

## Do Children and Adolescents Have Differential Response Rates in Placebo-Controlled Trials of Fluoxetine?

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### Abstract

*Objective:* Recent acute efficacy trials of antidepressants in youth have suggested that high placebo-response rates in children (<12 years of age) indicate that children may be more responsive to non-specific treatment interventions. Yet, these studies generally have not presented age-specific outcome data. The objective of this study was to compare the efficacy outcomes for children (<12 years of age) and adolescents ( $\geq 12$  years of age) using the combined data from two previously published double-blind, placebo-controlled trials of fluoxetine.

*Methods:* Children (<12 years of age) and adolescents ( $\geq 12$  years of age) with major depressive disorder were randomized to fluoxetine or placebo for 8–9 weeks of treatment. Outcome was assessed using the Children's Depression Rating Scale-Revised (CDRS-R) and Clinical Global Impressions scale.

*Results:* Random regression of the CDRS-R showed a treatment group by age group interaction ( $F_{1,338}=4.10$ ,  $P=.044$ ), indicating that the treatment effect was significantly more pronounced in children than adolescents. Within children, response at exit to fluoxetine was significantly better than placebo (56.9% vs 33.3%;  $P=.009$ ). Adolescent response rates at exit were not significantly different between the groups (51.1% vs 38.6%;  $P=.128$ ). Remission rates were low for both groups.

*Conclusion:* In the combined fluoxetine trials, drug-placebo difference was greater in children compared with adolescents. Contrary to expectations, the placebo-response rate was lower in the children than the adolescents.

### Introduction

Depression in children and adolescents is a serious disorder and causes substantial morbidity and mortality. Phenomenology and longitudinal studies<sup>1</sup> have demonstrated that children and adolescents do experience depressive episodes. Age-related symptom differences among younger children and adolescents are difficult to detect, if they do indeed exist. Kovacs<sup>2</sup> suggested children may have less hypersomnia, more appetite and weight changes, and delusions compared with adolescents. Despite the possible differences in symptom presentation, the criteria symptoms for major depressive disorder (MDD) are the same across the lifespan, with the exception that children and adolescents may have irritability with or without depressed mood.

Recently, there have been significant increases in research of psychopharmacologic treatments for pediatric depression, with randomized controlled trials (RCTs) serving as the gold standard in evaluating treatments. Prior to 1997, reports of RCTs in pediatric depression were minimal and included only ~250 participants. At that time, tricyclic antidepressants were the first-line medication treatment in adults. A meta-analysis of the pediatric data showed no difference between active medication and placebo.<sup>3</sup> With the development of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, paroxetine, and sertraline, new medication options became available, with potentially greater efficacy and better side-effect profiles. Since 1997, >2,500

depressed children and adolescents have participated in RCTs of SSRIs and other novel antidepressants (mirtazapine, nefazodone, and venlafaxine). As is often the case, new data have led to more questions.

Several of the SSRIs have shown some positive efficacy in pediatric populations.<sup>4-9</sup> However, the data seem to be more robust in adolescents than in children.<sup>8,10,11</sup> In fact, several reports of negative trials that included both children and adolescents have suggested that the high placebo-response rates in the child group (<12 years of age) result in the negative outcome for the overall trial.<sup>8,10-12</sup> Unfortunately, these trials are generally not powered to detect age differences. Only three medications have demonstrated positive efficacy in trials containing both children and adolescents (fluoxetine, citalopram, and sertraline), and one of those (sertraline) reported that the data for the child subgroup were not positive due to a high placebo-response rate (15% drug-placebo difference for adolescents but only 5% difference for children).<sup>8</sup>

Fluoxetine is the only antidepressant to have more than one positive RCT,<sup>4,5,7</sup> and two of the three trials included both children and adolescents.<sup>4,5</sup> In these individual trials with combined age groups, it was reported that there was not an age by treatment group interaction. However, primary and secondary outcomes for the age groups were not reported for the trials. Combining the data from these two trials provides a larger sample with which to evaluate efficacy outcomes by age.

