Anxiety As a Predictor of Treatment Outcome in Children and Adolescents with Depression

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Abstract

Objective: The aim of this study was to examine the impact of co-morbid illnesses on treatment outcomes in depressed children and adolescents aged 7–17 who were treated with fluoxetine.

Method: This data set was drawn from two large clinical trials involving children and adolescents with depression. Subjects with a diagnosis of major depressive disorder and depressive symptoms of at least moderate severity as defined by a Children's Depression Rating Score, Revised (CDRS-R) total score ≥ 40 and a Clinical Global Impressions–Severity (CGI-S) rating ≥ 4 were included. Subjects were randomized to receive fluoxetine or placebo over an 8-week period. Predictor analyses examining two primary outcomes were conducted: (1) Response based on Clinical Global Impressions–Improvement (CGI-I) score of 1 or 2, and (2) remission based on CDRS-R score of ≤ 28 . Logistic regression models were run to assess whether anxiety disorders were a predictor of response or remission.

Result: A total of 309 study participants were included. The only factor found to influence response was treatment with fluoxetine ($p = 0.022$, odds ratio [OR] = 2.08, 95% confidence interval [CI] 1.30, 3.31). Several factors were found to influence remission: Treatment with fluoxetine ($p < 0.0001$, OR = 3.17, 95% CI 1.80, 5.57), gender ($p = 0.024$, OR = 1.90, 95% CI 1.09, 3.30), and number of co-morbid diagnoses ($p = 0.026$, OR 0.73, 95% CI 0.55, 0.96).

Conclusion: Anxiety disorders alone did not predict response or remission, but the total number of co-morbid illnesses was associated with remission in depressed children and adolescents treated with fluoxetine.

Introduction

CO-MORBID DISORDERS IN CHILDREN and adolescents with depression are common (Kovacs and Devlin 1998). The rates of co-morbid attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders in depressed populations have ranged as high as 50–70% (Angold et al. 1999). In the largest adolescent depression study to date, Treatment for Adolescents with Depression Study (TADS), 50% of the sample met *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria for at least one other co-occurring condition, with the most frequent diagnoses being generalized anxiety disorder (GAD) and ADHD (March et al. 2004). Despite these high rates of co-occurrence, there is still limited understanding of the impact of common co-morbidities on treatment outcomes for pediatric depression.

Findings from naturalistic studies of children and adolescents have suggested that co-morbid conditions, including anxiety disorders, were related to prolonged depressive episodes and poorer outcomes (Sanford et al. 1995; Goodyer et al. 1997). This negative impact remains even when these patients receive active treatment. In studies of psychotherapy, adolescents with depression and any co-morbid conditions such as an anxiety disorder were generally less likely to respond to treatment (Ryan et al. 1986; Clarke et al. 1992; Brent et al. 1998; Jayson et al. 1998; Rohde et al. 2001). Studies of antidepressants, either alone or in combination with psychotherapy, have also examined the impact of co-morbid disorders such as anxiety on depression treatment outcomes, including an open-label trial (Tao et al. 2009) and several controlled trials (Kowatch et al. 1999; Curry et al. 2006; Asarnow et al. 2009). However, in contrast to the psychotherapy literature, the results from antidepressant trials have been mixed. In the largest adolescent

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depression study to date, TADS, co-morbid disorders (greater than 1 co-morbid disorder) or the presence of any anxiety disorder in depressed adolescents aged 12–17, treated with either cognitive behavioral therapy (CBT) and fluoxetine, fluoxetine alone, or CBT alone, predicted poorer treatment outcomes, regardless of treatment assignment (Curry et al. 2006). However, three other trials reported that co-morbid conditions such as anxiety disorders were not predictive of outcome. Kowatch and colleagues (1999) evaluated factors that were predictive of response to fluoxetine in children and adolescents (ages 7–17) with depression, and the number of co-morbid disorders was not found to be a predictor of treatment response. Similarly, findings from a recent analysis of data from an open trial involving 168 children and adolescents (ages 7–18) with depression treated with fluoxetine also did not suggest that co-morbid disorders such as an anxiety disorder predicted treatment outcome (Tao et al. 2009). In the most recent controlled trial, Treatment of Resistant Depression in Adolescents (TORDIA), which examined the benefit of combined CBT and medication in adolescents aged 12–18 years with treatment-resistant depression, Asarnow and colleagues similarly found no impact of co-morbid disorders such as anxiety disorders on treatment outcome (2009).

