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Secondary Outcomes From the Child/Adolescent Anxiety Multimodal Study: Implications for Clinical Practice

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Abstract

Background: Controlled evaluations comparing medication, cognitive-behavioral therapy (CBT), and their combination in the treatment of youth anxiety have predominantly focused on global ratings by independent evaluators. Such ratings are resource-intensive, may be of limited generalizability, and do not directly inform our understanding of treatment responses from the perspective of treated families. We examined outcomes from the perspective of treated youth and parents in the Child/Adolescent Anxiety Multimodal Study (CAMS).

Methods: Participants (N=488; ages 7–17 years) who had a primary diagnosis of separation, social, and/or generalized anxiety disorder were randomly assigned to a treatment condition in the CAMS trial. Linear mixed-effects and ANCOVA models examined parent- and youth-reported anxiety symptoms, impact of anxiety, broader internalizing and externalizing psychopathology, depressive symptoms, and family burden throughout the 12-week acute treatment phase and 6-month follow-up.

Results: At week 12, combination treatment showed superiority over placebo, sertraline, and CBT with regard to parent-reported youth anxiety symptoms, and sertraline and CBT as monotherapies showed superiority over placebo with regard to parent-reported youth anxiety. Combination therapy and sertraline also showed week 12 superiority over placebo with regard to parent-reported internalizing psychopathology, and superiority over placebo and CBT with regard to parent-reported impact of anxiety, family burden, and youth depressive symptoms. By week 36, parent reports of many youth outcomes were comparable across active conditions. Youth measures tracked parent measures on many outcomes.

Conclusions: Findings were drawn on brief, readily available questionnaires that in conjunction with clinician measures can inform patient-centered care and collaborative decision-making.

Trial Registry Name: Child and Adolescent Anxiety Disorders (CAMS)

Registry identification number: NCT00052078

Registry URL: <https://www.clinicaltrials.gov/ct2/show/NCT00052078>

Keywords

Child/Adolescent; Anxiety/Anxiety Disorders; CBT/Cognitive-Behavioral Therapy; Pharmacotherapy; Clinical Trials

Anxiety disorders are collectively the most prevalent class of mental disorders affecting youth (Kessler et al., 2012). These disorders commonly have an early onset (Franz et al., 2013) are associated with distress and disability across multiple domains (Swan & Kendall, 2016), and increase risk for comorbidities, chronic irritability, sleep problems, and suicidality over time (Cornacchio et al., 2016; Cummings et al., 2013; O'Neil Rodriguez & Kendall, 2014; Weiner et al., 2015). Moreover, anxiety disorders typically do not remit on their own (Costello et al., 2003). Poorly managed child anxiety is associated with substance misuse in young adulthood (Benjamin et al., 2013; Wu et al., 2010), and anxiety disorders persisting into adulthood are associated with reduced physical functioning (Lever-van Milligen et al., 2017) and quality of life (Comer et al., 2011).

Given the scope and burden of youth anxiety disorders, effective treatment is critical. Following two decades of intervention research supporting the efficacy of cognitive behavioral therapy (CBT) and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), the NIMH funded the Child/Adolescent Anxiety Multimodal Study (CAMS), a six-site, six-year randomized controlled efficacy trial evaluating sertraline (SRT), CBT, their combination (COMB), and pill placebo (PBO). Main outcomes found COMB produced the highest clinical global response rates (80.7%), with each monotherapy (CBT or SRT) showing comparable superiority over PBO following acute treatment and 6-month maintenance care (Piacentini et al., 2014; Walkup et al., 2008). Although long-term follow-up data underscore the continued need for further maintenance treatment for many children (Ginsburg et al., 2014), these main outcomes provide evidence that CBT, SRT, COMB are effective treatments for youth anxiety, with greatest responses associated with combination treatment.

Analyses supporting these primary outcomes were based on global evaluations by trained and reliable independent evaluators (IEs) masked to treatment assignment. Specifically, clinical response was defined as “very much improved” or “much improved” on the Clinical Global Impression-Improvement Scale (CGI-I; Guy & Bonato, 1970) and symptom reduction on the Pediatric Anxiety Rating Scale (PARS; RUPP Anxiety Study Group, 2002). Both the CGI and the PARS are clinician-rated, requiring expertise and time burden typically not feasible in clinical practice. These ratings were provided by supervised study staff with advanced training and expertise, and incorporated information obtained from specialized semi-structured interviews.

