Fluoxetine for the Treatment of Childhood Anxiety Disorders: Open-Label, Long-Term Extension to a Controlled Trial

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ABSTRACT

Objective: To assess the efficacy of fluoxetine for the long-term treatment of children and adolescents with anxiety disorders, including generalized anxiety disorder, separation anxiety disorder, and/or social phobia. **Method:** Children and adolescents (7–17 years old) with anxiety disorders were studied in open treatment for 1 year after they completed a randomized, controlled trial (RCT) comparing fluoxetine and placebo. The follow-up phase assessments included clinician, parent, and child ratings with measures of global severity, global improvement, and anxiety symptoms. **Results:** Subjects taking fluoxetine ($n = 42$) were compared with those taking no medication ($n = 10$) during follow-up on anxiety changes from the end of the RCT through the follow-up period. Statistical models included RCT assignment and follow-up psychological treatment. Excluded subjects took other medications ($n = 4$) or did not complete follow-up ($n = 18$). Compared with subjects taking no medication, subjects taking fluoxetine showed significantly superior follow-up outcomes on most measures, including clinician, parent, and child ratings. **Conclusions:** The results suggest that fluoxetine is clinically effective for the maintenance treatment of anxiety disorders in children and adolescents. A major limitation, however, was the lack of RCT methodology in the follow-up phase. RCTs are needed to determine the long-term risks and benefits of fluoxetine for this group. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(12):1263–1270. **Key Words:** anxiety disorders, fluoxetine, selective serotonin reuptake inhibitors.

Anxiety disorders are common in children and adolescents, are often accompanied by significant psychosocial impairment, and may persist into adulthood if not successfully treated (Clark et al., 1994; Kendall et al., 2001, 2004; Pine et al., 1998). Anxiety disorders frequently co-occur, with at least 60% of children with anxiety disorders having two and 30% having three of these conditions (Clark et al., 1994; Last et al., 1992; RUPP Anxiety Study Group, 2001). Cognitive-behavioral therapy (CBT) has been shown to be effective for these conditions (Compton et al., 2004), and outcome studies indicate that CBT confers long-term benefit (Kendall et al., 2004). Compared with CBT, pharmacotherapy has not been as thoroughly studied for these conditions (Williams and Miller, 2004). Particularly lacking are long-term outcome studies on pharmacological treatments for anxiety disorders in children and adolescents.

Several recent studies suggest that selective serotonin reuptake inhibitors (SSRIs) have therapeutic effects for anxiety disorders in children and adolescents. Small, randomized, placebo-controlled trials (RCTs) have

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demonstrated efficacy and tolerability of SSRIs for social phobia (SP) (n = 15) (Black and Uhde, 1994) and generalized anxiety disorder (GAD) (n = 22) (Rynn et al., 2001). A large-scale RCT (n = 319) has found paroxetine to be effective for social phobia in children and adolescents (Wagner et al., 2004). Because separation anxiety disorder (SAD), GAD, and SP often present in combinations, data on treatment of children and adolescents with SAD, GAD, and/or SP provide relevant guidance on the utility of SSRIs for these typical clinical presentations. Two RCTs have confirmed that SSRIs have benefit for children and adolescents with SAD, GAD, and/or SP. An 8-week RCT (RUPP Anxiety Study Group, 2001) showed that fluvoxamine was significantly more efficacious than placebo for the treatment of children and adolescents with SAD, GAD, and/or SP. In a 12-week RCT, Birmaher et al. (2003) showed that fluoxetine (n = 37) was significantly more efficacious than placebo (n = 37) for the treatment of children and adolescents with SAD, GAD, and/or SP. Birmaher et al. (2003) noted that despite improvement, many participating patients remained symptomatic. The present study reports the results of further fluoxetine treatment for these children and adolescents during a 1-year follow-up period.

