24- and 36-Week Outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS)

Dr. John Piacentini, Ph.D.,
University of California–Los Angeles (UCLA) Semel Institute for Neuroscience and Human Behavior

Dr. Shannon Bennett, Ph.D.,
Weill Cornell Medical College

Dr. Scott Compton, Ph.D.,

Correspondence to John Piacentini, PhD, UCLA Semel Institute, 760 Westwood Blvd, Rm 67-455, Los Angeles, CA 90024; jpiacentini@mednet.ucla.edu.

Dr. Compton served as the statistical expert for this research.

Duke University Medical Center

Dr. Phillip Kendall, Ph.D.,
Temple University

Dr. Boris Birmaher, M.D.,
Western Psychiatric Institute and Clinic-University of Pittsburgh Medical Center

Dr. Anne Marie Albano, Ph.D.,
New York State Psychiatric Institute–Columbia University Medical Center

Dr. John March, M.D., M.P.H.,
Duke University Medical Center

Dr. Joel Sherrill, Ph.D.,
Division of Services and Intervention Research, National Institute of Mental Health (NIMH)

Dr. Dara Sakolsky, M.D.,
Western Psychiatric Institute and Clinic-University of Pittsburgh Medical Center

Dr. Golda Ginsburg, Ph.D.,
Johns Hopkins Medical Institutions

Dr. Moira Rynn, M.D.,
New York State Psychiatric Institute–Columbia University Medical Center

Dr. R. Lindsey Bergman, Ph.D.,
University of California–Los Angeles (UCLA) Semel Institute for Neuroscience and Human
Behavior

Dr. Elizabeth Gosch, Ph.D.,
Philadelphia College of Osteopathic Medicine

Dr. Bruce Waslick, M.D.,
Baystate Medical Center

Dr. Satish Iyengar, Ph.D.,
Western Psychiatric Institute and Clinic-University of Pittsburgh Medical Center

Dr. James McCracken, M.D., and
University of California–Los Angeles (UCLA) Semel Institute for Neuroscience and Human
Behavior

Dr. John Walkup, M.D.
Weill Cornell Medical College

Abstract

Objective—We report active treatment group differences on response and remission rates and
changes in anxiety severity at weeks 24 and 36 for the Child/Adolescent Anxiety Multimodal
Study (CAMS).

Method—CAMS youth (N=488; 74% ≤ 12 years) with *DSM-IV* separation, generalized, or social
anxiety disorder were randomized to 12 weeks of cognitive behavior therapy (CBT), sertraline
(SRT), CBT+SRT (COMB), or medication management/pill placebo (PBO). Responders attended
6 monthly booster sessions in their assigned treatment arm; youth in COMB and SRT continued
on their medication throughout this period. Efficacy of COMB, SRT, and CBT (N=412) was
assessed at 24 and 36 weeks postrandomization. Youth randomized to PBO (n=76) were offered
active CAMS treatment if nonresponsive at week 12 or over follow-up and were not included

here. Independent evaluators blind to study condition assessed anxiety severity, functioning, and treatment response. Concomitant treatments were allowed but monitored over follow-up.

Results—Most (>80%) acute responders maintained positive response at both weeks 24 and 36. Consistent with acute outcomes, COMB maintained advantage over CBT and SRT, which did not differ, on dimensional outcomes; the 3 treatments did not differ on most categorical outcomes over follow-up. Compared to COMB and CBT, youth in SRT obtained more concomitant psychosocial treatments, while those in SRT and CBT obtained more concomitant combined (medication plus psychosocial) treatment.

Discussion—COMB maintained advantage over CBT and SRT on some measures over follow-up, while the 2 monotherapies remained indistinguishable. The observed convergence of COMB and monotherapy may be related to greater use of concomitant treatment during follow-up among youth receiving the monotherapies, although other explanations are possible. While outcomes were variable, most CAMS-treated youth enjoyed sustained treatment benefit. Clinical trial registration information— Child and Adolescent Anxiety Disorders (CAMS); http://clinicaltrials.gov; NCT00052078.

Keywords

Anxiety disorders are arguably the most common childhood onset psychiatric disorders with point prevalence ranging from 10–20%[1,2]. Twelve-month and lifetime-prevalence estimates in adolescence approach 25%[2] and 32%[3], respectively. Given their typically prepubertal onset and association with significant functional impact that can extend into adulthood, identifying safe, efficacious, and durable treatments for childhood anxiety disorders is important for providing both short and long term relief of suffering. Moreover, it may protect against accumulated disability over time[4,5]. To address the treatment needs of children and adolescents with anxiety disorders, the National Institute of Mental Health (NIMH) funded the Child/Adolescent Anxiety Multimodal Study (CAMS) to compare the acute efficacy (at 12 weeks) and durability (at 24 and 36 weeks postrandomization) of cognitive behavioral therapy (CBT), sertraline (SRT), a selective serotonin reuptake inhibitor (SSRI), their combination (COMB), and medication management with pill placebo (PBO) in youth with separation, generalized, and social anxiety disorders.

Earlier publications described the study protocol[6], baseline sample characteristics[4], acute safety and treatment response[7] and remission rates[8]. Briefly, all three active treatments (CBT, SRT, COMB) were more effective than PBO, and COMB was more effective than CBT or SRT alone[7]. Importantly, CAMS documented a relatively low placebo response rate suggesting that close monitoring and supportive care is ineffective for the vast majority of children with anxiety disorders. CAMS treatments were well tolerated and associated with minimal negative adverse events[7].

Several follow-up studies of cognitive-behavioral and pharmacological randomized, controlled trials for pediatric anxiety have been conducted[9,10,11,12]. However, existing research is limited by small to medium sample sizes and a focus on treatment completers and youth only receiving CBT. In addition, participants in treatment outcome study follow-ups often are exposed to off-protocol treatments following completion of the acute phase limiting what can reasonably be attributed to long-term benefit of acute treatments. Despite these limitations, existing data suggest that both CBT and SSRIs provide durable results for acute-phase responders. Kendall et al[10] found that youth who responded to CBT for their anxiety disorder demonstrated lower rates of anxiety symptoms at 7.4 year follow-up

compared to acute phase nonresponders. In addition, youth with a positive treatment response (i.e., no longer met criteria for their most troubling anxiety diagnosis) demonstrated significantly lower rates of substance use problems at follow-up than those youth with poorer acute outcomes. A similar finding was observed in subsequent analyses controlling for known predictors of substance use disorder[13]. Similarly, in a follow-up extension of the RUPP Anxiety Study[14], the largest SSRI monotherapy trial to date for separation, social, and generalized anxiety disorders, 94% (33 of 35) of acute-phase responders to SSRI treatment maintained their response over a 6-month open label follow-up[11].