Such an assessment regimen offers unparalleled benefits from an internal validity perspective (Comer & Bry, in press; Comer & Kendall, 2013), but the full application of such rigorous and lengthy methods are limited when used in clinical practice. Many practice settings lack the resources, expertise, and/or time to allow for semi-structured assessments common to RCTs. Constraints on clinician time, reimbursement ceilings, and patient burden limit the use of such research assessment methods. More brief parent- and youth-report

measures with strong psychometric properties are a feasible and cost-effective alternative in practice settings for informing treatment evaluation, planning, and monitoring.

The CGI is a generic measure that assesses a trained evaluator's global impressions of severity and improvement. Other rating scales examining particular symptom dimensions provide important complementary data that speak to focused aspects of children's functioning. Outcomes specifically assessing youth anxiety symptoms, anxiety impact, depressive symptoms, and broader internalizing and externalizing psychopathology may be obscured in the context of broad global impressions.

Although important for an RCT, IE ratings do not directly inform our understanding of treatment responses from the perspective of treated families. Capturing the direct perspectives of treated families is important given increased emphasis on patient-centered care—i.e., explicit partnerships among providers, patients, and families to routinely solicit patient input when making treatment-related decisions and ensure families participate in their own care (Institute of Medicine, 2001). Indeed, incorporating patient perspectives into clinical decision-making is associated with reduced dropout and improved outcomes (Swift & Callahan, 2009). Understanding patient appraisals of responses to CBT, SRT, and COMB informs patient-centered care for pediatric anxiety.

To provide patient and family perspectives on treatment responses across supported interventions, the present analysis examined secondary CAMS outcomes drawing on assessment instruments commonly used in practice. Specifically, we examined children's total anxiety symptoms, the impact of anxiety, family burden, depressive symptoms, and broader internalizing and externalizing psychopathology based on parent- and youth-reports. Consistent with the CAMS principal outcomes (Piacentini et al., 2014; Walkup et al., 2008), we hypothesized that both monotherapies would be associated with improvements across secondary youth- and parent-reported outcomes relative to PBO, and that combination treatment (CBT+SRT) would show a superior response.

Methods

Participants

The sample consisted of 488 youth (ages 7–17 years; $M=10.7$, $SD=2.8$; 50.4% male), and their parent(s), presenting for anxiety treatment at one of six university-affiliated clinics. Participants met criteria for a primary/co-primary diagnosis of DSM-IV-TR separation anxiety disorder (SAD), social phobia/social anxiety disorder (SP), and/or generalized anxiety disorder (GAD)—as determined by structured diagnostic interviews. Youth were required to have $IQ>80$, and could not have previously failed two adequate SSRI trials or a CBT course. Additional enrollment information is provided elsewhere (Compton et al., 2010).

Regarding race, 79.0% of the participants were white, 9.0% black, 2.5% Asian, 1.2% American Indian, 0.4% Native Hawaiian/Pacific Islander, and 8% identified as “other.” Roughly 12% were Hispanic. Most participants came from middle-/upper-middle class families (74.6%) and lived with both biological parents (70.3%). 54.0% had SAD, 81.9%

had SP, and 78.4% had GAD; 42.5% of youth had two of the study anxiety disorders and 35.9% had all three. Additional sample characteristics are provided elsewhere (Kendall et al., 2010).

Procedure

Procedures were conducted under approval and monitoring of each site's institutional review board, and a NIMH Data Safety and Monitoring Board. After obtaining informed consent/assent, families completed baseline evaluations, including IE-conducted semi-structured diagnostic interviews, and parent- and youth-report questionnaires. Eligible participants were randomized to 12 weeks of CBT (n=139), SRT (n=133), COMB (n=140), or PBO (n=76), and then completed week 12 (post-treatment), week 24, and week 36 (post-maintenance) evaluations. The present analysis examined parent- and self-report data collected at weeks 0 (baseline), 4, 8, 12 (post), and 36.

CAMS treatments.—Youth assigned to CBT received 12 weeks of *Coping Cat* (Kendall & Hedtke, 2005)—an empirically supported, skills-based anxiety management intervention emphasizing affective education, cognitive restructuring, problem solving, and graduated exposures to feared situations/stimuli (Kendall et al., 1997, 2008). All but two sessions are individual child sessions; parents attend two parent-only sessions, but play an active role in between-session homework and practice. SRT entailed eight 30–60 minute medication management sessions conducted by psychiatrists or nurse practitioners across 12 weeks and biweekly telephone check-ins. Medication diaries and pills counts assessed SRT compliance. A “fixed-flexible” dosing schedule linked to tolerability and clinical response was implemented with a 200mg maximum daily dose. Mean final sertraline doses were comparable across SRT and COMB. PBO youth participated in an identical medication management schedule. COMB youth received CBT and SRT regimens concurrently across 12 weeks.