Therefore, although several studies have examined the role of anxiety and other co-morbid conditions in predicting treatment outcomes, the results of these studies have been mixed. The largest trial to date, TADS, shows contradictory findings to other studies. This body of research is also heterogeneous, with studies differing in design (e.g., controlled versus open-label trials), sample characteristics (e.g., children and adolescents versus adolescents alone, treatment-resistant depression), and type of treatment (e.g., medication alone versus CBT and medication). Furthermore, these studies only reported on the impact of co-morbidities on response and not remission. Remission is a much more robust and optimal outcome, preferred by both patients and clinicians because it represents fuller improvement from the depressive illness (Thase 2001; McIntyre and O'Donovan 2004).

Finally, although there is a clear need for further understanding of the impact of common co-occurring conditions such as anxiety disorders on treatment outcomes, patients with co-morbid anxiety, as well as other co-morbid conditions, are frequently excluded from participation in depression treatment trials due to concerns regarding the potential confounding effects of their co-morbid condition—a practice that is supported by evidence from the adult depression literature. In the largest effectiveness antidepressant trial to date, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, adults with anxious depression were significantly less likely to remit compared to those with nonanxious depression (Fava et al. 2008). The impact of this extrapolation from the adult literature has further limited our understanding of the role of co-morbidities in the treatment of children and adolescents with depression.

Therefore, we report on the results of two randomized controlled trials of fluoxetine versus placebo in children and adolescents with major depressive disorder (MDD). The studies were combined *post hoc* to examine impact of co-morbid illnesses (and more specifically, co-morbid anxiety disorder) on treatment outcome. There are several advantages to using this combined sample. First, this is the largest child and adolescent sample to date used to examine this issue. Second, this sample includes both children and adolescents, thereby allowing us to examine the impact of age. Third, subjects were not excluded due to co-morbid conditions and therefore, the results will be more generalizable to youth presenting with depression. Finally, the study will examine both response and remission.

Methods

This combined data set was drawn from two large clinical trials involving children and adolescents with depression (Emslie et al. 1997; Emslie et al. 2002; Mayes et al. 2007). The first study (described in this paper as the single-site trial) was a trial funded by the National Institute of Mental Health conducted at the University of Texas Southwestern Medical Center at Dallas (UTSW). Of note, the study by Kowatch and colleagues described above also examined other predictors of response using the sample from this study. The second was a study funded by Eli Lilly (described in this paper as the multisite trial) and included academic hospitals and private research psychiatric clinics across the United States, including UTSW. Each study was approved by the institutional review board for each site. Consents were signed by both participants and their guardians/parents. Subjects may have provided consent or assent depending on the requirements of the institutional review board.

Both studies included children and adolescents aged 7–17 with a primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by the DSM-III-R (American Psychiatric Association 1987) or DSM-IV criteria, and depressive symptoms of at least moderate severity as defined by a Children's Depression Rating Scale-Revised (CDRS-R) total score ≥ 40 and a Clinical Global Impressions-Severity (CGI-S) rating of ≥ 4 (Guy 1976; Poznanski et al. 1996). All participants underwent a 2-week evaluation phase. During this phase, participants had three separate visits, which included a semistructured diagnostic interview administered to all enrolled participants and their parents at each interview to establish the diagnosis of MDD. The interviews were conducted by different interviewers, at least one of whom was a psychiatrist.

At the end of screening, participants entered a 1-week single-blind, placebo run-in period. Following the placebo run-in phase, those who responded to placebo were withdrawn from the study, and nonresponders were randomized to fluoxetine or placebo for 8 or 9 weeks of treatment. Only subjects who attended at least one postrandomization visit were included in these analyses. Dosing for the single-site study was 20 mg/day for the duration of the trial; dosing for the multisite trial was 10 mg/day for 1 week, with an increase to 20 mg/day for the remaining 8 weeks of the study.