One study to date has examined the effects of SSRIs on childhood anxiety disorders during an extended period. In a 6-month open treatment follow-up study (RUPP Anxiety Study Group, 2002a), patients treated with fluvoxamine or fluoxetine showed additional improvement. Among children and adolescents responding to fluvoxamine in the acute phase and continuing this medication in the follow-up period, 94% either retained their therapeutic response or showed additional improvement. Of placebo nonresponders, 56% improved with fluvoxamine. Although it included a sizable sample (n = 97) with systematic evaluations, the RUPP open treatment study did not include follow-up assessments for patients not receiving medication.

The goal of this study was to assess the long-term efficacy of fluoxetine for the treatment of anxiety symptoms among children and adolescents with GAD, SP, and/or SAD. We hypothesized that subjects receiving fluoxetine would show significantly greater improvement than subjects receiving no medication during a 1-year follow-up period.

METHOD

Sample and Recruitment

The sample for the RCT has been described in detail by Birmaher et al. (2003). In summary, children 7 to 17 years old with *DSM-IV* (American Psychiatric Association, 1994) GAD, SAD, and/or SP by Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) with significant functional impairment were recruited through advertisements and an outpatient clinic. Subjects with current major depressive, dysthymic, or disruptive behavior disorders; a history of other major mental disorders; significant developmental, medical, or neurological illness; prior use of fluoxetine; adequate trials of other SSRIs; or use of other psychotropic medications were excluded, as were pregnant girls. The University of Pittsburgh Institutional Review Board approved the protocol, and written informed consents were obtained from all parents and adolescents and assents were obtained from children.

To enter the study, all subjects needed to fulfill criteria for an anxiety disorder with functional impairment. Among the subjects examined in detail here (n = 52), most subjects had baseline CGI-S ratings of moderately ill (CGI-S = 4, n = 29, 56%) or markedly ill (CGI-S score of 5, n = 19, 36%), two subjects were rated mildly ill (CGI-S score of 3, 4%), one subject was rated severely ill (CGI-S score of 6, 2%), and one subject was rated among the most extremely ill patients (CGI-S score of 7, 2%).

RCT Procedures

The baseline evaluation included review of demographic characteristics, including age, ethnic group, sex, religion, school placement, and socioeconomic status, as derived from the Four-Factor Hollingshead Scale (Hollingshead, 1975). A screening physical examination and laboratory tests were conducted. At intake, the nurses, under the supervision of a child and adolescent psychiatrist, interviewed children and parents about their children using the K-SADS-PL (Kaufman et al., 1997). κ values for all psychiatric diagnoses were >0.80. Following the baseline evaluation, 74 children and adolescents (mean age 11.8 ± 2.8 years) were randomized to either fluoxetine (n = 37) or placebo (n = 37). Demographic characteristics for the complete sample have been presented (Birmaher et al., 2003). During the acute treatment trial, fluoxetine was administered at 10 mg/day for the first week, and, if tolerated, the dose was increased to 20 mg/day for the rest of the 12-week trial. Subjects were withdrawn from the study if they were taking <70% of study drug at each of two consecutive visits, missed two consecutive visits, had significant adverse reactions (e.g., severe headaches, agitation), had significant deterioration on their clinical symptomatology (e.g., suicidality, self-injury behaviors, persistent agitation), or had impairment in their functioning (e.g., ≥2 weeks absence from school). To ensure that fluoxetine and placebo groups received equivalent care, an adaptation of a standardized clinical management guide for adolescents with depression (Keller et al., 2001) was followed. During the RCT protocol, patients were not allowed concomitant medications or psychosocial interventions.

Follow-up Procedures

At the end of the RCT, after all of the measures were completed, subjects and their parents met with one of the child and adolescent psychiatrists (B.B. and D.A.) to open the blind. All subjects,

including those not completing the RCT, were offered free follow-up sessions every 4 months for 1 year. Subjects and their parents were informed that both medication and CBT have been shown to be useful for the treatment of anxiety disorders. The benefits and risks of the available treatment modalities were described. As depicted in Figure 1, 56 of 74 subjects completed the 1-year follow-up assessment. Of these 56, 42 received fluoxetine, 10 received no medication, and 4 received other medications. The subjects who received fluoxetine and those who received no medication were the focus of the analyses presented here.