CAMS is the largest randomized controlled, multi-site comparative treatment trial of CBT, an SSRI and their combination for child anxiety. CAMS included follow-up assessments from interviewers blind to acute response and treatment status to explore the durability and efficacy of 12 weeks of acute CBT, SSRI, and COMB over 6 months of maintenance treatment. Maintenance treatment was designed to reflect the manner in which the active CAMS treatments most appropriately be delivered in clinical settings. At study initiation we hypothesized that each of the three active treatments would be efficacious, with COMB treatment showing advantage over CBT and SSRI monotherapy, which would not differ from each other, both acutely and over follow-up. In this manuscript we present primary treatment outcomes at 24- and 36-weeks postrandomization. Although assessed throughout the follow-up period, youth initially randomized to PBO were intentionally excluded from these analyses, because they were offered their choice of 1 of the 3 active CAMS treatments following completion of the acute-phase or upon the absence of a response. Thus, the current study compared the active treatment groups on response and remission rates and changes in anxiety severity at weeks 24 and 36. We also examine response trajectories as determined by the pattern of response at weeks 12, 24, and 36.

METHOD

Participants

Children and adolescent (N=488) ages 7–17 (mean age 10.7) years who met *DSM-IV* criteria for separation anxiety disorder (SAD), generalized anxiety disorder (GAD), and/or social phobia (SOP) were recruited from 6 geographically diverse sites. Exclusionary criteria included comorbid mood, psychotic, or pervasive developmental disorder, and 1 failed prior CBT trial or 2 failed SSRI trials for anxiety[4]. All participants and at least one parent provided informed consent/assent. The institutional review board at each site approved and monitored the protocol. Safety monitoring was performed quarterly by the NIMH Data Safety and Monitoring Board.

Study Design

CAMS consisted of 2 phases: Phase I involved 12 weeks of acute treatment, while Phase II included 6 months of maintenance treatment. In Phase I, participants were randomized in a 2:2:2:1 ratio to 12 weeks of CBT (n=139), SRT (n=133), COMB (n=140), or PBO (n=76). SRT and PBO were double-blind conditions, although COMBO and CBT were masked to independent evaluators (IEs) but not to patients and therapists. During Phase II, assessments were completed at Weeks 24 and 36 by IEs who remained blind to initial treatment assignment and acute response status[6]. However, IE's were provided access to the results of the baseline assessment in order to facilitate improvement ratings which measured change since beginning treatment. IE continuity was maintained for most participants over the course of the study; staff changes and scheduling issues unavoidably led to assessor discontinuity in a small number of cases. Rigorous within- and cross-site training and supervision protocols served to maintain the reliability of study assessments over Phase II.

Study Treatments

Acute Phase—CAMS CBT was the *"Coping Cat"* program[15,16] adapted for CAMS[17] and involved 14, 60-minute sessions over 12 weeks. Treatment included training in anxiety management skills followed by behavioral exposure to anxiety-provoking situations. Parent(s) met briefly with their child's therapist for a check-in at the end of each session. Therapists completed training cases using the "Coping Cat" protocol, and received regular site-level and cross-site supervision over the course of the study. Youth assigned to the Pharmacotherapy conditions received 8, 30–60 minute sessions that included review and ratings of the participant's anxiety severity, treatment response, and adverse events. Sertraline and matching placebo were delivered using a "fixed-flexible" dosing schedule tied to clinical response and tolerability with a maximum daily dose of 200 mg. Pharmacotherapists consisted of experienced psychiatrists and nurse clinicians who were certified in the study pharmacotherapy protocol and also received regular site-level and cross-site supervision. Participants in COMB received both active SRT and CBT, which typically occurred in the same location and on the same day. COMB psychiatrists were purposely not blinded to CBT status in order to foster a collaborative care approach to combined treatment. Collaborative care approaches such as the one employed in CAMS have been associated with better outcomes, and in some cases, lower doses of medication used (the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) Study, the Treatment for Adolescents With Depression Study [TADS])[18,19].

Maintenance Phase—Participants rated as acute-phase responders (defined below) were maintained in their originally assigned condition over the 6-month maintenance period as described below. Maintenance and acute phase treatments differed in the following ways. Acute CBT was weekly with new material presented each session. Maintenance CBT was delivered monthly with no new material presented. New or worsening symptoms were addressed in booster session using the techniques previously learned during the acute phase. Acute medication treatment included weekly or biweekly clinic visits with dosing increases over time. Maintenance medication was maintained at end of acute phase doses with only dose decreases allowed for late emerging side effects. Visits were monthly as in CBT and any necessitated dosing increases led to subject's removal from the treatment phase of the study (although they continued in the assessment component of the study). CBT and Med maintenance strategies were designed to reflect how the two treatments would be delivered in clinical settings. Youth in maintenance COMB treatment received both CBT and medication according to the schedule and constraints associated with each individual treatment. Where possible, and in most cases, COMB youth attended their monthly CBT and med visits on the same day.

Study youth were also allowed up to 2 adjunctive services/attrition prevention (ASAP) sessions with their CBT and/or pharmacotherapists during each study phase (acute and maintenance). ASAP sessions were in addition to regularly scheduled treatment sessions and were designed to address emergent issues, including significant symptom worsening or environmental stressors (such as school expulsion, peer bullying, or parental divorce) that might pose safety concerns or increased risk of study attrition. Acute Phase nonresponders to active treatment were referred to community providers, while PBO nonresponders were offered their choice of an active CAMS treatment. PBO responders entered maintenance and attended monthly medication visits similar to active medication responders. PBO responders who relapsed during maintenance were offered the same choice of active CAMS treatment as initial PBO nonresponders. CAMS allowed the use of off-protocol (e.g., concomitant) interventions during maintenance to maximize sample retention for study analyses and to ensure that treatment was not withheld from a symptomatic child for an inordinate amount

of time during study participation. Off-protocol psychopharmacologic and psychosocial intervention use was carefully monitored over the course of the maintenance phase.

Assessments

Demographic data, anxiety and comorbid symptomatology, and psychosocial functioning were obtained using self- and parent-report and blinded IE-administered interviews of the parent and child at screening, baseline and weeks 4, 8, 12, 24, and 36. The Anxiety Disorders Interview Schedule for *DSM-IV- TR*, Child Version[20] established diagnostic eligibility. The primary categorical outcome was responder status based on dichotomized Clinical Global Impression-Improvement Scale[21]; youth who received ratings of 1 ("very much improved") or 2 ("much improved"), which reflected substantial, clinically meaningful improvement in anxiety severity, were categorized as responders. The primary continuous outcome was anxiety severity measured by the Pediatric Anxiety Rating Scale (PARS), computed by summing 6 items assessing anxiety severity, frequency, distress, avoidance, and interference over the previous week[22]. Total PARS scores range from 0–30, with scores above 13 indicating clinically meaningful anxiety[23]. In prior research, the PARS has demonstrated acceptable internal consistency (alpha = 0.64), strong inter-rater reliability (r=0.97), moderate retest reliability (r=0.55), and significant correlations, in the expected direction, with a range of validity indicators[22]. In the present sample, PARS internal consistency was good to excellent (intraclass correlation coefficients: Wk0 = .69; Wk12 = .90; Wk36 = .89). The Children's Global Assessment Scale[24] was used to rate overall functional impairment. Scores range from 1–100, with scores of 60 or lower considered indicative of significant dysfunction and need for treatment. The Clinical Global Impressions Severity scale (CGI-S) is a clinician rating of anxiety severity ranging from 1 (not at all ill) to 7 (extremely ill)[21]. A score of 1 or 2 reflects no to minimal symptoms. In Phase I, inter-rater agreement was high for anxiety severity as assessed by the PARS (r=0.85) and diagnostic status as assessed by the ADIS-C/P (ICCs=0.82–0.88) based on videotaped-review of 10% of baseline and week-12 IE assessments[7]. Inter-rater agreement (weighted kappa) for specific CAMS anxiety diagnoses were .87 for SAD, .78 for SOP, and .72 for GAD at week 12, and .88 for SAD, .84 for SOP, and .81 for GAD at week 36. PARS reliability was not assessed over follow-up.