Participants were assessed by a child psychiatrist who interviewed the participant and parent separately at each visit using the CDRS-R, the clinician-rated CGI-S, and the clinician-rated Clinical Global Impressions-Improvement scale (CGI-I), except at the baseline visit. Response to treatment was defined as a CGI-I score of 1 (very much improved) or 2 (much improved); remission was defined as a CDRS-R total score ≤ 28 . Additional information about participants, study design, and outcomes has been previously reported (Emslie et al. 1997; Emslie et al. 2002; Mayes et al. 2007).

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 senior author (Emslie). 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. Participants in the multisite trial had 1 week of 10 mg/day prior to increasing to 20 mg/day or 9 weeks of total medication exposure.

Statistical analyses for this study were conducted at Sunnybrook Health Sciences Centre, University of Toronto, Canada. All analyses were intent to treat. Descriptive statistics were calculated for all variables of interest. Continuous measures such as age were

summarized using means and standard deviations, whereas categorical measures such as gender were summarized using counts and percentages.

We conducted predictor analyses examining two primary outcomes: response based on CGI-I score of 1 or 2 and remission based on the CDRS-R score ≤ 28 . Logistic regression models were run to assess whether anxiety disorders (GAD, $n = 77$), separation anxiety disorder ($n = 22$), phobias ($n = 28$), obsessive compulsive disorder ($n = 4$), posttraumatic stress disorder ($n = 1$), either occurring in combination (e.g., GAD plus phobias) or individually (e.g., GAD alone), were a predictor of response or remission. The models included treatment group (fluoxetine/placebo), number of co-morbid diagnoses (including ADHD, oppositional defiant disorder [ODD], conduct disorder [CD], dysthymia, other [enuresis, alcohol abuse]), gender, age (age ≤ 11 or ≥ 12 years), baseline depression severity (based on CDRS-R total score), race (Caucasian, African American, Hispanic, or other), and study. To investigate the role of anxiety disorders as a moderator variable, an interaction term was included between anxiety disorders and treatment group. If this interaction was found to be nonsignificant, the models were rerun excluding anxiety disorders.

Secondary analyses examined the impact of other co-morbid illnesses as predictors. Separate logistic regression models were run to assess whether GAD, behavioral disorders (ADHD, ODD, CD), dysthymia, and "other disorders" were predictors of response or remission. These categories were chosen because of their higher prevalence in this sample. The models included the same variables as listed above and included an interaction term between type of disorders and treatment group. Any nonsignificant interactions terms were removed from the model. We also examined for differences in drug-placebo response rates between those with co-morbid anxiety and those without using the Mantel-Haenszel test. All analyses were carried out using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows the characteristics of the 309 study participants included in this *post hoc* analysis. Just under half of the participants were female, and most were Caucasian. Approximately 60% had at least one co-morbid disorder, and 1 in 3 had an anxiety disorder. There were no significant differences in demographic and clinical variables between those randomized to fluoxetine or placebo.

No significant differences were noted in demographic characteristics based on presence of an anxiety disorder. However, youths with an anxiety disorder had a higher mean baseline CDRS-R total score than those without an anxiety disorder (Table 2).

Treatment outcome

Figure 1 shows the reduction in CDRS-R for subjects who completed the study. The groups with anxiety generally start with more severe baseline severity and completed the study with more symptoms compared to those without anxiety disorders. This is consistent for those on fluoxetine as well as placebo.