## Methods

Data from two previously conducted trials<sup>4,5</sup> were combined to evaluate the efficacy outcomes of children (<12 years of age) and adolescents ( $\geq 12$  years of age). The first study was a single-site trial funded by National Institute of Mental Health and conducted at the University of Texas Southwestern Medical Center at Dallas (UTSW). The second, funded by Eli Lilly, was conducted by 15 investigators throughout the United States and included academic hospitals and private research psychiatric clinics, including UTSW. Each study, including informed consent/assent, was approved by the institutional review board for each site, and the consents were signed by participants' parents or guardians. Participants may have also provided consent or assent depending on the requirements of the institutional review board.

Generally, both studies included children and adolescents with a primary diagnosis of non-psychotic MDD (single or recurrent) as defined by *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised* or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, and depressive symptoms of at least moderate severity as defined by a CDRS-R total score  $\geq 40$  and a Clinical Global Impressions-Severity (CGI-S) rating of  $\geq 4$ . All participants underwent a 2-week, three-visit evaluation phase, which included a semi-structured diagnostic interview administered to all enrolled participants and their parents at each interview to establish the diagnosis of MDD. The interviews were conducted by three different interviewers, at least one of whom was a psychiatrist.

Following three evaluation visits, participants entered a 1-week single-blind, placebo-run-in period. Following the placebo-run-in phase, participants who responded to placebo were withdrawn from the study, and non-responders were randomized to fluoxetine or placebo for 8<sup>4</sup> or 9 weeks<sup>5</sup> of treatment. For inclusion in these analyses, participants must have attended at least one post-randomization visit.

Following randomization, visits in the single-site trial were weekly for 8 weeks; visits for the multi-site trial were at weeks 1, 2, 3, 5, 7, and 9. Dosing for the single-site study was 20 mg/day for the duration of the trial; dosing for the multi-site trial was 10 mg/day for 1 week, and then increased to 20 mg/day for the remainder of the study.

Participants were assessed by participant and parent report at each visit using the Childhood Depression Rating Scale-Revised (CDRS-R),<sup>13</sup> which was rated by the treating clinician. The CDRS-R measures symptom severity, with each item rated on a 1-5 or 1-7-point scale, with 1 describing absence of the given symptom and 5 or 7 indicating severe symptoms. The CDRS-R yields a total score from 17-113 with a score of  $\geq 40$  considered to symptomatic of depression. Five factors of the

CDRS-R have recently been reported: depressed mood (depressed mood, irritability, self-esteem, and excessive weeping); anhedonia (difficulty having fun and social withdrawal); somatic symptoms (difficulty with schoolwork, sleep disturbance, appetite change, fatigue, and physical symptoms); morbid thoughts (excessive guilt, morbid ideation, and suicidal ideation); and observed depressed mood (depressed facial affect, listless speech, and hypoactivity).<sup>14</sup> These factors were used to evaluate symptom presentation in the age groups. The factor score was defined to be the average of the item scores. Thus, the possible range for each factor score is 1–7 for all factors except somatic symptoms. For the somatic symptoms factor, the range is 1–6.2 because two of the items within this factor use a 5-point scale.

In addition to the CDRS-R, the clinicians rated the CGI-S<sup>15</sup> at each visit, as well as the CGI-Improvement scale (CGI-I),<sup>15</sup> which was assessed at each visit except the baseline visit. A CGI-I score of 1 (very much improved) or 2 (much improved) are considered response criteria. Additional information about participants, study design, and outcomes have been previously reported.<sup>4,5</sup>

## Statistical Analyses

Data from the two trials were combined by Eli Lilly for submission to the Food and Drug Administration, and were then provided to the principal investigator (GE). For the purposes of these post-hoc analyses, weeks of treatment are based on the number of weeks on fluoxetine 20 mg/day. Thus, week 8 refers to participants having been on fluoxetine 20 mg/day for 8 weeks. (Note: participants in the multi-site trial had 1 week of 10 mg/day prior to increasing to 20 mg/day; consequently, those participants will have had 9 weeks of total medication exposure.) Statistical analyses for this research were conducted at the UTSW site and then submitted to Eli Lilly for review. However, the decisions on what data to publish were made solely by the authors. All analyses were intent-to-treat. However, because subjects who did not return for at least one post-randomization visit were excluded, this is not a “pure” intent-to-treat analysis. All outcomes are post-hoc.