Treatment Response and Remission Definitions

In addition to positive treatment response (e.g., CGI-I = 1 or 2), Excellent Treatment Response was defined as a CGI-I score of 1 (very much improved). Two definitions of remission, initially developed to characterize acute-phase outcomes[8], were used. Remission-Severity (CGI-S = 1 or 2) indicated no or only occasional symptoms and the absence of any symptom-related impairment or need for accommodation. Remission-Diagnosis was indicated by the absence of ADIS SAD, SOP, and GAD diagnoses, although residual symptoms may have been present at a subdiagnostic level[8]. Each of the response and remission indicators was ascertained at both weeks 24 and 36, except for Remission-Diagnosis at week 24 since the ADIS was not administered at this time-point.

Six additional groups of treatment responders were identified. "Always Responders" were individuals who met positive response criteria at all three assessment points (Weeks 12, 24, and 36). "Always Non-Responders" were those who failed to meet response criteria at any of the three assessments, and "New Phase II Responder" was defined as a Week 12 nonresponder who became a responder by Week 24 or Week 36. Week 12 responders failing to meet these criteria at Week 24 or 36 were defined as "Phase II Relapse", while participants defined as "Phase II Regained" were Week 12 responders who lost response at Week 24 but regained it at Week 36. Finally, "Temporary Responders" were defined as Week 12 nonresponders who met criteria for responder at Week 24 but lost it at Week 36.

Statistical Analyses

Missing Data—Of the 412 eligible participants (e.g., those initially randomized to active treatment), 90 (21.8%) and 87 (21.1%) did not complete the Week 24 and 36 assessments, respectively. We employed a multiple imputation approach to replace missing values[25,26], using a sequential regression multivariate imputation algorithm as implemented in the IVEware[27] package for SAS. The imputation model included all baseline demographic characteristics; total scores on all parent- and child self-report measures at each assessment point; IE measures of clinical outcome at weeks 24 and 36; treatment condition; and treatment site as stratification variables. Using these variables, we generated 20 imputed data sets and then combined the results of identical analyses across these data sets using Rubin's established guidelines[25].

RESULTS

The mean age of the CAMS sample at pretreatment was 10.7±2.8 with 74.2% aged 12 or younger. Participants were predominantly white (78.9%), middle class (74.6%) youth, with a nearly equivalent number of males (50.4%) and females (49.6%). The majority of participants were diagnosed with 2 or more primary anxiety disorders (78.7%) and one or more secondary disorders (55.3%). Overall, 35.9% of the sample met criteria for all three targeted anxiety disorders, while the proportion of participants meeting criteria for only 1 targeted anxiety disorder was relatively small (3.3% SAD only, 11.3% SOP only, 6.8% GAD only). There were no significant differences in the distribution of anxiety diagnostic categories across the four treatment conditions. Overall, 74.9% were rated as markedly to severely ill on the CGI-S at baseline. See Kendall *et al.*[4] and Walkup *et al.*[7] for further details.

Acute Outcome

As reported by Walkup *et al.*[7], at the end of acute treatment (Week 12), COMB was associated with a significantly higher response rate (80.7%) on the CGI-I than either CBT-alone (59.7%) or SRT-alone (54.9%). Response rates for the 2 monotherapies did not differ from each other, and all 3 active treatments were superior to PBO (28.3%). An identical pattern of response was found for the PARS, CGAS, and CGI-S.

Attrition at Weeks 24 and 36

As noted, 370 (89.9%) of the 412 subjects randomized to active treatment at baseline completed the post-treatment assessment at week 12, 322 (78.2%) completed the week 24 assessment and 325 (78.9%) completed the final assessment at week 36. (Figure 1). There was no significant difference in the rate of study attrition based on treatment group assignment at week 24 (chi-square= 1.18, *p*=0.55), nor at week 36 (chi-square=2.50, *p*=0.29).

Outcomes at Weeks 24 and 36

Categorical Outcomes—Categorical Response rates for COMB, SRT, and CBT are presented in Table 1. Although the responder and excellent responder rates for COMB held steady through weeks 24 and 36, the rates for both SRT and CBT improved considerably such that the superiority of COMB over the monotherapies seen at week 12 failed to achieve statistical significance at weeks 24 and 36. A somewhat different pattern emerged with regard to remission status. Remission rates based on CGI-S severity were consistent across the three assessment points for COMB and at weeks 12 and 24 for CBT and SRT. However, these rates improved significantly for the monotherapies from week 24 to 36 such that the superiority of COMB seen at weeks 12 and 24 was no longer evident at week 36. In contrast,

remission based on the absence of any CAMS-targeted ADIS diagnosis (e.g., SAD, SOP, or GAD) evidenced minimal change from week 12 to week 36 for any treatment group such that COMB maintained superiority over both CBT and SRT at the final follow-up assessment.

Most youth who responded to acute phase treatment maintained a consistent positive response over the 6-month follow-up period, with 83% of COMB, 82% of SRT and 80% of CBT responders at week 12 achieving similar status at both weeks 24 and 36. Conversely, only 5% of youth receiving COMB and only 15–16% of those receiving monotherapy failed to achieve responder status at any point during study participation. There were no significant treatment condition differences in rates of new response, relapse, or inconsistent response patterns over follow-up, although there were few subjects falling into these categories.

Dimensional Outcomes—COMB maintained superiority over CBT and SRT on all 3 dimensional outcome measures (PARS, CGI-S, CGAS) at both week 24 and week 36 (Table 3, Figures 2–4). Effect sizes (Hedges'g) were computed for the PARS, CGI-S, and CGAS to document the magnitude and clinical significance of between group differences with regard to the three active CAMS treatments (Table 3). Effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large. At Week 24, the absolute effect sizes for COMB relative to both CBT and SRT ranged from 0.51 to 0.81 across the PARS, CGI-S, and CGAS indicating a generally moderate advantage of combined treatment over monotherapies at this time point. At week 36, however, the magnitude of the COMB-monotherapy comparison had attenuated (absolute effect sizes ranging from 0.34 to 0.41) suggesting a small clinical advantage of the former over latter treatments at 6 months post-acute treatment. The absolute effect sizes derived from comparison of CBT and SRT, ranging from 0.14 to 0.22 at Wk 24 and from 0.04 to 0.08 at Wk 36, did not favor one of these treatments over the other.