The only factor found to influence response (CGI-I of 1 or 2) was type of treatment, with participants on fluoxetine more likely to respond compared to those randomized to placebo ($p = 0.022$, odds ratio [OR] = 2.08, 95% confidence interval [CI] 1.30, 3.31), which has been previously reported (Emslie et al. 2002). Number of co-morbidities, co-morbid anxiety disorder (s), gender, age, baseline depression severity, and race were not associated with treatment outcome. These factors were also examined for interaction effects, and none was found to be statistically significant. Secondary analyses (behavioral disorders, GAD, dysthymia, "other disorders") were also not found to be significant predictors of treatment outcomes. Finally, those with and without anxiety disorder were equally responsive to active medication and placebo. That is, there was no statistically significant difference in drug-placebo differential

TABLE 1. CHARACTERISTICS OF SUBJECTS

	Fluoxetine ($n = 157$)	Placebo ($n = 152$)	Total ($n = 309$)	p value
Gender (% female)	76 (48.4%)	71 (46.7%)	147 (47.6%)	N.S.
Age ≥ 12 (%)	92 (58.6%)	83 (54.6%)	175 (56.6%)	N.S.
Mean Age (SD)	12.5 (2.6)	12.6 (2.7)	12.6 (2.6)	N.S.
Race (%)				N.S.
Caucasian	131 (83.4%)	119 (78.3%)	250 (80.9%)	
African American	10 (6.4%)	12 (7.9%)	22 (7.1%)	
Hispanic	11 (7.0%)	12 (7.9%)	23 (7.4%)	
Other	5 (3.2%)	9 (5.9%)	14 (4.5%)	
Trial (%)				
Single site ^a ($n = 95$)	48 (30.6%)	47 (30.9%)	95 (30.7%)	N.S.
Multisite trial ^b ($n = 214$)	109 (69.4%)	105 (69.1%)	214 (69.3%)	N.S.
Anxiety disorder (%)	61 (38.9%)	45 (29.6%)	106 (34.3%)	N.S.
Number of co-morbid illnesses (%)				N.S.
0	56 (35.7%)	65 (42.8%)	121 (39.2%)	
1	41 (26.1%)	39 (25.7%)	80 (25.9%)	
2	32 (20.2%)	26 (17.1%)	58 (18.8%)	
≥ 3	28 (17.8%)	22 (14.5%)	50 (16.2%)	
Response	84 (53.5%)	55 (36.2%)	139 (44.9%)	0.002
Remission	60 (38.2%)	29 (19.1%)	99 (32.0%)	0.0002

^aEmslie et al. (2002).

^bEmslie et al. (1997).

Abbreviations: N.S. = not significant; SD = standard deviation.

TABLE 2. INFLUENCE OF CO-MORBID ANXIETY DISORDER ON DEPRESSION SEVERITY AND TREATMENT OUTCOMES

	Anxiety disorder (n = 106)			No anxiety disorder (n = 203)		
	Fluoxetine (n = 55)	Placebo (n = 35)	Total (n = 90)	Fluoxetine (n = 102)	Placebo (n = 117)	Total (n = 219)
Baseline CDRS-R (SD)	61.1 (11.0)	62.0 (13.0)	61.4 (11.4)	55.8 (9.5)	54.1 (10.3)	54.9 (10.0)
Exit CDRS-R (SD)	37.7 (15.8)	49.3 (17.2)	42.2 (17.3)	35.3 (12.7)	40.2 (13.5)	37.9 (13.3)
Response (n) ^a	58.1% (32)	37.1% (13)	50.0% (45)	51.0% (52)	35.9% (42)	42.9% (94)
Remission (n) ^b	32.7% (18)	17.1% (6)	26.7% (24)	41.1% (42)	19.6% (23)	29.6% (65)

^aResponse based on Clinical Global Impressions–Improvement.

^bRemission based on Children’s Depression Rating Scale–Revised.

Abbreviations: CDRS-R = Children’s Depression Rating Scale–Revised; SD = standard deviation.

response rates (see Table 2) between those with co-morbid anxiety (21.0%) and those without anxiety (15.1%) ($\chi^2[1] = 0.21, p = 0.65$).

In examining remission, several factors influenced outcome. As with response, treatment with fluoxetine was the most significant ($p < 0.0001$, OR = 3.17, 95% CI 1.80, 5.57). In addition, being female led to increased likelihood of remission ($p = 0.024$, OR = 1.90, 95% CI 1.09, 3.30). Presence of any co-morbid disorder led to decreased chance of remission ($p = 0.026$, OR 0.73, 95% CI 0.55, 0.96). Similarly, participants with two or more co-morbid illnesses were statistically less likely to remit compared to those with no co-morbid illnesses or one co-morbid illness ($p = 0.04$, OR = 0.44, 95% CI 0.21, 0.95). Figure 2 shows the change in the outcome variable between those with two or more co-morbid illnesses versus those with less than two.

