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Andrea N. Niles, Kate B. Wolitzky-Taylor, Joanna J. Arch, Michelle G. Craske



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Applying a novel statistical method to advance the personalized treatment of anxiety disorders:

A composite moderator of comparative drop-out from CBT and ACT

Andrea N. Niles^a (Corresponding Author)
aniles@ucla.edu

Kate B. Wolitzky-Taylor^{b*}

Joanna J. Arch^{c*}

Michelle G. Craske^{a, b}

^aUniversity of California, Los Angeles, Department of Psychology, 1285 Franz Hall, Box
951563, Los Angeles, CA 90095-1563

^bUniversity of California, Los Angeles, Department of Psychiatry and Biobehavioral Science,
760 Westwood Plaza, Los Angeles, CA 90095

^cUniversity of Colorado Boulder, Department of Psychology, Muenzinger D244, 345 UCB,
Boulder, CO 80309-0345

* K. W.-T. and J. J. A. contributed equally to this work; thus, they share second authorship.

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Abstract

Background: No prior studies have examined moderators of dropout between distinct treatments for anxiety disorders. This study applied a novel statistical approach for examining moderators of dropout from traditional cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT).

Method: We combined data from two randomized controlled trials ($N = 208$) comparing CBT and ACT for patients with DSM-IV anxiety disorders. Adapting Kraemer's method for constructing and evaluating composite moderators (2013), 26 variables were examined for individual effect sizes. Forward-stepwise regression combined with k -fold cross validation was used to identify a model to predict treatment dropout.

Results: Four baseline variables comprised the final composite moderator: self-reported degree of control over internal anxiety, current psychiatric medication use, religiosity, and endurance in a voluntary hyperventilation stressor. This composite moderator predicted differential dropout from ACT vs. CBT with a medium effect size ($r = .28$), and had a significantly larger effect size than any individual moderator.

Conclusions: Findings reveal that specific patient profiles predict differential dropout from ACT vs. CBT for anxiety disorders. In the first investigation of a composite moderator with a dichotomous outcome, findings also support the superiority of composite over individual moderators.

Keywords: moderators; attrition; behavioral therapy; anxiety disorders; personalized medicine

Applying a novel statistical method to advance the personalized treatment of anxiety disorders:

A composite moderator of comparative drop-out from CBT and ACT

Personalized medicine represents the idea that a patient's individual characteristics can be used to select the best treatment for that patient. Originally focused on using patient genetics to inform treatment for medical disease (Ginsburg & Willard, 2009), this notion has been applied to the mental health field (Insel, 2009) in a manner that includes a broader range of biological and psychological patient characteristics to inform psychological treatment (Schneider, Arch, & Wolitzky-Taylor, 2015; Simon & Perlis, 2010). However, finding patient characteristics that consistently predict better outcomes in one psychological treatment over another – treatment moderators (Kraemer, Wilson, Fairburn, & Agras, 2002) – has been challenging. A recent review (Schneider et al., 2015), for example, demonstrated that across the twenty-four papers examining treatment moderators of cognitive behavioral therapy (CBT) for anxiety disorders, a first-line treatment, few consistent treatment moderators could be identified. Further, only one of twenty-four studies (4%) provided both high-quality moderator statistical tests *and* a moderately-sized or greater sample ($n = 60$ or more per condition), demonstrating that methodological and statistical power issues plague the vast majority of efforts to identify treatment moderators for anxiety disorders. Another review of treatment moderators for depression (Simon & Perlis, 2010) demonstrated similar methodological problems and limited moderator findings. In sum, advancing personalized medicine for the treatment of the most commonly occurring psychological disorders has been elusive.

What represents a promising path forward? Reviews have identified a strong need for larger sample sizes and better statistical methods (Schneider et al., 2015; Simon & Perlis, 2010). A novel statistical approach developed by Kraemer (2013) facilitates constructing *combined*

(composite) treatment moderators that are potentially more powerful than typical approaches that examine each moderator by itself. For example, applying Kraemer's method for creating a combined moderator, Wallace and colleagues (2013), compared psychotherapy to medication for the treatment of depression and calculated effect sizes for 32 potential moderators. The authors used principal component analysis to identify how many factors should be included in the combined moderator, and chose variables to represent each of those factors. The final moderator represented a combination of eight variables, and had an effect size of .31, which was substantially larger than the largest (single) moderator effect size of .12. Thus, by providing a fuller, multi-faceted profile of the types of patients that do better in one treatment versus another, combined moderators have preliminarily shown promise as a path toward identifying more robust treatment moderators.

In this paper, we apply an expanded version of this novel statistical approach to examine moderators of attrition for two distinct behavioral treatments for anxiety disorders, (traditional) CBT and acceptance and commitment therapy (ACT). Thus, this represents the first attempt to model a composite moderator for a dichotomous outcome (e.g., treatment attrition) – a challenge because dichotomous outcomes offer substantially less variability than continuous outcomes. Because treatment attrition represents an important outcome to clinical science and many outcomes in clinical fields more generally are dichotomous (e.g., survival, relapse, treatment response), this challenge is highly worthwhile. Expanding upon Kraemer's (2013) model, we drew upon statistical learning approaches and employed model selection with k -fold cross validation (James, Witten, Hastie, & Tibshirani, 2013). In addition, we used multiple imputation to estimate missing data on the purported moderators. We thus synergized two cutting-edge statistical approaches, in addition to Kraemer's (2013) approach, to maximize our ability to

identify treatment moderators for a dichotomous outcome (attrition). We combined data from two treatment studies, creating a larger sample size than in any published previous treatment moderator studies for anxiety disorders (see Schneider et al., 2015).

We selected treatment attrition as the moderated outcome because it represents a reliably measured behavior that perhaps more than any other, indicates a lack of good ‘treatment match’ from the perspective of the patient¹. Although dropout rates from CBT for anxiety disorders are somewhat lower than for pharmacological interventions, not all patients who initiate a course of CBT will complete it (Otto, Smits, & Reese, 2004). Data from efficacy studies and related meta-analyses (Gould, Buckminster, Pollack, Otto, & Massachusetts, 1997; Gould et al., 1997; Gould, Otto, & Pollack, 1995; Hofmann & Suvak, 2006; Kobak, Greist, Jefferson, Katzelnick, & Henk, 1998; Otto et al., 2004) indicate that a significant proportion of patient participants (ranging from 5% to 22%) do not complete the full CBT protocol. If we presume that the efficacy of CBT relies on gradual skill-building and practice, we would expect a dose-response relationship. Indeed, studies support the idea that completing more sessions of a cognitive behavioral or behavioral therapy results in superior outcomes (Craske et al., 2006; Glenn et al., 2013; Hansen, Lambert, & Forman, 2002; Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008). Thus, improving retention and completion of CBT – reducing premature dropout – would be expected to improve anxiety disorder outcomes. This highlights the importance of the current, novel aim to identify baseline patient characteristics that predict greater or lesser likelihood of dropping out of (or completing) distinct forms of behavioral therapy for anxiety disorders.