Measures

Measures examined parent- and youth-reported anxiety symptoms (Multidimensional Anxiety Scale for Children; Screen for Child Anxiety-Related Disorders), impact of anxiety (Child Anxiety Impact Scale), depression symptoms (Mood and Feelings Questionnaire), and internalizing and externalizing psychopathology (Child Behavior Checklist).

Multidimensional Anxiety Scale for Children (MASC; March et al., 1997).—The MASC and MASC-P—administered at weeks 0, 12, 24, and 36—are 39-item self- and parent-reports, respectively, of youth anxiety symptoms, and have demonstrated strong psychometric properties (March et al., 1997; Baldwin & Dadds, 2007; Wei et al., 2014). Internal consistency in this sample was high (Cronbach's $\alpha_{\text{Youth}}=0.92$; Cronbach's $\alpha_{\text{Parent}}=0.90$).

Screen for Child Anxiety-Related Disorders (SCARED).—The SCARED—administered at weeks 0, 4, 8, 12, 24, and 36—is a 41-item parent- and youth-report assessing youth anxiety symptoms. Strong internal consistency and discriminant validity

have been demonstrated (Birmaher et al., 1999; Hale et al., 2005; Wren et al., 2004). Internal consistency in this sample was high (Cronbach's $\alpha_{\text{Youth}}=0.94$; Cronbach's $\alpha_{\text{Parent}}=0.92$).

Child Anxiety Impact Scale (CAIS).—The CAIS—administered at weeks 0, 4, 8, 12, 24, and 36—is a brief parent- and youth-report measure of anxiety-related functional impairment, and has shown strong psychometric properties (Langley et al., 2014). Internal consistency in this sample was high (Cronbach's $\alpha_{\text{Youth}}=0.92$; Cronbach's $\alpha_{\text{Parent}}=0.92$).

Mood and Feelings Questionnaire (MFQ).—The MFQ—administered at weeks 0, 4, 8, 12, 24, and 36—is a 33-item self-report of depressive symptoms that has demonstrated strong psychometric properties (Angold et al., 1995; Kent et al., 1997). Internal consistency in this sample was high (Cronbach's $\alpha_{\text{Youth}}=0.93$; Cronbach's $\alpha_{\text{Parent}}=0.91$).

Child Behavior Checklist (CBCL).—The CBCL—administered at weeks 0, 12, 24, and 36—is a well-supported, standardized parent-report assessing internalizing and externalizing youth psychopathology (Achenbach & Rescorla, 2001). Empirically based scales, normed for age and gender, are generated, including Internalizing, Externalizing, and Total Problems, and an Anxious/Depressed syndrome scale that were presently analyzed.

Family Burden Assessment Scale (BAS).—The BAS—administered to parents at weeks 0, 12, 24, and 36—is a brief measure of subjective and objective consequences of disorder/illness on primary caretakers (Cronbach's $\alpha=0.92$ in present sample).

Statistical Analysis

Two data analytic model types tested week 12 hypotheses. For outcomes assessed at 3 time points, longitudinal regression models examined mean differences in outcomes. Each model included time (weeks since baseline), indicators of treatment condition, and all time X treatment group interactions as fixed effects. Random effects included intercept and linear slope terms. Residual error terms were assumed to follow a mean-0, normal distribution with an unstructured covariance structure to capture the within-person correlation over time. Each model also included 5 covariates (grand mean centered): youth age, gender, minority status, socioeconomic status, treatment site. Fitted models were used to report mean scores at week 12. For outcomes assessed <3 times (precluding estimates of change trajectories; Singer & Willett, 2003), ANCOVAs predicted week 12 outcomes for each treatment group, controlling for baseline scores and the same 5 covariates. By week 36, all measures had been administered 3 times and so similar linear mixed-effect models were employed. Because outcomes were found to not follow a linear trend, a quadratic term for time and all relevant interactions were added to each model.

At week 12, each treatment condition was compared to the others, for a total of six comparisons. Since placebo participants were given the option to begin active treatment after the acute treatment phase, week 36 contrasts did not include placebo youth, for a total of three tests comparing the active treatments. Sequential Hochberg correction was used to control the overall (familywise) error rate (Benjamini & Hochberg, 1995). All models were fit using PROC MIXED in SAS Statistical Software, version 9.4 TS Level 1M1 (SAS Institute Inc, Cary, North Carolina).

