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Moving to Second Stage Treatments Faster: Identifying Midtreatment Tailoring Variables for Youth with Anxiety Disorders

Jeremy W. Pettit, Ph.D.,

Department of Psychology, Florida International University, Miami, FL

Wendy K. Silverman, Ph.D., ABPP,

Child Study Center, Yale University, New Haven, CT

Yasmin Rey, Ph.D.,

Department of Psychology, Florida International University, Miami, FL

Carla Marin, Ph.D., and

Child Study Center, Yale University, New Haven, CT

James Jaccard, Ph.D.

New York University, New York, NY

Abstract

Objective—The current study presents an approach for empirically identifying tailoring variables at midtreatment of cognitive behavioral therapy (CBT) protocols for youth with anxiety disorders that can be used to guide moves to second stage treatments.

Method—Using two independent data sets (Study 1 $N = 240$, M age = 9.86 years; Study 2 $N = 341$; M age = 9.53 years), we examined treatment response patterns after eight sessions of CBT (i.e., CBT midtreatment).

Results—We identified and replicated three classes of response patterns at CBT midtreatment: Early Responders, Partial Responders, and Nonresponders. Class membership at CBT midtreatment was predictive of outcome at CBT post. Receiver operating characteristics curves were used to derive guidelines to optimize accuracy of assignment to classes at CBT midtreatment.

Conclusions—These findings support the promise of treatment response at CBT midtreatment to identify tailoring variables for use in abbreviating first stage treatments and facilitating moves to second stage treatments.

Correspondence concerning this manuscript should be addressed to Jeremy W. Pettit, Ph.D., Department of Psychology, Florida International University, 11200 SW 8th St., AHC I, Room 140, Miami, FL 33199. jpettit@fiu.edu.
(wendy.silverman@yale.edu)
(yrey@fiu.edu)
(carla.marin@yale.edu)
(jjaccard@nyu.edu)

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Despite the strong efficacy evidence for cognitive behavioral therapies (CBTs) to reduce anxiety disorders in children and adolescents (henceforth referred to as “youth”), up to 50% of youth continue to meet diagnostic criteria after a full course of treatment (Rapee, Schniering, & Hudson, 2009; Silverman, Pina, & Viswesvaran, 2008). No published empirical study has investigated augmentation strategies that may potentially help these youth who did not benefit from CBT. This is unfortunate because it means that a substantial proportion of youth, although having received an evidence based treatment, CBT, are continuing to suffer from the significant emotional distress and impairment associated with anxiety disorders (Silverman et al., 2008).

As discussed in this Special Section, adaptive and sequential designs allow for the evaluation of adaptive treatment strategies and have the advantage of mimicking what occurs in typical clinical practice (Collins, Murphy, & Bierman, 2004). In clinical practice, if a certain intervention does not work, then typically another treatment is tried as the next step, which might include augmentation (e.g., CBT + medication).

‘Short-circuiting’ Sequential Designs to Move to Second Stage Treatments Faster

Our review of sequential treatment designs in mental health research reveals the most common approach is to (1) begin patients in a first stage treatment, (2) require patients to go through the entire first stage treatment protocol, (3) ascertain patients’ status at a posttreatment (post) reevaluation, and (4) move patients to a second stage treatment if they did not show satisfactory improvement (Emslie et al., 2010; Fava et al., 2003; Rush et al., 2006; for an exception to the requirement that patients go through an entire first stage treatment before moving to second stage treatment, see Nahum-Shani et al., 2012). Although this approach mimics clinical practice, there are two scenarios in which it may not be ideal from the perspective of stakeholders including families, clinicians, and third party payers.

The first scenario is when CBT is not benefitting or only minimally helping the patient after a certain number of sessions, it is difficult to envision stakeholders desiring for the youth to continue. There would seem to be a strong desire to augment with a second stage treatment *before* the youth completes a full course of CBT. The second scenario is when CBT alone *is* effective, stakeholders likely will want to know if treatment can be terminated before completion of the entire protocol (typically 12 to 16 sessions). Stakeholders also will want to know whether the gains with a shortened first stage intervention are comparable to a full length intervention.

Data addressing either one of these two scenarios are lacking. This is unfortunate because under both scenarios, it is wasteful of time, money, and resources for patients and their families to continue a treatment that is not showing sufficient benefits, as well as to continue

when the anxiety has remitted. Further, under the first scenario, it is also likely frustrating and demoralizing to continue a treatment that is not of sufficient benefit. These two scenarios illustrate the potential need to move patients to second stage treatment augmentation or termination faster, rather than waiting for them to complete a full first stage treatment protocol.

Identifying and Testing Variables to Tailor Second Stage Treatment Strategies

Moving to second stage treatment augmentation or termination faster requires the identification of variables that provide information about a patient's eventual treatment outcome *before* the completion of a full first stage treatment protocol. In the adaptive treatment literature, these variables are referred to as intermediate tailoring variables (Almirall, Compton, Rynn, Walkup, & Murphy, 2012). Tailoring variables are used to generate decision rules, or cutpoints, which provide guidance about a second stage in treatment (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012; Collins et al., 2004).

