

FLUVOXAMINE FOR THE TREATMENT OF ANXIETY DISORDERS IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Background Drugs that selectively inhibit serotonin reuptake are effective treatments for adults with mood and anxiety disorders, but limited data are available on the safety and efficacy of serotonin-reuptake inhibitors in children with anxiety disorders.

Methods We studied 128 children who were 6 to 17 years of age; who met the criteria for social phobia, separation anxiety disorder, or generalized anxiety disorder; and who had received psychological treatment for three weeks without improvement. The children were randomly assigned to receive fluvoxamine (at a maximum of 300 mg per day) or placebo for eight weeks and were evaluated with rating scales designed to assess the degree of anxiety and impairment.

Results Children in the fluvoxamine group had a mean (\pm SD) decrease of 9.7 ± 6.9 points in symptoms of anxiety on the Pediatric Anxiety Rating Scale (range of possible scores, 0 to 25, with higher scores indicating greater anxiety), as compared with a decrease of 3.1 ± 4.8 points among children in the placebo group ($P < 0.001$). On the Clinical Global Impressions-Improvement scale, 48 of 63 children in the fluvoxamine group (76 percent) had a response to the treatment, as indicated by a score of less than 4, as compared with 19 of 65 children in the placebo group (29 percent, $P < 0.001$). Five children in the fluvoxamine group (8 percent) discontinued treatment because of adverse events, as compared with one child in the placebo group (2 percent).

Conclusions Fluvoxamine is an effective treatment for children and adolescents with social phobia, separation anxiety disorder, or generalized anxiety disorder. (N Engl J Med 2001;344:1279-85.)

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ANXIETY disorders are the most common psychiatric illnesses in children,¹⁻³ but most children with anxiety disorders do not receive treatment.^{4,5} Several studies have documented the safety and efficacy of drug therapy for children with obsessive-compulsive disorder, but there have been few studies of drug therapy for children with more prevalent anxiety disorders.^{6,7}

Social phobia, separation anxiety disorder, and generalized anxiety disorder in children cause substantial distress and interfere with academic as well as social functioning.^{1,2,8,9} Childhood anxiety disorders also foreshadow psychiatric illness later in life. Specifically, these disorders predict an increase by a factor of two to five in the risk of later anxiety disorders, major depression, suicide attempts, and hospitalization for psychiatric illness.^{1,2,10,11}

Selective serotonin-reuptake inhibitors are well-established treatments for virtually all anxiety disorders in adults.¹²⁻¹⁵ These drugs also appear to be effective in children with obsessive-compulsive disorder and major depression.^{6,7,16,17} Open trials suggest that selective serotonin-reuptake inhibitors may be effective in children with various anxiety disorders.^{18,19} On the basis of these reports, we carried out a randomized, double-blind trial of fluvoxamine and a placebo in children with social phobia, separation anxiety disorder, or generalized anxiety disorder. We recruited children with any of these disorders rather than one specific anxiety disorder because these conditions typically occur together.^{1-3,10,11} Therefore, a trial focusing on only one of these anxiety disorders would inevitably include children with the other two disorders. Fluvoxamine was selected since it was the only selective serotonin-reuptake inhibitor approved by the Food and Drug Administration for use in children at the time the study was designed in 1996.

METHODS**Patients**

This study was conducted between July 1997 and September 1999 at five medical centers — Johns Hopkins University, New York State Psychiatric Institute-Columbia University, New York University, Duke University, and the University of California at Los Angeles — under the auspices of the Research Unit on Pediatric Psychopharmacology (RUPP) network. The protocol was approved by the institutional review board at each center and by the data and safety monitoring board of the National Institute of Mental Health. Written informed consent was obtained from all parents, and assent was obtained from all children.

