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Latent Profiles of Cognitive and Interpersonal Risk Factors for Adolescent Depression and Implications for Personalized Treatment

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Abstract
A personalized approach to treatment with patients being matched to the best-fit treatment has been proposed as one possible solution to the currently modest treatment response rates for adolescent depression. Personalized treatment involves identifying and characterizing subgroups likely to respond differently to different treatments. We investigated the feasibility of this approach, by focusing on two key risk factors that are the purported treatment targets of cognitive behavioral therapy (CBT) and interpersonal psychotherapy for depressed adolescents (IPT-A): negative unrealistic cognitions and interpersonal relationship difficulties, respectively. We sought to learn whether subgroups high and low on the two risk factors, respectively, might be identified in a large sample of depressed, treatment-seeking adolescents. Latent class analysis (LCA) was conducted on measures of the two risk factors among 431 adolescents (age 12–17) in the Treatment for Adolescents with Depression Study. LCA identified three classes: (1) adolescents with high levels of problems in both family relationships and cognitions (21.6% of sample), (2) adolescents with moderate levels of problems in both domains (52.4%), and (3) adolescents with low levels of problems in both domains (26.0%). These subgroups did not predict treatment outcome with CBT or CBT + fluoxetine (COMB). The results challenge a current assumption about how treatments could be personalized, and they support a multi-causal model of depression rather than a risk-factor-specific model. Strategies other than risk factor-based personalizing for case assignment to CBT vs. IPT-A are discussed.

Keywords Adolescents · Depression · Treatment · Cognitions · Family

Depression is one of the most common and impairing psychiatric disorders in adolescents (Costello et al. 2006; Lewinsohn et al. 1993). It is associated with significant morbidity and functional impairment and it is the largest diagnostic predictor of death by suicide (Glied and Pine 2002; Lewinsohn et al. 1994). Decades of clinical trials have produced a number of evidence-based psychosocial treatments for adolescent depression (Weersing et al. 2017); however, a recent meta-analysis of randomized trials of youth psychotherapy found that psychotherapy for depression had the weakest effect size, on average, compared to psychotherapies for other common youth disorders and problems (Weisz et al. 2017). One

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proposed explanation for the poor treatment response rates is that there is likely heterogeneity in the risk factors that trigger underlying mechanisms of depression, and different mechanisms may require different treatment approaches (Ng and Weisz 2016; Simon and Perlis 2010). This personalized approach to treatment is the cornerstone of the Precision Medicine Initiative® led by NIH, as well as a key objective of the NIMH Strategic Plan (Objective 3.2, 2015).

Matching an adolescent correctly to a treatment that effectively targets the risk factor(s) most relevant for that adolescent can potentially lead to a successful treatment outcome and higher response rates. Developing guidelines for treatment matching requires identifying and characterizing subgroups of depressed adolescents who might respond differently to different treatment approaches. This involves identifying moderators of treatment, that is, patient characteristics that are present prior to treatment, are independent of the type of treatment the patient receives, and have an interactive effect with the type of treatment approach on treatment outcome (Kazdin and Nock 2003; Kraemer et al. 2002).

Two models have been proposed regarding the manner in which patient characteristics might moderate treatment response (Rude and Rehm 1991). The compensation model proposes that an intervention will be most effective for those individuals with the greatest difficulties in the areas targeted by the intervention (Rude and Rehm 1991). Following this model, cognitive therapy, for example, which aims to treat depression by modifying negative unrealistic cognitions, would be most effective for individuals who have high levels of negative cognitions. In contrast, the capitalization model proposes that an intervention will be most effective if it builds on the individual's strengths (Rude and Rehm 1991). In this case, cognitive therapy would be most effective for individuals who have low levels of dysfunctional cognitions. Under either model, treatment personalization is based on a single risk factor (in this example, dysfunctional cognitions). In keeping with this, prior treatment prediction studies have only examined single risk factors in isolation (e.g. Curry et al. 2006; Feeny et al. 2009; Jacobs et al. 2009). However, for these models to work, subgroups of depressed adolescents must exist that have a deficit in one domain but not in others (or a strength in one domain but not in others), such that that isolated domain can then be used to guide treatment selection. For example, to apply the compensation model of treatment assignment to cognitive therapy, there must be a subgroup of depressed adolescents who have high levels of dysfunctional cognitions *and* low levels of other risk factors. However, to our knowledge, no study has yet assessed whether there are subgroups of depressed adolescents that have a deficit in one domain, but not in others. We sought to address this knowledge gap by examining whether subgroups of depressed adolescents can be characterized based on two risk factors that are closely linked to two quite different empirically supported approaches to depression treatment, and employing a large sample of depressed, treatment-seeking adolescents.