¹ This holds true at least if different levels of attrition exist between two treatments administered in the same location at the same frequency for the same fee, and patients did *not* report feeling so much better than they no longer needed treatment - conditions that were met here.

Although some studies have examined treatment attrition for psychotherapy across a variety of disorders (Barrett, Chua, Crits-Christoph, Gibbons, & Thompson, 2008), fewer studies have examined predictors of attrition within CBT for anxiety disorders; and *no* studies to our knowledge have examined *moderators of attrition* between two or more distinct evidence-based psychological treatments for a psychiatric disorder, as proposed currently. Findings from the existing predictor studies of attrition in CBT for anxiety disorders are mixed, offering few conclusions: most studies find no significant predictors of dropout (Eskildsen, Hougaard, & Rosenberg, 2010). Others examining demographic variables have found that female gender (Herbert et al., 2005; McEvoy, 2007) and younger age (Garcia, Kelley, Rentz, & Lee, 2011; Herbert et al., 2005; McEvoy, 2007) predicted dropout. Greater baseline severity has been associated with greater odds of dropout in some studies (Garcia et al., 2011; Rosser, Issakidis, & Peters, 2003) but not others (Erwin, Heimberg, Juster, & Mindlin, 2002; Keijsers, Kampman, & Hoogduin, 2001; van Velzen, Emmelkamp, & Scholing, 1997). Similarly, findings are mixed with regard to the role of depression symptoms or comorbid diagnoses in predicting attrition from CBT for anxiety disorders (Erwin et al., 2002; Hofmann & Suvak, 2006; Ledley et al., 2005; van Minnen, Arntz, & Keijsers, 2002). Taken together, few conclusions can be drawn from the extant literature to understand the prognostic factors leading to dropout of CBT for anxiety disorders. These inconsistencies preclude researchers from developing any useful summaries that can directly aid practicing clinicians in treatment decision-making practices. Thus, efforts are needed to help clinicians choose treatments that offer the greatest likelihood that a patient will complete the treatment, which should lead to greater symptom improvement (Glenn et al., 2013; Hansen et al., 2002; Wolitzky-Taylor et al., 2008). In addition, these prescriptive recommendations must be user-friendly and offer simple, cost-effective utility for

real-world clinicians who may not have access to putative biological moderators/predictors. By examining moderators of attrition between two distinct psychological treatments using cutting-edge statistical approaches within a large sample, the current study aims to address these important aims.

In order to provide prescriptive recommendations to clinicians based on which treatment a patient is most likely to complete, CBT must be compared to other evidence-based approaches that, when completed, yield similar effect sizes for the treatment of anxiety disorders.

Acceptance and commitment therapy (Hayes, Strosahl, & Wilson, 1999) has recently developed an evidence base for the treatment of anxiety disorders and represents a promising alternative treatment to traditional CBT (Landy, Schneider, & Arch, 2015). No studies to our knowledge have examined predictors of attrition in ACT for anxiety disorders. However, prior work successfully identified pre-treatment patient characteristics – treatment moderators – that predicted better *symptom* outcomes in CBT or ACT, among those who *completed* the full course of therapy (Craske et al., 2014; Wolitzky-Taylor, Arch, Rosenfield, & Craske, 2012). The current study builds on this previous work by applying more powerful statistical tools in a larger sample to identify moderators of attrition between CBT and ACT. In doing so, we aim to advance the personalized medicine for anxiety disorders and provide useful treatment decision-making options for clinicians.

In sum, the aim of the current study was to use a novel statistical approach to identify a composite moderator (based on several putative moderators) that will predict the degree to which someone will drop out of (traditional) CBT relative to ACT. This method was recently used to successfully identify a composite moderator of treatment outcome for anxiety disorders between an evidence-based CBT and medication program or usual care in primary care settings (Niles et

al., under review). Our goal in the current study is to use this novel statistical program to create a robust composite moderator of attrition in CBT relative to ACT, informing future clinical resources that improve prediction of whether someone will drop out of (or complete) one form of behavioral treatment over another. Thus, this study represents the first to apply cutting-edge statistical learning, composite moderator, and multiple-imputation approaches to compare distinct forms of behavioral therapy. As noted, this study also represents the first to apply such cutting-edge moderator approaches to predict treatment attrition or to a dichotomous patient outcome more generally.

Method

Participants

Two-hundred eight patients diagnosed with anxiety disorders participated in two randomized treatment studies between 2005 and 2013 at the Anxiety and Depression Research Center at the University of California, Los Angeles. Both studies compared acceptance and commitment therapy to (traditional) cognitive behavioral therapy for the treatment of anxiety disorders across 12 individual sessions. Given that moderators tend to have small effect sizes and because we had many of the same measures across the two studies, we combined the samples to increase power. Patients in the first study (mixed anxiety disorder study) met DSM-IV criteria for panic, social, generalized anxiety, obsessive compulsive, or post-traumatic stress disorders or specific phobia. Participants in the second study (social phobia study) met DSM-IV criteria for generalized social phobia and social phobia was the principal or co-principal anxiety diagnosis. Participants were screened used the Anxiety Disorders Interview Schedule IV (T. A. Brown, Di Nardo, & Barlow, 1994) and had a clinical severity rating of 4 or greater for their

principal diagnosis. Participants were recruited in the Los Angeles area in response to local flyers, Craigslist and local newspaper advertisements, and referrals.

Participants were either psychotherapy or medication free, were stabilized on non-behavioral treatment that was not focused on their anxiety disorder or were stabilized on medication for three months (1 month for benzodiazepines and beta blockers). Exclusion criteria included active suicidal ideation, severe depression (clinical severity rating > 6 on a 0 to 8 point scale), history of bipolar disorder or psychosis, substance abuse or dependence within the last 6 months, or diagnosis of a respiratory, cardiovascular, pulmonary, neurological, muscular-skeletal disease, or pregnancy. Patients with asthma, high blood pressure, or thyroid diseases were included only if they were receiving treatment and were stabilized for these conditions. If a patient's medical status was unclear, confirmation was obtained from the patient's medical doctor. See Craske et al. (2014) for further details about the social phobia sample, and Arch et al. (2012) for details regarding the mixed anxiety sample.

Because we were interested in examining moderators of dropout (dropout was our dependent variable), all participants, including those who dropped from the study, were included in analyses. Post-treatment data were not analyzed, and therefore, no measures were taken to account for missing data on post-treatment measures. We did not include participants who dropped prior to completing at least one therapy session because they had no exposure to the treatment prior to dropout.