Finally, we examined whether youth age or primary baseline diagnosis moderated responses across groups. ANCOVAs predicted week 12 and 36 scores from treatment condition, putative moderators, and interactions of treatment condition and moderators (controlling for baseline scores and the same covariates as above).

Multiple imputation techniques (Rubin, 1987) addressed missing data in ANCOVA models. Twenty data sets were generated. Results reported below were calculated using Rubin's rules for combining the results of identical analyses performed on each of the 20 imputed data sets. Multiple imputation was not necessary for linear mixed-effects models, given that maximum likelihood estimation produces unbiased estimates when incomplete data are assumed missing at random.

Results

Tables 1 and 2 present the details of youth- and parent-reported outcomes, respectively.

Anxiety Symptoms

Youth Reports. Analyses of the youth MASC and SCARED week 12 and 36 outcomes revealed one significant between-group difference. Namely, SRT was superior to PBO ($b = -4.68$, $t = -2.80$, $adj\ p = 0.03$), but only on the week 12 MASC. All other pairwise comparisons on these two youth-report measures were not statistically different.

Parent Reports. Parent reports of youth anxiety symptoms differed by treatment condition across both the SCARED and MASC at week 12, with some MASC differences persisting through week 36. Specifically, on the week 12 MASC, COMB ($b = -15.7$, $t = -6.4$, $adj\ p < .001$), SRT ($b = -11.1$, $t = -4.4$, $adj\ p < .001$), and CBT ($b = -7.0$, $t = -2.9$, $adj\ p < .001$) were each superior to PBO. Comparisons between the active treatment conditions revealed that COMB was superior to SRT ($b = -4.5$, $t = -2.2$, $adj\ p < .04$) and CBT ($b = -8.7$, $t = -4.5$, $adj\ p < .001$) and SRT was superior to CBT ($b = -4.1$, $t = -2.1$, $adj\ p < .04$). On the week 36 MASC, COMB ($b = -3.3$, $t = -5.9$, $adj\ p < .01$) and SRT ($b = -6.8$, $t = -2.9$, $adj\ p < .01$) continued to be superior to CBT. However, unlike week 12 findings, COMB and SRT were not statistically different ($adj\ p = .98$).

On the week 12 Parent SCARED, COMB ($b = -9.8$, $t = -5.9$, $adj\ p < .001$) and SRT ($b = -7.9$, $t = -4.7$, $adj\ p < .001$) proved superior to PBO, whereas CBT ($adj\ p = .26$) did not. Comparisons between the active treatment conditions revealed that COMB ($b = -7.3$, $t = -5.4$, $adj\ p < .001$) and SRT ($b = -5.9$, $t = -4.2$, $adj\ p < .001$) were each superior to CBT, while differences between COMB and SRT were not statistically significant ($adj\ p = .32$). Analyses of week 36 parent SCARED outcomes revealed no differences between active treatment conditions.

Functional Impact of Anxiety

Youth Reports.—Analyses of the youth CAIS outcomes revealed no differences between the conditions at week 12 or week 36.

Parent Reports.—On the week 12 Parent CAIS, COMB ($b = -7.7$, $t = -5.2$, $adj\ p < .001$) and SRT ($b = -6.1$, $t = -4.0$, $adj\ p < .001$) proved superior to PBO, whereas CBT ($adj\ p = .27$) did not. Comparisons among the active treatment conditions revealed that COMB ($b = -6.1$, $t = -5.0$, $adj\ p < .001$) and SRT ($b = -4.4$, $t = -3.6$, $adj\ p < .001$) were superior to CBT, while differences between COMB and SRT were not significant ($adj\ p = .27$). On the week 36 CAIS, COMB ($b = -3.7$, $t = 3.1$, $adj\ p < .01$) and SRT ($b = -3.0$, $t = -2.4$, $adj\ p < .04$) continued to be superior to CBT. Differences between COMB and SRT on the week 36 CAIS continued to not be statistically different ($adj\ p = .53$).

Depressive Symptoms

Youth Report.—Analyses of youth MFQ outcomes found no differences between conditions at week 12 or week 36.

Parent reports.—Analyses of the parent MFQ at week 12 revealed a similar ordering of outcomes to that found on the parent SCARED and parent CAIS. Specifically, COMB ($b = -3.9$, $t = -3.7$, $adj\ p < .001$) and SRT ($b = -3.0$, $t = -2.8$, $adj\ p < .001$) proved superior to PBO, whereas CBT ($adj\ p = .91$) did not. Comparisons between the active treatment conditions revealed that COMB ($b = -4.0$, $t = -4.7$, $adj\ p < .001$) and SRT ($b = -3.1$, $t = -3.6$, $adj\ p < .001$) were superior to CBT, whereas differences between COMB and SRT were not statistically significant ($adj\ p = .63$). However, by week 36 parent reports of their children's depressive symptoms were comparable across the three active treatment conditions.