Two psychotherapy approaches both currently meet criteria for a *well-established* intervention for adolescent depression: cognitive behavioral therapy (CBT) and interpersonal psychotherapy for depressed adolescents (IPT-A) (Weersing et al. 2017). CBT aims to treat depression symptoms by addressing depressive thought patterns and deficient reinforcing behavioral patterns (TADS Team 2004). CBT protocols (e.g., TADS 2004) heavily emphasize changes in depressive and unrealistic negative cognitions (Weisz et al. 2006). IPT-A aims to treat depression symptoms by helping adolescents improve their relationships and interpersonal interactions by targeting their identification and expression of emotions, communication skills, and interpersonal problem-solving skills (Mufson et al. 2004). CBT can also address family relationships. For example, the CBT manual used in the Treatment for Adolescents with Depression Study (TADS) included conjoint family sessions to address family problems if parental behaviors were perceived to be associated with the emergence or maintenance of their child's depression (TADS Team 2003). These sessions focused on family problem solving, family communication, family contingency management and positive reinforcement, and family attachment and commitment. Similarly, additional CBT studies for adolescent depression included combined parent-child sessions that focused on family communication and problem solving (Brent et al. 1997; Clarke et al. 1999; Lewinsohn et al. 1990). However, while CBT can address family problems with optional family component sessions, it is not a primary or required component. Based on the proposed primary mechanisms of action of these two therapies, we were interested in determining whether we could identify subgroups of depressed adolescents who demonstrated deficits in one domain, but not in the other (e.g. elevated unrealistic negative cognitions and healthy family relationships, adaptive cognitions and impaired family relationships). If we could identify these subgroups, it would provide support for the notion that these two constructs might guide selection of a cognitively-focused intervention versus an interpersonally-focused intervention. The primary aim of the current study was to determine whether we could characterize subgroups of depressed adolescents based on level of unrealistic negative cognitions and level of family relationship difficulties. To determine whether these subgroups of depressed adolescents exist, we used data from the Treatment for Adolescents with Depression Study (TADS), a large multisite study of cognitive-behavioral therapy (CBT), fluoxetine (FLX), combination of CBT and FLX (COMB), and placebo (PBO) (TADS Team 2004). The unusually large sample (N = 439) and number of cognitive and family relationship-focused measures administered in the trial enabled us to characterize subgroups of depressed adolescents using multiple measures of these two key risk factors at the baseline assessment time

point. In addition, we assessed whether these subgroups predicted outcome within the treatment conditions that included CBT (CBT and COMB). As discussed earlier, previous research has examined cognitive biases and interpersonal functioning separately as predictors of CBT (Curry et al. 2006; Feeny et al. 2009; Jacobs et al. 2009). Studies that have examined cognitive biases as predictors of CBT have generally suggested that CBT is more effective for adolescents who report low levels of cognitive biases (e.g. Weersing and Gonzalez 2009), and studies that have examined interpersonal functioning as predictors of CBT have found that CBT is more effective for adolescents who report more positive family relationships (e.g. Feeny et al. 2009). However, it is unclear how these two constructs interact in relation to outcome with CBT.

Method

Participants

TADS was a multi-site randomized clinical trial designed to evaluate the effectiveness of CBT, FLX, COMB, and PBO (TADS Team 2003). Participants were 439 adolescents (age 12–17) with a primary DSM-IV (American Psychiatric Association 1994) diagnosis of current major depressive disorder (MDD). The study design, methods, inclusion criteria, sample characteristics, and treatment outcomes have been described in previous papers (TADS Team 2003, 2004, 2005, 2007, 2009). Out of the total $N = 439$, eight participants had missing data on all baseline measures of family relations and cognitions. Therefore, these cases were excluded from the analyses. The eight participants were 75% male ($n = 6$) and 75% Caucasian (n = 6). Their mean age was 15.00 years ($SD = 0.93$). They were randomly assigned to CBT ($n = 3$), COMB ($n = 1$), FLX ($n = 2$), and PBO (n = 2). Their mean CDRS-R score was 60.88 ($SD = 11.73$, $n = 8$) and was not significantly different from that of the analysis sample ($n = 431$, CDRS-R $M = 60.09$, $SD = 10.38$, $t(437) = 0.21$, $p = .830$).