Materials

Moderators. Twenty-six possible moderators were examined including demographic variables and clinical features. Potential moderators were selected if they were present across both treatment samples and were either demographic or clinical variables. Descriptive statistics

for all moderators analyzed are included in Table 1. No significant difference was found between ACT and CBT on any moderator examined. Potential demographic moderators included age, gender (0 = female, 1 = male), education (highest grade level completed; continuous), number of children, ethnicity (White, Hispanic, Asian), marital status (0 = single, separated, or divorced, 1 = married or cohabitating), employment status (0 = unemployed, 1 = employed), and whether or not participants were religious (0 = non-religious, 1 = religious). Potential clinical moderators included depressive symptom severity, anxiety symptom severity, current medication use (0 = no, 1 = yes), past or current therapy (0 = no, 1 = yes), mindfulness, psychological flexibility, quality of life, anxiety control, emotion regulation, negative affect in response to a stressor and duration of engagement with a stressor (see procedure for description of the stressor task). We also assessed whether participants were responding truthfully or misrepresenting themselves in order to manage self-presentation (i.e. social desirability).

Depressive and anxiety symptoms were assessed with the Mood and Anxiety Symptom Questionnaire (Watson & Clark, 1991). Anxiety symptoms were also assessed using the Penn State Worry Questionnaire (T. A. Brown, Antony, & Barlow, 1992), and the Anxiety Sensitivity Index (Peterson & Heilbrunner, 1987). Mindfulness was assessed using the Mindfulness Attention Awareness Scale (K. W. Brown & Ryan, 2003). Psychological flexibility was assessed with the Acceptance and Action Questionnaire-II (Hayes et al., 2004). Because the two studies included slightly different versions of the Acceptance and Action Questionnaire, we standardized scores on each measure separately in the two samples and used the standardized scores in subsequent analyses. Quality of life was measured using the Quality of Life Inventory (Frisch, 1994). Anxiety control was measured using the Anxiety Control Questionnaire (T. A. Brown, White, Forsyth, & Barlow, 2004), and we assessed both internal and external subscales

separately. Emotion regulation was assessed using the Emotion Regulation Questionnaire (Gross & John, 2003), and we tested the suppression and reappraisal subscales separately. Finally, we assessed social desirability using the Marlowe-Crowne Social Desirability Scale (Crowne & Marlowe, 1960).

Insert Table 1

Outcome. For the current moderator analysis, dropout (0 = completer, 1 = drop) was used as the outcome measure. Participants who dropped out of treatment were those who completed at least 1 therapy session but who did not complete all 12 sessions. Treatment completers finished all 12 therapy sessions. The majority of participants (62%) who dropped from treatment did so prior to session 6, and 25% of participants dropped out of treatment after only 1 session. Of the participants assigned to CBT, 34 out of 116 dropped (29%) and of those assigned to ACT, 25 out of 92 dropped (27%). A chi-squared analysis revealed that groups did not significantly differ in terms of dropout ($p = .734$)

Randomization

After a baseline diagnostic assessment, completion of questionnaires, and a behavioral laboratory assessment, participants were randomized to receive either ACT or CBT. For more details about patient flow from eligibility screening through randomization, see Craske et al. (2014), and Arch et al (2012).

Treatments

Participants in both studies received 12 weekly 1-hour therapy sessions based on detailed treatment manuals. ACT and CBT were matched on the amount of exposure, but framing and intent of exposures differed between the two treatments. Sessions were audio taped and later

rated for adherence and competency by independent raters. Therapists were graduate level clinical psychology doctoral candidates, and completed intensive two-day trainings in either ACT or CBT. Therapists administered either ACT, CBT or both (but never at the same time). Therapists received 90 minutes of weekly group supervision. For CBT, supervision was lead by professors and post-doctoral fellows at UCLA, and for ACT, supervision was lead via Skype by advanced therapists at University of Nevada, Reno where ACT was originally developed, or by the author of the ACT for anxiety disorders treatment manual (Eifert & Forsyth, 2005). Therapists adhered closely to the designated treatments in both CBT and ACT (Arch, Eifert, et al., 2012; Craske et al., 2014). Therapists also completed monthly 25-minute follow-up booster phone calls for six months following treatment completion to provide support and coaching as necessary.

Cognitive Behavioral Therapy. CBT followed a manual written by Craske (2005), which included branching mechanisms for the different anxiety disorders. For the social phobia study, therapists were trained on the social phobia section of the manual, which was updated from the 2005 version to include interoceptive exposure. Session 1 included assessment, psychoeducation, and self-monitoring. Sessions 2-4 included cognitive restructuring and hypothesis testing, self-monitoring, and breathing retraining. Exposure was introduced in session 5, was tailored to the patient's primary disorder, and included in-vivo, interoceptive, and imaginal exposures. Exposure was the primary focus of treatment in sessions 6-11. Session 12 focused on relapse prevention.

Acceptance and Commitment Therapy. ACT followed a manual focused on the treatment of anxiety disorders written by Eifert and Forsyth (2005). Session 1 included psychoeducation, experiential exercises, and introduced the concepts of acceptance, creative

hopelessness, and valued action. Creative hopelessness included a discussion of what had not previously “worked” to control and reduce anxiety and how these efforts had minimized valued life activities. Acceptance was introduced as an alternative to controlling anxiety.

Sessions 2-4 further explored the concepts of acceptance and creative hopelessness.

Sessions 4 and 5 included mindfulness, acceptance, and cognitive defusion, which included practice with present moment awareness, non-judgment of negative thoughts and feelings, and getting “unstuck” from anxious and negative thoughts. Sessions 6-11 continued to include practice of mindfulness, acceptance, and cognitive defusion, but also included identification of values and initiation of behavioral exercises to help the patient pursue valued actions.

Behavioral exposures including interoceptive, in-vivo, and imaginal were used to practice acceptance of and “willingness” to experience anxiety, and to encourage the patient to move in valued directions. Session 12 reviewed what worked and included discussion of additional areas for practice.

Procedure

Participants interested in the study were screened over the phone. Those eligible after the phone screening completed a diagnostic assessment to determine eligibility. Enrolled participants then completed questionnaires and a laboratory assessment that included an attentional bias task, an emotional reactivity task, and a hyperventilation task. Because the attentional bias and emotional reactivity tasks followed slightly different protocols in the two studies, only the hyperventilation task was included in the current analyses. In the hyperventilation task, participants were instructed to hyperventilate (i.e. breath quickly and deeply) for 60 seconds, paced by a metronome. They then completed questionnaires including the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988). Participants were

then instructed to hyperventilate again and were asked to continue hyperventilating as long as they were “willing” to continue with the task (for a maximum of 3 minutes, though they were not informed of the maximum ahead of time). In the current analysis, negative affect scores following the first hyperventilation period, and the duration of time participants engaged in the second hyperventilation period, were examined as moderators of drop out.