We studied 128 children 6 to 17 years of age who met the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition)²⁰ for social phobia, separation anxiety disorder, or generalized anxiety disorder on the basis of comprehensive, semistructured psychiatric interviews. There were three other criteria for inclusion. First, the child had to have clinically important symptoms of anxiety according to the Pediatric Anxiety Rating Scale.^{21,22} With this scale, the clinician assesses the child's degree of suffering and limitation in functioning associated with

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anxiety during the previous week. Second, the child had to have clinically important impairment according to the Children's Global Assessment Scale (a score of less than 60).²³ This scale assesses the degree to which psychiatric symptoms impede functioning. Third, both the child and a parent had to agree to attend the clinic weekly. Criteria for exclusion included current therapy with any psychoactive substance; a current diagnosis of major depression, Tourette's syndrome, obsessive-compulsive disorder, post-traumatic stress disorder, conduct disorder, or panic disorder; a history of or a current diagnosis of mania, psychosis, or pervasive developmental disorder; current suicidal ideation; mental retardation (an IQ of less than 70) as assessed with the Kaufman Brief Intelligence Test²⁴; previous treatment with a selective serotonin-reuptake inhibitor; or a current diagnosis of attention-deficit-hyperactivity disorder of sufficient severity to require drug therapy.

We initially evaluated 153 children who presented, with their families, for treatment of anxiety at a participating center (Fig. 1). The children and their families underwent three weeks of open treatment with supportive, psychoeducational therapy. As described previously,^{25,26} psychoeducational therapy is designed to teach families about the origins and typical course of mental illness while emphasizing the good outcome in many cases. During this three-week phase, we identified five children whose conditions improved with brief psychotherapeutic interventions and who therefore did not require drug therapy. Another 20 children were excluded because they could not attend weekly sessions. The remaining 128 children were randomly assigned to receive fluvoxamine or placebo for eight weeks, during which time supportive psychotherapy

continued. The dose of fluvoxamine was increased by approximately 50 mg per week to a maximum of 300 mg per day in adolescents and 250 mg per day in children less than 12 years of age. The capsules of placebo and fluvoxamine were identical in appearance, so that the clinicians who were treating the children and who adjusted the doses of the study drug were unaware of the treatment-group assignments. Dose escalation was delayed in children who had adverse effects or a remission of their anxiety disorder.

The treating clinicians saw the children and parents weekly during weeks 1 through 6 and at the end of week 8. During each visit, the clinician administered supportive psychotherapy, assessed the severity of symptoms using the Pediatric Anxiety Rating Scale, and monitored the patient for adverse effects. Clinical indications for removal from the trial were determined before the study began; decisions to remove children were based on the consensus of a group of expert clinicians, including both clinicians who treated the children and clinicians who did not, all of whom remained unaware of the treatment-group assignments.

Diagnosis and Outcome Measures

The criteria for inclusion and exclusion according to diagnosis were assessed by experienced clinicians in semistructured interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children.²⁷

The two primary outcome measures were the change in the score on the Pediatric Anxiety Rating Scale, which was assessed each week, and the score on the Clinical Global Impressions-Improvement scale at the end of the study.

