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Impact of Treatments for Depression on Comorbid Anxiety, Attentional, and Behavioral Symptoms in Adolescents With Selective Serotonin Reuptake Inhibitor–Resistant Depression

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Abstract

Objective—To assess the relative efficacy of antidepressant medication, alone and in combination with cognitive behavioral therapy (CBT), on comorbid symptoms of anxiety, attention, and disruptive behavior disorders in participants in the Treatment of Resistant Depression in Adolescents (TORDIA) trial.

Method—Adolescents with selective serotonin reuptake inhibitor (SSRI)–resistant depression (N = 334) were randomly assigned to a medication switch alone (to another SSRI or to venlafaxine) or to a medication switch plus CBT. Anxiety, attention-deficit/hyperactivity disorder (ADHD), and disruptive behavior disorder (DBD) symptoms were assessed by psychiatric interview and self-report at regular intervals between baseline and 24 weeks. The differential effects of medication and of CBT, and the impact of remission on the course of comorbid symptoms and diagnoses, were assessed using generalized linear mixed models.

Results—Remission was associated with a greater reduction in scalar measures of anxiety, ADHD, and DBDs, and a greater decrease in the rate of diagnosed anxiety disorders. The correlations between the changes in symptoms of depression on the CDRS-R and anxiety, ADHD, and oppositional symptoms were modest, ranging from r = 0.12 to r = 0.28. There were no significant differential treatment effects on diagnoses, or corresponding symptoms.

Conclusion—The achievement of remission had a beneficial effect on anxiety, ADHD, and DBD symptoms, regardless of the type of treatment received. There were no differential effects of medication or CBT on outcome, except for a nonsignificant trend that those adolescents treated

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with SSRIs showed a greater decrease in rates of comorbid DBDs relative to those treated with venlafaxine.

Keywords

antidepressants; cognitive behavioral therapy (CBT); comorbidity; Treatment of Resistant Depression in Adolescents (TORDIA); secondary outcomes

In community and clinically referred samples, adolescent depression is frequently comorbid with anxiety, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or conduct disorder (CD). [1–3] Comorbid conditions in adolescent depression may contribute to functional impairment and/or poorer treatment response; therefore it is important to know how current depression treatments affect comorbid conditions. [4–7]

To our knowledge, there have been no reports on the efficacy of treatments that target adolescent depression, with respect to the relief of comorbid symptomatology, in large clinical trials. We now report on the impact of the treatments for depression in the Treatment of Selective Serotonin Reuptake Inhibitor (SSRI)–Resistant Depression in Adolescents (TORDIA) study.[8] In TORDIA, adolescents with depression who had not responded to an adequate trial of an SSRI antidepressant were randomly assigned to either a switch to another SSRI or to venlafaxine, with or without cognitive behavioral therapy (CBT). We now briefly review the extant literature on the treatment of comorbid conditions in depression to formulate hypotheses about expected treatment response; this includes comparing the effects of venlafaxine to those of SSRIs, and of CBT plus medication to medication monotherapy with respect to anxiety, ADHD, and disruptive behavioral disorders (DBDs), the latter consisting of either conduct or oppositional defiant disorders.

Anxiety

Venlafaxine was initially thought to be superior to the SSRIs for the treatment of adult depression comorbid with anxiety, although later studies did not find a significant difference between drug classes.[9–13] Although venlafaxine and SSRIs have not been directly compared with respect to their effects on anxiety in children and adolescents, it appears that the impact of the SSRIs may be more robust than the impact of venlafaxine.[14,15] CBT has been shown to be efficacious for the treatment of pediatric anxiety disorders, both alone and with SSRI pharmacotherapy.[16] Although the CBT used in TORDIA had a different focus and did not routinely use exposure therapy, comorbid anxiety was a positive moderator of the therapeutic effects of CBT on depression.[17–21]

ADHD

Some preliminary evidence from open and small randomized controlled trials supports the efficacy of venlafaxine for the treatment of ADHD, because of its noradrenergic effects.[22,23] An open series trial reported that SSRIs reduced ADHD symptomatology.[24] However, the impact of venlafaxine versus SSRIs on ADHD symptoms has never been directly compared. The combination of SSRIs and stimulants, although reported as well tolerated by subjects with depression comorbid with ADHD may, in animal studies, potentiate central changes in gene expression related to the action of stimulants.[25–27] CBT has been reported to be helpful for the symptoms of adolescent ADHD, albeit with a different clinical focus than the TORDIA CBT.[28] Nevertheless, elements of the TORDIA CBT, such as problem solving, communication training, emotion regulation, and social skills training, may be beneficial to youth with comorbid ADHD.

DBDs

Currently, no pharmacological studies of DBDs in children or adolescents have focused on venlafaxine or SSRIs. However, we have found that venlafaxine was more problematic than the SSRIs in terms of agitation and self-injury in youth with high suicidal ideation in TORDIA; therefore, it is possible that venlafaxine is more problematic than SSRIs for patients with DBDs, although this has never been explicitly studied. [5,29] Randomized clinical trials in adults suggest that SSRIs may be useful in patients with intermittent explosive disorder.[30] Previous reports found that treatment of depression in youth with comorbid conduct disorder can result in a reduction in conduct symptoms.[31] One treatment study of youth with both depression and conduct disorder demonstrated the helpfulness of elements of CBT, such as problem solving, communication training, and social skills training, in the treatment of DBDs.[32]

Remission of Depression

Since pharmacological treatment of depression is similar to that for anxiety, it is reasonable to anticipate that successful treatment of depression would also result in reduction in anxiety symptoms. Less is known about the impact of treatment of depression comorbid with ADHD or DBDs, although there is a report that successful treatment of depression resulted in relief of symptoms of DBDs.[31]

In light of the extant literature, we hypothesized the following: first, venlafaxine and SSRIs would have similar impacts on anxiety disorders and symptoms, venlafaxine would be superior to the SSRIs for ADHD, and SSRIs would be superior to venlafaxine for DBDs; second, CBT would be superior to medication monotherapy for all three conditions; and third, remission of depression would be associated with a reduction in all three sets of symptoms and diagnoses.