After completion of the lab assessment, participants in the social phobia study also completed an fMRI scan (data not included in current analyses). Participants were then randomized to receive ACT or CBT. Participants were assessed following treatment, and at 6- and 12-month follow-up (from baseline) time points. Data from the baseline assessment and information regarding dropout were used in the current analyses.

Statistical Analyses

See Figure 1 for a flow chart of statistical analyses. The statistical analyses combined methods described by Kraemer (2013) and James, Witten, Hastie & Tibshirani (2013). Analyses were conducted using Stata 13 and RStudio. Kraemer’s method was used to determine effect sizes for the 26 moderators assessed. Model selection combined with k -fold cross-validation with three folds as described by James and colleagues was used to identify how many and which variables were to be included in the final model. Because we were missing data on a number of the moderator variables (see *Multiple Imputation*, below), we used multiple imputation with three imputations to estimate missing data. Each of the three imputed dataset were used as one of the three datasets in the k -fold cross validation. Results were then averaged across the three datasets according to Rubin’s rule, which states that population parameters of interest (e.g. regression coefficients) obtained from each imputed dataset can be averaged to estimate the overall point estimate of the multiply imputed datasets (2004).

Multiple Imputation. Twenty-five of the 26 moderators examined contained missing data, with percentage of missing data ranging from .4% to 27%; we thus chose to impute missing data prior to running the moderation analyses. In Stata 13, we used multiple imputation with multivariate normal regression and three imputations (Rubin, 2004; Schafer, 1997). Because we needed to use the imputed datasets in the next step of our analysis (*k*-fold cross validation), we were only able to use three imputations. However, a small number of imputations is unlikely to produce biased results because an insufficient number of imputations leads to biased standard errors, but not regression coefficients (Rubin, 2004), and this approach relies primarily on regression coefficients and not *p*-values. We included main effects of all purported moderators as well as interaction effects of each moderator with group in the imputation model. The dependent variable (dropout) was also included in the model and had no missing data.

***k*-Fold Cross-Validation.** Empirically driven statistical methods can sometimes capitalize on chance associations within a single dataset making it difficult to replicate findings across studies. To protect against capitalization on chance associations, we used the method of *k*-fold cross validation (Kohavi, 1995). In RStudio, we randomly divided the 208 observations into three sections of equal size. We chose 3-fold cross validation because we had a small sample size and small effect sizes of our moderators and therefore needed a large enough validation sample to detect differences in the performance of our models. Two sections were used to train the model (i.e. identify the best moderators of dropout) while the remaining section was used to validate the model (i.e. test how well the moderators would predict outcome in a new sample). This process was repeated three times where the model was trained on 2/3 of the data and validated on the remaining third, and results were averaged across the three repetitions. To identify the fit of our models, in the validation dataset, we calculated the Brier Score (a

measure of error for models with a dichotomous outcome). To obtain less variable results with more stable estimates of prediction error, we repeated the k -fold cross validation 50 times and averaged the error estimates.

Combined Moderator. Following the method of Kraemer (2013) in the training datasets, we paired every patient assigned to CBT with every patient assigned to ACT. As indicated by Kraemer, in the paired dataset, the correlation between the difference in outcome (O) and the average moderator (AM) for each pair, represented as $r(\Delta O, AM)$, is the moderator effect size. This produces an effect size equivalent to a correlation coefficient that falls between -1 and +1, with null value 0 and greater magnitudes indicating stronger moderation. Therefore, within the paired dataset, for all 26 moderators assessed, we calculated the average value of the moderator and the difference in the outcome (which was dropout in the current analysis) for each pair in the dataset. We then ran pairwise correlations between the difference in dropout and each of the averaged moderators to determine the individual effect size for each moderator.

To identify the combined moderator, in the paired dataset, we ran forward stepwise ordinary least squares (OLS) regression predicting dropout from each of the 26 moderators. We used OLS regression because a logistic regression approach to Kraemer's method has not yet been established. OLS regression produces nearly identical results for dichotomous outcomes as does logistic regression, and violations of the homoscedasticity assumption appear to be "of little importance" (Hellevik, 2009). Forward stepwise regression is generally not appropriate for hypothesis testing. However when combined with k -fold cross validation, which protects against capitalizing on chance, this method is appropriate (James et al., 2013). We allowed the forward stepwise regression to continue adding predictors until all 26 variables had been included, resulting in 26 models with increasing numbers of variables from 1 to 26. In the unpaired

dataset, we then used beta coefficients from each of the 26 models to create 26 composite moderators M_1 through M_{26} , calculated using the following equations:

$$M_1 = B_1 X_1$$

$$M_2 = B_1 X_1 + B_2 X_2$$

...

$$M_{26} = B_1 X_1 + B_2 X_2 \dots B_{26} X_{26}$$

M_i is the combined moderator, B_i is the beta coefficient obtained from the regression model, and X_i is the individual moderator.

After creating 26 composite moderators M_1 through M_{26} , we ran logistic regression models in which the dependent variable was dropout, and the predictors were Group (CBT = 0, ACT = 1), M_i , and Group $\times M_i$, where i was the model number ranging from 1 to 26. We calculated the Brier Score for each of the 26 regression models using the equation:

$$BS = \frac{1}{n} \sum_{i=1}^n (f_i - o_i)^2$$

where f_i is the predicted probability of dropout for participant i , and o_i is the actual outcome (0 = completer, 1 = drop out) for participant i . We plotted the Brier Score for moderators M_1 through M_{26} resulting in a curve representing the fit of models 1 through 26 in the validation datasets. We then identified the minimum on the curve to choose a model that would minimize the Brier Score (error). This allowed us to identify the number of variables to include in the final composite moderator that would minimize error but not overfit the model.

Once we identified the number of variables to include in the final model, to maximize the amount of data used to determine the final model weights, we ran forward-stepwise regression on the full imputed dataset (following the guidelines of Wood, White and Royston (2008) for

running stepwise regression on imputed data) including only the number of variables identified by the k -fold cross-validation results. Following the method described by Kraemer (2013), we then used the beta coefficients obtained from the model to create our combined moderator M^* . Finally, we calculated the predictive power of the combined moderator, using a regression analysis predicting dropout from the combined moderator M^* , treatment group, and the interaction between M^* and treatment group. We then graphed the results, and characterized participants who were less likely to drop from one treatment over the other.