ASAP and Concomitant "Off-Protocol" Treatment—Approximately 6% of participants received at least one Adjunctive Services/Attrition Prevention (ASAP) session over follow-up. For COMB, 29 (23.9%) youth attended any ASAP session over follow-up, with 18 (14.9%) attending a session between week 12 and week 24 and 14 (12.2%) attending a session between week 24 and week 36. The rates for CBT were weeks 12–24 = 7 (5.5%), weeks 24–36 = 8 (6.5%), Total = 13 (10.2%), while those for SRT were weeks 12–24 = 8 (7.5%), weeks 24–36 = 6 (5.9%), and Total = 13 (12.1%).

Utilization of off-protocol treatment for all CAMS participants was monitored throughout the 6-month follow-up, although these data were missing for 57 (13.8%) of youth randomized to active treatment. For those for whom data were available, receipt of off-protocol treatment during maintenance was reported by 15.7% (19 of 121) of those receiving COMB, 36.4% (39 of 107) of the SRT group, and 29.9% (38 of 127) of those randomized to CBT (Table 4). With respect to new psychosocial treatments, pairwise comparisons revealed that more SRT participants obtained nonCAMS psychosocial treatment when compared to COMB participants (chi-square=12.43, $p<0.001$) and CBT (chi-square=7.72, $p<0.01$). There were no differences between COMB and CBT participants with respect to obtaining additional non-CAMS psychosocial treatments during maintenance (chi-square=0.50, p=0.48). There were no statistically significant differences between COMB, SRT, and CBT with respect to seeking new psychopharmacological treatments during maintenance. However, both SRT and CBT participants were more likely to initiate both non-CAMS psychosocial and non-CAMS psychopharmacological treatment during maintenance when compared to COMB (chi-square=7.369, p<0.007, chi-square=9.88, p<0.002, respectively. There were no differences between SRT and CBT in the number of participants who sought both non-CAMS psychosocial and non-CAMS psychopharmacological treatment (p=0.70). Thus, findings suggest that SRT participants were more likely to seek non-CAMS

psychosocial treatments during maintenance, and both SRT and CBT participants were more likely to seek both non-CAMS psychosocial and non-CAMS psychopharmacological treatment.

DISCUSSION

The current study examined the relative effectiveness and durability of CBT (Coping Cat), sertraline (SRT), and their combination (COMB) over six months of maintenance treatment following 12 weeks of acute treatment. Positive outcomes observed at the end of acute treatment (week 12) were largely maintained or enhanced across all 3 treatment conditions over the subsequent 6 months with COMB maintaining superiority over CBT and SRT on some outcomes, while the monotherapies effectively caught up with COMB on others. Also similar to the pattern of acute phase response, CBT and SRT were indistinguishable over follow-up across all outcomes studied. These findings significantly enhance current knowledge regarding the 6-month outcomes associated with evidence-based interventions for anxiety. Moreover, the large sample size, relatively high subject retention, age distribution, broad eligibility criteria, and geographic distribution of study sites all contribute to the generalizability of these findings. Conversely, the exclusion of youth with significant depressive symptoms, a relatively common feature of anxiety in older youth[1], limits study generalizability.

Of interest, between treatment conditions, differences in outcome were largely related to the nature of the outcome indicator with COMB less likely to outperform monotherapy over time on categorical measures of response, as opposed to continuous measures. Although COMB maintained both statistical and clinical superiority over CBT and SRT, which did not differ, on continuous measures of anxiety severity (PARS, CGI-S) and functional status (CGAS) at weeks 24 and 36, there was some attenuation of this difference with moderate effect sizes for COMB superiority at week 24 as compared to small effect sizes for COMB superiority at week 36. In contrast, the significant between group differences in absolute rates of response, excellent response, and remission based on severity favoring COMB at week 12 following completion of acute treatment disappeared by week 36. It is of interest to note that a similar pattern of findings has also been observed in the treatment literature for depressive disorders[28]. This convergence was due to an increase in response rates for the monotherapies in light of little or no change in the corresponding rates for COMB. Although COMB appears best for prompt benefit, all 3 treatment conditions appear beneficial at 6 months. COMB did demonstrate efficacy over CBT and SRT in the proportion of youth consistently classified as responders at each of the three outcome assessments, although this was not wholly unexpected given that these classifications were heavily influenced by status at week 12.

The current findings are largely consistent with the acute phase findings[7], but the specific pattern of outcomes reported herein needs to be considered in light of the concomitant (e.g., off-protocol) treatments received by some study youth during maintenance Dealing with off-protocol treatments is a notable challenge of follow-up studies[10,29,30], and CAMS was no exception. As noted, concomitant interventions were allowed, but tracked, during maintenance to maximize sample retention for study analyses and to ensure that treatment was not withheld from a symptomatic child for an inordinate amount of time over the course of study participation.

Although the absolute rate of youth receiving concomitant treatment was moderate, with 27% of study youth receiving at least one non-CAMS treatment over the follow-up interval, there were significant differences in this rate across the 3 CAMS treatment groups. SRT showed the highest rate of outside treatment use (36.4%) versus 29.9% for CBT and only

13.5% for COMB. In addition, youth randomized to SRT were more likely than those randomized to COMB or CBT to seek non-CAMS psychosocial treatment during maintenance while those randomized to SRT and CBT were more likely to receive both non-CAMS medication and psychosocial treatments (although not necessarily at the same time) as COMB. The relative attenuation in COMB superiority, which as noted, was due to increased benefits from monotherapy, as opposed to reduced benefits from COMB, may be related to the higher cumulative concomitant treatment rates reported for the two monotherapy groups over the course of follow-up. Unfortunately, data regarding the quality and potential efficacy of the concomitant treatments received is not available limiting our ability to directly assess the potential benefits accrued from these interventions. In addition, it is also impossible to rule out the possibility that the benefits of the monotherapies increased over time and effectively "caught up" to COMB by the end of the study. The fact that this attenuation was most pronounced for the categorical outcomes may be due to lower statistical power associated with analysis of dichotomous versus continuous variables.

Study limitations include the lack of a placebo comparison group at the week 24 and 36 assessments, concomitant treatment usage, sample characteristics that might limit generalizability, and differential expectations and treatment contact across conditions. As noted earlier, ethical and attrition concerns did not allow us to withhold active treatment during follow-up from those youth initially randomized to PBO, and 79% of these youth received an active CAMS treatment at some point during study participation. As such, the resultant lack of a PBO control does not allow us to rule out the possibility that the continued benefits of the CAMS treatments over follow-up were due to maturation or the passage of time. However, such concerns may be at least partially mitigated by the observed superiority of COMB over the monotherapies on some of our outcome measures. Although allowed by the study protocol, concomitant treatment usage during maintenance complicated our ability to examine the absolute and relative durabilities of the three active CAMS treatments over follow-up and contributed to the observed convergence of outcomes across these treatment arms. CAMS used relatively broad inclusion criteria and enrolled a reasonably diverse sample. However the sample was predominantly pre-teen, did not include the most socioeconomically disadvantaged children, and excluded youth with major depressive and pervasive developmental disorders, which limits the generalizability of study findings.