METHOD

Participants

Participants were 334 adolescents 12 to 18 years of age with moderately severe (Clinical Global Impression–Severity [CGI-S][33] subscale ≥4 and a Children's Depression Rating Scale Revised [CDRS-R][34] ≥ 40) major depressive disorder or dysthymia, who did not respond to treatment with an SSRI of at least 8 weeks, with the last 4 weeks at a dose of at least 40 mg of fluoxetine or its equivalent (40 mg of paroxetine, 40 mg of citalopram, 20 mg of s-citalopram, or 150 mg of sertraline).[8] Excluded were potential participants with diagnoses of bipolar spectrum disorder, psychosis, pervasive developmental disorder or autism, substance abuse or dependence, eating disorders, or hypertension (diastolic blood pressure ≥90 mm Hg). Other exclusionary criteria included history of nonresponse to CBT (≥7 sessions) or venlafaxine (at least 4 weeks at ≥150 mg/d); 2 or more adequate trials of an SSRI; and use of antipsychotics, mood stabilizers, or other classes of antidepressants. Female adolescents who were pregnant, breast-feeding, or sexually active and not using contraception were also excluded. Informed assent/consent was obtained from participants and families. This study was approved by the institutional review boards of all sites.

Randomization and Treatment

Participants were randomly assigned to 12 weeks of treatment using a 2×2 balanced design of medication (new SSRI or venlafaxine) and therapy (CBT or no CBT). All participants received family psychoeducation and supportive management. Participants previously treated with fluoxetine and randomized to an SSRI switch received paroxetine and vice versa. Participants previously treated with other SSRIs (e.g., sertraline) and randomized to

an SSRI switch were assigned to either fluoxetine or paroxetine. Following international concerns about the safety and efficacy of paroxetine that emerged midway through the study, after 181 participants had been enrolled, citalopram was substituted for paroxetine in the protocol. The dosage schedule for all SSRIs began with 10 mg per day for the first week, 20 mg for weeks 2 to 6, with an optional increase to 40 mg at week 6 if there was inadequate clinical improvement (CGI Improvement subscale [CGI-I] ≥3). More than half of those adolescents treated with venlafaxine (60.8%) or an SSRI (56.2%) received a dose increase at week 6. Those assigned to venlafaxine received 37.5 mg for week 1, and for weeks 2 to 4, 75 mg, 112.5 mg, and 150 mg, respectively, with an optional increase from 150 to 225 mg at week 6. From week 6 through week 12, the average daily doses of study medications were: paroxetine, 35.2 mg(SD=8.7);citalopram,31.2mg(SD=10.1);fluoxetine, 33.8mg(SD=9.3); and venlafaxine, 200.9mg(SD= 35.2). By design, randomization balanced across treatment cells with respect to comorbid anxiety disorders. Participants who entered the study with ADHD and were on a stable dose of a stimulant were allowed to remain on it (n = 31). An additional 20 participants began a stimulant during open treatment. Participants were also allowed to have benzodiazepines prescribed as clinically indicated (n = 12).

Assessments

Mood and comorbid *DSM-IV* diagnoses were assessed at baseline, 12, and 24 weeks using the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL)[35] and grouped as follows: anxiety disorders (generalized anxiety, separation anxiety, social phobia, panic, agoraphobia, or posttraumatic stress disorder), ADHD, and DBDs (oppositional defiant or conduct disorder). Inter-rater reliability of diagnoses was conducted by tape review, and ranged from 0.62 to 0.70 across diagnoses. The K-SADS-PL can also generate scales based on the symptom ratings for attentional and disruptive symptoms ($\alpha = 0.80$ and $\alpha = 0.83$, respectively). Symptoms of anxiety disorders were assessed using the self-reported Screen for Child Anxiety Related Disorders (SCARED)[36] and were recorded at baseline, 6, 12, and 24 weeks. Parent–child conflict was assessed using the Conflict Behavior Questionnaire, Adolescent and Parent versions (CBQ-A and CBQ-P).[37]

Remission at 24 weeks was defined as at least 3 or more weeks with no more than one clinically significant symptom and no associated functional impairment.[5,38]

Data Analysis

Demographic and clinical correlates of comorbid diagnoses at baseline were identified using χ^2, Fisher exact, or Student t-tests as appropriate. We also examined the univariate relationship of demographic and clinical characteristics to the course of anxiety, ADHD, and DBD diagnoses using mixed effects logistic regression with the main effects of characteristic, time, and their interaction. Similarly, we examined the relationship of the above-noted characteristics to the course of anxiety, ADHD, and DBD symptoms using mixed effects linear regression. The impact of treatment and remission on comorbid diagnoses and symptoms was tested with mixed effect logistic or linear regressions as appropriate, testing for group-by-time interactions and controlling for the variables associated with the outcome of interest at the univariate level. Given the exploratory nature of these analyses, the α value was set at ≤ 0.05 without attempts to correct for multiple comparisons. Analyses were conducted using SPSS 17.0 and STATA 11.2.