Broader Internalizing and Externalizing Psychopathology—On the week 12 CBCL Total Problems subscale, the two medication conditions proved superior to PBO (COMB: $b = -4.6$, $t = 2.7$, $adj\ p = .03$; SRT: $b = -4.6$, $t = 2.8$, $adj\ p = .03$) whereas CBT alone was not ($adj\ p = .06$). Contrasts between the active treatment conditions revealed no significant differences. The pattern of findings on the week 12 CBCL Internalizing Problems subscale were identical to that found on the week 12 CBCL Total Problems subscale. Specifically, COMB ($b = -5.7$, $t = 3.4$, $adj\ p < .01$) and SRT ($b = -6.8$, $t = 4.0$, $adj\ p < .001$) were superior to PBO whereas CBT ($adj\ p = .11$) was not, with no significant differences between the three active treatment conditions. Analyses of the week 12 CBCL Externalizing Problems subscale revealed no significant differences between any of the conditions. Analyses of the week 12 CBCL Anxious/Depressed subscale yielded a different pattern of findings. Specifically, COMB ($b = -4.8$, $t = 3.8$, $adj\ p < .001$), SRT ($b = -4.7$, $t = 3.8$, $adj\ p < .001$), and CBT ($b = -3.6$, $t = 2.9$, $adj\ p < .02$) were superior to PBO, with no statistically significant differences between the three active treatment conditions. At week 36, all CBCL subscale improvements were comparable across the active treatment conditions.

Family Burden Measure (BAS)—By week 12, parent measures of family burden showed significant differences between conditions. However, by week 36, differences between the active treatment conditions were not statistically different. Specifically, on the week 12 BAS, COMB ($b = -10.3$, $t = -5.3$, $adj\ p < .001$), SRT ($b = -7.1$, $t = -3.5$, $adj\ p < .003$), and CBT ($b = -4.7$, $t = -2.4$, $adj\ p < .05$) were superior to PBO. Comparisons between the active treatment conditions revealed that COMB was superior to SRT ($b = -3.2$, $t = -2.2$, $adj\ p = .03$).

$p < .05$) and CBT ($b = -5.7$, $t = -4.2$, $adj\ p < .001$), whereas SRT and CBT did not differ statistically ($p = .08$).

Moderation Analyses

Neither primary diagnosis nor youth age reliably moderated treatment impact on any of the week 12 or 36 outcomes (all p 's $< .05$).

Discussion

The present findings add the perspective of patients and families to the growing body of literature supporting the short-term efficacy of three active therapies—combination therapy with both CBT and sertraline, sertraline alone, and CBT alone—for redressing the problems of youth anxiety disorders (Birmaher et al., 2003; RUPP Anxiety Study Group, 2001; Walkup et al., 2008). These data have implications for the assessment and monitoring of youth anxiety in clinical settings. Mostly consistent with primary CAMS outcomes based on global impressions of IEs (Walkup et al., 2008), combination treatment showed acute superiority over placebo and CBT with regard to parent-reports of youth anxiety, however the superiority of COMB over SRT seen in the IE-completed measures was less evident from the perspective of parents. Sertraline and CBT as monotherapies both showed acute superiority over placebo with regard to parent reports of youth anxiety. Combination therapy and sertraline also showed acute superiority over placebo with regard to parent reports of broader internalizing psychopathology, and acute superiority over placebo and CBT with regard to parent reports of the impact of anxiety, family burden, and youth depressive symptoms. The absence of age moderation effects is consistent with findings showing treatments for anxious youth over the age of 7 are comparably efficacious across children and adolescents (Kendall & Peterman, 2015).

It is important to note that the parent-reported acute superiority of medication treatments over CBT with regard to family burden did not endure across the maintenance phase. In fact, by week 36, parent reports of many outcomes were comparable across the three active treatments. Future work examining treatment sequences and adaptive regimens (Comer & Barlow, 2013) are needed to inform individualized courses of care for youth anxiety.