The research nurses, under the supervision of a child psychiatrist (B.B. and D.A.), observed all of the patients for psychiatric symptomatology and functioning using the instruments described below. At each appointment, the nurse recorded the amount of drug dispensed, taken, and returned to monitor medication compliance. Side effects were clinically monitored and clinically significant problems were noted. During the follow-up period, the psychiatrists and nurses were also available for emergencies. Although treatment visits were provided without cost, fluoxetine and other medications were obtained through insurance or were purchased by these families. During follow-up, nurses remained blind to acute treatment assignment.

At the termination of the acute phase of the RCT, all of the subjects were offered referrals for psychosocial interventions. Patients and their families were particularly encouraged to pursue this referral when additional treatment was judged to be needed. Because the follow-up phase was open clinical treatment, the extent to which families elected to pursue these referrals and the psychosocial interventions provided by referral sources varied considerably. Of the 52 subjects considered here, 12 received psychosocial interventions during the follow-up period. Among these 12 subjects, the types of treatment provided included CBT ($n = 7$), family therapy ($n = 1$), or general individual psychotherapy ($n = 4$). These interventions were not standardized, and sufficient information to quantify treatment provided was not available. For the purpose of including psychosocial interventions as a covariate in the analyses, a psychosocial intervention variable was constructed based on a classification as to whether subjects had received psychosocial interventions during follow-up.

At each follow-up visit, the nurses administered the Pediatric Anxiety Rating Scale (PARS), and children and parents completed the Self-Report for Childhood Anxiety Related Disorders (SCARED). At the final RCT visit and at the final follow-up visit, the nurses administered Clinical Global Impressions (CGI) scales. The same raters participated through the acute phase and follow-up phase procedures.

Measures

Clinician-Rated Anxiety Instruments. The CGI scales (Guy et al., 1976) were used to measure global improvement and severity. CGI-Improvement (CGI-I) provides a rating of clinical improvement ranging from 1 (very much improved) to 7 (very much worse). CGI-Severity (CGI-S) provides a rating of baseline severity ranging from 1 (not at all ill) to 7 (extremely ill). The PARS includes a seven-item anxiety severity rating scale that has been shown to have good psychometric properties (RUPP Anxiety Study Group, 2002b). Ratings were obtained for the parent report on the child (i.e., PARS-P), the child's report (PARS-C), and a rater summary (PARS-R). In the acute treatment trial (Birmaher et al., 2003), this PARS scale had excellent interrater consistency ($\kappa = 0.80$).

Child- and Parent-Rated Anxiety Scales. The parent- and child-rated anxiety symptoms used the SCARED, including indicators for parent report (SCARED-P) and child report (SCARED-C). This instrument is a 41-item self-report instrument that assesses *DSM-IV* symptoms of panic, SAD, SP, GAD, panic, specific phobias, and school refusal. The SCARED has shown good psychometric properties in clinical and community samples (Birmaher et al., 1997, 1999; Monga et al., 2000; Muris et al., 1998) and sensitivity to treatment effects (Birmaher et al., 2003; RUPP Anxiety Study Group, 2001). A score of 25 has been found to be an optimal threshold for discriminating children with anxiety disorders from children without anxiety disorders (Birmaher et al., 1999).

Data Analyses

For descriptive purposes, demographic and clinical characteristics between the group that completed follow-up and those who did not complete the follow-up phase were compared using χ^2 or t tests as appropriate. Similarly, subjects receiving fluoxetine and those receiving no medication during follow-up were compared on baseline characteristics. For hypothesis testing, the primary focus was comparing follow-up medication conditions (i.e., follow-up-fluoxetine versus follow-up-no medication) on change from the end of the RCT (i.e., end of acute or RCT phase) to the end of the follow-up period. Covariates examined in statistical models included demographic variables, RCT medication assignment (i.e., RCT-fluoxetine or RCT-placebo), and participation in psychotherapy during follow-up. All values were reported as either percentages or mean ± SD. All p values are based on two-tailed tests with $\alpha = .05$.