The average age of the sample ($N = 431$) used in this study was 14.60 years ($SD = 1.56$) and the proportion of females was 55.0%. The ethnic composition of the sample was 73.8% White/Caucasian, 12.5% African American/Black, 8.9% Hispanic/Latino, 0.7% Asian, 0.5% Pacific Islander, and 3.7% other.

Measures: Cognitive Measures

Children's Attributional Style Questionnaire (CASQ) (Seligman et al. 1984) The CASQ is a 48-item self-report questionnaire designed to assess children's attributional style across three dimensions (internal-external, stable-unstable, global-specific). Positive or negative hypothetical events are provided (e.g., "you get a bad grade in school") and children are asked to give causal explanations for why they believe the event may have happened. A forced choice format is used to assess children's causal attributions of the events. There are an equal number of positive (24) and negative (24) events, with 16 questions assessing each dimension of attributional style. Positive and negative composite scores and an overall composite score are determined. The overall composite score was used in the current study. Over a one-year period, test-retest reliability has been shown to be 0.54 for the positive and 0.48 for the negative composite scores (Gotlib et al. 1993). The CASQ has been found to have good concurrent criterion-related validity (Gladstone and Kaslow 1995). Reliability (Chronbach's alpha) of the overall composite score in the current sample was 0.74.

Children's Negative Cognitive Error Questionnaire (CNCEQ) (Leitenberg et al. 1986) The CNCEQ is a 24 item self-report questionnaire designed to assess four types of negative cognitive errors (e.g., catastrophizing, overgeneralizing, personalizing and selective abstraction) based on Beck's adult theory of depression. Children are given hypothetical events or situations across three areas (e.g., social, academic, athletic) and a statement about the event demonstrating one of the types of cognitive errors. They are then asked to rate the similarity of what they would think if they imagined themselves in the situation on a 5-point scale (1 = almost exactly like I would think, to 5 = not at all like I would think). An example of an item that assesses personalizing in the academic area is, "Your team loses a spelling contest. The other team won easily." You think 'If I were smarter, we wouldn't have lost.' Items are reverse coded so that higher scores are associated with higher ratings of cognitive errors. A total cognitive error score is computed, as well as subscales scores for each type of cognitive error and each content area. The CNCEQ has been found to have adequate test-retest reliability (0.65) and moderate to high internal consistencies (0.89 for total score; 0.60–.071 for the four error types; 0.75–0.82 for the three content areas) (Leitenberg et al. 1986). The CNCEQ has demonstrated construct validity with the TADS sample of participants and the use of the CNCEQ as a clinically valid tool for the use with adolescents (ages 12–18) has been established (Kingery et al. 2009). Reliability (Chronbach's alpha) in the current sample was .94.

Cognitive Triad Inventory for Children (CTI-C) (Kaslow et al. 1992) The original CTI-C is a 36-item self-report questionnaire that assesses the cognitive triad of negative cognitions developed by Beck using three subscales (12 items for each):

View of the Self, View of the World and View of the Future. The version of the measure used in this study was 24-items and excluded the View of the Future subscale due to similarity with what was assessed by another measure used in the original data collection for the TADS study (Beck Hopelessness Scale). Lower scores on the measure represent more negative views. Adequate internal consistency reliability and concurrent validity have been established for the measure (Kaslow et al. 1992). The View of the Self scale (Chronbach's alpha = 0.83) measures children's view of themselves and their self-esteem (e.g., "I can't do anything right."). The View of the World scale (Chronbach's alpha = 0.76) measures children's views of their world (e.g., "The world is a very mean place.").