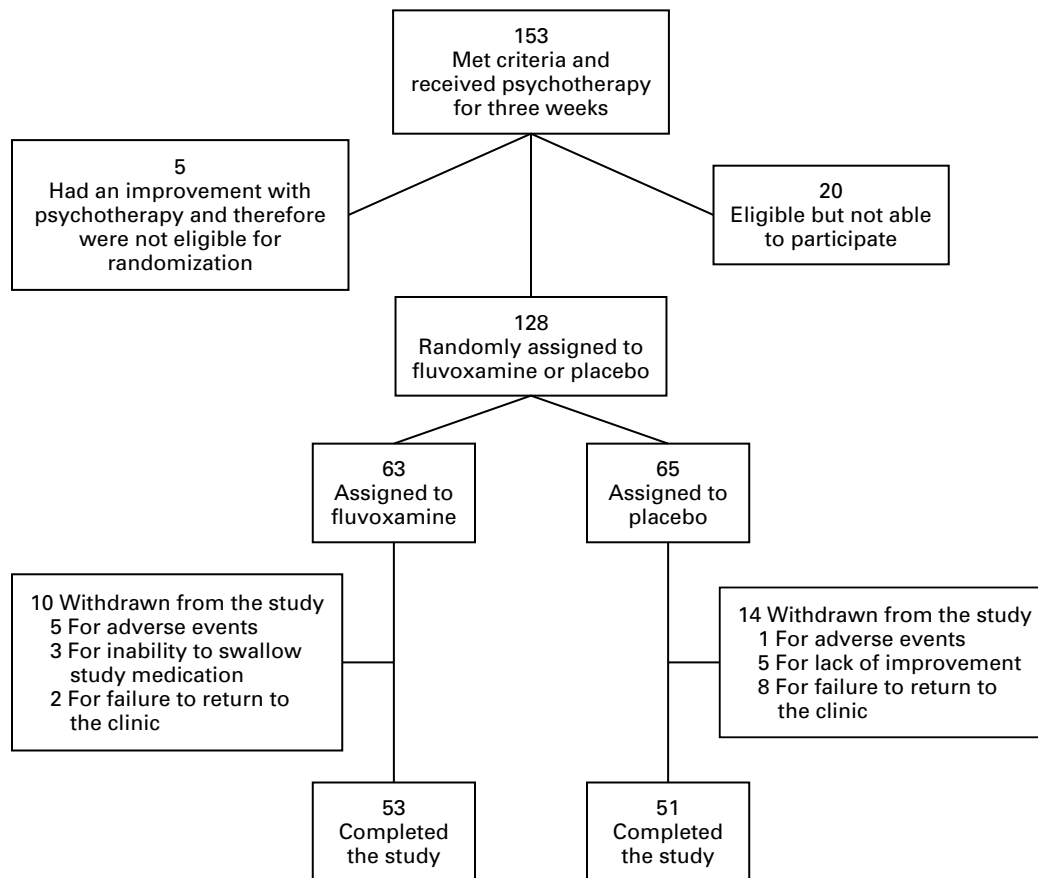


Figure 1. Numbers of Children with Anxiety Disorders during Each Phase of the Study.

Symptoms of Anxiety

Before the trial, a clinician-rated scale was not available for assessing the symptoms of the targeted disorders.²¹ To meet this need, the Pediatric Anxiety Rating Scale was developed and validated in children with clinically significant anxiety disorders, who were identified through standardized interviews with clinicians.²² With this scale, the clinician uses a checklist of questions regarding the symptoms of anxiety during the past week to elicit responses from parents and children. After completing this checklist, the clinician rates five general items: the severity of the child's distress due to anxiety, the frequency of anxiety, the degree to which the child avoided anxiety-provoking situations, and the degree to which the anxiety limited the child's participation in typical daily activities both at home and in other environments, such as school. The sum of the scores on these five items, which can range from 0 to 25, served as the primary continuous outcome measure. A rating of 10 indicates mild but clinically meaningful levels of anxiety, whereas a rating of 20 indicates extremely high levels of anxiety.

Global Improvement

During each visit, global improvement was rated by the treating clinician on the Clinical Global Impressions-Improvement scale with the use of data from all other measures in the study. An eight-point scale was used, as in prior studies of children.^{28,29} Children who received scores of 3 (improved), 2 (much improved), or 1 (free of symptoms) were defined as having had a clinically meaningful response to the treatment. This meant that the clinician would recommend continuing the medication rather than changing to an alternative treatment.

Other Measures

At base line and at weeks 4 and 8, each child completed the Multidimensional Anxiety Scale for Children,³⁰ and both the child and a parent rated the condition of the child with the Screen for Child Anxiety Related Emotional Disorders.³¹ These scales record the answers of the child and parent to written questions concerning the child's level of anxiety; the reliability of these scales has been established.^{30,31} At the same times, clinicians also assigned a score for global functional impairment²³ and physiologic symptoms of anxiety.³² To assess the interrater reliability of the ratings made by the clinicians participating in the trial, each clinician rated 16 children using all scales. Acceptable interrater reliability (an intraclass correlation of more than 0.80) was obtained for all scales.

At each visit, the frequency, severity, and effect on treatment of adverse events were rated, in order to screen for possible adverse effects of the drug.