For CGI variables, considered the primary outcome measures, the last RCT assessment was used as the initial assessment for the follow-up period, and the 12-month follow-up assessment was used as the outcome evaluation. Interim assessments of most subjects using the CGI were not done, and therefore linear mixed models were used as the statistical modeling approach. For CGI variables, group differences in the assessments at the end of the RCT and at 1-year follow-up were examined. In these models, covariates included demographic variables, RCT medication assignment, and psychosocial treatment during follow-up. Because the RCT medication assignment may have combined with follow-up medication conditions to produce unique

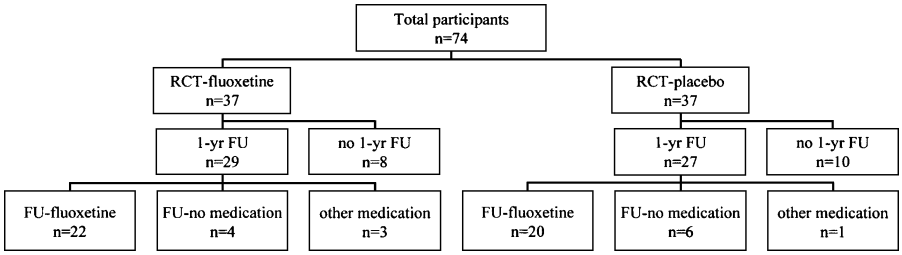

Fig. 1 Randomized, controlled trial (RCT) and follow-up (FU) medication categories for children and adolescents with anxiety disorders.

effects, the statistical interaction between RCT medication assignment and follow-up medication condition was also examined.

The PARS and SCARED variables, considered secondary outcome measures, were analyzed using piecewise growth models (Muthen and Muthen, 2004). For each measure, a two-piece growth model was evaluated: The first piece was composed of the RCT assessments, and the second piece was composed of the last RCT assessment and the four assessments of the follow-up period (i.e., 3, 6, 9, and 12 months). The results focus on the second piece, comprising changes in the follow-up period. RCT medication conditions were specified as a covariate influencing the slope of the acute phase (i.e., the first piece). Follow-up medication conditions were specified as a covariate influencing the slope and end point of the follow-up period (i.e., the second piece). Other variables examined as covariates were the demographic variables, including age, sex, race, and socioeconomic status and the presence or absence of psychotherapy during the follow-up period. These models allow for missing data. Evaluation of the models was accomplished using Mplus version 3 (Muthen and Muthen, 2004).

RESULTS

A flow chart depicting the standing of subjects throughout the RCT and follow-up phases is presented in Figure 1. Fifty-six of 74 (76%) subjects completed the 1-year follow-up assessment. There were no significant differences between those with and without follow-up assessments on age (t = 0.6, df = 72, p = .6), sex (χ^2 = 0.2, df = 1, p = .7), socioeconomic status (χ^2 = 0.6.1, df = 4, p = .2), ethnic group (χ^2 = 0.1.7, df = 1, p = .2), presence of comorbid disorders (χ^2 = 0.2, df = 1, p = .6), CGI-S (t = 0.4, df = 72, p = .7), or drug assignment in the acute trial (χ^2 = 0.3, df = 1, p = .6). In addition, four subjects were treated with medications other than fluoxetine and were not included in the subsequent analyses.

The following analyses included the 52 subjects completing the 1-year follow-up assessment. Of these 52 subjects, 42 received fluoxetine and 10 received no medication during the follow-up phase. The characteristics of these two groups are presented in Table 1. The two groups were not significantly different on sex, age, socioeconomic status, ethnic group, age of anxiety disorder onset, number of anxiety disorders (i.e., SAD, GAD, and/or SP), number of anxiety disorder symptoms at baseline, or drug assignment during the acute treatment trial. Among these cases, all combinations of SAD, GAD, and/or SP were represented. The most common was GAD and SP (n = 14, 27%), followed by SP only (n = 10, 24%), SAD and GAD (n = 8, 15%), GAD only (n = 7, 13%), SAD only (n = 5,