In the youth mental health literature, rationally derived tailoring variables and decision rules have been proposed to guide moves from first stage treatments to second stage treatments among youths with ADHD (Nahum-Shani et al., 2012) and youths with bipolar disorder (Dawson, Lavori, Luby, Ryan, & Geller, 2007). In the youth anxiety literature, we are aware of no published research that has reported on tailoring variables before the completion of a first stage treatment protocol. The literature on predictors of youth anxiety CBT response points toward anxiety symptom severity as a potentially promising tailoring variable; more severe anxiety at pretreatment (pre) or early in treatment significantly predicts poorer response at post (e.g., Compton et al., 2014). Unfortunately, research on other predictors of youth anxiety treatment response has yielded null or highly inconsistent findings (Nilsen, Eisemann, & Kvernmo, 2013; Silverman et al., 2008). In light of the difficulty identifying and replicating predictors of treatment response measured before treatment begins, efforts to inform moves to second stage treatment augmentation or termination may concentrate on identifying predictors measured *during* first stage treatment.

In this study we present an approach for identifying tailoring variables at midtreatment (mid) for use in 'short-circuiting' the first stage of adaptive treatment strategies among youth with anxiety disorders. We addressed three issues. First, we sought to empirically identify tailoring variables *before* the completion of full first stage CBT protocols. To address this issue, we evaluated the existence of distinct patterns (i.e., classes) of treatment response at CBT mid, as indicated by patients' scores on anxiety rating scales. Evidence in support of the existence of distinct classes of treatment response at CBT mid would provide the basis for a potential tailoring variable. We focused on anxiety severity as a potential tailoring variable given the evidence supporting anxiety severity as a predictor of treatment response (Compton et al., 2014).

Second, we evaluated the validity of treatment response at CBT mid as a tailoring variable. To address this issue, we examined the associations between treatment response class and (a)

clinical characteristics of patients at a pre evaluation (i.e., pre covariates) and (b) treatment outcomes at CBT post, including targeted anxiety disorder diagnosis. Evidence of significant associations between class membership and youths' clinical characteristics, such as levels of impairment, presence of comorbid diagnoses, and levels of depressive symptoms, would support the validity of identified classes because these clinical characteristics have been significantly associated with anxiety symptom severity in past research (Berman, Weems, Silverman, & Kurtines, 2001; Liber et al., 2010). Further, evidence that treatment response class at CBT mid predicts outcomes at CBT post would support the predictive validity of mid response status as a tailoring variable by providing valuable prospective information about patients' probable response by the end of treatment. Treatment response class at CBT mid thus could be used to guide decisions about whether to continue, augment, or terminate treatment.

Third, we derived guidelines for classifying patients based on mid response status. To address this issue, we statistically identified cutpoints on mid response status that had maximum accuracy for classifying patients' treatment response class. With guidelines in hand, researchers would be positioned to make empirically informed decisions about the second stage in studies designed to evaluate strategies for youth anxiety CBT augmentation and CBT abbreviation. Specifically, researchers would have data to guide which patients should be assigned to which second stage option, as well as data to guide the timing of a move to a second stage. These data thus will facilitate the development and evaluation of adaptive treatment strategies, which will lead to more efficient, personalized treatment approaches for youth with anxiety disorders.

We addressed these three issues using data from two independent trials of CBT for youth anxiety disorders. The CBTs used are prototypes of those used in past trials and have a wealth of evidence of producing positive treatment effects (Silverman et al., 2008). Indeed, both trials were conducted not to evaluate outcomes, but to evaluate mediators of treatment outcome. The first data set will be described in Study 1 and the second data set will be described in Study 2.

Study 1

Method

Participants—Participants consisted of 240 youths (55% male) ages 6 to 16 years ($M = 9.86$; $SD = 2.29$) and their parents (mostly mothers) who were referred for difficulties with excessive fear or anxiety. One-hundred eighty-three youths (76.25%) completed treatment. All youths met criteria for a primary anxiety disorder on the basis of the Anxiety Disorders Interview Schedule for Children (Child and Parent Versions) for *DSM-IV* (ADIS-IV: C/P; Silverman & Albano, 1996). The most common primary diagnoses were separation anxiety disorder (SAD; 41%), social phobia (SOP; 25%), specific phobia (SP; 15%), and generalized anxiety disorder (GAD; 13%). Seventy-two percent had at least one comorbid diagnosis, with SAD (21%), GAD (19%), SP (17%), and SOP (16%) being most common. Youths with developmental delays (e.g., autism), psychosis/schizophrenia, or current involvement in another psychosocial treatment were excluded. Youths with other comorbid diagnoses (e.g., major depression, ADHD) were included as long as those comorbid

diagnoses were not primary, were treated with a stable dose of medication, and received a clinician severity rating < 4. The majority (75%) of youths was Hispanic/Latino, 20% were European American, 3% were African American, and 2% reported “other” ethnicity. Fourteen percent had an annual family income of less than \$20,000.

Measures

Diagnostic interview administered to youths and parents at pre and post: The ADIS–IV: C/P was administered to assess anxiety and related disorders. The anxiety disorder deemed most interfering was viewed as primary and was targeted in treatment. The ADIS–IV: C/P has satisfactory test-retest reliability for specific diagnoses, excellent retest reliability over a two week interval, and strong correspondence with youths’ anxiety self-ratings (Silverman, Kurtines, Jaccard, & Pina, 2009; Silverman, Saavedra, & Pina, 2001).