The interpretation of study findings may also be complicated by certain design elements of the CAMS trial. First, youth in COMB received somewhat greater treatment contact by virtue of needing to meet separately with their CBT therapist and psychopharmacologist on a regular basis during both acute and maintenance study phases. Second, CBT and COMB, but not SRT, were unblinded conditions which may have also influenced treatment expectations. Finally, although CAMS youth received monthly treatment sessions during maintenance, medication was taken continually as opposed to instruction in CBT techniques which was only provided during scheduled treatment sessions. These design elements, which are not unique to the present study[18,19], need to be considered against the overall goal of CAMS which was to maximize the ecological validity of CAMS treatments to the extent possible within a primarily efficacy trial.[6] Consistent with this approach, maintenance treatment was designed to maximize the generalizability of study findings by reflecting the way these treatments were delivered in the "real world"; i.e., acute medication responders typically stay on their medication over time, while acute CBT responders typically stop or taper this treatment returning to clinic to address emergent or worsening symptoms as needed. Although it is not possible to determine the potential impact of treatment intensity and duration on outcome in the present study, the fact that CBT and SRT outcomes did not differ over follow-up and in some cases, caught up to COMB, supports the benefits of these interventions.

Finally, the present analyses focused on treatment response and remission and did not address safety, secondary outcomes, predictors (e.g., clinical characteristics) of response over the 36 week follow-up period, outcomes for youth in the placebo group, and site differences across the CAMS treatment centers. Additional reports addressing these important topics are currently being prepared by CAMS investigators.

The present study extends CAMS acute phase findings[7] and supports the efficacy and durability of CBT and sertraline either in combination or as monotherapies for youth with commonly occurring and moderately severe childhood anxiety disorders. Our findings are consistent with the existing anxiety treatment follow-up literature, which suggests that response to both CBT[7] and SSRI monotherapy[11] is highly durable over follow-up. Although the combination of CBT and sertraline yielded a somewhat more positive outcome over the monotherapies even in the face of higher rates of concomitant therapy in the CBT and SRT groups, each of the three CAMS treatments are viable alternatives with the ultimate choice dependent on treatment availability, cost, burden, and family preference.

Acknowledgments

References

1. Costello J, Egger H, Angold A. The developmental epidemiology of anxiety disorders: Phenomenology, prevalence, and Comorbidity. Child Adol Clinics North America. 2005; 14:631–648.

2. Kessler RC, Avenevoli S, Costello JE, et al. Prevalence, Persistence and Sociodemoraphic Correlates of DSM-IV Disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry. 2012; 69:372–380. [PubMed: 22147808]

3. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010; 49:980–989. [PubMed: 20855043]

4. Kendall P, March J, Sherrill J, Walkup J, Albano AM, Birmaher B, Compton S, Ginsburg G, Rynn M, McCracken J, Gosch E, et al. Clinical characteristics of anxiety disordered youth. J Anx Dis. 2010; 24:360–65.

5. Ramsawh HJ, Chavira DA, Stein MS. Burden of anxiety disorders in pediatric medical settings: prevalence, phenomenology, and research agenda. Arch Ped Adol Medicine. 2010; 164:965–972.

6. Compton S, Walkup J, Albano AM, et al. Rationale, design, and methods of the Child/Adolescent Anxiety Multimodal Study (CAMS). CAPMH. 2010; 4:1. (http://www.capmh.com/content/4/1/1). [PubMed: 20051130]

7. Walkup J, Albano AM, Piacentini J, et al. Cognitive-behavioral therapy, sertraline and their combination for children and adolescents with anxiety disorders: acute phase efficacy and safety. NEJM. 2008; 359:2753–2766. [PubMed: 18974308]

8. Ginsburg G, Kendall P, Sakolsky D, et al. Remission after acute treatment in children and adolescents with anxiety disorders: Findings from the CAMS Study. J Cons Clin Psychol. 2011; 79:806–813.

9. Kendall PC, Hudson JL, Gosch E, Flannery-Schroeder E, Suveg C. Cognitive behavioral therapy for anxiety disordered youth: a randomized clinical trial evaluating child and family modalities. J Cons Clin Psychol. 2008; 76:282–297.

10. Kendall PC, Safford S, Flannery-Schroeder E, Webb A. Child anxiety treatment: outcomes in adolescence and impact on substance use and depression at 7.4 year follow-up. J Cons Clin Psychol. 2004; 72:276–287.

11. The Research Units on Pediatric Psychopharmacology Anxiety Study Group. Treatment of pediatric anxiety disorders: An open-label extension of the Research Units on Pediatric Psychopharmacology Anxiety Study. J Child Adol Psychopharmacology. 2002; 12:175–188.

12. Saavedra LM, Silverman WK, Morgan-Lopez AA, Kurtines WM. Cognitive behavioral treatment for childhood anxiety disorders: long-term effects on anxiety and secondary disorders in young adulthood. J Child Psychol Psychiatry. 2010; 51:924–934. [PubMed: 20345838]

13. Puleo CM, Conner BT, Benjamin CL, Kendall PC. CBT for childhood anxiety and substance use at 7.4-year follow-up: A reassessment controlling for known predictors. J Anx Disorders. 2011; 25:690–696.

14. Pine DS, Walkup JT, Labellarte MJ, et al. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. NEJM. 2001; 344:1279–1285. [PubMed: 11323729]

15. Kendall, PC.; Hedtke, KA. Cognitive behavioral therapy for anxious children: therapist manual. 3. Ardmore, PA: Workbook Publishing; 2006.

16. Kendall, PC.; Hedtke, KA. Coping Cat workbook. 2. Ardmore, PA: Workbook Publishing; 2006.

17. Kendall PC, Gosch E, Furr JM, Sood E. Flexibility within fidelity. J Am Acad Child Adolesc Psychiatry. 2008; 47:987–993. [PubMed: 18714195]

18. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999; 56:1073–1086. [PubMed: 10591283]

19. TADS Study Team. Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression: Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial. JAMA. 2004; 292:807–820. [PubMed: 15315995]

20. Albano, AM.; Silverman, WK. Clinician Manual. New York: Oxford University Press; 1996. The Anxiety Disorders Interview Schedule for DSM- IV, Child Version.

21. Guy, W.; Bonato, R., editors. CGI: Clinical Global Impressions. Chevy Chase, Maryland: National Institute of Mental Health; 1970.