The CDRS-R was analyzed as a continuous outcome using a random-regression model (SAS Proc Mixed<sup>16</sup>). The model contained main effects for treatment group (fluoxetine/placebo), time (weeks 1–8 as previously defined), and age group (child/adolescent), and covariates for gender, baseline CDRS-R, and Study (single site vs multi-site). Length of illness and diagnosis of an anxiety disorder or behavior disorder were considered as covariates. Two-way interaction terms were included if they were significant or part of a three-way interaction. Thus, terms for week by treatment group, age group by treatment group, week by age group, and week by study were included. The week by treatment group by age group interaction was included because the purpose of the analysis was to determine if the treatment effect was different in the two age groups. In the model, week was replaced by  $\log(\text{week} + 1)$  to obtain a more linear relationship between CDRS-R and time.

For comparisons of pre-post continuous measures, analysis of variance was used. Means presented are adjusted means based on covariates. Fisher exact test was used for dichotomous outcomes: response (CGI-I: 1 or 2) and remission (CGI-I: 1 or 2 and CDRS-R:  $\leq 28$ ).

## Results

A total of 315 children and adolescents were randomized in the two studies. Six subjects (one in the single-site trial and five in the multi-site trial) did not have a post-randomization visit, and were therefore excluded from the analyses. All six subjects were randomized to placebo. Thus, 309 youth with at least one post-randomization visit were included in the analyses (134 children [ $<12$  years of age and 175 adolescents [ $\geq 12$  years of age]).

Females comprised 47.7% of the sample, and the sample was predominantly white (80.9%). Table 1 provides the baseline demographic and clinical characteristics by age group. There were more females represented in the adolescent age group (54.3%) compared with children (38.8%;  $P = .007$ ). As expected, children had an earlier age of onset ( $8.3 \pm 1.7$  vs  $12.1 \pm 2.5$ ;  $P < .001$ ). In both age groups, the majority of subjects (over two thirds) were in their first episode of depression.

Other illness characteristics, such as duration of episode and comorbid diagnoses, were similar for the age groups. However, comorbid behavior disorders (attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder) were more common in children (39.6% vs 26.3%;  $P=.014$ ). Adolescents also had a extended length of illness ( $22.6\pm 24.1$  weeks vs  $17.3\pm 20.3$  weeks;  $P=.036$ ) and more severe depression at baseline based on CDRS-R ( $59.5\pm 11.1$  vs  $53.2\pm 9.2$ ;  $P<.001$ ).

**TABLE 1.**  
**Baseline Demographic and Clinical Characteristics by Age Group\***

	Children (n=134)	Adolescents (n=175)	P
Gender (% female)	38.8% (52)	54.3% (95)	.007
Race (%)			.176
White	85.1 (114)	77.7 (136)	
Black	6.7 (9)	7.4 (13)	
Hispanic	3.7 (5)	10.3 (18)	
Other	4.5 (6)	4.6 (8)	
Age (years)	10.1±1.1	14.5±1.6	<.001
Age of onset (years)	8.3±1.7	12.1±2.5	<.001
Duration of episode (weeks)	41.3±61.8	51.4±74.3	.196
Length of illness (months)	17.3±20.3	22.6±24.1	.036
Number of episodes			.116
1	70.1 (94)	68.0 (119)	
2	21.6 (29)	16.6 (29)	
≥3	8.2 (11)	15.4 (27)	
Comorbid disorders			
None	33.6 (45)	43.4 (76)	.079
Dysthymia	24.6 (33)	24.6 (43)	.991
Anxiety	33.6 (45)	26.9 (47)	.211
Behavior	38.8 (52)	25.7 (45)	0.019
CDRS-R	53.2±9.2	59.5±11.1	<.001

\* Children: <12 years of age; adolescents: ≥12 years of age.