Anxiety rating scale administered to youths at pre, mid, and post: The *Revised Children’s Manifest Anxiety Scale* (RCMAS; Reynolds & Richmond, 1978) is a self-rating scale that assesses anxiety symptoms and was a primary outcome measure in past trials (e.g., Kendall, 1994; Silverman et al., 1999). Each of 28 items is scored 1 or 0; items are summed to yield a Total Anxiety score. Convergent validity has been supported via significant correlations between the Total Anxiety scale, trait anxiety, and fear ($r_s = .63$ to $.88$) (Ollendick, 1983). The measure has been found to discriminate between youth with anxiety and youth with no psychiatric problems, although it has not been found to discriminate between youths with different types of psychiatric problems (Perrin & Last, 1992). The alpha coefficient for this sample was $.84$.

Anxiety rating scales administered to parents at pre, mid, and post: In the *Revised Children’s Manifest Anxiety Scale* (Parent Version; RCMAS/P), the wording of RCMAS items was changed from *I* to *my child*, as done in past research (Kendall, 1994; Silverman et al., 1999). The alpha coefficient for this sample was $.78$.

The *Child Behavior Checklist* (CBCL; Achenbach & Rescorla, 2001) is a 118-item parent rating scale designed to measure specific child behavioral and emotional problems. Items are rated on a 3-point scale (0 = *not true*; 1 = *somewhat or sometimes true*; 2 = *very true or often true*). In the present study, we examined T scores on parent ratings on the CBCL Internalizing scale (CBCL-I). Significant correlations have been found between the CBCL-I and youth anxiety disorder diagnoses (Aschenbrand, Angelosante, & Kendall, 2005).

Measures of covariates collected at pre: In latent profile and latent transition analyses (see Data Analysis), the term covariate refers to a variable that predicts membership in latent classes (Collins & Lanza, 2010). The following variables assessed at a pre evaluation were examined as covariates of class membership for the purpose of evaluating the validity of latent classes: presence versus absence of a comorbid diagnosis, clinician rated interference, and child self rated depressive symptoms. Presence of a comorbid diagnosis at the pre evaluation was coded as a dichotomous variable (0=absent, 1=present) and included any comorbid anxiety or non-anxiety diagnosis based on the ADIS–IV: C/P.

Clinician rated interference was assessed using the interview schedule's clinician severity rating (CSR) scale, a 0- to 8-point rating of the severity of a diagnosis and the amount of interference it causes in the youth's functioning. Satisfactory interrater and retest reliability have been demonstrated (correlations ranging from .74 to .88; Silverman & Eisen, 1992).

Depressive symptoms were assessed using the 27-item Children's Depression Inventory (CDI; Kovacs, 1985). Each item is scored on a 0 to 3 scale; total scores range from 0 to 81. The CDI possesses good internal consistency and convergent validity has been demonstrated via significant correlations with clinician rated and self rated measures of depressive symptoms (Klein, Dougherty, & Olino, 2005). The alpha coefficient for this sample was .87.

Treatment Conditions—Participants were randomly assigned to 14-16 sessions of either CBT involving parents or group CBT. A mid evaluation was conducted following session eight and a post evaluation was conducted within one week of the final session. Treatment strategies for reducing anxiety were the same in both conditions and consisted of 1) gradual exposures to anxiety-provoking situations related to the primary diagnosis and 2) behavioral and cognitive strategies to facilitate the exposures. Additional details about the randomization procedures, treatment conditions, and therapists are provided in (Silverman, Marin, Rey, Jaccard, & Pettit, 2014). Study findings and conclusions did not differ when treatment condition was included as a covariate in analyses. Treatment condition thus was excluded from the analyses presented below.

Data Analysis

To gain perspective on patterns of mid response that could be used to tailor second stage treatment strategies in future studies, we identified homogeneous classes of youths based on anxiety symptom profiles at mid (CBT session eight). To evaluate the validity of mid class assignment, including the predictive validity of mid class assignment on post outcomes, we also identified the existence of homogenous classes of patients based on anxiety symptom profiles at pre and at post. Three measures of anxiety were used as indicators of class membership at pre, mid, and post: parent ratings of youth anxiety on the CBLC-I parent ratings of youth anxiety on the RCMAS/P, and youth self ratings of anxiety on the RCMAS.

Latent profile analysis (LPA) was used to identify classes based on anxiety symptom profiles using the statistical software program Mplus, Version 7 (Muthén & Muthén, 1998-2012). We tested the fit of one-class through five-class models at each of the three assessment waves. The Bayesian Information Criterion (BIC) and Bootstrap Likelihood Ratio Test (BLRT) were used to determine the best fitting model in terms of the number of classes because simulation studies indicate they provide the best and most consistent statistical indicators for determining number of classes (Nylund, Asparouhov, & Muthén, 2008). Lower BIC values are indicative of better model fit, and differences in BIC values > 10 provide strong evidence in support of the model with the lower BIC value (Raftery, 1995). Statistically significant BLRT values indicate the k class model provides a superior model fit than the $k-1$ class model. We also examined entropy, which provides a weighted average of participants' posterior probabilities of membership in a given class. Because entropy values can decrease

simply as function of an increasing number of classes, we gave preference to the BIC and BLRT in model selection (Collins & Lanza, 2010).