RESULTS

Prevalence and Correlates of Comorbid Diagnoses Of the participants enrolled in TORDIA, 169/327 (51.7%) had at least one comorbid diagnosis; 119 (36.4%) had comorbid anxiety,

52 (15.7%) had ADHD, and 33 (10%) had DBDs. In all, 287 participants (85.9%) completed the week-12, and 261 (78.1%) competed the week-24 assessment; among those who completed the 24-week assessments, 122 of 254 (48%) had at least one comorbid diagnosis upon entry into the study: 87 of 254 (34.3%) had comorbid anxiety, 40 of 259 (15.4%) had ADHD, and 23 of 259 (8.9%) had DBDs. Participants with an anxiety disorder were more likely to be female ($p = .02$), to have elevated baseline interview-related depression scores ($p = .003$), and to have a history of sexual abuse ($p = .001$). Individuals with ADHD were more likely to be male ($p < .001$). Those with DBDs were more likely to have a history of drug or alcohol use (Drug Use Screening Inventory–Drug and Alcohol Use section,[39] $p = .01$), and to have higher levels of parent–child conflict as reported by both the adolescent ($p = .04$) and the parent ($p < .001$) (Table 1).

Anxiety Diagnoses and Symptoms

Although the rate of anxiety diagnoses significantly decreased over time (odds ratio [OR] = 0.88, 95% confidence interval [CI] = 0.84–0.92, z = −5.63, $p < .001$; Figure 1), there was no differential decrease between the SSRI and venlafaxine groups (medication-by-time interaction, $p = .19$) after adjusting for baseline covariates (Table 2). Since response has been shown in this sample to be dose and concentration sensitive in SSRIs, participants were stratified into those who did or did not receive a dose increase at 6 weeks, with similar results.[40] There was also no statistically significant decrease in anxiety diagnoses between the medication only and CBT groups ($p = .25$; Figure 1) after controlling for the above-mentioned variables (Table 2). Similarly, there was a decline in self-reported anxiety symptoms in both medication groups, but no group-by-time interaction ($p = .09$), after adjusting for baseline anxiety severity and self-reported depression (Figure 2a). There was no differential efficacy attributable to the addition of CBT on anxiety symptoms ($p = .38$) (Figure 2b).

The rate of anxiety disorders significantly decreased over time (36.4% to 9.3%; OR = 0.84, 95% CI = 0.81–0.89, z = −7.00, $p < .001$; Figure 1) and as expected, participants receiving benzodiazepines were still more likely meeting criteria for anxiety at the end of treatment (OR = 1.13, 95% CI = 1.03–1.25, z = 2.48, $p = .01$). Removal of those adolescents who received benzodiazepines did not change the results.

ADHD Diagnosis and Symptoms

There were significant reductions in ADHD diagnoses from intake through weeks 12 and 24 (15.7% to 4.8%; OR = 0.86, 95% CI = 0.80–0.93, z = −3.98, $p < .001$; Figure 1) but no medication-by-time interaction ($p = .53$). These results did not change when adjusting for the impact of stimulant use ($p = .87$); a three-way interaction among medication, stimulant use, and time was not statistically significant ($p = .51$). The rates of ADHD decreased both in the CBT and medication-only group, with no significant difference between groups ($p = .07$). There was no differential impact of an antidepressant dose increase on ADHD symptoms ($p = .65$). In examining the impact of medication treatment on a dimensional measure of ADHD symptoms, there were significant reductions in symptoms in both medication treatments (SSRI and venlafaxine), but no medication by time interaction ($p = .27$), indicating no differential effect of medication on symptoms (Figure 3a). Similar findings resulted when stratifying for those already on treatment with stimulants ($p = .70$) and not ($p = .19$), and in those who received an antidepressant dose increase ($p = .17$) or not ($p = .78$). The reduction in ADHD symptoms was similar in the medication only and combination group (treatment by time interaction, $p = .53$; Figure 3b).

DBD and Symptoms

There were significant reductions in the rates of DBDs over time (10% to 2.8%; OR = 0.95, 95% CI = 0.89–1.00, z = −1.99, $p = .046$; Figure 1). Participants treated with SSRIs showed a trend toward a greater reduction in the rates of DBDs over time than those treated with venlafaxine (OR = 0.90, 95% CI = 0.81–1.00, z = −1.89, $p = .06$; Figure 1). There were no differential effects of medication on DBD symptoms ($p = .51$; Figure 4a). There was also no significant differential reduction in DBD diagnoses for those who received medication only or medication and CBT ($p = .26$), and no effects of CBT compared to medication alone on continuously measured symptoms ($p = .75$; Figure 4b).

Impact of Remission

Both remitted and nonremitted participants showed statistically significant decreases in anxiety diagnoses (OR = 0.85, 95% CI = 0.78–0.93, z = −3.60, $p < .001$). There was no differential impact of remission on changes in the rates of either ADHD diagnoses ($p = .22$), or DBD ($p = .15$). For self-reported anxiety, there was no main effect for remission ($p = .94$), but there was a significant main effect of time ($p < .001$), and a significant remission-by-time interaction ($p = .003$), meaning that self-reported anxiety showed a greater rate of decrease over time in those who achieved remission (Figure 5a). Similarly, remitters showed greater reduction in attentional symptoms (group-by-time interaction, $p = .001$; Figure 5b) and in disruptive symptoms from baseline through week 24 ($p = .048$; Figure 5c). The decline in the CDRS-R from 0 to 12 weeks and from 12 to 24 weeks was modestly correlated with a decline in the SCARED (r = 0.28 and r = 0.24; p's < .001), symptoms of oppositional disorder (r = 0.20 and r = 0.21, p's < .001), and ADHD (r = 0.18 and 0.24, p's < .001).

DISCUSSION

Nearly half of the participants in this study of adolescent treatment resistant depression had at least one comorbid disorder. Remission was associated with reductions in anxiety, ADHD, and DBD symptomatology. The effects of venlafaxine and SSRIs were similar with respect to anxiety and attention, but trended toward a reduction of DBD diagnoses in the SSRI group. CBT showed no differential benefit over medication monotherapy on any outcomes. We discuss these results after putting them in the context of the study's strengths and limitations.