CDRS-R=Childhood Depression Rating Scale-Revised.

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Baseline demographic and clinical characteristics were also similar for both treatment groups within each age group. However, within the child subgroup, those on fluoxetine were more likely to have an anxiety disorder than those randomized to placebo (46.2% vs 21.7%;  $P=.003$ ). No other baseline differences were found between the fluoxetine and placebo groups for either age group.

Baseline depressive symptomatology was also compared for children and adolescents for the CDRS-R factor scores, as outlined by Guo and colleagues.<sup>14</sup> Table 2 lists the mean scores for each of the factors as well as each of the individual items within those factors. In all categories, adolescents endorsed greater symptom severity than children, with all of the factors reaching significance except morbid thoughts. Depressed adolescents scored significantly higher than children on all items of observed depressed mood. Generally, morbid thoughts and observed depressed mood were lower in severity than the other factors for both age groups.

**TABLE 2.**  
**Baseline Depressive Symptoms by Age Group (CDRS-R Factors and Individual Items)**

	Children (n=134)	Adolescents (n=175)	P
<i>Reported Depressed Mood</i>	4.0±1.0	4.3±1.0	.003
8. Irritability	4.4±1.4	4.9±1.4	.005
10. Low Self-Esteem	4.4±1.3	4.6±1.4	.150
11. Depressed Feelings	3.8±1.2	4.5±1.3	0.001
14. Excessive Weeping	3.3±1.7	3.3±1.9	.949
<i>Anhedonia</i>	3.9±1.1	4.3±1.2	.007
2. Difficulty Having Fun	4.3±1.2	4.7±1.3	.005
3. Social Withdrawal	3.6±1.3	3.9±1.4	.048
<i>Somatic Symptoms</i>	3.3±0.9	3.8±0.9	<.001
1. Schoolwork	3.7±1.7	4.4±1.8	<.001
4. Sleep Disturbance	3.4±1.4	3.5±1.4	.238
5. Appetite Disturbance	2.7±1.3	2.8±1.3	.734
6. Excessive Fatigue	3.8±1.6	4.7±1.6	<.001
7. Physical Complaints	3.0±1.6	3.0±1.6	.081
<i>Morbid Thoughts</i>	2.1±0.8	2.3±1.0	.075
9. Excessive Guilt	2.3±1.2	2.5±1.4	.122
12. Morbid Ideation	2.1±1.2	2.3±1.4	.400
13. Suicidal Ideation	1.9±1.1	2.0±1.1	.202
<i>Observed Depressed Mood</i>	2.2±0.8	2.7±1.0	<.001
15. Depressed Facial Affect	3.0±1.2	3.6±1.5	<.001
16. Listless Speech	1.7±0.7	1.9±0.9	.024
17. Hypoactivity	2.0±1.0	2.6±1.3	<.001

\* Children: <12 years of age; adolescents: ≥12 years of age.  
CDRS-R=Childhood Depression Rating Scale-Revised.  
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## Outcomes

Individual study results were previously reported.<sup>4,5</sup> When combined, results were similar. Fluoxetine led to greater improvement in CDRS-R total score compared with placebo ( $-21.5 \pm 14.1$  vs  $-13.6 \pm 14.3$ ;  $P < .001$ ). The effect size for fluoxetine versus placebo was medium (effect size: .56). Response rates were significantly better with fluoxetine than placebo (53.5% vs 36.2%;  $P = .003$ ) in the full sample, and fluoxetine was superior to placebo on rates of remission at exit, although remission rates were low for both groups (36.3% vs 19.1%;  $P = .001$ ).