Statistical Analysis

The total score on the Pediatric Anxiety Rating Scale was the primary continuous outcome measure, and the proportion with a score of less than 4 on the Clinical Global Impressions-Improvement scale was the primary categorical outcome measure. For the Pediatric Anxiety Rating Scale, the effect of treatment was analyzed with the use of a mixed model, with treatment group and center as fixed effects and the time of treatment as a random effect.³³ Efficacy was evaluated by tests of the interaction of treatment with time; all interactions were included (treatment with center, time with center, and treatment with time with center). Estimates of regression slopes and intercepts for individual subjects were generated in the mixed model with the use of all available data. Although the results for children with missing data were weighted less heavily than the results for those with complete data, having missing data did not exclude a child from the analysis.³³ However, the results from four children were excluded from this analysis because of scoring errors. For the Clinical Global Impressions-Improvement scale, we used logistic-regression analysis for all 128 children to assess the effect of treatment on the ratings at week 8, carrying forward the last available rating and including the center as an independent variable. Analyses were performed accord-

ing to the intention-to-treat principle and included all children, with the exception of the four children who were excluded from the Pediatric Anxiety Rating Scale analysis. All statistical tests were two-tailed.

RESULTS

The base-line characteristics of children in the fluvoxamine and placebo groups were similar (Table 1). The scores on the Pediatric Anxiety Rating Scale indicated that the children in both groups had high levels of anxiety. The children in the fluvoxamine group

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 128 CHILDREN IN THE FLUVOXAMINE AND PLACEBO GROUPS.*

CHARACTERISTIC	FLUVOXAMINE (N=63)	PLACEBO (N=65)
Demographic characteristics		
Age of 6-12 yr — no. (%)	48 (76)	47 (72)
Male sex — no. (%)	32 (51)	33 (51)
Race or ethnic group — no. (%)		
White	41 (65)	40 (62)
Black	6 (10)	3 (5)
Hispanic	12 (19)	12 (18)
Other	4 (6)	10 (15)
Total annual family income — no. (%)		
<\$25,000	9 (14)	10 (15)
\$25,000-\$39,999	10 (16)	10 (15)
\$40,000-\$59,999	9 (14)	9 (14)
≥\$60,000	28 (44)	27 (42)
Unknown	7 (11)	9 (14)
Two parents in home — no. (%)	47 (75)	45 (69)
Mean age — yr	10.4±2.8	10.3±3.1
Psychiatric profile		
Current separation anxiety disorder — no. (%)	40 (63)	36 (55)
Current generalized anxiety disorder — no. (%)	32 (51)	41 (63)
Current social phobia — no. (%)	39 (62)	45 (69)
Past or current attention-deficit-hyperactivity disorder — no. (%)	11 (17)	9 (14)
Past or current oppositional defiant disorder — no. (%)	4 (6)	3 (5)
Past conduct disorder — no. (%)	0	2 (3)
Past obsessive-compulsive disorder — no. (%)	3 (5)	3 (5)
Past major depressive disorder — no. (%)	3 (5)	3 (5)
Past enuresis — no. (%)	3 (5)	5 (8)
Past encopresis — no. (%)	3 (5)	0
Past tics — no. (%)	1 (2)	0
Past post-traumatic stress disorder — no. (%)	1 (2)	2 (3)
MASC total score	54.8±18.5	53.6±19.0
SCARED-P total score	35.9±14.4	37.3±12.4
SCARED-Y total score	31.0±12.9	32.1±14.8
Dose of medication or placebo and participation in study		
Average dose — mg/kg of body weight†	2.9±1.3	3.8±1.7
Last dose — mg/kg‡	4.0±2.2	5.9±2.8
No. of visits during trial	7.7±2.0	7.8±1.7

*Plus-minus values are means ±SD. MASC denotes the Multidimensional Anxiety Scale for Children (range of scores, 0 to 117), and SCARED the Screen for Child Anxiety Related Emotional Disorders, parent rated (P) or child rated (Y) (range of scores, 0 to 82). Higher scores indicate more anxiety. Except as noted, P>0.05.

†P=0.001.

‡P<0.001.

were prescribed lower doses of drug than the children in the placebo group. Given that dose escalation continued only in children with symptoms of anxiety, this difference in doses is consistent with the superior efficacy of fluvoxamine as compared with placebo.