This study included a large, clinically representative sample of treatment-resistant, depressed participants, allowing the exploration of secondary treatment effects. On the other hand, the study was not designed to assess treatment effects on these conditions, and the sample size, except for those with anxiety symptoms, was only sufficient to detect only differential treatment effects with a large effect size. In addition, there may be other measures of attention and behavior disorders, more sensitive to change that TORDIA didnotuse, simply because these symptoms were not the main treatment focus. Because of the exploratory nature of these analyses, we did not correct for multiple comparisons; consequently, results must be interpreted cautiously and should be replicated. Because this study involved a sample of youth with chronic, treatment-resistant depression, these findings may notgeneralize to all depressed youth.

The most significant finding in TORDIA was that patients who achieved remission had a much more pronounced reduction in anxiety, attentional, and disruptive symptoms. The reduction in anxiety symptoms may be because antidepressants are at least as efficacious for anxiety as for depressive disorders. [14,15] The reduction in ADHD and DBD symptoms may result from shared symptomatology between depression and these conditions, or youth with

these conditions may have become more symptomatic when participants were also depressed. For example, improvement in depressive symptoms could include better motivation and concentration, which could affect the presentation of ADHD. A decline in the rate of DBD diagnoses could be related to the reduction in irritability and parent–child conflict because of depression, which could contribute to oppositional behavior and conduct disorder. In fact, efficacious treatment of depression has been reported to reduce the rate of conduct disorder and parent-reported parent–child conflict. [31,45] Alternatively, it is possible that youth with persistent comorbid conditions were less likely to have their depressive disorder remit, rather than vice versa. We do not believe that the main explanation for these findings is due to shared symptomatology because we counted a symptom toward both a depressive and a comorbid condition only if (assuming that the comorbid condition antedated the depression) the "shared" symptom (e.g., attention) worsened with the onset of depression. Also, the correlations between the changes in symptoms in depression and anxiety, modest oppositional disorder, and ADHD symptoms were explaining 2% to 6% of the shared variance.

Venlafaxine and SSRIs had strong and similar efficacy in the reduction of symptoms of anxiety disorders. The similar efficacy of these two classes of antidepressants is consistent with more recent studies in adults and the strong performance of SSRIs as anti-anxiety agents in pediatric clinical trials.[14,16] The rate of diagnoses and corresponding symptoms of ADHD showed similar reductions in both medication classes, although often participants with a history of ADHD entered into the study on a steady dose of a stimulant. Thus, with or without the concomitant administration of a stimulant, there was no evidence that venlafaxine provided any additional benefit for ADHD symptoms over the SSRIs, or vice versa.

We found a trend that SSRIs were associated with a greater reduction in DBD diagnoses than venlafaxine, which, given the number of contrasts, must be interpreted with caution. These findings may be consistent with other indications of greater activation associated with venlafaxine and other selective serotonin norepinephrine reuptake inhibitors (SNRIs), such as higher rates of suicide events and self-harm behaviors in those with high suicidal ideation.[29,46] That SSRIs may be of benefit for DBDs is also consistent with studies of adults with intermittent explosive disorder, finding beneficial effects of fluoxetine.[30]

CBT did not show differential effects on secondary symptoms or diagnoses relative to medication monotherapy, possibly because of its relatively low dosage (9 visits on average) and primary focus on cognitive restructuring.[19] The modest effect of CBT on anxiety might have been greater had there been a component of exposure, which many CBT theorists now believe to be the most important active therapeutic ingredient in the treatment of anxiety.[21] Similarly, although CBT in TORDIA also included problem-solving and social skills training, the "dose" of these modules relative to what is used in psychosocial interventions targeting ADHD or DBD was probably inadequate. In addition, there was relatively little family work in this protocol, which is a critical domain to target for the treatment of DBDs. Previous, more specialized protocols successfully targeted comorbid conduct disorder and depression in adolescents.[32] Recent work suggests that a modular approach to treatment, in which different evidence-based psycho-therapies are applied in a logical and hierarchical way, may help to optimize the treatment of comorbid symptomatology.[47]

In summary, these findings support the importance of attaining remission in the treatment of depression, and suggest that comorbid symptoms are likely to improve as depression abates, independent of treatment modality. These findings may suggest that an SSRI may be more beneficial than venlafaxine as a second-line intervention if a first SSRI does not work in depressed adolescents comorbid with DBDs. Otherwise, venlafaxine and SSRIs had similar

effects. The addition of CBT to antidepressant treatment, despite being important in improving depression in a treatment-resistant population,[8] did not add to the effects of medication alone with regard to comorbid conditions. In addition, these findings show that these interventions for depression are robust to comorbidity and that if remission is attainable, these interventions can reduce comorbid symptomatology as well. the importance of finding novel interventions, or sequences of interventions, to improve and accelerate the achievement of remission in depressed youth, especially in those with comorbid disorders.

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Clinical Guidance

- In adolescents with treatment-resistant depression, remission was associated with an improvement in comorbid symptoms of attention-deficit/hyperactivity disorder (ADHD), anxiety, and disruptive behavior disorders (DBDs), regardless of the type of treatment received.
- Although this study cannot address the mechanisms by which treatment for depression resulted in a decline in comorbid symptomatology, these findings highlight yet another reason why the ideal clinical endpoint for the treatment of depression should be complete remission.