## Age Group Differences

As noted, the CDRS-R was analyzed as a continuous outcome using a random-regression model, with main effects for treatment group (fluoxetine/placebo), time (weeks 1–8, as previously defined), age group (children/adolescents), and covariates for gender, baseline CDRS-R, and Study (single site vs multi-site). Length of illness and presence of an anxiety disorder or behavior disorder were not significant covariates and, therefore, were not included. The week by treatment group by age group interaction was significant ( $F_{1,338} = 4.10$ ,  $P = .0436$ ), indicating that the treatment effect (treatment group by week interaction) is different in the two age groups. To illustrate, the estimated mean change from baseline (CDRS-R scores estimated from the model) is shown in the Figure, which demonstrates a larger treatment effect among children than adolescents. Single site versus multi-site did not impact outcome (study by week by treatment group interaction:  $F_{1,521} = 0.01$ ,  $P = .917$ ).

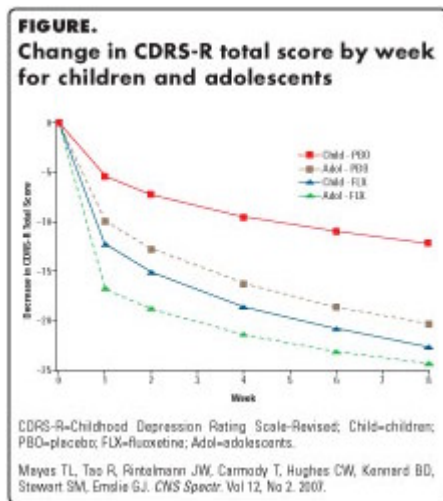


Table 3 shows additional outcomes, including baseline and exit scores for the CDRS-R (total score) and CDRS-R mean factor scores for both age groups (by treatment). Change scores are also presented for each variable. On the CDRS-R, adolescents started with higher scores. Improvement on fluoxetine was similar in children and adolescents. However, on placebo, adolescents had a greater response than children, resulting in a greater drug-placebo difference in the children than in the adolescents. The effect size for change in CDRS-R total score was medium for children (effect size: 0.71), but small for adolescents (effect size: 0.39).

**TABLE 3.**  
**Mean Changes on CDRS-R Total and Factor Scores (Baseline to Exit) by Age Group\***

	Children							
	Fluoxetine (n=65)			Placebo (n=69)			P	Effect Size
	Baseline	Exit	Change	Baseline	Exit	Change		
CDRS-R total	53.9±8.4	31.8±10.5	-22.1±14.0	52.5±10.0	41.3±13.4	-11.3±13.7	<.001	0.71
Reported depressed mood (Factor 1)	4.0±0.8	2.2±1.1	-1.8±1.3	4.0±1.0	3.1±1.3	-0.9±1.4	<.001	0.65
Anhedonia (Factor 2)	4.0±0.9	2.1±1.1	-1.9±1.3	3.9±1.2	3.1±1.5	-0.8±1.5	<.001	0.75
Somatic symptoms (Factor 3)	3.4±0.9	2.1±0.9	-1.3±1.2	3.3±0.9	2.6±0.9	-0.7±1.0	.001	0.56
Morbid thoughts (Factor 4)	2.2±0.8	1.4±0.5	-0.8±0.9	2.0±0.7	1.6±0.6	-0.4±0.7	.001	0.57
Observed depressed mood (Factor 5)	2.2±0.8	1.5±0.6	-0.8±0.8	2.2±0.7	1.8±0.7	-0.5±0.8	.04	0.36
	Adolescents							
	Fluoxetine (n=92)			Placebo (n=83)			P	Effect Size
	Baseline	Exit	Change	Baseline	Exit	Change		
CDRS-R total	60.3±10.4	39.2±15.1	-21.1±14.3	58.7±11.8	43.2±16.1	-15.5±14.5	.011	0.39
Reported depressed mood (Factor 1)	4.4±1.0	2.7±1.2	-1.6±1.2	4.2±1.1	3.1±1.3	-1.1±1.3	.005	0.44
Anhedonia (Factor 2)	4.5±1.1	2.7±1.4	-1.8±1.5	4.0±1.2	2.8±1.4	-1.2±1.4	.006	0.42
Somatic symptoms (Factor 3)	3.7±0.9	2.5±1.1	-1.2±1.0	3.8±0.9	2.8±1.2	-1.0±1.1	.187	0.20
Morbid thoughts (Factor 4)	2.2±0.9	1.5±0.7	-0.6±0.9	2.4±1.0	1.7±0.8	-0.7±1.0	.427	-0.12
Observed depressed mood (Factor 5)	2.9±1.0	1.9±0.9	-1.0±1.0	2.5±1.0	2.1±0.8	-0.4±0.9	<.001	0.55