Efficacy

The children in the fluvoxamine group had greater reductions in symptoms of anxiety and higher rates of clinical response than the children in the placebo group (Table 2 and Fig. 2 and 3). On the Pediatric Anxiety Rating Scale, significant differences between the treatment groups were detectable by week 3 and increased through week 6, with little change during the final two weeks of the trial. At the end of the trial, the average rating on the Pediatric Anxiety Rating Scale in the fluvoxamine group was below 10 — a score that indicates no more than mild anxiety — whereas the rating in the placebo group remained high (above 14). On the Clinical Global Impressions–Improvement scale, 48 of 63 children in the fluvoxamine group (76 percent) had scores of less than 4, as compared with 19 of 65 children in the placebo group (29 percent). For both measures, these effects of treatment with fluvoxamine are considered large, given the results of other treatment studies of mood and anxiety disorders in children.^{6,7,16,17,34} Neither analysis revealed interactions of the center with treatment.

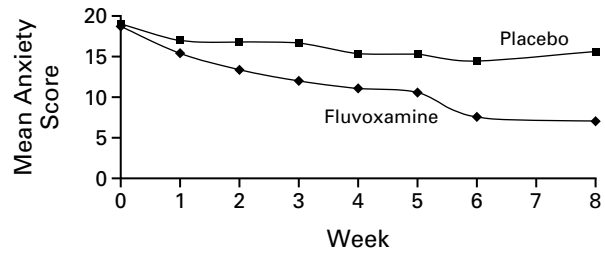


Figure 2. Mean Total Score on the Pediatric Anxiety Rating Scale in the Fluvoxamine and Placebo Groups during the Eight-Week Trial.

Curves were estimated with the use of random regression for 61 children in the fluvoxamine group and 63 children in the placebo group (P<0.001 for the interaction of treatment with time). The score on the Pediatric Anxiety Rating Scale can range from 0 to 25, with a score of 10 indicating mild but clinically meaningful levels of anxiety and a score of 20 indicating severe anxiety.

Adverse Events

Adverse events that were recorded at any time during the trial are listed in descending order of prevalence in Table 3. Abdominal discomfort was significantly more prevalent in the fluvoxamine group than in the placebo group (P=0.02); there was also a trend toward a greater frequency of increased motor activity in the fluvoxamine group (P=0.06).

TABLE 2. CHANGE IN SCORES ON THE PEDIATRIC ANXIETY RATING SCALE AND CLINICAL GLOBAL IMPRESSIONS–IMPROVEMENT SCALE IN THE FLUVOXAMINE AND PLACEBO GROUPS.*

VARIABLE	WEEK OF STUDY										P VALUE FOR INTERACTION OF TREATMENT WITH TIME
	0	1	2	3	4	5	6	8	END OF STUDY†		
Weeks from base line	0.0±0.0	1.1±0.3	2.1±0.3	3.1±0.4	4.2±0.4	5.2±0.5	6.2±0.5	8.3±0.7	7.5±2.0		
Fluvoxamine											
No. tested	61	55	53	56	52	49	47	50	61		
Pediatric Anxiety Rating Scale score	18.7±2.9	15.4±5.4	13.4±5.7	12.0±5.4	11.1±6.0	10.6±6.1	7.6±5.6	7.1±6.1	9.0±7.0	<0.001	
Placebo											
No. tested	63	60	55	54	56	55	54	49	63		
Pediatric Anxiety Rating Scale score	19.0±3.0	17.0±3.6	16.8±4.3	16.7±4.0	15.4±4.6	15.3±4.4	14.5±5.0	15.7±5.4	15.9±5.3		
Fluvoxamine											
No. tested		58	56	58	54	51	49	52	63		
Clinical Global Impressions–Improvement scores <4 (% of patients)		19	38	59	59	69	84	86	76	<0.001	
Placebo											
No. tested		64	58	56	59	57	54	50	65		
Clinical Global Impressions–Improvement scores <4 (% of patients)		5	17	12	29	25	30	32	29		

*Plus–minus values are means ±SD. The possible range of Pediatric Anxiety Rating Scale scores was 0 to 25, with higher scores indicating greater anxiety. The possible range of Clinical Global Impressions–Improvement scores was 1 to 8, with a score less than 4 indicating a response to treatment.