Dysfunctional Attitudes Scale (DAS) (Weissman and Beck 1978) The DAS is a 40-item self-report questionnaire assessing maladaptive or dysfunctional beliefs seen as characteristic of depression. The measure uses a 7-point Likert scale (1 = totally agree, 5 = totally disagree). An example of an item includes, "If I do not do well all the time, people will not respect me." The measure was originally designed for use with adults, though it has been used broadly with adolescents (Ackerson et al. 1998; Williams et al. 2001). The DAS has been found to have good internal consistency and excellent stability over 8 weeks in adults and adolescents (Garber et al. 1993; Marton and Kutcher 1993). Reliability (Chronbach's alpha) in the current sample was 0.93.

Measures: Family Measures

Conflict Behavior Questionnaire (CBQ-20) (Robin and Foster 1989) The CBQ-20 is a 20-item self-report measure that assesses parent-child conflict and problems in communication in the previous two weeks. Higher scores indicate higher levels of conflict and negative communication. Adolescents completed the CBQ-20 separately for each parent. Only adolescents' reports on the mother-adolescent relationship are included in these analyses because 18% of adolescents did not report on their relationships with their fathers. The CBQ-20 has been found to have good validity and internal consistency (Robin and Foster 1989). Reliability (Chronbach's alpha) in the current sample was 0.91.

Family Assessment Measure (FAM) (Skinner et al. 1983) The FAM is a 50-item self-report measure that is designed to assess the functioning of the family as a whole. The measure includes 7 subscales (task accomplishment, role performance, communication, affective expression, involvement, control, and values & norms), as well as a total score that provides a global assessment of the family environment. The total score was used in the current analyses. Higher scores indicate more problems in family functioning. The FAM has been found to have good internal consistency (Skinner et al. 1983). In the current sample, reliability (Chronbach's alpha) was 0.78.

Issues Checklist (IC) (Robin and Weiss 1980) The IC is a self-report measure of parent-adolescent conflict. It lists 44 issues representing typical areas of parent-adolescent conflict (e.g. doing homework, cleaning up the bedroom). For each issue, adolescents indicate whether it was a topic of discussion during the last month and the intensity of the discussion (ranging from 1 = calm to 5 = angry). Number of conflicts and mean intensity ratings are calculated for each participant. In the current study, a weighted average of number of conflicts and mean intensity rating was used.

Measures: Outcome Measures

Children's Depression Rating Scale - Revised (CDRS-R) (Poznanski and Mokros 1996) The CDRS-R is a clinician-administered semi-structured interview that assesses 17 symptom areas related to depression, including those that serve as criteria in the DSM-IV. It provides an overall index of severity of depression and a depressive symptom profile. Interviews are conducted separately with the adolescent and the parent and scores are integrated to create a summary score for each item. Higher scores indicate more severe depression. The CDRS-R was administered at baseline, week 6, and week 12 by evaluators who were blind to treatment assignment. The measure has been found to have good reliability and validity (Poznanski et al. 1984). In TADS, interrater reliability on the CDRS-R at baseline was reported to be high (intraclass correlation coefficient = 0.95 (TADS Team 2005).

Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Life- Time Version (KSADS–PL) (Kaufman et al. 1997) The KSADS-PL was used to evaluate past and current *DSM–IV–TR* diagnoses. The KSADS-PL was administered at baseline and week 12 by evaluators who were blind to treatment assignment. For current diagnosis of MDD, 94.1% of reviewed tapes met the criteria of at least 80% agreement between raters. In the current study, the binary variable indicating whether the participant continued to meet criteria for a diagnosis of MDD at week 12 was utilized.

Analytic Strategy

Latent profile analysis (LPA) was used to identify latent classes of adolescents who showed distinct patterns of problems in family relationships and cognitions. LPA models specifying 1–4 classes were fit to the three family relationship variables and five cognitive variables. Positive cognitive scales (CASQ,

CTI-self, CTI-world) were reversed in the LPA models so that higher scores indicated greater cognitive problems. We used Mplus v6.11 (Muthen and Muthen 2010) to conduct the analyses. Site was included in the models as a nesting variable to account for the non-independence of individuals within sites using the TYPE = COMPLEX option in Mplus.