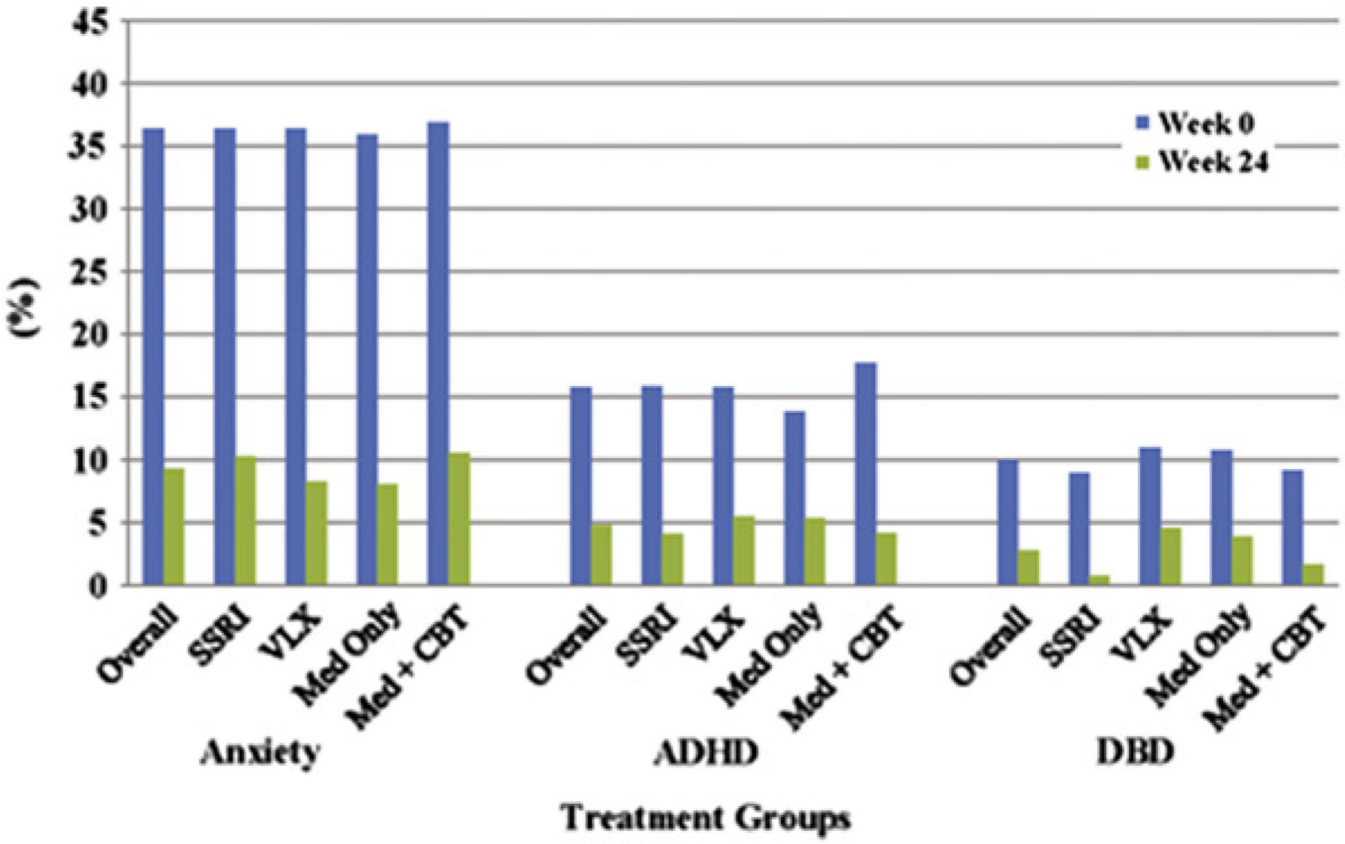

FIGURE 1.
Rates of anxiety, attention-deficit/ hyperactivity disorder (ADHD), and disruptive behavior disorder (DBD) diagnoses over time. Note: CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor; VLX = venlafaxine.

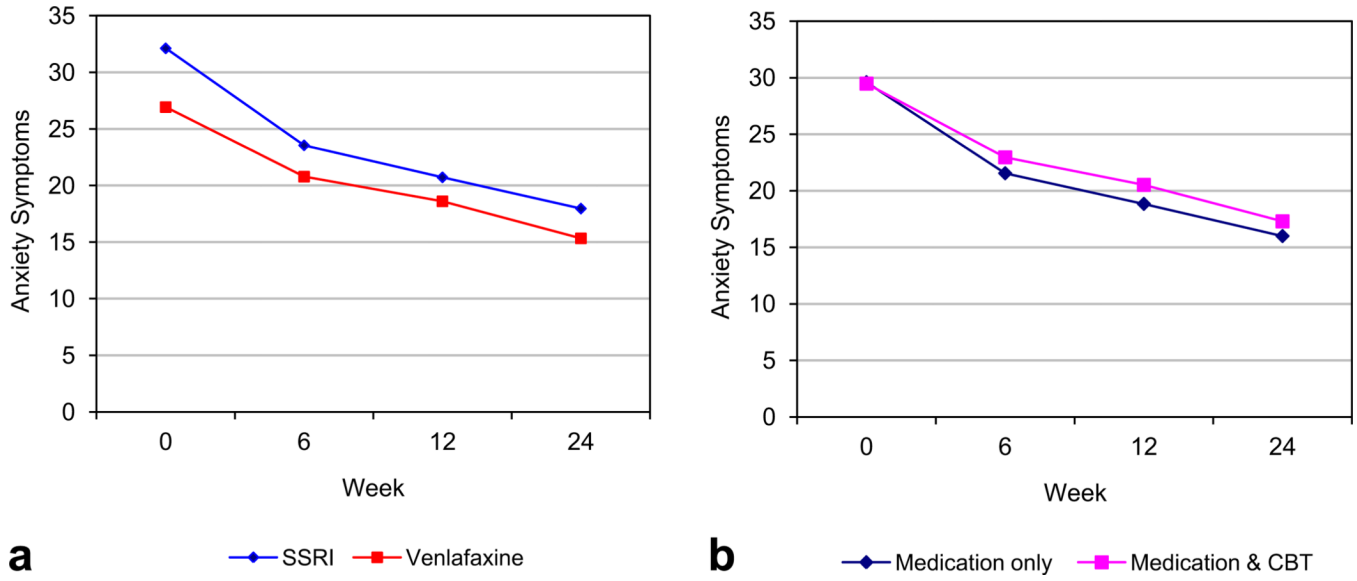

FIGURE 2.