TABLE 1
Subject Characteristics at Baseline by Follow-up Medication Group

	Follow-up-Fluoxetine (n = 42)		Follow-up-No Medication (n = 10)				
	No.	%	No.	%	χ^2	df	p
Sex							
Female	24	57	5	50	0.2	1	0.7[a]
Male	18	43	5	50			
Ethnic group							
White	39	93	10	100	0.8	1	0.9[a]
Other	3	7	0	0			
No. of diagnoses							
1	17	40	5	50	0.6	2	0.9[a]
2	21	50	4	40			
3	4	10	1	10			
RCT medication assignment							
Fluoxetine	22	52	4	40	0.5	1	0.7
Placebo	20	48	6	60			
	Mean	SD	Mean	SD	t	df	p
Age, yr	12.2	3.0	10.8	3.2	1.4	50	0.2
SES	48.1	12.8	39.0	16.8	1.8	39	0.09
No. of anxiety symptoms	12.7	5.1	12.8	4.3	0.1	50	0.95

Note: Number of anxiety symptoms and number of disorders include generalized anxiety disorder, separation anxiety disorder, and social phobia. RCT = randomized, controlled trial; SES = socioeconomic status.

[a] Fisher's exact test because of small cells.

10%), SAD, GAD, and SP (n = 5, 10%), and SAD and SP (n = 3, 6%). The follow-up-fluoxetine and follow-up-no medication groups were not significantly different for this pattern (χ^2 = 11.8, df = 6, p = .07).

Clinical Outcome

CGI-S. In the linear mixed model examining change on the CGI-S from the end of acute treatment through 1-year follow-up, the acute RCT medication assignment by follow-up medication condition interaction was statistically significant (F = 4.1, df = 1, 93, p = .047; Fig. 2). The greatest improvement in severity was noted in the group receiving placebo in the acute period followed by fluoxetine in the follow-up period. In contrast, the greatest worsening in severity occurred in the group receiving placebo in the acute period followed by no medication in the follow-up period. Having accounted for this interaction, the main effects of follow-up medication (F = 1.5, df = 1, 93, p = .2) and acute medication assignment (F = 1.7, df = 1, 93, p = .2) did not account for significant additional variance; however, a significant effect was noted for psychosocial treatment (F = 5.5, df = 1, 93, p = .02). The proportion of subjects achieving the landmark of a CGI-S score indicating "normal, not at all ill" (CGI-S = 1) was significantly different among groups (χ^2 = 4.9, df = 1, p = .03), with the highest proportion in the RCT-fluoxetine/follow-up-fluoxetine group (n = 7, 32%), followed by RCT-placebo/follow-up-fluoxetine group (n = 2, 10%), and none from the RCT-fluoxetine/follow-up-no medication group or RCT-placebo/follow-up-no medication group.

Improvement. Similarly, in the linear mixed model examining change on the CGI-I from the end of acute treatment through 1-year FU, the acute medication assignment by FU medication condition interaction was statistically significant (F = 6.7, df = 1, 93, p = .01; Fig. 3). Having accounted for this interaction, the main effects of FU medication (F = 2.2, df = 1, 103, p = .1) did not account for significant additional variance, while acute medication assignment (F = 4.1, df = 1, 103, p = .045) accounted for significant variance. A significant effect was also noted for psychosocial treatment (F = 7.4, df = 1, 103, p = .008). The proportion of subjects achieving the CGI-I score indicating "very much improved" (CGI-I = 1) was significantly different among groups (χ^2 = 5.0, df = 1, p = .03), with the highest proportion in the RCT-fluoxetine/FU-fluoxetine group (n = 13, 59%), followed by RCT-placebo/FU-fluoxetine group (n = 5, 25%), the RCT-fluoxetine/FU-no medication group (n = 1, 25%) and the RCT-placebo/FU-no medication group (n = 1, 17%). Since demographic variables did not account for significant variance in either CGI analysis, demographic variables were not included in these models.