Selection of the optimal number of classes was based on a combination of statistical fit and interpretability. For model fit, we used the Akaike Information Criterion (AIC) (Akaike 1987), the Bayesian Information Criterion (BIC) (Schwarz 1978), the sample-size-adjusted BIC (ABIC) (Sclove 1987), and the bootstrap likelihood ratio test (BLRT) (Feng and McCulloch 1996), where smaller values of AIC and BIC indicate better fit and a significant BLRT shows model improvement with the additional class. In addition, we examined entropy of each model to assess class separation, and used the Vuong-Lo-Mendell-Rubin likelihood ratio test (Lo et al. 2001) to examine model fit between two nested models that differ by one class.

Once the optimal number of classes was determined, participants were categorized into class with the highest posterior probability of class membership. The class information was used to examine whether the profile classes had differential impact on depression outcomes. To test the effect of class groups as a predictor of depression outcome for those who received CBT, mixed model regression analyses were conducted on CDRS-R (baseline, 6-week, 12-week) and major depression diagnosis (12-week) within the CBT group and within the COMB group separately. A three-level mixed model was applied to CDRS-R using SAS PROC MIXED (SAS Institute 2008) where repeatedly measured outcomes were nested within individuals who were nested within sites. A two-level mixed model was conducted on the major depression diagnosis (1 vs. 0) assessed at Week 12, where individuals were nested within sites. SAS GLIMMIX for binomial data (Littell et al. 2006) was used for the analysis. All mixed models included age and gender as covariates to control for their effects.[1] A significance level of alpha < 0.05 was applied to all mixed model analyses. Correction for multiple testing was not applied to the alpha level because of the exploratory nature of this study.

Results

Identification of the Latent Profiles of Adolescents' Family Relationships and Cognition

Table 1 provides Pearson's correlations among family relationship and cognitive variables. Model fit statistics for models with one to four latent profiles are presented in Table 2. The information criteria (AIC, BIC, and ABIC) fit indices for the four-class solution were smaller than those found for the other three solutions, suggesting the 4-class model fit the data best. However, the VLMR likelihood ratio test results indicated the 4-class model was not significantly different from the 3-class model ($p = .791$). The 3-class solution had an approaching significant VLMR ($p = 0.065$) when compared to the 2-class model, and had the highest entropy, which indicated that three classes should be extracted. The bootstrapped likelihood ratio test failed to discriminate solutions. Because the four-class model had small cell sizes for the four treatment groups and because the three-class model yielded more clinically meaningful profiles compared to the four-class model, a decision was made to select the three-class solution as the final model.

The three-class latent profiles are displayed in Fig. 1. Because measures were on different scale units, scores were transformed into z-scores for clearer depiction of each class profile. The first class (21.6%) was labeled high-problems and consisted of participants with high levels of problems in both family relationships and cognitions. The second class (52.4%), and the largest class, was labeled moderate-problems and included participants with moderate levels of problems in both domains. The third class (26.0%) was characterized as low-problems and consisted of participants with low levels of problems in both family relationships and cognitions. Means and standard deviations of the LPA variables and baseline depression scores for the three classes are presented in Table 3. One-way ANOVAs showed significant main effect of class on all of the variables (Table 3). Frequencies and percentages of each class membership by treatment conditions are presented in Table 4.

Class Effects on Depression Outcomes: CBT Group

Descriptive statistics on the depression outcomes for the CBT and COMB groups are shown in Table 5. The longitudinal mixed regression analysis on the CDRS-R for those who were randomized to CBT group showed that there were no significant interaction effects of time × class [$F(2,181) = 0.02$, $p = .979$]. Main effects of time [$F(1, 181) = 194.56$, $p < 0.001$] and class [$F(2,181) = 4.42$, $p = 0.013$] were statistically significant. Logistic mixed regression analysis using the binary major depression diagnosis assessed at Week 12 revealed no significant class effect [$F(2, 72) = 0.13$, $p = .881$]. Overall the results indicated that within the CBT group all three classes showed significant improvement in depression over time and there were no significantly different rates of change in depression by class membership.

[1] Mixed models including race and SES in addition to age and gender as covariates yielded similar results. Because of the smaller sample size from missing data in race and SES, results using only age and gender as covariates are reported.