Limitations

The CAMS trial entailed the largest randomized evaluation to date examining youth anxiety treatments and recruited a racially, ethnically, and geographically diverse range of families from across multiple centers and locations, but several limitations merit comment. First, the present analyses relied exclusively on parent- and youth-report data, which, relative to IE ratings, can be biased by knowledge of treatment condition. However, such concerns are tempered by the fact that parent and youth subjective accounts of treatment response are specifically what we were presently interested in, and so questionnaire-based methods offer the appropriate measurement strategy for the present purposes. Further, recent findings suggest parents and youth are indeed able to provide accurate improvement ratings (Lewin et al., 2012). Second, our analyses only examined week 12 and week 36 data. Long-term follow-up evaluations of parent and youth data are beyond the scope of the present analysis.

However, preliminary naturalistic long-term follow-up evaluations (Ginsburg et al., 2014) underscore the continued need for further maintenance treatment for many youth treated with the active CAMS treatments. Indeed, in the present analyses several between-treatment effects at posttreatment did not endure across the maintenance period. It is possible that further care will be needed for long-term maintenance of parent-reported gains. Third, the acute superiority of combination treatment may have been due to the additional contact with providers youth had in this condition relative to other conditions, or the fact that participants in combination treatment knew they were taking sertraline (i.e., the CAMS design did not include a combination regimen of CBT+PBO). Finally, interpretation of the six-month findings is complicated by relatively high rates of off-protocol treatment during this naturalistic follow-up period (Piacentini et al., 2014).

Recommendations for Clinicians

Shifting health care policies in recent years have placed an increasing emphasis on patient-centered care, in which treatment-related decisions are to be made collaboratively with the input of patients and their families. In the treatment of youth anxiety, it is often parents who first identify anxiety symptoms, present youth for services, bring youth to weekly appointments, and ensure youth complete homework assignments or adhere to prescribed medication doses. Given the role of parents in treating youth anxiety, as well as evidence that incorporating patient and family perspectives into clinical decision-making reduces drop-out and enhances treatment responses (Swift & Callahan, 2009), the present findings offer the perspective of parents on three well-supported treatment strategies that—in careful combination with expert clinical ratings—can meaningfully inform patient-centered collaborative decision-making and help parents of anxious youth actively participate in decision-making about their youth's care.

Although all three active treatments showed acute superiority over placebo with regard to parent reports of youth anxiety, the present findings suggest that, from the perspective of parents, medication treatments may be associated with a broader range of favorable acute outcomes. The more favorable acute response associated with medication treatments for depressive symptoms relative to CBT is not surprising given that sertraline is an effective antidepressant medication (Wagner et al., 2003) whereas effective CBTs for youth depressive symptoms have different components and targets than the CBT provided in the CAMS. That parent reports suggest medication treatments yield greater acute response on the functional impact of youth anxiety and family burden is noteworthy, given it is often the impact of youth anxiety and associated interference—rather than anxiety symptoms themselves—that prompt parents to initially seek treatment. For optimal collaborative treatment planning, parents should be informed of possible differences in acute outcomes between medication versus CBT as noted by parents and as noted by trained evaluators, as well as side effects of medications. Given meta-analytic findings showing patients prefer psychological treatments over pharmacologic interventions (McHugh et al., 2013), the present findings suggest that parents who initially select psychological treatment for their anxious child, but who after an adequate CBT course still experience considerable burden associated with child anxiety, could be encouraged to consider SSRI augmentation of their child's CBT.

Despite significant differences observed between many parent-reported outcomes of youth who received CBT as a monotherapy versus youth who received medication therapy, it is important to note that all three active treatments demonstrated relative superiority over placebo. Many treatment-seeking families—after factoring in personal preferences, limited availability of child psychiatrists, costs associated with medication regimens, and the relatively higher rates of adverse events associated with SSRIs—may choose CBT as their initial treatment. The CAMS findings provide robust evidence to support “CBT-first” as a well-supported treatment recommendation for such families.

In contrast to parent-reported appraisals of treatment response, the present findings suggest that, across treatment conditions, treatment-related gains may go largely unnoticed by youth. Specifically, youth-reports revealed minimal differences, with only one significant finding: sertraline was associated with lower week 12 anxiety than placebo. The absence of differences based solely on youth’s reports is consistent with previous clinical trials evaluating youth anxiety treatment (Kendall et al., 2008), and may be the result of a number of factors, including: (a) reluctance or limitations in youth’s ability to identify or self-report anxiety-related problems (Comer & Kendall, 2004) or treatment-related improvements; (b) failure to include measures that assess outcomes of greater relevance to youth; and/or (c) important ways in which the active CAMS treatments failed to attend to outcomes of importance to anxious youth. Given the need for youth engagement, compliance, and adherence for positive treatment response, providers will do well to routinely solicit input directly from treated youth regarding their personal treatment goals and the clinical targets of greatest relevance to them.