Anxiety symptoms Screen for Child Anxiety Related Emotional Disorders (SCARED)[36] and treatment. Note: a) Medication: β = −0.53, SE = 0.72, z = −0.74, p = .46; Time: β = −4.19, SE − 0.42, z = −10.01. p < .001; Interaction: β = 1.00, SE − 0.60, z = 1.67, p= .09. b) CBT: β = −0.36, SE = 0.72, z = −0.50, p= .62; Time: β = −3.95, SE = 0.42, z = −9.48, p < .001; Interaction: β = 0.53, SE = 0.60, z = 0.88, p= .38. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor.

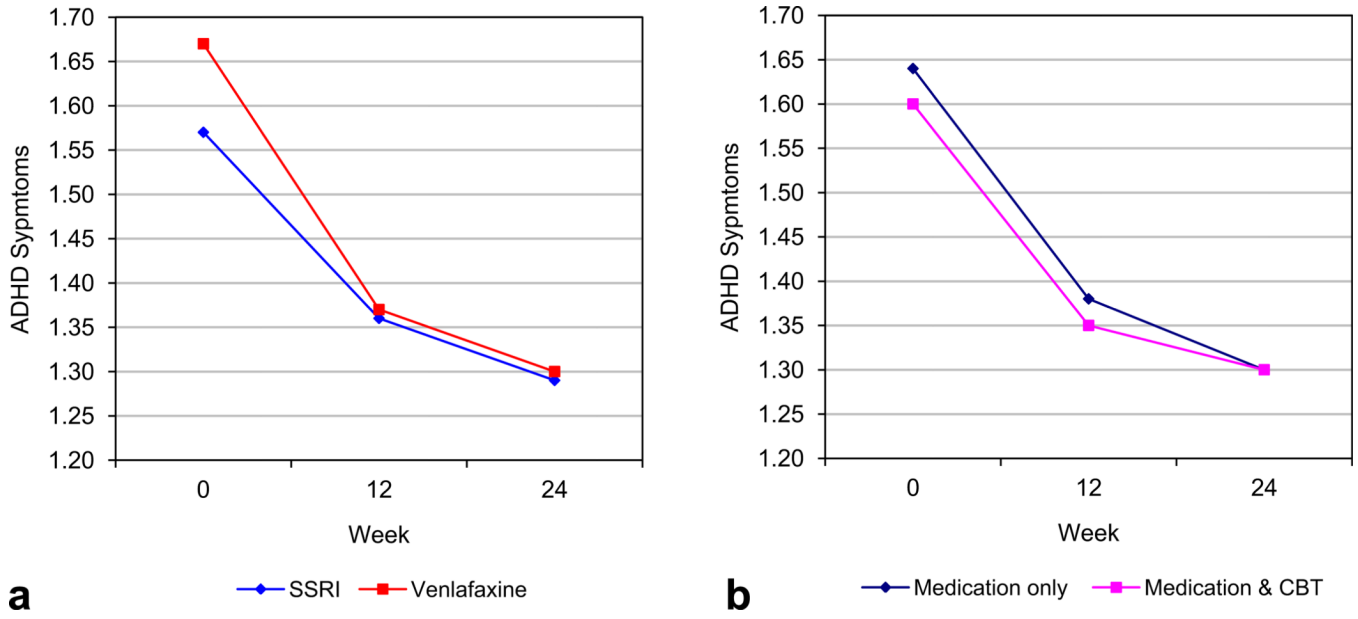

FIGURE 3.

Attention-deficit/hyperactivity disorder (ADHD) symptoms and treatment. Note: a) Medication: β = 0.08, SE = *0.07*, z = 1.28, *p* = .20; Time: β = −0.08, SE = 0.02, z = −5.32, *p* < .001; Interaction: β = −0.02, SE = 0.02, z = − 1.11, *p* = .27. b) CBT: β = −0.04, SE = *0.07*, z = −0.61, *p* = .54; Time: β = −0.10, SE = 0.01, z = −6.75, *p* < .001; Interaction: β = 0.01, SE = 0.02, z = 0.63, *p* = .53. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor.