Table 1 Bivariate correlations among family relationship and cognitive functioning variables

Variable	1	2	3	4	5	6	7
1. FAM	–						
2. CBQ	0.59***	–					
3. ICA	0.35***	0.40***	–				
4. CNCE	014**	0.10*	0.12*	–			
5. DAS	0.14**	0.08	0.09	0.64***	–		
6. CASQ[a]	−0.30***	−0.25***	−0.11	−0.29***	−0.36***	–	
7. CTI-self[a]	−0.29***	−0.17***	−0.16**	−0.55***	−0.58***	0.52***	–
8. CTI-world[a]	−0.37***	−0.31***	−0.26***	−0.39***	−0.42***	0.48***	.73***

Ns = 261–427. FAM, Family Assessment Measure; CBQ, Conflict Behavior Questionnaire; ICA, Issues Checklist - adolescent report; CNCE, Children's Negative Cognitive Error Questionnaire; DAS, Dysfunctional Attitudes Scale; CASQ, Children's Attributional Style Questionnaire; CTI, Cognitive Triad Inventory

[a] Original scale with higher score indicating positive cognitive style

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Class Effects on Depression Outcomes: COMB Group

Comparisons of the CDRS-R trajectories between the three class groups for those who were randomized to COMB showed that the interaction effect of time × class was not significant [$F(2, 187) = 1.49$, $p = .228$]. There was a significant main effect of time [$F(1, 187) = 277.96$, $p < 0.001$] and a non-significant main effect of class [$F(2, 187) = 2.81$, $p = 0.063$]. The results of the logistic mixed regression on the binary major depression diagnosis at Week 12 indicated that there was no significant class effect [$F(2, 77) = 1.06$, $p = .351$]. Similar to the CBT group, the overall results indicated that all three classes showed significant decrease in depression over time and class membership did not significantly predict differential rates of change in depression within the COMB group.

Discussion

Psychotherapy effects for youth depression are modest and lag significantly behind psychotherapies for other youth conditions; thus, youth depression should be a priority for future treatment development and evaluation (Weisz et al. 2017). A common explanation for the modest effect of therapy is that the risk factors underlying depression differ across individuals, and a solution often proposed is for treatment to be personalized to fit the risk factor (see e.g., Ng and Weisz 2016). This personalized approach to treatment is the cornerstone of the Precision Medicine Initiative® led by NIH, as well as a key objective of the NIMH Strategic Plan (Objective 3.2, 2015). Development of personalized treatment requires identifying and characterizing subgroups of depressed adolescents who can be expected to respond differently to different treatments. Efforts thus far have focused on identifying subgroups based on a single risk factor in isolation, rather than in the context of the individual's values on other potential relevant risk factors. This implicitly assumes that there will be adolescents who display elevations on one of these risk factors, but not the other. However, no study has yet assessed whether there are subgroups of depressed adolescents that have deficits in one domain but not in others, such that that the isolated deficit can then be used to guide treatment selection. To our knowledge, the present study is the first to address this question empirically among adolescents with depression. We focused specifically on two key risk factors of depression that are the purported treatment targets of CBT and IPT-A: negative unrealistic cognitions and interpersonal difficulties. The findings showed that in a sample of clinic-referred, depressed adolescents, there did not appear to be subgroups who demonstrated deficits in one domain, but not in the other

Table 2 Latent profile analysis fit statistics

Number of Classes	AIC	BIC	Adjusted BIC	VLMR p value	Entropy	BLRT	BLRT p value
One	22,103.12	22,168.18	22,117.40	–	–		
Two	21,542.97	21,648.69	21,566.18	0.001	0.753	580.15	0.0000
Three	21,301.55	21,447.93	21,333.68	0.065	0.824	261.42	0.0000
Four	21,192.09	21,379.13	21,233.16	0.791	0.793	129.45	0.0000

AIC, Akaike information criterion; BIC, Bayesian information criterion; VLMR, Vuong-Lo-Mendall-Rubin likelihood difference test; BLRT, bootstrap likelihood ratio test