Although the CAMS trial did not evaluate alternative sequences of treatment, the issue of non-response and treatment sequencing merits special comment. Although both monotherapy treatment strategies were associated with favorable outcomes in CAMS, a considerable proportion of youth were, nonetheless, non-responders. In the face of non-response or inadequate response to one of the monotherapies, providers and families are confronted with the difficult decision as to whether to transition to a combined regimen (augmentation strategy), or whether to discontinue the current treatment and switch to the other monotherapy (switching strategy). Future sequential multiple assignment randomized trials (SMARTs) are needed to optimally guide such decisions, but, in the interim, the stronger gains associated with combined treatment relative to either of the monotherapies suggests that in the event of step 1 non-response, a step 2 augmentation strategy may be particularly promising. It is important to also consider *when* in a course of treatment it is best to determine that an alternative treatment strategy is warranted. The CAMS findings do suggest that many treatment-related changes begin to occur as early as 4 or 8 weeks into treatment. Accordingly, weekly monitoring of symptoms is critical in order to identify youth by midtreatment who may not be showing adequate progress. If there are clear early signals of non-response, it may not be necessary for youth to endure a full monotherapy course prior to switching or augmenting treatment.

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Table 1.
Youth-reported outcomes across time, by treatment condition, in the Child/Adolescent Multimodal Study

	Baseline	Week 4	Week 8	Week 12	Week 36
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
Total Anxiety Symptoms					
<i>MASC</i>					
COMB	52.5(12.8)	-	-	39.5(10.8) ^{a,b}	34.1(11.7) ^a
SRT	51.1(13.3)	-	-	38.2(10.7) ^b	33.4(12.0) ^a
CBT	51.2(11.0)	-	-	40.9(10.4) ^{a,b}	36.4(11.5) ^a
PBO	50.3(13.2)	-	-	42.9(11.8) ^a	-
<i>SCARED</i>					
COMB	24.4(15.7)	18.3(11.6)	13.8(10.7)	9.4(11.6) ^a	7.6(11.1) ^a
SRT	22.3(15.3)	17.4(11.6)	13.4(10.8)	9.3(11.9) ^a	7.2(11.4) ^a
CBT	23.6(14.0)	19.7(11.5)	16.1(10.5)	12.4(11.4) ^a	8.7(10.8) ^a
PBO	23.1(15.8)	19.4(11.6)	16.6(10.9)	13.8(12.1) ^a	-
Anxiety Impact					
<i>CAIS</i>					
COMB	18.6(14.3)	13.8(9.5)	10.9(9.3)	8.1(11.0) ^a	8.3(12.5) ^a
SRT	15.2(12.2)	12.6(9.6)	10.1(9.5)	7.7(11.3) ^a	6.9(12.9) ^a
CBT	15.6(11.3)	13.7(9.5)	11.4(9.3)	9.1(10.7) ^a	7.3(12.2) ^a
PBO	16.8(14.4)	14.8(9.6)	13.0(9.6)	11.2(11.5) ^a	-
Depressive Symptoms					
<i>MFQ</i>					
COMB	18.0(12.5)	12.0(8.3)	8.4(7.4)	4.8(8.1) ^a	4.7(8.3) ^a
SRT	17.9(11.3)	12.0(8.4)	8.3(7.5)	4.6(8.3) ^a	5.2(8.5) ^a
CBT	18.1(11.8)	12.2(8.3)	8.8(7.3)	5.3(7.9) ^a	5.0(8.0) ^a
PBO	16.6(11.7)	12.4(8.4)	9.4(7.6)	6.4(8.5) ^a	-

Note: Within each measure/subscale, week 12 values with different superscript letters are significantly different. Similarly, within each measure/subscale, week 36 values with different superscript letters are significantly different. MASC=Multidimensional Anxiety Scale for Children; SCARED=Screen for Child Anxiety-Related Disorders; CAIS=Child Anxiety Impact Scale; MFQ=Mood and Feelings Questionnaire. Data based on multiple imputation models.

Table 2.