Two steps were taken to evaluate the validity of class membership. First, we examined the associations between relevant covariates (comorbid diagnosis, clinician rated interference, and depressive symptoms) and class membership at pre. Second, we examined the associations between class membership at post and targeted anxiety disorder diagnostic status at post.

Following LPA, latent transition analysis (LTA) was used to examine the movement of patients between latent classes from pre to mid and from mid to post. Of greatest interest was the probability of membership in a given class at post based upon membership in a given class at mid. A high transition probability from a given class at mid to a given class at post would provide evidence to support the predictive validity of mid status on treatment response at post.

Because all participants were receiving active treatment, we did not assume the number or nature of latent classes would be invariant across assessment waves. Indeed, the assumption of class invariance across waves was rarely met; constraining class indicator intercepts to equality across waves almost always led to a decrement in model fit. Unless stated otherwise, class indicator intercepts were freed to vary across waves. Because classes were not invariant across waves, we focused on patterns of movement between classes across waves rather than alternative analytic approaches that assume invariance such as mover-stayer models.

All 240 youths assigned to treatment were included in analyses. Missing data were assumed to be missing at random and comprised on average 16.67% of the sample. Missing data were imputed using maximum likelihood multiple imputation, averaged over 40 imputations (Graham, 2009). Ancillary analyses including only treatment completers resulted in comparable findings that did not impact conclusions in Study 1 or Study 2 (results available upon request).

Results

Class enumeration—Fit indices for LPA class solutions at each wave are provided in Table 1. At each wave, the BIC provided evidence a three class model was preferred and the BLRT provided evidence a four class model was preferred. The four class solutions at each wave resulted in a class < 10% of the total sample that was challenging to interpret and a BIC < 10 compared to the three class solution. We thus retained the three class solution at each wave.

Mean scores on class indicators at each wave are presented in Table 2. Class assignments were made based on the highest of the posterior probabilities; class labels were made based on mean scores on class indicators. At pre, classes were labeled Mild (12.71%), Moderate (48.76%), and Severe (38.53%). At mid, classes were labeled Early Responders (ERs; 21.51%), Partial Responders (PRs; 57.30%), and Nonresponders (NRs; 21.19%).¹ At post, classes were labeled Full Responders (FRs; 41.67%), PRs (42.50%), and NRs (15.83%).

Pre covariates—In a conditional LPA, presence of a comorbid diagnosis and CSR scores, but not CDI scores, were significantly associated with class membership at pre. The odds of being assigned to the Severe class relative to the Mild class (OR=1.83, 95% CI=1.23, 2.72) and the Moderate class (OR=1.70, 95% CI=1.17, 2.47) significantly increased as CSR scores increased. The odds of being assigned to the Severe class relative to the Mild class (OR=6.44, 95% CI=2.57, 16.16) and the Moderate class (OR=4.41, 95% CI=2.09, 9.26) was significantly higher in the presence of a comorbid disorder.

Post diagnostic status—Post diagnostic status was examined as an outcome of class membership at post. The odds of meeting diagnostic criteria for the targeted anxiety disorder at post was significantly higher in the NR class relative to the FR class (OR=11.81, 95% CI=5.12, 27.22), in the PR class relative to the FR class (OR=3.44, 95% CI=1.36, 8.70), and in the NR class relative to the PR class (OR=3.43, 95% CI = 1.24-9.47).

Evaluating class assignment at mid as a potential tailoring variable—Based on findings from the LPA, we first ran an unconditional LTA with no covariates or outcome variables. The same three class models identified in the LPAs replicated in the LTA. The NR class intercept at mid was constrained to be equal to the NR class intercept at post, as it was the only equality constraint that did not lead to significant decrement in model fit. We then ran a conditional LTA with pre covariates that were significant in the LPA model and with post diagnostic status as an outcome variable.

In the conditional LTA, presence of a comorbid diagnosis, but not CSR scores, was significantly associated with class membership. Class membership at post continued to be significantly associated with diagnostic status at post. We examined transition probabilities from pre classes to mid classes and from mid classes to post classes (Table 3). These transition probabilities represent the probability that patients in a specific class at one wave were in a specific class at the subsequent wave. Transition probabilities from mid to post are most relevant for evaluating the predictive validity of class assignment at mid as a potential tailoring variable. As shown in Table 3, 97% of patients in the ER class at mid transitioned to the FR class at post. The majority (76%) of PRs at mid transitioned to the PR class at post, and the remainder (24%) transitioned to the NR class. Slightly more than half (53%) of NRs at mid transitioned to the PR class at post, and the remainder (47%) transitioned to the NR class.

Deriving guidelines at mid—To identify an optimal cutpoint for classification of youths at mid as either candidates for CBT abbreviation (ERs) or candidates for CBT augmentation (PRs and NRs), we converted raw scores on class indicators at mid to T-scores with a mean of 50 and standard deviation of 10 so all three indicators would be on the same metric. We then summed T-scores on the three indicators to create a composite index. A receiver operating characteristics (ROC) curve was used to calculate the sensitivity and

¹To evaluate the possibility that classes identified at mid were redundant with symptom severity at pre, we ran an analysis of covariance on each class indicator at mid using class assignment as a between-subjects factor and the class indicator at pre as a covariate. Each pairwise comparison between classes was statistically significant. These findings indicate class membership at mid represented mean symptom severity at mid and mean level of covariate adjusted pre to mid changes in symptom severity. Similar findings were obtained in Study 2.

specificity when using each value of the composite index to predict membership in the PR class or NR class at mid (lumped) versus membership in the ER class at mid (Steidtmann et al., 2013). The composite index significantly discriminated between members of PR or NR and members of ER (area under the curve = .87, 95% CI = .83-.92, $p < .001$). A value of 146 on the composite index maximized sensitivity (.82) and specificity (.80). Youths who scored < 146 on the composite score were classified as ERs and youths who scored > 146 were classified as PRs or NRs.