 Insert Figure 1

Results

Model selection results from the k -fold cross validation are displayed in Figure 2. A local minimum occurred at model 4 (model zero includes no moderators), and the global minimum occurred at model 7. Due to the large standard errors, we chose a simpler model with 4 predictors.²

 Insert Figure 2

Independent effect sizes for each moderator are displayed in Table 2. Effect sizes ranged from .002 (education) to -.173 (anxiety control internal). Negative values indicate lower predicted probability of dropout in CBT than in ACT (for higher values of the moderator), and positive values indicate lower predicted probability of dropout in ACT than CBT (for higher values of the moderator).

² Please see the online supplement for a description of the 7-variable model

To create the combined moderator, we used forward stepwise regression, as described in the *Methods*, to identify the first four variables to include in the final model. The variables selected in order from first to fourth were anxiety control internal, current medication use (0 = no, 1 = yes), religious (0 = no, 1 = yes), and number of seconds of hyperventilation. We then used the regression coefficients from the regression in the paired database as the weighting values (see Table 2 for weights) to create our combined moderator M^* . The combined moderator effect size was $r = .28$.

Insert Table 2

To visualize the effect of the combined moderator and to identify a cut point that would allow us to characterize patients more likely to drop from one treatment over the other, using an imputed database with 20 imputations, we ran a logistic regression predicting dropout from group, M^* and the interaction between group and M^* (Figure 3). We tested a dummy variable representing research study (0 = social phobia study; 1 = mixed anxiety disorder study) as a covariate, but it was not a significant predictor of dropout, and was therefore not included in the model described below. The lines crossed at $M^* = -.02$. Participants above the cut point were more likely to drop from CBT than from ACT, and participants below the cut point were more likely to drop from ACT than CBT. The odds ratio for dropout from ACT compared to CBT across the whole sample was .90. However, when the sample was stratified into those above and below the cut point, for those above the cut point the odds ratio for dropout was .45, and for those below the cut point, the odds ratio for dropout was 1.88, suggesting that the composite moderator substantially improved how well we predicted attrition from one treatment versus the other.

We next compared the combined moderator M^* to our strongest individual moderator (Anxiety Control Internal, see Table 2). Using “seemingly unrelated regression” (Zellner, 1962) to combine non-nested logistic models, we compared the model testing the interaction of M^* with Group to the model testing the interaction of Anxiety Control Internal with Group (all main effects were also included). Using a Wald test, we compared the coefficients associated with the interaction term in the model. The beta associated with the $M^* \times \text{Group}$ term ($b = 1.46$) was significantly larger than the beta associated with the Anxiety Control Internal \times Group term ($b = .73$); $\chi^2(1, N = 208) = 4.35, p = .037$.

Insert Figure 3

In terms of individual variables included in the combined moderator, participants higher on internal anxiety control, who were taking medication, who were religious, and who were more avoidant of the hyperventilation task were more likely to drop out of ACT than CBT, whereas participants who were lower on internal anxiety control, who were medication free, not religious and who were less avoidant of the hyperventilation task were more likely to drop out of CBT than ACT. Based on the value of M^* where the lines crossed, we classified participants into one of two groups: those less likely to drop from CBT than from ACT ($n = 93$), and those less likely to drop from ACT than CBT ($n = 115$). Descriptive statistics for the four variables included in the combined moderator for the two groups are shown in Table 3.

Insert Table 3

Discussion

The current study advances the field of treatment moderator research by combining statistical and computational approaches in a novel way that improve our ability to detect moderators for dichotomous outcomes, in this case, to determine whether a patient will be more likely to drop out of (traditional) CBT or ACT for the treatment of anxiety disorders. Our aims thus were to implement a novel statistical approach to more powerfully model treatment moderators, and to specifically increase our understanding of the factors that predict whether a patient is more likely to drop out of CBT or ACT. Our statistical approach extends pioneering work by Kraemer (2013) by integrating two additional statistical methods - statistical learning (model selection with k -fold cross validation), and multiple imputation for missing data - that increased our capacity to identify treatment moderators for a dichotomous outcome. Our findings provide relevant clinical prescriptive information to aid clinicians in selecting a behavioral approach to treating anxiety disorders that will minimize treatment dropout. Thus, both of these goals converge on our overarching aim to improve personalized mental health care.

Advantages of the Novel Composite Moderator Approach

We identified a composite profile of patients who were more likely to drop out of CBT or ACT, and this composite patient profile was more effective in making this prediction than any individual moderator examined. Thus, given that greater patient engagement and retention in a particular behavioral treatment for anxiety disorders is associated with better outcomes (Craske et al., 2006; Glenn et al., 2013; Hansen et al., 2002; Wolitzky-Taylor et al., 2008), these findings have direct and straightforward clinical decision-making utility. Consistent with a study that identified a combined moderator of response to psychotherapy compared to medication for depression (Wallace et al., 2013), our *combined* moderator effect size ($r = .28$), a medium effect, was significantly larger than the largest *individual* moderator effect size (largest $r = .17$). The

comparatively small moderator effect sizes for individual variables render prescriptions based on a single moderator variable problematic. In addition, testing individual moderators only allows for the use of one characteristic in treatment prescription at a time, whereas when moderators are combined, multiple characteristics can be used simultaneously and inter-correlations between them are accounted for. Specific to the current analysis, when examining moderators of treatment attrition, power was reduced by limited variability of the attrition outcome, which can take on only two possible values. Thus, the current study represents a particularly stringent and conservative test of the potential for a composite approach to boost capacity to identify treatment moderators. Given the many challenges to identifying treatment moderators that are sufficiently robust to inform clinical decision-making (see Schneider et al, 2015), the current study provides further support for the utility of composite moderators.

In addition to increasing moderator power, this statistical approach allowed us to identify a cut point for M^* above which dropout was more likely in ACT vs. CBT and vice versa. Across the whole sample, the odds of dropout from ACT were 10% less than the odds of dropout from CBT. However, when the sample was stratified by the moderator, for those above the cut point, the odds of dropout from ACT were 55% less than the odds of dropout from CBT. For those below the cut point, the odds of dropout from CBT were 88% less than the odds of dropout from ACT. Given the magnitude of the difference in odds ratios when the moderator is accounted for and when it is not, our results suggest that this moderator may be valuable for reducing rates of dropout. Although these findings require confirmation in an independent dataset designed to test the composite moderator, this cut-point approach allows for a straightforward interpretation about who will be more likely to drop out of one treatment over another.