Parent-reported outcomes across time, by treatment condition, in the Child/Adolescent Multimodal Study

	Baseline	Week 4	Week 8	Week 12	Week 36
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
Total Anxiety Symptoms					
<i>MASC</i>					
COMB	65.6(15.0)	-	-	33.4(16.9) ^a	26.8(18.9) ^a
SRT	62.3(16.9)	-	-	37.9(17.3) ^b	27.5(19.4) ^a
CBT	65.4(14.4)	-	-	42.1(16.1) ^c	34.3(18.4) ^b
PBO	64.7(15.6)	-	-	49.1(16.9) ^d	-
<i>SCARED</i>					
COMB	32.1(12.0)	23.5(10.6)	16.6(10.1)	9.6(11.4) ^a	8.7(11.2) ^a
SRT	31.0(13.7)	23.4(10.7)	17.2(10.2)	11.0(11.7) ^a	9.4(11.5) ^a
CBT	33.4(12.8)	28.0(10.6)	22.5(10.0)	16.9(11.2) ^b	11.1(10.9) ^a
PBO	31.9(12.8)	26.8(10.7)	23.2(10.3)	19.5(11.8) ^b	-
Anxiety Impact					
<i>CAIS</i>					
COMB	25.7(13.5)	18.5(10.0)	13.0(9.1)	7.4(10.2) ^a	6.5(10.2) ^a
SRT	22.0(13.4)	16.8(10.0)	12.9(9.2)	9.1(10.5) ^a	7.3(10.4) ^a
CBT	24.8(13.6)	21.3(9.9)	17.4(9.0)	13.5(10.0) ^b	10.3(9.8) ^b
PBO	24.3(12.7)	20.9(10.0)	18.0(9.4)	15.2(10.7) ^c	-
Internalizing and Externalizing Psychopathology, and Depressive Symptoms					
<i>CBCL Total Problems</i>					
COMB	62.2(7.4)	-	-	51.2(10.9) ^a	47.8(12.5) ^a
SRT	59.6(7.8)	-	-	51.2(10.5) ^a	45.8(12.9) ^a
CBT	61.4(8.0)	-	-	51.7(10.1) ^{ab}	48.1(12.0) ^a
PBO	59.6(9.5)	-	-	55.8(11.7) ^b	-
<i>CBCL Internalizing Problems</i>					
COMB	69.2(6.6)	-	-	55.7(11.6) ^a	48.9(13.2) ^a
SRT	67.0(7.5)	-	-	54.5(11.2) ^a	47.9(13.8) ^a

	Baseline	Week 4	Week 8	Week 12	Week 36
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
CBT	67.7(7.3)	-	-	57.7(10.8) ^{a,b}	51.6(12.7) ^a
PBO	66.2(9.3)	-	-	61.3(12.0) ^b	-
<i>CBCL Externalizing Problems</i>					
COMB	54.2(10.2)	-	-	47.6(9.9) ^a	46.6(10.7) ^a
SRT	51.4(10.1)	-	-	47.3(9.8) ^a	44.1(11.0) ^a
CBT	53.1(10.5)	-	-	47.7(9.6) ^a	45.0(10.4) ^a
PBO	51.8(11.3)	-	-	50.3(10.6) ^a	-
<i>CBCL Anxious/Depressed</i>					
COMB	68.6(9.0)	-	-	57.9(8.7) ^a	52.8(8.3) ^a
SRT	67.5(8.0)	-	-	58.0(8.2) ^a	52.5(8.8) ^a
CBT	68.5(8.6)	-	-	59.1(8.2) ^a	55.1(8.0) ^a
PBO	67.2(10.8)	-	-	62.7(8.7) ^b	-
<i>MFQ</i>					
COMB	15.1(10.7)	10.8(7.3)	7.4(6.6)	4.1(7.2) ^a	4.6(6.8) ^a
SRT	13.4(10.0)	10.1(7.4)	7.6(6.7)	5.0(7.4) ^a	4.2(7.0) ^a
CBT	14.9(10.6)	13.1(7.3)	10.6(6.5)	8.1(7.1) ^b	5.3(6.6) ^a
PBO	13.2(9.1)	11.4(7.4)	9.7(6.7)	8.0(7.5) ^b	-
Family Burden					
<i>BAS</i>					
COMB	49.2(14.8)	-	-	33.7(11.5) ^a	30.5(11.2) ^a
SRT	43.4(13.0)	-	-	36.9(12.0) ^{a,b}	31.8(11.5) ^a
CBT	46.6(13.3)	-	-	39.4(11.2) ^{b,c}	33.9(10.9) ^a
PBO	49.2(12.2)	-	-	44.1(14.7) ^c	-

Note: Within each measure/subscale, week 12 values with different superscript letters are significantly different. Similarly, within each measure/subscale, week 36 values with different superscript letters are significantly different. MASC=Multidimensional Anxiety Scale for Children; SCARED=Screen for Child Anxiety-Related Disorders; CAIS=Child Anxiety Impact Scale; CBCL=Child Behavior Checklist; MFQ=Mood and Feelings Questionnaire; BAS=Family Burden Assessment Scale. Data based on multiple imputation models.