Discussion

Distinct classes based on anxiety symptom profiles were found at pre, mid, and post. Validity of the classes was supported by significant associations with the presence of a comorbid diagnosis at pre and with targeted anxiety disorder diagnostic status at post, and expected patterns of movement between classes across waves. All but one patient assigned to the ER class at mid was assigned to the FR class at post. No patient assigned to the NR class at mid was assigned to the FR class at post. A composite score on the CBCL-I, RCMAS/P, and RCMAS at CBT mid thus provides a potential variable for tailoring second stage treatment strategies for youth with anxiety disorders, with a composite score of 146 offering maximum sensitivity and specificity.

Study 2

Method

Participants—Participants consisted of 341 youths (53% male) ages 7 to 16 years ($M = 9.53$; $SD = 2.48$) and their parents (mostly mothers) who were referred with excessive fear or anxiety. Of the 341 youths, 253 (74.19%) completed treatment. Inclusion criteria and exclusion criteria were identical to those in Study 1. The most common primary diagnoses were SAD (27%), GAD (23%), SOP (23%), and SP (15%). Seventy-two percent had at least one comorbid diagnosis, with SOP (29%), SAD (24%), GAD (24%), and SP (22%) being most common. The majority (82%) of youths was Hispanic/Latino, 11% were European American, 2% were Asian American, 1% were African American, 2% reported “other” ethnicity, and 2% did not report ethnicity. Sixteen percent had an annual family income of less than \$20,000.

Measures

Diagnostic interview administered to youths and parents at pre and post: The ADIS-IV: C/P was administered to assess anxiety and related disorders.

Anxiety rating scales administered to youths at pre, mid, and post: A brief version of the RCMAS (B-RCMAS) was derived by selecting RCMAS items with the highest correlation with the RCMAS Total Anxiety score using data from previous case files at our clinic. The BRCMAS contained seven items rated on a five point scale (1=*not at all*, 2=*a little bit*, 3=*some*, 4=*quite a bit*, and 5=*very much*); total scores ranged from 7 to 35. B-RCMAS items were: “I get nervous when things do not go the right way;” “Others seem to do things easier than I can;” “I worry a lot of the time;” “I feel alone even when there are people with me;” “I worry about what is going to happen;” “My feelings get hurt easily

when I am fussed at;" and "I often worry about something bad happening to me." The correlation between the B-RCMAS and the full RCMA Total Anxiety score at the pre evaluation was $r = .58$, $p < .001$. The alpha coefficient was .79.

The *Multidimensional Anxiety Scale for Children* (MASC; March, Parker, Sullivan, Stallings, & Conners, 1997) is a 39 item youth self rating scale of anxiety symptoms. A brief version of the MASC (B-MASC) was derived by selecting items with the highest correlation with the total MASC score using data obtained from previous case files at our clinic. The BMASC included five items rated on a five-point scale (1=*not at all*, 2=*a little bit*, 3=*some*, 4=*quite a bit*, 5=*very much*): "I worry about other people laughing at me;" "The idea of going away to camp scares me;" "I worry about what other people think of me;" "I stay away from things that upset me;" and "My hands shake." Total scores ranged from 5 to 25. The correlation between the B-MASC and the full MASC total score at the pre evaluation was $r = .64$, $p < .001$. The alpha coefficient was .69.

Anxiety rating scale administered to parents at pre, mid, and post: A parent version of the brief RCMA (B-RCMA/P) was created by changing the wording of B-RCMA items from *I* to *my child*. The correlation between the B-RCMA/P and the full RCMA/P Total Anxiety score at the pre evaluation was $r = .73$, $p < .001$. The alpha coefficient was .83.

Measures of covariates collected at pre: The same pre covariates described in Study 1 were measured at a pre evaluation in Study 2: presence of a comorbid diagnosis based on the ADIS-IV: C/P, clinician rated interference (CSR), and depressive symptoms (CDI; $\alpha = .83$).

Treatment Conditions—Participants in this RCT (Silverman, Pettit, Rey, Marin, & Jaccard, 2015) were randomly assigned to 12-14 sessions of individual youth CBT or one of two CBTs involving parents. The treatment strategies for reducing anxiety were similar in all three conditions and consisted of 1) gradual exposures to anxiety-provoking situations related to the primary diagnosis and 2) behavioral and cognitive strategies to facilitate the exposures. The two parent involved treatment conditions also targeted specific parenting behaviors relevant to youth anxiety. Study findings and conclusions did not differ when treatment condition was included as a covariate in analyses. Treatment condition thus was excluded from the analyses presented below. A mid evaluation was conducted following session eight and a post evaluation was conducted within one week of the final session.