SCARED-P. In the structural growth models, SCARED-P showed significant differences by follow-up medication group on slopes and end points. For SCARED-P, the follow-up-fluoxetine group (compared with the follow-up-no medication group) showed greater improvement and a lower score at the end point signifying lower anxiety symptoms (Table 2). RCT medication assignment accounted for significant variance in slope (z = 1.97, p < .05) but not end point (Z = 0.5, p > .05). Psychosocial intervention accounted for significant variance in both slope (Z = 2.3, p < .05) and end point (Z = 3.4, p < .01). Race was the only significant covariate (slope: Z = 2.3, p < .05; end point: Z = 3.5, p < .01).

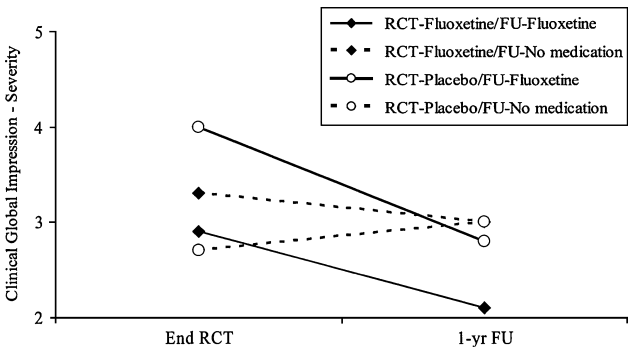

Fig. 2 CGI-S: follow-up (FU) phase changes by medication group. RCT = randomized, controlled trial.

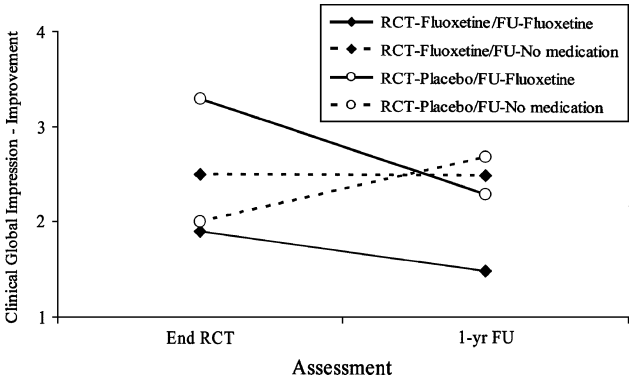

Fig. 3 CGI-I: follow-up (FU) phase changes by medication group. RCT = randomized, controlled trial.

TABLE 2
Clinical Response to Fluoxetine and No Medication During 1-Year Follow-up Period

	End RCT (mean ± SD) (n = 52)	4-Mo Follow-up (mean ± SD) (n = 43)	8-Mo Follow-up (mean ± SD) (n = 43)	12-Mo Follow-up (mean ± SD) (n = 52)	Structural Growth Model[a]			
					Slope		End Point	
					Z	p	Z	p
SCARED-P[b]								
Fluoxetine	21.3 ± 13.3	15.4 ± 12.1	16.1 ± 9.8	13.7 ± 12.0	3.07	<.01	3.21	<.01
No medication	19.1 ± 14.3	23.0 ± 16.0	19.8 ± 13.6	21.8 ± 13.0				
SCARED-C								
Fluoxetine	13.9 ± 13.6	9.9 ± 8.4	11.0 ± 8.9	10.5 ± 13.8	2.07	<.05	2.14	<.05
No medication	10.2 ± 12.3	11.0 ± 11.6	15.0 ± 21.5	14.8 ± 19.6				
PARS-P								
Fluoxetine	13.4 ± 7.8	12.5 ± 17.7	6.7 ± 4.9	8.6 ± 6.8	2.21	<.05	2.95	<.01
No medication	11.4 ± 7.5	8.6 ± 6.2	10.2 ± 6.7	12.2 ± 8.4				
PARS-C								
Fluoxetine	8.4 ± 6.6	6.6 ± 5.0	6.8 ± 5.1	5.6 ± 5.2	2.06	<.05	1.80	NS
No medication	4.8 ± 3.7	11.3 ± 10.3	9.4 ± 7.2	7.2 ± 7.6				
PARS-R								
Fluoxetine	13.6 ± 7.6	9.6 ± 6.1	10.5 ± 6.4	9.4 ± 6.4	1.56	NS	2.51	<.05
No medication	11.8 ± 6.9	15.0 ± 13.2	15.6 ± 6.5	11.8 ± 8.1				