22. Research Units on Pediatric Psychopharmacology Anxiety Study Group. The Pediatric Anxiety Rating Scale (PARS): Development and psychometric properties. J Am Acad Child Adolesc Psychiatry. 2002; 41:1061–9. [PubMed: 12218427]

23. Ginsburg GS, Keeton CK, Drazdowki T, Riddle M. The utility of clinicians' ratings of anxiety using the Pediatric Anxiety Rating Scale (PARS). Child and Youth Care Forum. 2011; 40:93–105.

24. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry. 1983; 40:1228–1231. [PubMed: 6639293]

25. Little, RJA.; Rubin, DB. Statistical analysis with missing data. 2. New Jersey: John Wiley & Sons, Inc; 2002.

26. Rubin DB. Multiple imputation after 18+ years. J Am Statistical Assoc. 1996; 91:473–489.

27. Raghunathan, TE.; Solenberger, PW.; Van Hoewyk, J. IVEware: imputation and variance estimation software. University Michigan, Ann Harbor: Survey Research Center, Institute for Social Research; 2002.

28. March JS, Silva S, Petrycki S, et al. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007; 64:1132–43. [PubMed: 17909125]

29. Emslie G, Mayes T, Porta G, et al. Treatment of Resistant Depression in Adolescents (TORDIA): Week 24 Outcomes. Am J Psychiatry. 2010; 167:782–791. [PubMed: 20478877]

30. Jensen P, Arnold E, Swanson J, et al. 3-year follow-up of the NIMH MTA Study. J Am Acad Child Adolesc Psychiatry. 2007; 46:989–1002. [PubMed: 17667478]

Clinical Guidance

- The majority of youth with separation, generalized or social anxiety disorder who responded to acute treatment with CBT, sertraline, or their combination and received continued treatment with monthly cognitive behavior therapy (CBT) booster sessions, sertraline, or their combination maintained a positive response 3 and 6 months later.

- Youth assigned to acute and maintenance combination treatment showed better outcomes on some measures and utilized less concomitant treatment than those assigned to CBT or sertraline.

- This study's findings are consistent with the existing anxiety treatment literature which has suggested that response to both CBT and selective serotonin reuptake inhibitor (SSRI) are durable with maintenance treatment.
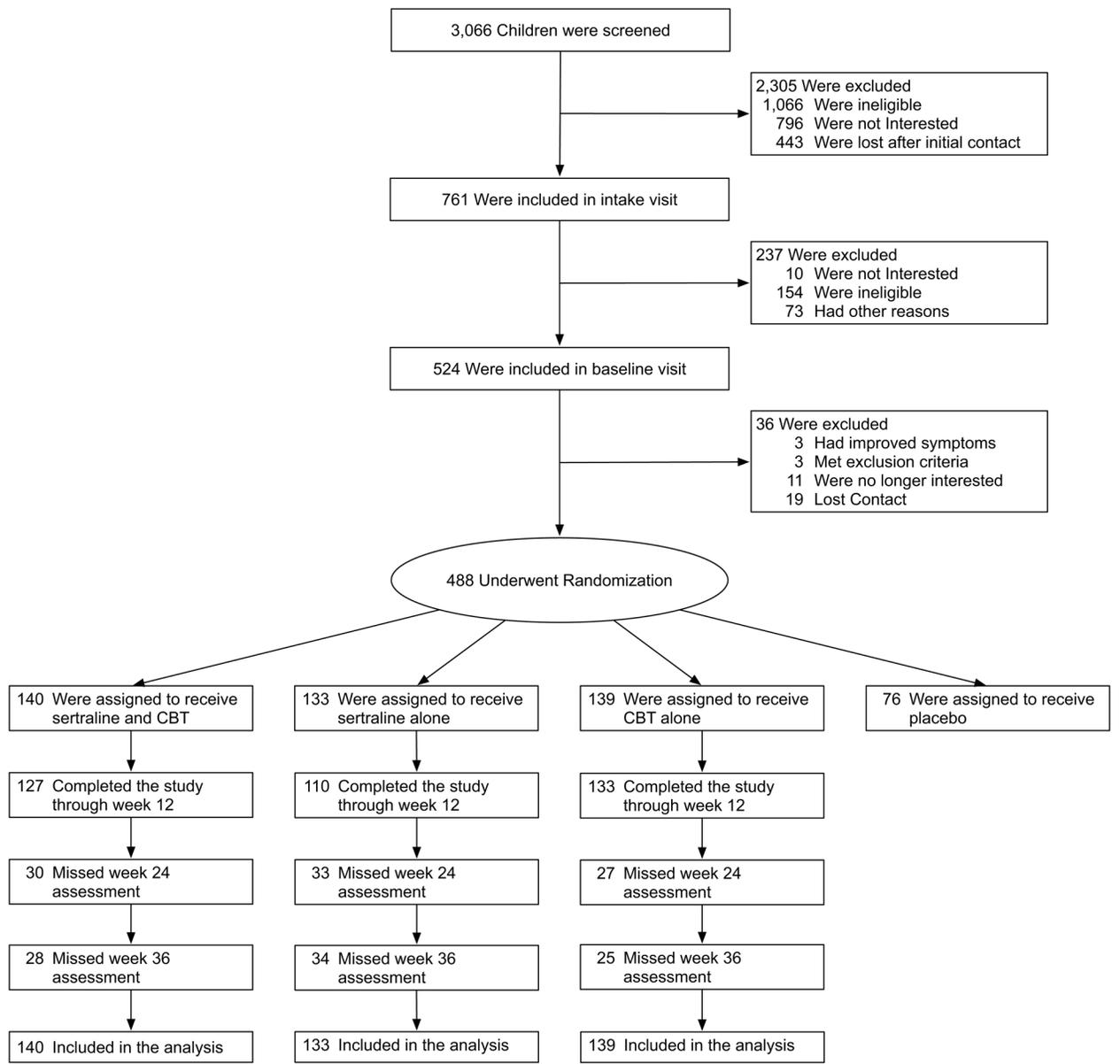
Figure 1.
Consort diagram.
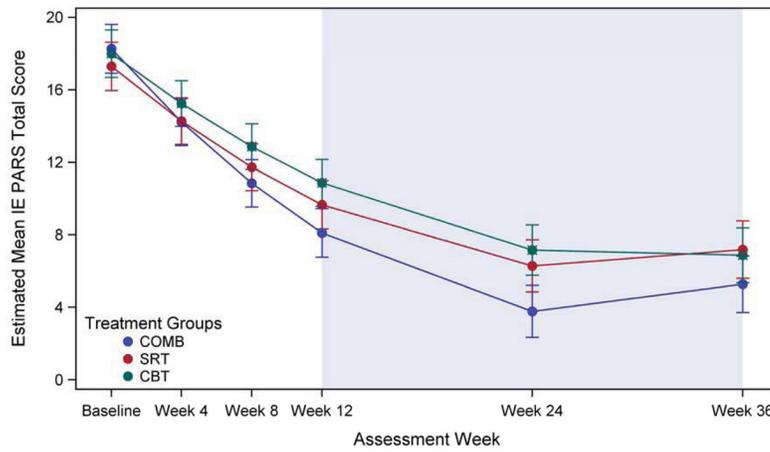
FIGURE 2.
Estimated mean scores for the Pediatric Anxiety Rating Scale (PARS) by treatment group over 36 weeks. Note: Shaded area indicates follow-up period. CBT = cognitive behavior therapy; COMB = combined (CBT+sertraline) treatment; SRT = sertraline.