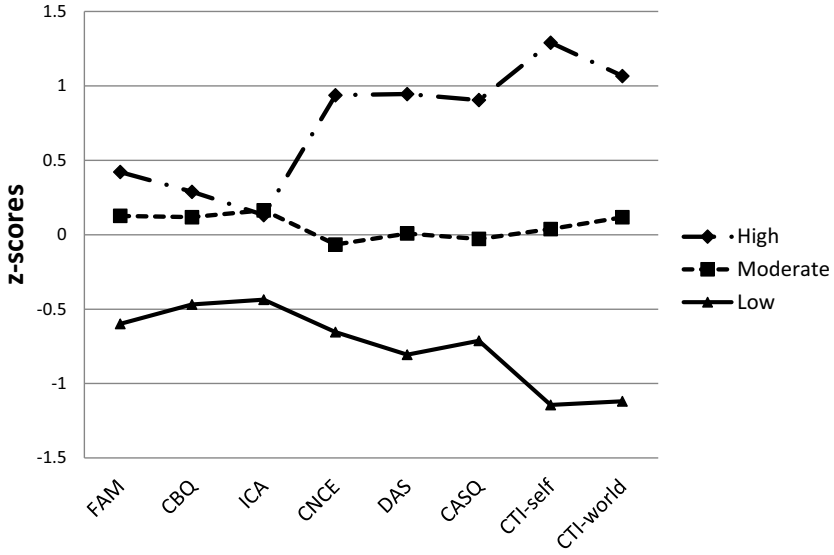

Fig. 1 Latent profiles of adolescents' relationship and cognition. FAM = Family Assessment Measure, CBQ = Conflict Behavior Questionnaire, ICA = Issues Checklist - adolescent report, CNCE = Children's Negative Cognitive Error Questionnaire, DAS = Dysfunctional Attitudes Scale, CASQ = Children's Attributional Style Questionnaire, CTI = Cognitive Triad Inventory

(e.g. elevated unrealistic negative cognitions and healthy family relationships, adaptive cognitions and impaired family relationships). Instead, we found that adolescents with high levels of unrealistic negative cognitions also had high levels of interpersonal family difficulties and adolescents with low levels of unrealistic negative cognitions also had low levels of interpersonal family difficulties. Most adolescents had moderate levels of difficulties in both domains. These subgroups did not predict treatment outcome with CBT or COMB. These findings are significant, as they indicate that a current assumption about how treatments could be personalized, at least employing these commonly used measures of negative cognitions and family relationships, is not likely to be feasible or effective, as high-low subgroups were not identified in our study.

These results have implications for the nature of psychopathology in depressed youth. The findings may provide support for a multi-causal etiology of depression, with multiple risk factors contributing to the development of the disorder in any given individual. The results may also reflect bidirectional relations between depression risk factors. In addition to increasing risk for depression, risk factors may contribute to the development of other risk factors. Negative cognitions may not only increase risk for depression, but they may also increase risk for interpersonal difficulties, if inaccurate perceptions and

Table 3 Means and SDs of the LCA variables and depression score by profile class

Variables	Profile class			
	Low problems (n = 112)	Moderate problems (n = 226)	High problems (n = 93)	
	M (SD)	*M (SD)*	*M (SD)*	*p*
Family Relationships				
FAM	44.18 (11.01)	55.51 (13.43)	59.03 (15.37)	< 0.001
CBQ	4.88 (4.92)	8.45 (5.70)	9.45 (6.03)	< 0.001
ICA	2.01 (0.86)	2.60 (0.97)	2.52 (1.00)	< 0.001
Cognitions				
CNCE	49.12 (15.34)	61.27 (17.53)	82.20 (18.23)	< 0.001
DAS	117.82 (29.39)	148.68 (27.53)	185.01 (29.28)	< 0.001
CASQ[a]	12.53 (3.00)	10.06 (3.01)	6.65 (2.53)	< 0.001
CTI-self[a]	19.96 (2.42)	13.59 (2.77)	6.69 (2.94)	< 0.001
CTI-world[a]	17.10 (2.63)	11.53 (2.65)	7.36 (3.13)	< 0.001
CDRS-R				
Baseline	56.60 (8.36)	59.75 (10.12)	65.11 (11.30)	< .001