Profiles of Patients More Likely to Drop Out of ACT or CBT

In addition to the statistical strengths of our approach over previous treatment moderator research (see Schneider et al., 2015; Simon & Perlis, 2010 for reviews), our findings provide practical directions for clinical decision-making. Specifically, the findings, which included data from multiple randomized clinical trials comparing CBT to ACT for anxiety disorders, identified “profiles” of patients who are more likely to continue one treatment approach over another. Notably, within the combined moderator, the contribution of each individual variable must be interpreted in conjunction with the other variables included in the moderator. These findings suggest that patients who perceived that they had high control of their internal anxiety states, were taking medication for anxiety, identified as religious, and discontinued a hyperventilation task earlier (i.e., were more avoidant of the physiological arousal symptoms of anxiety) were more likely to drop out of ACT than CBT. In contrast, those who perceived having less internal control over their anxiety, did not take medication, were not religious, and continued a hyperventilation task longer (i.e., were less avoidant of physiological arousal) were more likely to drop out of CBT than ACT. Notably, when examined individually, only anxiety control was a significant moderator, but when examined as a composite, these four variables accounted for significantly more variance in attrition than anxiety control alone. Thus, individual variables with limited predictive power still provided a valuable contribution to the prediction of treatment outcome when included in the composite moderator. The composite moderator thus facilitated integrating more types of clinical information into boosting our capacity to predict differential attrition between two treatments.

Although speculative, these profiles appear to represent two groups: The first, who are more likely to drop out of ACT than CBT (e.g., are more likely to be *retained* in CBT), appear to be “anxiety managers.” This profile included patients who took medication for anxiety,

perceived that they have some control over anxiety, and were more avoidant of an anxiety-inducing task. These characteristics represent some aspect of anxiety mitigation, avoidance, or management. Greater religiosity has been associated with greater needs for closure and predictability (Saroglou, 2002), which may be linked more broadly with greater need for control. Thus, traditional CBT for anxiety disorders, which focuses on fear reduction as a goal of exposure and coping skills (e.g., cognitive restructuring) to manage and control anxiety (Beck, Emery, & Greenberg, 1985; Foa & Kozak, 1986; Foa & McNally, 1996), appears to be more acceptable to individuals who even before treatment begins, already perceive that they can control or are motivated to maintain control of their anxiety. Perceiving at least some control over anxiety, along with use of medication for anxiety, and avoidance of provoking anxiety in an anxiety-inducing task, thus may reflect beliefs about the importance of controlling and reducing anxiety due to it being harmful or threatening. Thus, CBT (at least in traditional forms) may fit well within such patients' priority to control, manage, and reduce anxiety.

Notably, in a clinically significant, treatment-seeking anxiety disorder population, "high" perceived control of anxiety is relative: in our sample, the mean (11.7) was well below the mean of a healthy control group (26.9). Thus, in this sample, high perceived control over internal anxiety is likely to represent a moderate perceived ability to control anxiety in the general population. Thus, in line with a previous examination of moderators of treatment outcome between CBT and ACT (Wolitzky-Taylor et al., 2012), a *moderate* level of a treatment target may be optimal – in this case for treatment retention.

The second profile represents those who favor continuing in ACT over CBT, and appear to fall into an "anxiety acceptor" profile; that is, at baseline they do not perceive having control over internal anxiety states, do not take medication, and continue the interoceptive task longer,

all of which represent (whether willingly or not) a “relinquishing of control” over anxiety. Possibly, these individuals have difficulty managing anxiety but believe that either their anxiety cannot be controlled, that it is not important to control it, or that they have greater willingness to experience it; thus, they allow themselves to experience the anxiety associated with the interoceptive task. Not surprisingly then, patients falling into this category may be more engaged in ACT, an approach that cultivates the notion that anxiety *need not* be controlled and managed to live a meaningful life. Thus, individuals who have trouble controlling their anxiety may respond more favorably to an intervention that is not aimed at improving this “deficit,” but instead teaches new ways of approaching, accepting, and relating to anxiety.

Taken together, these findings suggest that anxiety disorder treatment approaches that tap into and enhance baseline patient strengths (e.g., greater ability and desire to control anxiety in the case of CBT; greater willingness to experience anxiety in ACT) rather than overcome or make up for patient deficits, better resonate with patients. These findings are consistent with previous moderator analyses of *treatment outcome* within one of the two treatment samples we combined for the present analysis (Craske et al., 2014). Specifically, high self-reported experiential avoidance, or an unwillingness to experience uncomfortable internal experiences, was associated with better outcome in CBT than in ACT. Therefore, patients with more difficulty accepting negative thoughts and feelings benefited more from CBT, which aims to increase control over anxiety, and less from ACT, which promotes greater acceptance of anxiety. Possibly, patients may have more positive outcome expectancies and greater self-efficacy to remain in a treatment approach that is in line with their perceived strengths and perceptions about how to manage anxiety. Indeed, positive treatment expectancies and greater self-efficacy are associated with greater treatment adherence (Bouchard, Bastien, & Morin, 2003) and

outcomes (Chambless, Tran, & Glass, 1997; Price, Anderson, Henrich, & Rothbaum, 2008; Safren, Heimberg, & Juster, 1997; Sotsky et al., 2006). Future research that examines whether these moderating effects are mediated by constructs such as self-efficacy and outcome expectancies would provide additional information to guide clinicians in developing appropriate treatment plans likely to maximize patient adherence and engagement.

Despite many strengths, the current study has a number of limitations. Although this study included a relatively large sample size compared to most randomized controlled trials of psychotherapy for anxiety disorders, identification of reliable moderators requires a large number of observations because moderator effect sizes tend to be small. In addition, statistical learning via k -fold cross validation requires splitting the sample into two sections, one used to train the model, and the other used to validate it. Therefore, through the process of cross-validation, the sample size was reduced. An additional challenge in the current study was examining moderators of treatment dropout. A dichotomous outcome has limited variability, which limits power to detect significant effects. Given all of these factors, this statistical approach to moderator analysis will be most useful in larger samples, though we do not yet know how large a sample is ideal. Another possible limitation with the current analysis is that Kraemer's approach was developed for analysis of continuous outcomes, and we unfortunately do not yet have tools developed specifically for dichotomous outcomes. Although OLS regression produces nearly identical results for dichotomous outcomes as does logistic regression, and violations of the homoscedasticity assumption appear to be "of little importance" (Hellevik, 2009), the development of novel approaches for dichotomous outcomes would be of value. Despite these challenges however, we successfully identified a composite moderator that predicted treatment drop out with a larger effect size than any individual moderator. That said, although k -fold cross

validation protects against overfitting and provides confidence that our model will replicate, we had no method to predict the effect size of the moderator in new data from different studies. Follow-up studies that assign participants to conditions based on a composite moderator will allow for a rigorous assessment of the composite moderator's utility. More specifically, the composite moderator could be used to develop a calculator that would estimate the likelihood of each patient completing ACT vs. CBT. Then the patient could be randomly assigned to either the treatment that the calculator predicts they would most likely complete, or to the treatment that the calculator predicts they would be most likely to drop out of. We could then assess the validity of the calculator's predictions by comparing actual dropout between the two groups. The use of graduate student therapists also represents a potential study limitation in that they were relatively inexperienced. On the other hand, research demonstrates that in the context of evidence-based, manualized treatment of anxiety and related disorders, inexperienced and experienced therapists can produce similar therapy outcomes (van Oppen et al., 2010). Finally, because many variables were examined, 122 out of 208 participants were missing data on at least one variable. Although the majority of participants required imputation of at least one datapoint, out of 5,616 possible data points, only 466 or 8.3% were imputed. Bennet (2001) states that imputation of up to 10% of data produces valid results.