\* Children: <12 years of age; adolescents: ≥12 years of age.  
 CDRS-R=Childhood Depression Rating Scale-Revised.  
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Examining factor scores, children showed greater improvement with fluoxetine than placebo on all factors, while adolescents showed greater improvement with fluoxetine than placebo on only three factors (reported and observed depressed mood and anhedonia). Overall, the biggest drug-placebo

difference in both age groups was in anhedonia. The effect sizes are listed in Table 3. All factors showed a medium effect size in the children; only observed depressed mood showed a medium effect size in the adolescents, while most other factors (except morbid ideation) showed a small effect size in adolescents.

While the exit response and remission rates to fluoxetine were not significantly different for the two age groups, the drug-placebo difference was greater in the children for both response and remission. Fluoxetine response rates were significantly greater than placebo rates within the child subgroup (56.9% vs 33.3%;  $P=.009$ ), but not in the adolescent group (51.1% vs 38.6%;  $P=.128$ ). Similarly, remission rates were higher with fluoxetine than placebo in both age groups, although only significant within children (41.5% vs 15.9%;  $P=.001$ ) but not adolescents (32.6% vs 21.7%;  $P=.128$ ). Remission rates were relatively low over the 8-week trial for both age groups, even within the fluoxetine condition (Table 4).

**TABLE 4.**  
**Response and Remission Rates in Children and Adolescents\***

	Children				Adolescents			
	FLX (n=65)	PBO (n=69)	Difference	P	FLX (n=65)	PBO (n=69)	Difference	P
Response	56.9% (37)	33.3% (23)	23.6%	.009	51.1% (47)	38.6% (32)	12.5%	.128
Remission	41.5% (27)	15.9% (11)	25.6%	.001	32.6% (30)	21.7% (18)	10.9%	.128

\* Children: <12 years of age; adolescents: >12 years of age.  
FLX=fluoxetine; PBO=placebo.

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To examine changes of suicidality in these age groups, we examined CDRS-R suicide item 13 (Table 5). For purposes of these analyses, a score of  $\geq 3$  was identified as presence of suicidal behaviors. Baseline presence of suicidality occurred in ~23% of the full sample. It was similar in children (21.6%) and adolescents (24.0%). In subjects who presented with baseline suicidal behaviors (n=71), most improved regardless of treatment assignment. Of the subjects who had minimal or no suicidal thoughts at baseline (CDRS-R item 13:  $\leq 2$ ) (n=238), most remained unchanged or improved. In subjects who had minimal or no baseline suicidality, worsening of suicidality (CDRS-R item 13 increase:  $\geq 1$  points) was noted in 12.3%, with no differences between fluoxetine (11.5%) and placebo (13.2%) ( $P=.730$ ). No differences were found between children and adolescents on worsening of suicidality (9.7% children, 14.3% adolescents;  $P=0.294$ ).