Note: RCT = randomized, controlled trial; SCARED-P = Self-Report for Childhood Anxiety Related Disorders, parent report; SCARED-C = Self-Report for Childhood Anxiety Related Disorders, child report; PARS-P = Pediatric Anxiety Rating Scale, parent report; PARS-C = Pediatric Anxiety Rating Scale, child report; PARS-R = Pediatric Anxiety Rating Scale, rater report; NS = not significant.

[a] All test statistics controlled for acute trial medication assignment and psychotherapy during follow-up.

[b] Race included in models for this variable.

SCARED-C. Similarly, SCARED-C showed significant differences by follow-up medication group on slopes and end points, with the follow-up-fluoxetine group showing relatively greater improvement and a lower score at the end point signifying lower anxiety symptoms. For SCARED-C, RCT medication assignment did not account for significant variance (slope: $Z = 0.3$, $p > .05$; end point: 0.3, $p > .05$). Psychosocial intervention accounted for significant variance in slope ($Z = 2.2$, $p < .05$) and end point ($Z = 2.5$, $p < .05$). For SCARED-C, demographic variables did not account for significant variance and were not included in models.

PARS-P. In the structural growth models, the PARS-P showed significant differences by follow-up medication group on slopes and end points. For PARS-P, the follow-up-fluoxetine group (compared with the follow-up-no medication group) showed greater improvement and a lower score at the end point signifying lower anxiety symptoms. For PARS-P, RCT medication assignment did not account for significant variance (slope: $Z = 0.4$, $p > .05$; end point: 0.8, $p > .05$). Psychosocial intervention accounted for significant variance in end point ($Z = 3.7$, $p < .01$) but not slope ($Z = 1.5$, $p > .05$).

PARS-C. For PARS-C, the follow-up-fluoxetine group (compared with the follow-up-no medication group) showed greater improvement as indicated by a significant group difference on the slopes, but the end points were not significantly different. For PARS-C, RCT medication assignment did not account for significant variance (slope: $Z = 0.7$, $p > .05$; end point: 1.3, $p > .05$). Psychosocial intervention accounted for significant variance in slope ($Z = 2.5$, $p < .05$) and end point ($Z = 2.6$, $p < .01$).

PARS-R. For PARS-R, the follow-up medication groups did not show a significant difference in the rates of improvement as indicated by the slopes, but the end points were significantly different, favoring those receiving fluoxetine. For PARS-R, RCT medication assignment did not account for significant variance (slope: $Z = 0.3$, $p > .05$; end point: 1.2, $p > .05$). Psychosocial intervention accounted for significant variance in end point ($Z = 3.2$, $p < .01$) but not slope ($Z = 1.4$, $p > .05$). Because demographic variables did not account for significant variance for any PARS analysis, demographic variables were not included in these models.

Side Effects. Side effects were clinically ascertained during the course of follow-up. No subjects made

suicide attempts or had clinically significant suicidal ideation. Two subjects were noted to have clinically significant events potentially attributable to fluoxetine in the follow-up period. One subject had a 30-lb weight gain. Because the weight gain occurred after initiating contraceptive medication, the weight gain was clinically attributed to that medication change and fluoxetine was continued; a 1-year follow-up assessment was conducted and the subject was included in analyses. Another subject with a diagnosis of SAD during the acute phase showed signs of bipolar disorder during follow-up. In the latter case, fluoxetine was discontinued.

DISCUSSION

In this study, children and adolescents with anxiety disorders taking fluoxetine were increasingly less symptomatic than those taking no medication during the course of a long-term treatment period. This positive result was generally consistent across clinician, parent, and child ratings. Among those receiving fluoxetine, only 5% were judged by clinicians to be not improved at 1-year follow-up, in contrast to 30% of the group receiving no medication. On parent, child, and clinician anxiety ratings, the fluoxetine group showed greater improvement than the no medication group during the 1-year follow-up period.