Data Analysis

The data analytic approach was identical to that described in Study 1. The three variables used as class indicators were youth self ratings of anxiety on the B-MASC and B-RCMA and parent ratings of youth anxiety on the B-RCMA/P. All 341 youths assigned to treatment were included in analyses. Missing data were assumed to be missing at random and comprised on average 20.90% of the sample.

Results

Class enumeration—Fit indices for LPA class solutions at each wave are provided in Table 4. The BIC provided evidence the three class model was preferred at each wave. The

BLRT provided evidence the four class model was preferred at mid and post, but the solution resulted in a class < 10% of the total sample that was challenging to interpret and a BIC < 10 compared to the three class solution. We thus retained the three class solution at each wave.

Mean scores on the three class indicators are presented in Table 5. At pre, the classes were labeled Mild (35.49%), Moderate (51.33%), and Severe (13.18%). At mid, the classes were labeled ERs (40.17%), PRs (44.58%), and NRs (15.25%). At post, the classes were labeled FRs (50.34%), PRs (37.60%), and NRs (12.06%).

Pre covariates—As was the case in Study 1, CSR scores and CDI scores were significantly associated with class membership. The presence of a comorbid diagnosis was not significantly associated with class membership. The odds of being assigned to the Severe class relative to the Mild class significantly increased as CSR scores increased (OR=1.82, 95% CI=1.28, 2.58) and as CDI scores increased (OR=1.49, 95% CI=1.35, 1.63). The odds of being assigned to the Moderate class relative to the Mild class significantly increased as CSR scores increased (OR=1.46, 95% CI=1.19, 1.80) and as CDI scores increased (OR=1.36, 95% CI=1.25, 1.48). Finally, the odds of being assigned to the Severe class relative to the Moderate class significantly increased as CDI scores increased (OR=1.09, 95% CI=1.04, 1.15).

Post diagnostic status—Post diagnostic status was significantly associated with class membership. The odds of meeting diagnostic criteria for the targeted anxiety disorder at post was significantly higher in the NR class relative to the FR class (OR=4.05, 95% CI=1.90, 8.64) and in the PR class relative to the FR class (OR=3.07, 95% CI = 1.77-5.35).

Evaluating class assignment at mid as a potential tailoring variable—Based on findings from the LPA, we ran an unconditional LTA with no covariates or outcome variables. The same three class models identified in the LPAs replicated in the LTA. We then ran a conditional LTA with pre covariates that were significant in the LPA model and with post diagnostic status as an outcome variable.

In the conditional LTA, CDI scores but not CSR scores were significantly associated with class membership. Class membership at post continued to be significantly associated with diagnostic status at post. We examined transition probabilities from pre classes to mid classes and from mid to post (Table 6). As shown in Table 6, 95% of patients in the ER class at mid transitioned to the FR class at post. The majority (55%) of PRs at mid transitioned to the PR class, 33% transitioned to the FR class, and 12% transitioned to the NR class. Approximately half (51%) of NRs at mid transitioned to the PR class at post and slightly less than half (44%) transitioned to the NR class at post. Only 5% of NRs at mid transitioned to the FR class.

Deriving guidelines at mid—We used the same procedures described in Study 1 to identify an optimal cutpoint for classification of youths as members of the PR class or NR class at mid (lumped) versus members in the ER class at mid. The composite index significantly discriminated between members of PR or NR and members of ER (area under

the curve = .97, 95% CI = .95-.98, $p < .001$). A value of 143 on the composite index maximized sensitivity (.93) and specificity (.90). Youths who scored < 143 on the composite score were classified as ERs and youths who scored > 143 were classified as PRs or NRs.

Discussion

As in Study 1, distinct classes based on anxiety symptom profiles were found at pre, mid, and post. Validity of the classes was supported by significant associations with depressive symptoms at pre and with targeted anxiety disorder diagnostic status at post, and expected patterns of movement between classes across waves. All but three patients assigned to the ER class at mid were assigned to the FR class at post. Only three patients assigned to the NR class at mid were assigned to the FR class at post. A composite score on the summed B-MASC, BRCMAS, and B-RCMAS/P at CBT mid thus provides a potential variable for tailoring second treatment strategies for youth with anxiety disorders, with a composite score of 143 offering maximum sensitivity and specificity.

General Discussion

Using two independent data sets, we identified and replicated three classes of treatment response at CBT mid for youth with anxiety disorders: Early Responders, Partial Responders, and Nonresponders. We further demonstrated treatment response status at CBT mid predicted outcome at CBT post. Across Study 1 and Study 2, almost all (95% to 97%) youths classified as Early Responders at CBT mid were classified as Full Responders at CBT post, and Full Responders at CBT post were significantly more likely to show diagnostic recovery relative to Nonresponders and Partial Responders. The majority of youths classified as Partial Responders at CBT mid also were classified as Partial Responders at CBT post, although 24% to 45% transitioned to Full Responder or Nonresponder status at CBT post. Finally, few (0% to 5%) youths classified as Nonresponders at CBT mid were classified as Full Responders at CBT post.

