% (24 of 298) for the drug and 3.7% (11 of 294) for placebo. In adolescents, the composite from the four placebo-controlled studies reporting this AE was 3.6% (30 of 838) for the SSRIs versus 2.8% (18 of 650) for placebo. In adults, only 1 of 22 placebo-controlled SSRI trials listed vomiting as an AE and the rate was 3.4% (5 of 149) for sertraline and 1.3% (2 of 150) for placebo (Reimherr et al. 1990). These data suggest that vomiting is more common as a SSRI-associated AE in children.

*Suicidal behavior associated with SSRIs: Children versus adolescents*

Preadolescents, as a group, were not distinguished statistically from adolescents in respect to their *risk* for the SSRI AE suicidality (Hammad 2004, p. 16). In the fluoxetine cases reported by King et al. (1991), 3 were ages 10-12 years and 3 were ages 14-17. In the Kremer et al. (2004) report on suicidality associated with sertraline trials, 3 of 86 with this AE were children and 2 of 103 were adolescents. In exclusively adolescent SSRI trials, the rates of suicidality AEs are as follows: 5 of 93 paroxetine versus 0 of 87 placebo (Keller et al. 2001; Whittington et al. 2004), 14 of 121 citalopram versus 5 of 112 placebo (CSM 2004; 68), and 15 of 216 fluoxetine versus 9 of 223 placebo/CBT (TADS 2004; CSM 2004; 67, 70). These are the only age-

TABLE 2A. RATE OF SOMNOLENCE ADVERSE EVENTS FROM SSRIs: CHILDREN VERSUS ADOLESCENTS

Investigators and diagnoses	SSRI and duration	Children		Adolescents	
		SSRI	Placebo	SSRI	Placebo
Wagner et al. 2002 Depression (3 studies) OCD (1 study)	Paroxetine 8–12 weeks	2% <sup>a</sup> (< 5%/108)	2% (< 5%/104)	14% (50/362)	6% (18/283)
Wagner et al. 2003 Depression	Sertraline 10 weeks	2% (< 5%/86)	2% (< 5%/88)	2% (< 5%/103)	2% (< 5%/96)
Wagner et al. 2004 Social Anxiety Disorder	Paroxetine 16 weeks	9% (4/46)	11% (5/45)	15% (17/117)	5% (6/111)
Geller et al. 2004 OCD	Paroxetine 10 weeks	2% (< 5%/58)	2% (< 5%/57)	2% (< 5%/40)	2% (< 5%/48)
	<b>Total</b>	<b>3.0%</b> <b>(9/298)</b>	<b>3.4%</b> <b>(10/294)</b>	<b>11.3%</b> <b>(70/622)</b>	<b>5.0%</b> <b>(27/538)</b>

SSRIs = selective serotonin reuptake inhibitors; OCD = obsessive-compulsive disorder.

<sup>a</sup>The midpoint of 2% was arbitrarily selected for purposes of comparison.

TABLE 2B. RATE OF SOMNOLENCE ADVERSE EVENTS FROM SSRIs: EXCLUSIVELY ADOLESCENTS

Investigators and diagnoses	SSRI and duration	Rate of SSRI activation ADE	
		SSRI	Placebo
Keller et al. 2001 Depression	Paroxetine 8 weeks	17% (10/93)	3% (3/87)
TADS 2004 Depression	Fluoxetine 12 weeks	4% (8/216)	1% (1/112)
	<b>Totals</b>	<b>5.8% (18/309)</b>	<b>2.0% (4/199)</b>

SSRIs = selective serotonin reuptake inhibitors.

grouped rates of suicidality that were located in the literature.

#### *Discontinuation from treatment owing to AEs*

Discontinuations owing to AEs from short-term clinical trials of SSRIs are fairly common. In the placebo-controlled trials of SSRIs that separated the findings of children from adolescents, the average SSRI discontinuation rates owing to AEs were as follows: Children 12.1% (36 of 298) for the SSRI versus 1.4% (4 of 294) for placebo; adolescents 7.6% (43 of 567) for SSRI versus 3.3% (18 of 538) for placebo. Activation was the major AE associated with withdrawal from the trial for children in two of the four studies that listed age-grouped findings separately (Geller et al. 2004; Wagner et al. 2002). It is also the major cause of discontinuation in a number of other SSRI clinical reports of youths (Martin et al. 2003; Raches et al. 2002; Birmaher et al. 2003; Dummit et al. 1996).

Discontinuation rates for adults owing to SSRI AEs were variable across trials and ranged from 8% to 19% for SSRIs and 2%–6% for placebo. In the 10 adult SSRI studies that listed causes of the AE discontinuation, the major reasons were somnolence, nausea, and insomnia. Lower administered SSRI doses led to fewer AE discontinuations—which were most clearly apparent in adult fixed-dose studies (Beasley et al. 2000; Burke et al. 2002; Feighner and Overo 1999; Liebowitz et al. 2002b).

#### *Pharmacokinetic SSRI considerations in relation to age*

Children typically metabolize drugs more rapidly than adults (Soldin and Steele 2000).

Consistent with this general finding, a shorter half-life has been reported in children given paroxetine (Findling et al. 1999) or given sertraline (Alderman et al. 1998). This fact could justify more frequent drug administration for children, but it might also result in more problems with withdrawal and thus to more discontinuations owing to AEs. However, when doses of sertraline, paroxetine, and fluoxetine are adjusted for body weight, the resultant plasma concentration in children is similar to that in adolescents (Alderman et al. 1998; Findling et al. 2005; Wilens et al. 2002).

In the four placebo-controlled, clinical trials when SSRI daily doses were compared (Table 1A), adolescents received 17%–35% higher average doses than children. In two of the four trials with available data to assess mg/kg dosing, dosage in mg/kg was 27% higher in children than adolescents (Table 1A). Available data on SSRI pharmacokinetic and dosing parameters from clinical trial data, at this point, are insufficient to reveal a clear *age-group* relationship between these drug-dose measurement differences and AEs.

#### *Limitations*

The major studies on which this review is based were in the published literature, and there are numerous unpublished studies that bear on the findings that have not been presented (Whittington 2004). Safety issues in the clinical trial literature are strikingly under-reported (Ioannidis and Lau 2001; Papanikolaou et al. 2004). Furthermore, clinical trial studies of SSRIs tend to report lower AE rates than case series and community reports because of case selection and selective reporting differences. For ex-

ample, the frequency of withdrawal from SSRI treatment is consistently higher in case series studies and reports based on follow-up telephone interviews than in reports based on drug trials (e.g., Bull et al. 2002; Tierney et al. 1995).

## CONCLUSIONS

Age vulnerabilities to medication AEs are well known (Brent et al. 2004). It may be that since activation is more common during childhood, this age group would be more vulnerable than older youths and adults to activation AEs. Likewise, vomiting—which is more common in childhood than in adulthood (Lee 2002)—may also represent a developmental vulnerability to SSRIs.

The reporting of AEs in clinical trials is unfortunately not standardized, although efforts are underway to rectify this—at least in government-sponsored trials of psychotropic drugs involving youths (Greenhill et al. 2004). Using cut-offs above 5% and 10% in the reporting of AE rates makes for shorter “side effect” tables, but it limits the reporting of less frequent, but possibly more serious, AEs, such as suicidal behavior.

## DISCLOSURES

Drs. Daniel J. Safer and Julie Magno Zito have no conflicts of interest.

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