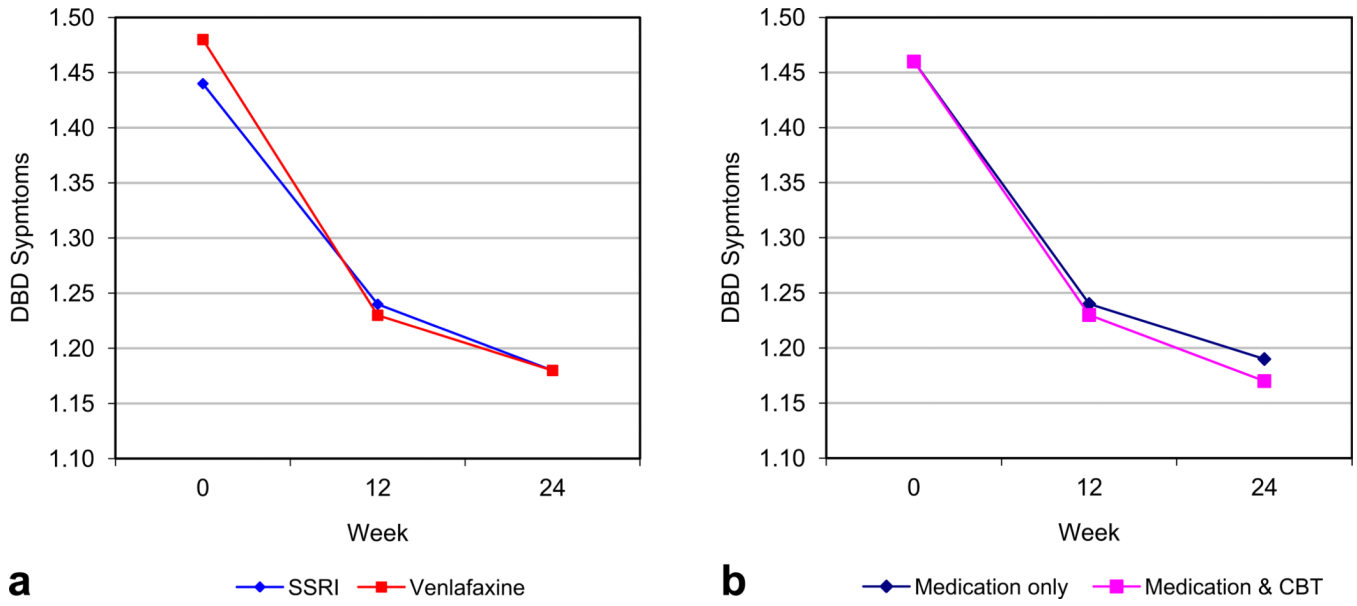

FIGURE 4.

Disruptive behavior disorder (DBD) symptoms and treatment. Note: a) Medication: β = 0.04, SE = 0.04, z = 0.80, *p*= .42; Time: β = −0.08, SE = 0.01, z = *−7.52. p* < .001; Interaction: β = −0.01, SE = 0.01, z = −0.65, *p* = *51.* b) CBT: β = 0.04, SE = 0.05, z = 0.97, *p*= .33; Time: β = −0.08, SE = 0.01, z = −7.88, *p* < .001; Interaction: β = −0.004, SE = 0.01, z = −0.32, *p*= .75. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor.

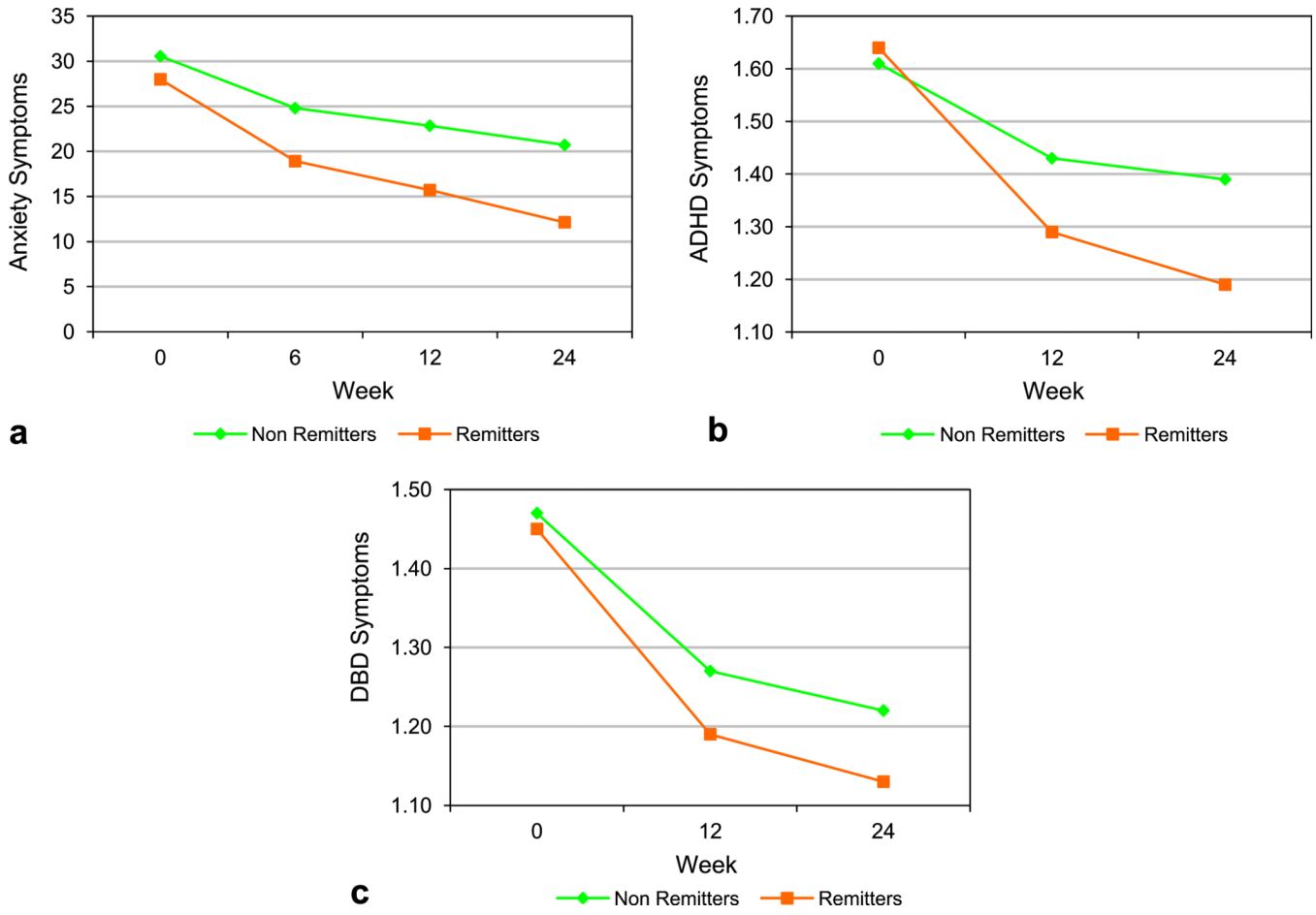

FIGURE 5.