†These are the last values obtained for each subject.

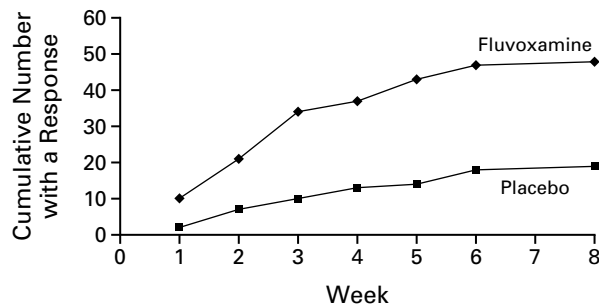


Figure 3. Cumulative Response Rates on the Clinical Global Impressions–Improvement Scale during the Eight-Week Trial in the Fluvoxamine and Placebo Groups.

Data are from 63 patients in the fluvoxamine group, 48 of whom had a response (76 percent), and 65 patients in the placebo group, 19 of whom had a response (29 percent, $P < 0.001$ for the difference in response rates between the two treatments). On the eight-point Clinical Global Impressions–Improvement scale, a score of less than 4 was defined as a response to treatment (symptoms of anxiety had improved or ceased).

Premature Discontinuation of Treatment and Worsening of Anxiety

A total of 10 of the 63 children in the fluvoxamine group (16 percent) withdrew from the trial, as compared with 14 of the 65 children in the placebo group (22 percent). The reasons for withdrawal from the fluvoxamine group were failure to return to the clinic (two children), inability to swallow medication (three children), and adverse events (sedation, somatic discomfort, or hyperactivity; five children). The reasons for withdrawal from the placebo group were irritability and insomnia (one child), failure to return (eight children), and lack of efficacy (five children). The Clinical Global Impressions–Improvement ratings indicated that anxiety did not increase after the initiation of treatment with fluvoxamine, as has been reported in some trials of selective serotonin-reuptake inhibitors in adults.¹²⁻¹⁵ Specifically, in the first three weeks of the trial, the condition of 3 of 63 children in the fluvoxamine group (5 percent) was rated worse than at base line on the Clinical Global Impressions–Improvement scale, as compared with 6 of 65 children in the placebo group (9 percent).

DISCUSSION

Our report demonstrates the efficacy of fluvoxamine in the treatment of children with social phobia, separation anxiety disorder, or generalized anxiety disorder. Fluvoxamine treatment was generally well tolerated but was associated with significantly more gastrointestinal symptoms, as found in other trials,^{6,7,13-17} and with greater increases in children’s levels of activity than was placebo. Effects on activity have been found in previous trials of selective serotonin-reuptake inhibitors in children, particularly in children younger

TABLE 3. ADVERSE EVENTS THAT OCCURRED AT ANY TIME DURING THE TRIAL IN THE FLUVOXAMINE AND PLACEBO GROUPS.

ADVERSE EVENT	FLUVOXAMINE (N=63)	PLACEBO (N=65)	TOTAL	P VALUE*
	no. (%)	no. (%)		
Headache	27 (43)	24 (37)	40	NS
Abdominal discomfort	31 (49)	18 (28)	38	0.02
Increased motor activity	17 (27)	8 (12)	20	0.06
Difficulty falling asleep	12 (19)	13 (20)	20	NS
Nasal congestion	11 (17)	12 (18)	18	NS
Drowsiness or sedation	13 (21)	10 (15)	18	NS
Nausea	12 (19)	9 (14)	16	NS
Diarrhea	9 (14)	10 (15)	15	NS
Influenza or upper respiratory symptoms	12 (19)	7 (11)	15	NS
Vomiting	12 (19)	6 (9)	14	NS
Sore throat	10 (16)	6 (9)	12	NS
Tiredness or fatigue	11 (17)	5 (8)	12	NS
Muscle or joint pain	11 (17)	5 (8)	12	NS
Coughing	6 (10)	9 (14)	12	NS
Skin irritation	6 (10)	9 (14)	12	NS
Decreased appetite	10 (16)	4 (6)	11	NS