In sum, our study provides support for a novel approach to developing more highly powered methods to identify treatment moderators, including for important, understudied dichotomous outcomes such as attrition. Thus, we advanced the field of personalized treatment for anxiety disorders by identifying composite moderator profiles that indicate whether a patient will drop out of one evidence-based behavioral treatment over another. Ultimately, these findings could be applied to create user-friendly tools for clinical decision-making. We encourage

researchers to utilize and expand upon our methodological approaches to developing treatment prescription tools across treatments and disorders in order to improve our understanding of treatment moderators across the full range of psychopathology.

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Figure 1. Flow chart of study methods

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Figure 2. Brier Score (measure of model fit for logistic regression models) in Validation Datasets from k -fold Cross Validation Analysis with Standard Error Bars Showing Variability Across 150 Validation Datasets (3 datasets over 50 repetitions)

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Figure 3. Predicted Probability of Dropout for Participants in ACT and CBT Across Values of the Combined Moderator M^* with 95% Confidence Interval

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Table 1. Descriptive statistics for all moderators analyzed

	Mean (SD)	
	CBT	ACT
Demographics		
Age	34.1 (10.3)	34.1 (11.5)
Gender (% Female)	53	48
Education (years)	15.3 (2.0)	15.4 (2.0)
Employed (%)	67	64
Married (%)	29	24
Number of Kids	.38 (1.0)	.31 (0.7)
Religious (%)	49	50
Race (%)		
Asian	12	13
Hispanic	15	14
White	59	62
Clinical Variables		
Emotion Regulation Reappraisal	24.7 (7.2)	24.6 (8.0)
Emotion Regulation Suppression	14.4 (5.9)	14.7 (6.0)
Anxiety Control Internal	11.3 (5.4)	11.7 (5.3)
Anxiety Control External	19.9 (6.7)	20.2 (6.3)
Anxiety Sensitivity Index	27.4 (11.3)	31.2 (12.0)
Penn State Worry Questionnaire	45.2 (12.2)	46.3 (12.6)
MASQ – Anhedonic Depression	47.7 (13.8)	47.6 (16.6)
MASQ – General Anxiety	15.6 (7.7)	16.1 (8.3)
Marlow-Crowne Social Desirability	4.0 (2.2)	4.4 (2.6)
Quality of Life	0.4 (2.0)	0.1 (2.2)
Mindfulness Attention and Awareness Scale	37.9 (12.4)	40.4 (14.9)
Hyperventilation Duration	137.2 (48.7)	139.2 (54.1)
Hyperventilation Negative Affect	9.0 (3.9)	9.0 (4.0)
Current Medications (%)	37.9	33.7
Past or Current Therapy (%)	68	71

Table 2. Effect sizes and final model weights for moderators

Variable	Individual Effect Size (<i>r</i>)	Weight in Final Model
Included in Final Model (in order of inclusion in the stepwise regression)		
Anxiety Control Internal	-0.1729	-.1367
Current Medications	-0.1176	-.1359
Religious	-0.1211	-.1179
Hyperventilation Duration	0.1080	.1080
Not Included in Final Model		
Marlowe-Crowne Social Desirability	0.1088	
Employed	-0.0872	
MASQ – General Anxiety	0.0862	
White Race	0.0817	
Hyperventilation Negative Affect	0.0687	
Male Gender	-0.0644	
Penn State Worry Questionnaire	0.0629	
MASQ – Anhedonic Depression	0.0552	
Hispanic Race	-0.0455	
Emotion Regulation Suppression	-0.0377	
Anxiety Sensitivity Index	0.0369	
Age	-0.0364	
Past or Current Therapy	-0.0355	
Married	-0.0287	
Quality of Life	0.0192	
Number of Kids	-0.0187	
Emotion Regulation Reappraisal	0.0160	
Anxiety Control External	-0.0131	
Asian Race	0.0120	
Mindfulness Attention and Awareness Scale	0.0033	
Acceptance and Action Questionnaire	-0.0023	
Education	0.0018	

Note. MASQ = Mood and Anxiety Symptom questionnaire; Positive effect sizes indicate that higher values of the moderator are associated with lesser likelihood of dropout from ACT than CBT and negative effect sizes indicate that higher values of the moderator are associated with greater likelihood of dropout from CBT than ACT

Table 3. Descriptive statistics for variables included in the final model by preferred treatment

	CBT Preferable to ACT ($M^* < -.02$; $n = 93$)	ACT Preferable to CBT ($M^* \geq -.02$; $n = 115$)
Anxiety Control Internal	14.1 (5.3)	9.3 (4.4)
Current Medications	58%	18%
Religious	69%	34%
Hyperventilation Duration	121.4 (56.4)	152.8 (40.5)

ACCEPTED MANUSCRIPT

Flow Chart of Study Methods

1. Calculate Individual Effect Sizes

- a. Using non-imputed data, create paired dataset
- b. Calculate the average of the moderators across the pairs and the difference of dropout across pairs
- c. Run a correlation between the average of each moderator and difference of dropout across pairs