These findings lay the groundwork for intriguing innovations in approaches to designing and implementing adaptive treatment strategies. Rather than waiting for patients to complete an entire first stage intervention before re-evaluating their status, we have identified variables at mid which predict post status and suggested guidelines for classification of patients at mid. These findings thus provide a possible empirical justification for ‘short circuiting’ the more common design for evaluating adaptive treatment strategies. With this information in hand, researchers have preliminary empirical guidance to pursue studies designed to evaluate adaptive treatment strategies for youth with anxiety disorders. Some example study designs are depicted in Figure 1. All youths would be assigned to CBT as the first stage treatment. In this example study design, the decision to initiate treatment with CBT is consistent with the large evidence base supporting CBT for youth anxiety (Silverman et al., 2008) and with data indicating patients and their families prefer psychosocial over pharmacological treatments (Chavira, Stein, Bailey, & Stein, 2003; Young et al., 2006). All youths would be evaluated on the tailoring variables at CBT mid and the second stage would be determined according to the guidelines.

To address questions related to CBT abbreviation, youths classified as Early Responders at CBT mid could be randomized to either an abbreviated CBT condition or a continued CBT condition. Youths in both conditions would be assessed at the end of the second stage (see Figure 1) and statistical comparisons would be made between these two conditions. An example hypothesis that could be tested would be that youths assigned to abbreviated CBT would display a treatment response that is not inferior to youths assigned to continued CBT. Promising findings at the end of the second stage would provide an impetus to evaluate the long term maintenance of gains attained in abbreviated CBT.

To address questions related to CBT augmentation, youths classified as Nonresponders and/or Partial Responders at CBT mid could be randomized to different conditions depending on the research question of interest. For example, to evaluate a specific augmentation strategy such as sertraline, youths classified as Partial Responders and Nonresponders could be randomized to either a continued CBT plus sertraline augmentation condition or a continued CBT alone condition (Figure 1). Statistical comparisons could be made between these conditions to test a hypothesis that youths assigned to continued CBT plus sertraline augmentation would show a superior treatment response than youths assigned to continued CBT alone. Alternative research questions may lead investigators to include conditions that would permit comparisons of multiple augmentation strategies (e.g., CBT plus sertraline versus CBT plus Attention Bias Modification).

These findings offer empirical documentation that coincides with clinicians' anecdotal reports when using CBT with anxious youth: Some patients improve early on, some never improve, and some only partially improve. These findings also increment a literature documenting that lower anxiety severity at pre and early response to treatment predict better outcomes at post (Compton et al., 2014). Further, these findings extend past research by identifying specific classes of youth at CBT mid that may guide the design of studies to evaluate adaptive treatment strategies. We identified a class of youth Nonresponders who could be hypothesized as likely to benefit from augmentation because CBT alone was ineffective at mid and mid status predicted post status. We also identified a class of youth Early Responders who could be hypothesized as likely to be good candidates for CBT abbreviation because CBT alone was found to be effective at mid and mid status predicted post status. Between these classes was a third class of youth who partially responded at mid and showed a mixed pattern of responding at the end of CBT.

The results of this study should be interpreted in light of its strengths and limitations, as well as the assumptions underlying the data analytic approach. Strengths include the multisource assessment approach and replication of findings in two independent data sets. The data analytic approach, LPA, assumes the association among observed indicators of anxiety is accounted for by a categorical latent variable. It remains unclear whether anxiety is truly categorical, continuous, or both (Haslam, Holland, & Kuppens, 2012). This study has presented an empirical approach to facilitate decisions about next steps in treatment. We encourage future studies to consider this approach and alternative empirical approaches.

One limitation was our inability to examine predictors of transitions from class membership at mid to class membership at post. It would be of interest to know, for example, what

variables predict which youth Partial Responders at mid will transition to Full Responders versus Partial Responders at post. The interaction analyses needed to address that type of research question are computationally complex, especially given the dimensional nature of our class indicators, and exceeded the sample sizes of classes available in this study.

Another limitation concerns the timing and measurement of tailoring variables. We were constrained to the measures and assessment schedules of the two data sets used for analyses, including abbreviated measures with modest internal consistency in Study 2 (α ranged from .69-.83). We were unable to evaluate tailoring variables prior to CBT mid, which potentially could inform even earlier shifts to second stage treatment. Further, the use of parent report and child report measures as indicators of the same latent class variable emphasized common variance among the measures and did not take into account possible informant source effects.

Finally, the tailoring variables in each study were derived using three measures. Although the measures are relatively short and could be administered by treating clinicians, the collection of and integration of scores across three measures may not be practical in some settings. Future research is encouraged to empirically identify tailoring variables that pose minimal burden on clinicians and patients (Almirall, Compton, Gunlicks-Stoessel, et al., 2012), as well as to investigate tailoring variables in other populations of youth with anxiety disorders.

In spite of these limitations, this study provides an empirical effort to identify variables before the completion of a full first stage treatment protocol that can be used to tailor second stage treatments in adaptive treatment strategies for youth with anxiety disorders. The framework presented in this study offers an example for researchers interested in developing and evaluating adaptive treatment strategies for youth with anxiety disorders.

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Figure 1. Example design of randomized trial of CBT augmentation and CBT abbreviation as adaptive treatment strategies. CBT = Cognitive behavioral therapy.

Table 1

Study 1 criteria to decide on optimal solution for number of latent classes.