Impact of remission on symptoms. Note: a) Remission: β = 0.06, SE = *0.74*, z = 0.08, *p* = .94; Time: β = −2.93, SE = 0.39, z = *−7.52, p* < .001; Interaction: β = −1.77, SE = 0.59, z = −2.97, *p*= .003. b) Remission: β = 0.04, SE = 0.07, z = 0.56, p = .58; Time: β = −0.06, SE = 0.01, z = −4.70, *p* < .001; Interaction: β = −0.07, SE = 0.02, z = −3.18, *p*= .001. c) Remission: β = 0.007, SE = 0.05, z = 0.16, *p*= .87; Time: β = −0.07, SE = 0.01, z = *−7.27, p* < .001; Interaction: β = −0.03, SE = 0.02, *z*= −1.98, *p*= .048. ADHD = attention-deficit/hyperactivity disorder; DBD = disruptive behavior disorder.

TABLE 1

Descriptors of Comorbidity: Significant Contrasts of Participants With and Without a Comorbid Diagnosis at Baseline[a]

	No Comorbid Dx[b]	Comorbid Dx[b]	Test	df	*p*
Anxiety, n	208	119			
Sex, female, n (%)	137 (65.9)	93 (78.2)	χ^2 =5.48	1	.02
CDRS-R	57.5 ±10.1	61.1 ± 10.4	t=−3.04	325	.003
Sexual abuse, n (%)	24 (11.9)	31 (26.3)	χ^2=10.84 χ	1	.001
ADHD, n	279	52			
Sex, male, n (%)	72 (25.8)	28 (53.8)	χ^2=16.34 χ	1	<.001
DBD, n	293	33			
Drug use, n (%)	153 (52.2)	25 (75.8)	χ^2=66.3 χ	1	.01
CBQ-A (M ± SD)	8.7 ± 6.2	11.1 ±6.1	t=−2.05	321	.04
CBQ-P (M ± SD)	9.0 ± 5.9	13.5 ± 5.1	t=−4.03	312	<.001

Note: ADHD = attention-deficit/hyperactivity disorder; CBQ-A = Conflict Behavior Questionnaire—Adolescent version [37] ; CBQ-P = Conflict Behavior Questionnaire—Parent version [37] ; CDRS-R = Children's Depression Rating Scale—Revised[34] ; DBD = disruptive behavior disorder; Dx = diagnosis.

[a] Includes only significant differences.

[b] f (%) or mean ± SD.

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2013 August 29.

TABLE 2

Baseline Demographic and Clinical Characteristics Associated to the Course of Anxiety, Attention-Deficit/Hyperactivity Disorder (ADHD) and Disruptive Behavior Disorder (DBD) Diagnosis and Symptoms

	Covariate				Time				Covariate× Time			
	β	SE	z	*p*	β	SE	z	*p*	β	SE	z	*p*
Anxiety Dx												
CDRS-R	0.08	0.02	3.09	.002	−0.38	0.10	−3.86	<.001	0.004	0.001	2.48	.01
CGAS	−0.08	0.03	−2.52	.01	0.13	0.11	1.25	.21	−0.01	0.002	−2.59	.009
SCARED	0.10	0.02	5.41	<.001	−0.14	0.04	−3.40	.001	0.000	0.001	−0.32	.75
Dysthymia	0.22	0.55	0.41	.68	−0.18	0.02	−7.53	<.001	0.09	0.03	2.76	.006
History of abuse	2.38	0.58	4.10	<.001	−0.14	0.02	−6.59	<.001	−0.02	0.03	−0.71	.48
ADHD Dx												
Age	−0.31	0.19	−1.64	.10	0.29	0.20	1.45	.15	−0.03	0.01	−2.04	.04
SIQ-Jr	−0.04	0.02	−2.78	.005	−0.17	0.05	−3.56	<.001	0.001	0.001	1.15	.25
No. of MDD episodes	0.81	0.46	1.77	.08	0.03	0.06	0.42	.68	−0.12	0.05	−2.34	.02
DBD Dx												
CGI-S	0.75	0.34	2.19	.03	0.27	0.17	1.63	.10	−0.08	0.04	−2.15	.03
Drug use–severity	0.02	0.01	2.34	.02	−0.11	0.03	−3.62	<.001	0.001	0.001	0.89	.37
CBQ-P	0.16	0.05	3.48	.001	−0.03	0.05	−0.58	.56	−0.01	0.004	−1.26	.21
MRS	0.17	0.05	3.80	<.001	−0.06	0.03	−1.80	.07	−0.01	0.004	−1.40	.16
Anxiety Sx												
SCARED	1.02	0.02	44.00	<.001	0.86	0.57	1.49	.14	−0.16	0.02	−9.04	<.001
BDI	0.65	0.06	10.20	<.001	−2.73	0.52	−5.21	<.001	−0.05	0.02	−2.24	.03
ADHD Sx												
MRS	0.04	0.01	5.63	<.001	−0.08	0.01	−5.70	<.001	−0.004	0.002	−2.02	.04
Parent at least college graduate	−0.22	0.07	−3.28	.001	−0.12	0.01	−8.35	<.001	0.05	0.02	2.49	.01
DBD Sx												
Drug use (yes/no)	0.20	0.05	4.20	<.001	−0.06	0.01	−5.46	<.001	−0.04	0.01	−2.98	.003
CBQ-P	0.03	0.004	8.86	<.001	−0.03	0.01	−1.91	.06	−0.01	0.001	−4.95	<.001
Age at onset MDD	0.004	0.001	−4.10	<.001	−0.22	0.05	−4.53	<.001	0.001	0.000	2.77	.006

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Note: BDI = Beck Depression Inventory[41] ; CBQ-P = Conflict Behavior Questionnaire—Parent version[37] ; CDRS-R = Children's Depression Rating Scale—Revised[34] ; CGAS = Children's Global Assessment Scale[42] (lower scores indicate more functional impairment); CGI-S = Clinical Global Impressions Scale—Severity[33] ; Dx = diagnosis; MDD = major depressive disorder; MRS = Mania Rating Scale[43] ; SCARED = Self-Report for Childhood Anxiety Disorders[36] ; SIQ-Jr = Suicidal Ideation Questionnaire[44] ; Sx = symptoms.