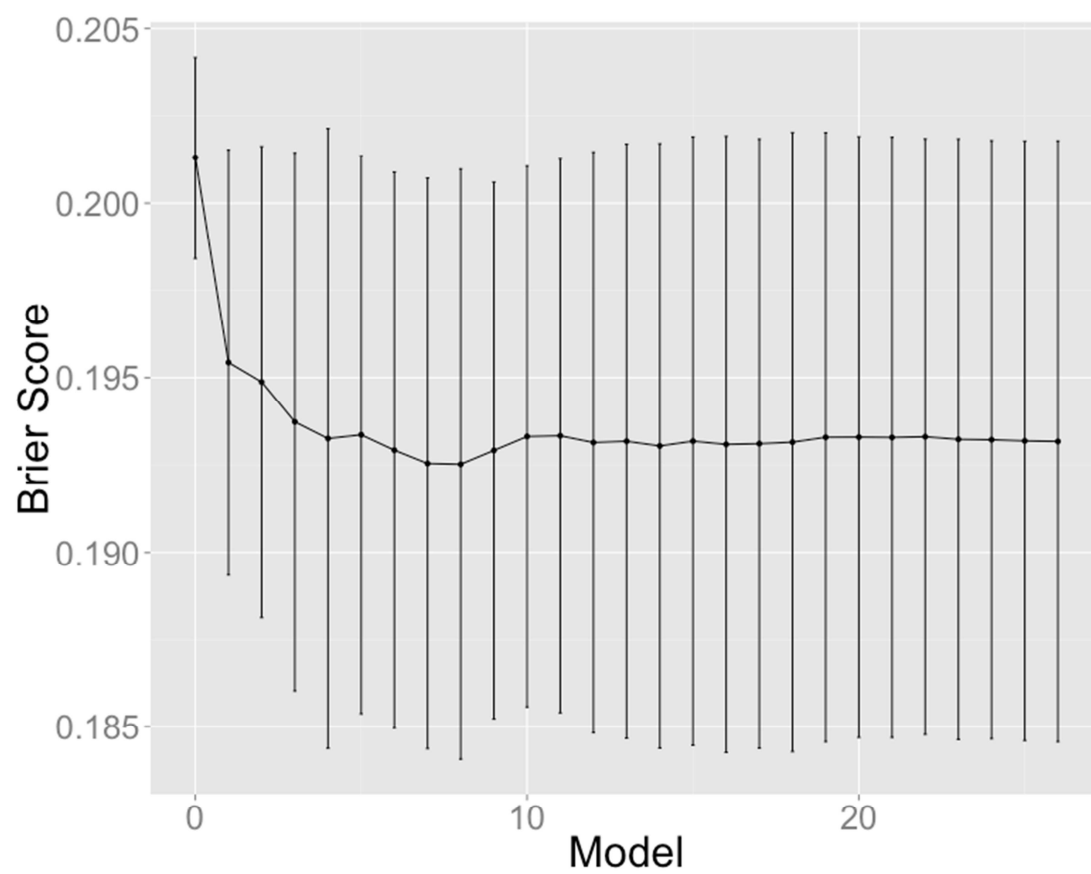
2. Identify Number of Variables to Include in Final Model

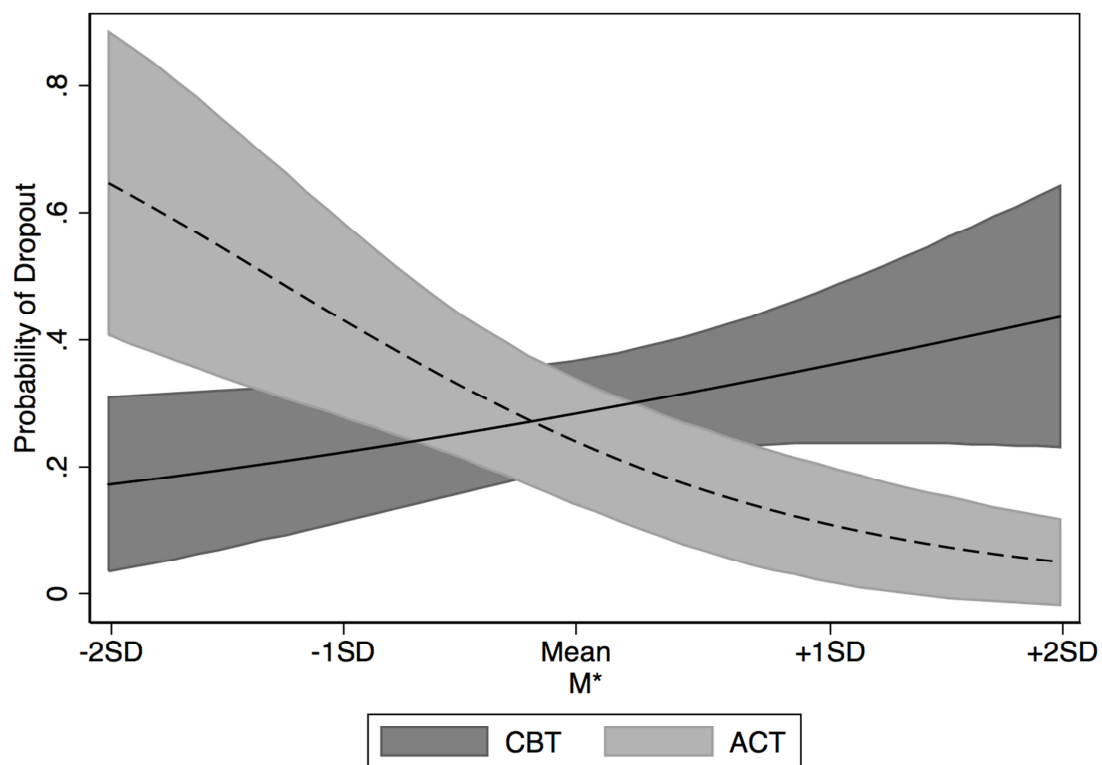
- a. Create 'k' variable and randomly assign values 1, 2 and 3 in equal parts to all observations in the data
- b. Impute data with multivariate normal approach and three imputations
- c. Using k, split three complete imputed datasets into two parts with two thirds included in one dataset and one third included in the other (train and test datasets)
- d. Create paired dataset with the training data for each of the three imputed datasets
- e. Run forward stepwise regression in each training dataset
- f. Using the betas from the forward stepwise regressions, calculate M_1 through M_{26} in the testing datasets
- g. Run logistic regressions predicting dropout from group, M_i , and the group by M_i interaction for M_1 through M_{26} and calculate the Brier Score for each of the 26 models across the three imputed datasets
- h. Average the Brier Scores across the three datasets and calculate standard errors
- i. Repeat the process above 50 times then average the Brier Scores and standard errors
- j. Graph
- k. Choose model based on local or global maximum taking into account parsimony

3. Create Final Model

- a. Using full imputed data, pair each of the 3 complete imputed datasets
- b. Stack paired imputed datasets and run forward stepwise regression
- c. Use beta weights from the model with 4 variables to calculate M^* in unpaired data
- d. Run logistic regression predicting dropout from group, M^* , and the group by M^* interaction in an imputed dataset with 20 imputations
- e. Graph results and identify cut points
- f. Calculate effect size of M^* using method in 1 above







- No research exists on moderators of attrition from therapy for anxiety disorders
- We identified baseline patient characteristics moderating dropout from ACT vs CBT
- We used a novel moderator approach for creating composite moderators
- We combined 4 patient characteristics to form a composite moderator of attrition
- Our composite moderator had a larger effect than any individual moderator