**TABLE 5.**  
**Changes in Suicidality**

<i>Suicidality at Baseline (CDRS-R Item 13: <math>\geq 3</math>)</i>						
	Fluoxetine			Placebo		
	Children (n=16)	Adolescents (n=23)	Total (n=39)	Children (n=13)	Adolescents (n=19)	Total (n=32)
Improvement of $\geq 1$ points	87.5% (14)	78.3% (18)	82.1% (32)	76.9% (10)	73.7% (14)	75% (24)
Worsening of $\geq 1$ points	6.3% (1)	13.0% (3)	10.3% (4)	0% (0)	5.3% (1)	3.1% (1)
Unchanged	6.3% (1)	8.7% (2)	7.7% (3)	23.1% (3)	21.1% (4)	21.9% (7)
<i>No Suicidality at Baseline (CDRS-R Item 13: <math>\leq 2</math>)</i>						
	Fluoxetine			Placebo		
	Children (n=49)	Adolescents (n=69)	Total (n=118)	Children (n=56)	Adolescents (n=64)	Total (n=120)
Improvement of $\geq 1$ points	24.5% (12)	29.0% (20)	27.1% (32)	12.5% (7)	23.4% (15)	18.3% (22)
Worsening of $\geq 1$ points	8.2% (4)	14.5% (10)	11.9% (14)	14.3% (8)	17.2% (11)	15.8% (19)
Unchanged	67.3% (33)	56.5% (39)	61.0% (72)	73.2% (41)	59.4% (38)	65.8% (79)

CDRS-R=Childhood Depression Rating Scale-Revised.

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## Discussion

Children <12 years of age showed a more robust active medication response and lower placebo response than adolescents on symptom severity, response, and remission, despite initial lower severity scores. Reduction of specific symptoms was similar for both age groups. These findings are important because they suggest that previously reported differences in antidepressant response between children and adolescents may be due to methodological issues in the prior antidepressant trials (eg, dosing) rather than differences in the underlying illness between the age groups (ie, that depression in children is significantly less severe, and, therefore, more placebo-responsive).

Clinical trials generally are not powered to determine differences between age subgroups. Several previous trials reported higher placebo response in the younger age group.<sup>8,10</sup> Fluoxetine is the only antidepressant to demonstrate better efficacy than placebo in children <12 years of age. The question that remains is whether this is due to differences in the medication or other methodological issues, such as inadequate dosing used in the trials. Most studies were conducted without extensive data on what the correct dose would be for children and adolescents. In fact, dosing decisions for trials generally were primarily based on extrapolating from adults.<sup>17</sup> Serendipitously, the dosing strategy may have worked for fluoxetine in the child subgroup because 20 mg/day seems to be an ideal dose for increasing medication efficacy, while not increasing adverse events (at least in the child group). The fluoxetine trials were essentially fixed-dose studies (20 mg/day). In fact, the more marked drug-placebo difference in TADS<sup>7</sup> in adolescent subjects may be due to the fact that a higher dose was used (mean: ~33 mg/day) than in these two studies. Contrary to these findings, in the paroxetine trial, there was substantial dropout in the children in that trial.<sup>6</sup> Whether lower doses (with the shorter half-life of paroxetine) would have resulted in a different outcome is unknown.

Other methodological differences between these studies and other antidepressant trials that may have impacted drug-placebo differences include number of sites, number of subjects per site, extended evaluation period, quality of sites, and use of child-sensitive outcome measures (see Cheung and colleagues<sup>18</sup>). Also, the first fluoxetine trial was started in 1990. Later trials in children have a tendency toward higher placebo rates overall. Clearly, assessment of depression in children and ability to detect change requires substantial clinical acumen.

Changes in specific symptoms of depression between children and adolescents seem similar, with the biggest changes in anhedonia. With increased concerns about suicidal behaviors, of note, is that suicidal ideation occurred in the age groups, and both age groups showed improvement in suicidal ideation and behavior.

It is important to recognize that remission (at least over 8 weeks) was low in both groups, though lower in adolescents. The adolescent group had a longer duration of illness and higher baseline severity, which may have led to more negative consequences of depression.

## Conclusion

It is premature to say that antidepressants are not very effective in children (either not effective or that they show high placebo-response rates, implying that this age group is more responsive to non-specific interventions). While it appears appropriate to initiate psychosocial interventions prior to initiating medication, how long to continue such interventions and when to initiate medication is not clear. Future RCTs in children should be conducted after adequate assessment of appropriate doses specifically for children.

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