Presence of a co-morbid anxiety disorder was not a predictor or moderator of remission, and differential drug–placebo remission

rates were similar for those with and without an anxiety disorder. Likewise, the variables examined in the secondary analyses (behavioral disorders, GAD, dysthymia, “other disorders”) were not found to be significant predictors of treatment outcomes.

Discussion

Many clinical trials have strict exclusion criteria regarding co-morbidities because of concerns, including subjects with co-morbid illnesses that act as a confounder. However, the evidence is inconsistent regarding the impact of co-morbidities on the treatment outcomes of children and adolescents with depression. The results of the current study supports the findings from TADS that presence of co-morbid conditions may lead to reduced remission rates, although having an anxiety disorder or any other specific disorder does not affect likelihood of remission. Furthermore, although not

FIG. 1. Reduction in Children’s Depression Rating Score, Revised (CDRS-R) for subjects who completed the study.

FIG. 2. Change in the outcome variable between subjects with two or more co-morbid illnesses versus those with less than two. CDRS-R = Children's Depression Rating Score, Revised; comorb = co-morbid.

statistically significant, we did find numerically that subjects with anxiety disorders generally started with more severe baseline depression and completed the study with more symptoms compared to those without anxiety disorders

These findings are also consistent with the clinical indications that co-morbid pediatric depression and anxiety can be effectively treated by fluoxetine because it is approved by the Food and Drug Administration (FDA) for use in this population for both anxiety disorders and depressive disorders. However, the findings of this study, as well as earlier studies, are contradictory to that observed in the adult depression literature, where co-morbid anxiety has been observed to be a predictor of poorer outcome in participants treated with antidepressants (Fava et al. 2008; Papakostas et al. 2008; Howland et al. 2009). This difference between adult and pediatric depression may be related to a greater differentiation of depressive and anxiety disorders as a child ages.

Although this analysis did not demonstrate that co-morbid anxiety predicts or moderates depression treatment response or remission, it is important to note that it may have a different impact on outcome when other treatment modalities are used. In particular, adolescents with treatment-resistant depression and a co-morbid anxiety disorder have been shown to respond more favorably to combination therapy with both CBT and antidepressant treatment compared to antidepressant treatment alone (Asarnow et al. 2009). This potential difference is also supported by previous research, which suggests that depressed patients with co-morbid anxiety may respond more favorably to CBT compared to other forms of psychotherapy (Brent et al. 1998). However, results remain mixed.

Limitations

There are several limitations to this study. First, this study is a *post hoc* analysis of two clinical trials of antidepressants in the pediatric population, which were conducted several years apart. Second, the studies included a wide range of subjects, including age range and type of co-morbidity. Participants with any anxiety disorder, including simple phobia, were included within the anxiety group, regardless of severity. Although the anxiety disorder was only considered present if it met full diagnostic criteria, it is possible that the results would be different if only those of moderate or greater severity were included. However, these studies did not assess severity or impairment of the co-morbid disorders; rather, they assess simply whether or not a co-morbid disorder was present. For example, simple phobia may not cause significant impairment, whereas OCD can at times be very impairing. In this study, no distinction was made between these disorders. Larger samples are needed to examine the impact of each individual disorder on treatment outcome.

In sum, the results suggest that the overall burden of illness from co-morbid conditions has a greater impact on treatment outcomes in children and adolescents with depression than individual illnesses. Although specific co-morbid conditions may not impact treatment outcome, patients and parents will benefit from understanding that the greater number of disorders a child has, the less likely he or she may be to remit from depression, at least within 8 weeks. This finding, along with the similar result in the TADS study, may represent a relationship between the overall burden of illness and remission. In these instances, it may be important for

clinicians to use multimodal treatment interventions if the depression does not remit with a single intervention. However, further research is needed to better understand the optimal treatments for depressed youth suffering from multiple co-morbidities.

Disclosures

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