Assessment Wave	Number of classes	LL	BIC	BLRT	Entropy
Pre	1	-2426.40	4885.68	--	--
	2	-2366.47	4787.74	119.86 [*]	.73
	3	-2338.44	4753.60	56.06 [*]	.75
	4	-2326.13	4750.92	24.61 [*]	.76
	5	-2318.85	4758.28	14.56	.82
Mid	1	-2463.68	4960.24	---	---
	2	-2408.15	4871.11	111.06 [*]	.66
	3	-2381.93	4840.58	52.45 [*]	.75
	4	-2370.41	4839.49	23.02 [*]	.71
	5	-2364.45	4849.47	11.97	.76
Post	1	-2444.19	4900.39	---	---
	2	-2367.07	4788.95	154.25 [*]	.78
	3	-2344.54	4765.82	45.06 [*]	.79
	4	-2331.57	4761.80	25.94 [*]	.83
	5	-2323.97	4768.94	15.20	.86

Note. LL = log likelihood; BIC = Bayesian Information Criteria; BLRT = Bootstrap likelihood ratio test; Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.

^{*}
p < .001.

Table 2

Study 1 mean scores on latent class indicators.

Pre			
	Mild Class	Moderate Class	Severe Class
CBCL-I	50.42	65.08	74.37
RCMAS/P	4.35	11.17	18.00
RCMAS	12.46	12.19	15.46

Mid			
	ER Class	PR Class	NR Class
CBCL-I	44.24	57.55	68.02
RCMAS/P	4.47	12.14	18.80
RCMAS-C	6.27	9.13	14.82

Post			
	FR Class	PR Class	NR Class
CBCL-I	46.95	60.02	66.96
RCMAS/P	3.94	10.88	17.72
RCMAS	6.88	7.84	12.40

Note. CBCL-I = Parent rating on Child Behavior Checklist Internalizing T-Score; RCMAS/P = Reynolds Child Manifest Anxiety Scale - Parent rating; RCMAS = Reynolds Child Manifest Anxiety Scale - Child self rating; ER=Early Responder; PR = Partial Responder; NR = Nonresponder; FR = Full Responder; Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.

Table 3

Study 1 transition probabilities from pre to mid and from mid to post.

Mid Class			
	ER	PR	NR
Pre Class			
Mild	.82	.12	.06
Moderate	.35	.65	.00
Severe	.16	.29	.55

Post Class			
	FR	PR	NR
Mid Class			
ER	.97	.03	.00
PR	.00	.76	.24
NR	.00	.53	.47

Note. ER=Early Responder; PR = Partial Responder; NR = Nonresponder; FR = Full Responder. Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.

Table 4

Study 2 criteria to decide on optimal solution for number of latent classes.

Assessment Wave	Number of classes	LL	BIC	BLRT	Entropy
Pre	1	-3295.19	6625.38	--	--
	2	-3199.02	6456.36	192.36 ^{**}	.76
	3	-3173.72	6429.08	50.61 ^{**}	.80
	4	-3166.05	6437.07	15.34	.73
	5	-3161.02	6450.34	10.05	.77
Mid	1	-3284.42	6603.83	---	---
	2	-3185.83	6429.99	197.17 ^{**}	.72
	3	-3156.61	6394.87	58.55 ^{**}	.74
	4	-3144.74	6394.46	23.74 ^{**}	.81
	5	-3138.50	6405.30	12.49	.81
Post	1	-3278.73	6592.44	---	---
	2	-3146.02	6350.36	265.42 ^{**}	.82
	3	-3102.09	6285.84	84.23 ^{**}	.86
	4	-3086.83	6278.64	30.53 ^{**}	.81
	5	-3074.28	6276.86	25.11 [*]	.83

Note. LL = log likelihood; BIC = Bayesian Information Criteria; BLRT = Bootstrap likelihood ratio test; Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.

^{**}
p < .001

^{*}
p < .01.

Table 5

Study 2 mean scores on LPA indicators.

Pre			
	Mild Class	Moderate Class	Severe Class
MASC	7.97	13.99	20.73
B-RCMAS/P	18.81	21.96	20.80
B-RCMAS	12.49	22.18	26.44

Mid			
	ER Class	PR Class	NR Class
MASC	8.33	13.78	19.09
B-RCMAS/P	18.19	20.42	23.30
B-RCMAS	11.81	20.41	29.07

Post			
	FR Class	PR Class	NR Class
MASC	7.93	13.43	18.41
B-RCMAS/P	13.29	17.12	15.34
B-RCMAS	10.28	20.22	29.40

Note. MASC = Child self rating on Multidimensional Anxiety Scale for Children; B-RCMAS/P = Brief Reynolds Child Manifest Anxiety Scale - Parent rating; B-RCMAS = Brief Reynolds Child Manifest Anxiety Scale - Child self rating; ER=Early Responder; PR = Partial Responder; NR = Nonresponder; FR = Full Responder; Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.

Table 6

Study 2 transition probabilities from pre to mid and from mid to post.

Mid Class			
	ER	PR	NR
Pre Class			
Mild	.86	.09	.05
Moderate	.22	.67	.11
Severe	.01	.50	.49

Post Class			
	FR	PR	NR
Mid Class			
ER	.95	.04	.01
PR	.33	.55	.12
NR	.05	.51	.44

Note. ER=Early Responder; PR = Partial Responder; NR = Nonresponder; FR = Full Responder; Pre = Pretreatment; Mid = Midtreatment; Post = Posttreatment.