*Values were determined by means of a chi-square statistic with Yates’ correction. NS denotes not significant.

than 13 years of age,⁷ but such effects typically have not been found in adults.¹²⁻¹⁴ This increase in activity in children may relate to subjective effects in adults taking these drugs, who sometimes report increases in energy. Regardless of the mechanism, the side effects in the fluvoxamine group were usually mild. Only 5 of the 63 children in the fluvoxamine group discontinued treatment as a result of adverse events, as compared with 1 of the 65 children in the placebo group.

The efficacy of treatment with selective serotonin-reuptake inhibitors for anxiety in children in our trial is consistent with data obtained in studies of adults. Panic disorder, social phobia, and obsessive–compulsive disorder are the three specific anxiety disorders in adults whose treatment with these drugs has been studied most intensively.¹²⁻¹⁵ In general, approximately 50 to 70 percent of patients with these disorders respond to therapy with selective serotonin-reuptake inhibitors; response rates in patients with panic disorder are usually higher than in patients with the other disorders. The results of our trial in children with social phobia, separation anxiety disorder, and generalized anxiety disorder are also consistent with the results of trials of these drugs in children with obsessive–compulsive disorder and major depression.^{6,7,16,17,26}

Trials of cognitive–behavioral psychotherapy for children with anxiety disorders have found response rates in the range of 70 to 80 percent.^{35,36} The response rates in trials of supportive therapies that pro-

vide encouragement and education to patients and their families about symptoms are similar to those for cognitive-behavioral therapy, although supportive therapies may include techniques of cognitive-behavioral therapy.³⁶ Without direct systematic comparisons between selective serotonin-reuptake inhibitors and psychotherapy, the relative merits of each treatment remain unknown. There is a particular need for studies of the comparative efficacy of treatment methods in children with anxiety, since such children have a more robust response to psychotherapy than children with other psychiatric disorders, such as attention-deficit-hyperactivity disorder.³⁷

Treatment recommendations might follow from the current finding of a clinically meaningful effect of fluvoxamine on the symptoms of anxiety in children, for three main reasons. The study design satisfies standard criteria of evidence-based medicine for the generalizability of results.³⁸ The treatment had a large effect on symptoms.³⁹ Finally, fluvoxamine was generally well tolerated. Given these results, treatment with a selective serotonin-reuptake inhibitor becomes an important option for the treatment of children with anxiety disorders.

Our study had at least three limitations. First, the children were recruited if they met the criteria for any one of three anxiety disorders but not if they had several other disorders that often coexist with anxiety disorders. Second, the study lasted only eight weeks. Long-term trials and follow-up studies are needed, given the evidence from studies in animals of developmental plasticity in serotonergic neurons.⁴⁰ For example, treatment with selective serotonin-reuptake inhibitors in immature rodents may alter cortical and hippocampal synapses.^{41,42} It is important to note that basic-science research has also established the long-term effects of stress, which is an integral aspect of anxiety in children, on the developing nervous system.⁴³ Stress has been shown to have long-term effects on behavior, neurochemistry, autonomic control, and hormonal regulation in developing rodents and primates.⁴³⁻⁴⁵ Therefore, untreated anxiety in children may also have neurodevelopmental effects. Since there is a range of outcomes in children with anxiety disorders, from remission to chronic illness,^{1,2,10,11} a study of maintenance treatment with selective serotonin-reuptake inhibitors is needed to assess the benefits and risks of long-term use. Moreover, given the evidence of neurodevelopmental effects of these drugs in animals, it will be important to study the effects of anxiety, stress, and selective serotonin-reuptake inhibitors on brain structure and function in children. Finally, despite a large therapeutic effect, the results of this trial must be interpreted cautiously, since the treating clinicians — rather than independent evaluators — rated both clinical outcome and adverse events, a design that may have created opportunities for bias in favor of active treatments.⁴⁶

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