FIGURE 3.
Estimated mean scores for the Clinical Global Impressions-Severity Scale (CGI-S) by treatment group over 36 weeks. Note: Shaded area indicates follow-up period. CBT = cognitive behavior therapy; COMB = combined (CBT+sertraline) treatment; SRT = sertraline.

FIGURE 4.
Estimated mean scores for the Children's Global Assessment Scale (CGAS) by treatment group over 36 weeks. Note: Shaded area indicates follow-up period. CBT = cognitive behavior therapy; COMB = combined (CBT+sertraline) treatment; SRT = sertraline.
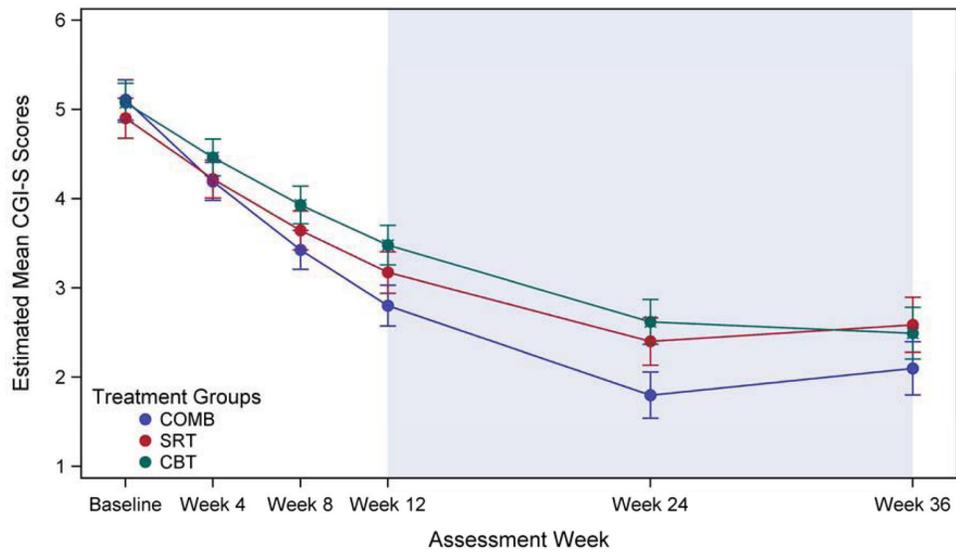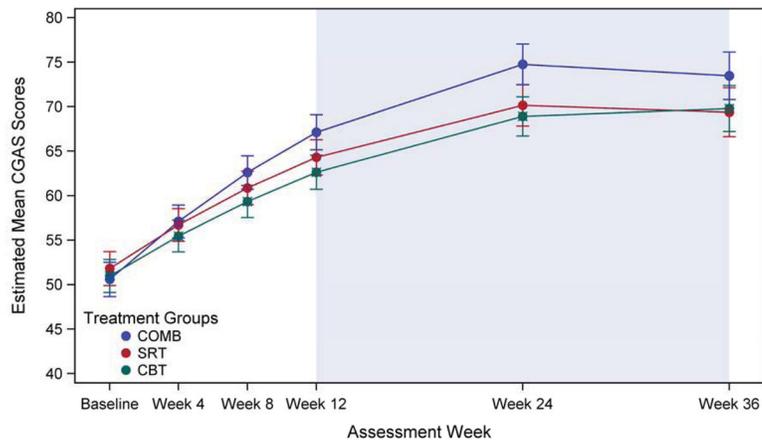
TABLE 1

Response/Remission Rates for Various Categorical Phase II Outcomes Among COMB, SRT, and CBT

Variable	COMB (N=140)	SRT (N=133)	CBT (N=139)	p-values for Pairwise Comparisons		
				COMB vs. SRT	COMB vs. CBT	SRT vs. CBT
Responder (CGI-I = 1 or 2)						
Week 12	80.71	54.89	59.71	<0.001	<0.001	0.419
Week 24	81.24 (71.51–90.98)	67.62 (52.78–82.45)	69.37 (57.08–81.66)	0.092	0.162	0.859
Week 36	82.69 (72.77–92.61)	70.49 (55.17–85.82)	71.54 (62.30–80.78)	0.176	0.144	0.931
Excellent Response (CGI-I = 1)						
Week 12	45.46 (35.50–55.41)	33.15 (24.41–41.88)	19.36 (12.69–26.04)	0.068	<0.001	0.013
Week 24	46.48 (37.94–55.03)	36.55 (25.28–47.83)	33.90 (24.55–43.25)	0.171	0.055	0.723
Week 36	47.42 (38.90–55.93)	42.57 (31.12–54.03)	41.27 (32.36–50.18)	0.506	0.331	0.864
Remission - Severity (CGI-S = 1 or 2)						
Week 12	65.50 (55.82–75.19)	46.14 (35.10–57.18)	35.35 (27.19–43.52)	0.011	<0.001	0.125
Week 24	64.56 (52.54–76.58)	48.78 (35.99–61.58)	44.59 (35.30–53.88)	0.010	0.012	0.609
Week 36	66.74 (54.91–78.57)	62.86 (48.39–77.34)	58.39 (48.33–68.45)	0.685	0.305	0.612
Remission - Diagnosis (No ADIS SAD, SOP or GAD Diagnosis)						
Week 12	69.23 (60.30–78.17)	45.71 (37.03–54.39)	46.10 (37.33–54.87)	<0.001	<0.001	0.950
Week 36	73.42 (62.49–84.36)	51.53 (42.56–60.50)	52.01 (43.51–60.50)	<0.005	<0.006	0.940
Other Response Outcomes						
Consistent Response	67.08 (58.13–76.02)	45.42 (36.22–54.62)	48.20 (39.31–57.09)	0.002	0.005	0.663
Consistent Non-Response	5.41 (0.01–10.87)	15.71 (7.57–23.85)	15.29 (7.31–23.27)	0.063	0.084	0.942
New Phase II Response	8.74 (0.01–15.96)	19.52 (7.58–31.47)	17.86 (9.98–25.75)	0.115	0.115	0.884
Phase II Relapse	7.42 (0.01–12.71)	4.97 (0.01–10.34)	6.99 (2.14–11.85)	0.485	0.917	0.538
Phase II Regained	6.18 (1.39–10.97)	3.98 (−0.66 to 8.63)	3.96 (−0.04 to 7.95)	0.465	0.476	0.610
Temporary Response	3.75 (−1.94 to 9.44)	7.67 (−1.23 to 16.56)	4.89 (−1.20 to 10.98)	0.354	0.577	0.394