These findings are consistent with the positive results reported for the 6-month follow-up with fluvoxamine or fluoxetine for children and adolescents with SP, GAD, and/or SAD conducted by the RUPP Anxiety Study Group (2002a). In the RUPP study, however, no reference group was reported. In the present study, a comparison group declining medication after the acute trial participated in follow-up assessments and functioned as a reference group. Compared with the reference group receiving no medication, patients receiving fluoxetine in the present study showed greater improvement across most measures, including clinician, parent, and child reports. Although not as definitive as a long-term RCT, the results are informative in suggesting that continued fluoxetine treatment during a 1-year period may be beneficial.

Limitations

The study had several additional limitations. A major limitation was the lack of RCT methodology in the follow-up phase. As with the RUPP Anxiety Study Group (2001) follow-up study, this study was an open-treatment trial subject to the biases inherent in such designs. The children, parents, and clinicians were not blind to treatment condition during the follow-up period, and bias in outcome assessments may have occurred. In addition, assignment to the no medication group was not determined by random assignment and these subjects may have differed from those taking medication on unmeasured variables relevant for interpreting the results. The reasons for electing to continue or discontinue treatment with fluoxetine were not systematically collected during the follow-up period, nor were these reasons available in our records. Although fluoxetine at 20 mg/day was probably a reasonable dose for most subjects (Wilens et al., 2002), higher doses may have been more efficacious for some.

Psychosocial treatments were not methodically assigned, systematically administered, or thoroughly measured. The analyses included only a rudimentary variable indicating whether psychosocial interventions had been provided in the follow-up period. Inclusion of this characteristic was intended to provide a statistical covariate for the purpose of improving the specification and interpretation of medication effects. The study was not well suited to providing observations on the influences of psychosocial interventions on outcomes during the follow-up period, and therefore a more detailed interpretation has not been presented.

The results of this study cannot be generalized to all children and adolescents with anxiety disorders because the sample was predominantly white and anxiety disorder patients with common comorbid mental disorders, such as major depression, were excluded. Future studies should investigate the generalizability of these results to other ethnic groups and to children and adolescents with comorbid mental disorders. The sample was not of sufficient size to examine variation in effects by specific anxiety disorders and their combinations. The evaluation of side effects was not sufficiently systematic to support definitive statements about adverse effects. Psychosocial treatments were not thoroughly measured and therefore could not be evaluated in more detail. These limitations further emphasize the need for more long-term research on the use of SSRIs in children and adolescents with anxiety disorders.

Clinical Implications

In several acute treatment trials using SSRIs for anxiety disorders in children and adolescents, patients

typically showed significant improvement but remained symptomatic (Birmaher et al., 2003; Black and Uhde, 1994; RUPP Anxiety Study Group, 2001; Rynn et al., 2001), indicating that long-term treatment may confer additional benefit. These results suggest that fluoxetine may typically be beneficial and well tolerated for the long-term treatment of anxiety disorders in children and adolescents. Because CBT has been shown to be efficacious for the acute and continuation treatment of anxious youths (Compton et al., 2004; Flannery-Schroeder and Kendall, 2000; Kendall et al., 1997; Silverman et al., 1999), studies need to be carried out to evaluate the effects of separate and combined applications of medication and CBT for these disorders. Until such comparison studies are available, a clinically prudent course is to initiate treatment with a CBT intervention. SSRIs may be added for patients who do not show a favorable response to a course of CBT. SSRIs may be reasonably offered with or without CBT for patients with severe anxiety disorders, those with limited ability to participate in psychotherapy, families and patients who are not motivated to pursue treatment with CBT, or patients for whom CBT is not available. Although these results suggest that fluoxetine administered during a 1-year period may be beneficial for children and adolescents with anxiety disorders, RCTs are needed to more definitively determine the long-term risks and benefits of fluoxetine for this group.

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