Note: These models are derived from imputed data so there is a range in the response outcomes with the exception of Week 12 Responder status which is from Walkup et al.[7] and based on last-observation-carried-forward (LOCF) analyses. Week 12 values for Excellent Response, Remission-Severity, and Remission-Diagnosis differ from those reported in Ginsburg et al.[8] because site was included as a covariate in the present analyses but not previously reported analyses. For Remission-Diagnosis, the Anxiety Disorders Interview Schedule (ADIS) was not administered at Week 24. Consistent Response indicates that the subject had a Clinical Global Impressions–Severity scale (CGI-I) less than or equal to 2 at Weeks 12, 24, 36. Consistent Non-Response is its counter. New Phase II Response is a Week 12 nonresponder who was a responder at Weeks 24 and 36. Phase II Relapse is a Week 12 responder who was no longer a responder at Week 24 or a Week 36 or a Week 24 responder who was no longer a responder at Week 36. Phase II Regained is a Week 12 responder who lost response at week 24 but regained it by Week 36. Temporary Responder is a Week 12 nonresponder who had a response by Week 24 but lost it at Week 36. All data derived from the intent-to-treat (ITT) sample. CBT = cognitive behavior therapy; COMB = combined (CBT+sertraline) treatment; SRT = sertraline.

TABLE 2

Model-Based Means at Each Assessment Point During Phase I and II

PARS	COMB	SRT	CBT
Baseline	19.05 (17.89–20.20)	18.07 (16.92–19.21)	18.81 (17.70–19.93)
Week 4	15.01 (13.92–16.10)	15.05 (13.96–16.13)	16.06 (15.01–17.11)
Week 8	11.62 (10.52–12.72)	12.51 (11.41–13.60)	13.69 (12.63–14.75)
Week 12	8.89 (7.74–10.03)	10.44 (9.29–11.58)	11.69 (10.59–12.79)
Week 24	4.56 (3.30–5.81)	7.07 (5.80–8.34)	7.98 (6.77–9.19)
Week 36	6.06 (4.66–7.45)	7.97 (6.54–9.39)	7.69 (6.35–9.04)

CGI-S	COMB	SRT	CBT
Baseline	5.11 (4.88–5.33)	4.90 (4.68–5.13)	5.07 (4.86–5.29)
Week 4	4.19 (3.98–4.41)	4.22 (4.01–4.43)	4.46 (4.26–4.67)
Week 8	3.43 (3.21–3.64)	3.64 (3.43–3.86)	3.93 (3.72–4.14)
Week 12	2.80 (2.57–3.03)	3.17 (2.94–3.40)	3.48 (3.26–3.70)
Week 24	1.80 (1.54–2.06)	2.40 (2.14–2.67)	2.62 (2.37–2.87)
Week 36	2.10 (1.80–2.40)	2.59 (2.28–2.89)	2.49 (2.20–2.78)

CGAS	COMB	SRT	CBT
Baseline	50.59 (48.67–52.52)	51.80 (49.89–53.72)	50.98 (49.11–52.84)
Week 4	57.09 (55.25–58.93)	56.71 (54.87–58.54)	55.46 (53.68–57.24)
Week 8	62.60 (60.72–64.48)	60.87 (58.99–62.75)	59.35 (57.53–61.16)
Week 12	67.12 (65.15–69.10)	64.30 (62.31–66.29)	62.63 (60.73–64.54)
Week 24	74.75 (72.48–77.03)	70.16 (67.83–72.48)	68.91 (66.70–71.11)
Week 36	73.48 (70.81–76.15)	69.39 (66.63–72.14)	69.80 (67.21–72.39)

Note: CBT = cognitive behavior therapy; CGAS = Children's Global Assessment of Functioning; CGI-S = Anxiety Disorders Interview Schedule; COMB = combined (CBT+sertraline) treatment; PARS = Pediatric Anxiety Rating Scale; SRT = sertraline.

TABLE 3

P-Values and Effect Size Estimates (95% CI) for Between Treatment Condition Pairwise Comparisons at Each Assessment Point During Phase II

PARS	Week 24		Week 36	
	p-value	ES (95% CI)	*p*-value	ES (95% CI)
COMB vs SRT	<0.001	0.58 (0.28–0.87)	0.017	0.39 (0.07–0.71)
COMB vs CBT	<0.001	0.78 (0.50–1.07)	0.034	0.34 (0.03–0.65)
SRT vs CBT	0.161	−0.21 (−0.50 to 0.08)	0.728	0.06 (−0.26 to 0.37)

CGI-S	Week 24		Week 36	
	p-value	ES (95% CI)	*p*-value	ES (95% CI)
COMB vs SRT	<0.001	0.59 (0.32–0.87)	0.007	0.41 (0.11–0.71)
COMB vs CBT	<0.001	0.81 (0.54–1.08)	0.024	0.34 (0.04–0.63)
SRT vs CBT	0.124	−0.22 (−0.49 to 0.06)	0.604	0.08 (−0.22 to 0.38)

CGAS	Week 24		Week 36	
	p-value	ES (95% CI)	*p*-value	ES (95% CI)
COMB vs SRT	<0.001	−0.51 (−0.79 to −0.23)	0.013	−0.38 (−0.67 to −0.08)
COMB vs CBT	<0.001	−0.65 (−0.92 to −0.38)	0.021	−0.34 (−0.62 to −0.05)
SRT vs CBT	0.323	0.14 (−0.14 to 0.42)	0.800	−0.04 (−0.33 to 0.26)

Note: CBT = cognitive behavior therapy; CGAS = Children's Global Assessment of Functioning; CGI-S = Clinical Global Impressions–Severity scale; COMB = combined (CBT+sertraline) treatment; PARS = Pediatric Anxiety Rating Scale; SRT = sertraline.

TABLE 4

Proportion of Subjects Receiving Concomitant Off-Protocol Treatment During Phase II

Type of Treatment	COMB N (%)	SRT N (%)	CBT N (%)
None	102 (72.9)	68 (51.1)	89 (64.0)
New Psychosocial Only	10 (7.1)	26 (19.6)	12 (8.6)
New Medication Only	7 (5.0)	4 (3.0)	12 (8.6)
Both New Psychosocial and New Medication	2 (1.4)	9 (6.8)	14 (10.1)
Information Missing	19 (13.6)	26 (19.6)	12 (8.6)
Total	140	133	139

Note: New Psychosocial includes both cognitive behavior therapy (CBT) and other psychotherapeutic interventions targeting mental health symptoms or adjustment. New Medication includes any pharmacologic treatments, both sertraline and otherwise, targeting mental health symptoms and adjustment. For youth receiving both New Psychosocial and New Medication, these treatments were not necessarily delivered concurrently or in coordinated fashion. COMB = combined (CBT+sertraline) treatment; SRT = sertraline.