[a] Original scale with higher score indicating positive cognitive style. *P* values are from one-way (class) ANOVAs. FAM, Family Assessment Measure; CBQ, Conflict Behavior Questionnaire; ICA, Issues Checklist - adolescent report; CNCE, Children's Negative Cognitive Error Questionnaire; DAS, Dysfunctional Attitudes Scale; CASQ, Children's Attributional Style Questionnaire; CTI, Cognitive Triad Inventory; CDRS-R, Children's Depression Rating Scale – Revised

Table 4 Class membership by treatment condition

Class	Treatment Condition			
	CBT n (%)	FLX n (%)	COMB n (%)	Placebo n (%)
High problems	20 (18.5)	16 (15.0)	27 (25.5)	30 (27.3)
Moderate problems	54 (50.0)	55 (51.4)	57 (53.8)	60 (54.5)
Low problems	34 (31.5)	36 (33.6)	22 (20.8)	20 (18.2)

CBT, Cognitive behavioral therapy; FLX, fluoxetine; COMB, CBT + fluoxetine

interpretations of interpersonal events lead adolescents to engage in interpersonal behaviors that contribute to interpersonal difficulties (Hammen 1991; Safford et al. 2007). Similarly, the experience of chronic interpersonal difficulties may lead adolescents to develop negative beliefs about themselves, others, and their ability to exert change in their interpersonal relationships (Auerbach and Ho 2012). If so, this poses challenges for personalization of treatment, as by the time an adolescent presents to a clinic, multiple risk factors may be present. Consequently, it may be difficult to identify a single key underlying risk factor that should be the focus of treatment, at least using the constructs and assessment measures that have been commonly used in clinical research and treatment so far.

The results of this study might mean either that personalizing treatment for youth depression is not a realistic objective, or that other strategies or tools for personalizing are needed. In support of the latter view, it seems likely that some adolescents will benefit more from CBT, others more from IPT-A, but we may not have the tools yet to determine membership in those two groups. There may be other risk factors besides negative cognitions and quality of family relationships that could be used to guide decisions to treat with CBT versus IPT-A. To date, there has not been a clinical trial directly comparing CBT and IPT-A for adolescent depression that also included assessment of moderators of treatment outcome. Trials like these are needed to assess the utility of other depression risk factors for guiding selection between CBT and IPT-A.

An additional strategy for personalizing treatment that may prove fruitful is focusing on the malleability of a given risk factor and not just its magnitude prior to treatment. If adolescents with depression are likely to enter treatment with deficits in more than one domain, perhaps some of these deficits are more malleable than others. If the more malleable risk factor can be identified and targeted first, this may not only bring about symptom relief, but could also lead to downstream improvements in the other risk factors. The challenge will be determining how to measure the malleability of the risk factors – this will be an important direction for future research. An additional strategy could be focusing on the risk factor that is most salient to the adolescent. Some adolescents may place a greater value on how their relationships are going, while others may be more focused on or distressed by their thoughts and how their thoughts are impacting their mood. Incorporating adolescents' attitudes about the salience of the risk factors and their motivation to address them may be also a promising method of personalized treatment planning.

It is also possible that the failure to identify subgroups of depressed adolescents in this study may be due to the exclusive reliance on self-report measures. Depression, like any type of psychopathology, is best understood through assessment across multiple levels of analysis including biological, behavioral, and cognitive indicators (Berenbaum 2013; Kendler 2008). Self-reports provide one perspective, and are useful for understanding individuals' consciously accessible feelings and experiences;

Table 5 Descriptive statistics on depression outcomes by class for the CBT and COMB groups

Variables	Profile class		
	Low problems	Moderate problems	High problems
CBT group	*M (SD)*	*M (SD)*	*M (SD)*
CDRS-R BL	54.18 (5.51)	61.28 (9.16)	63.90 (9.27)
CDRS-R Wk6	40.77 (10.51)	46.23 (11.11)	49.63 (13.61)
CDRS-R Wk12	36.28 (12.97)	42.48 (13.41)	46.06 (16.66)
	%	%	%
MDD Wk12	32.0	41.3	44.4
COMB group	*M (SD)*	*M (SD)*	*M (SD)*
CDRS-R BL	55.50 (7.97)	60.32 (11.99)	65.74 (11.61)
CDRS-R Wk6	38.90 (8.55)	37.04 (14.53)	40.84 (11.33)
CDRS-R Wk12	32.79 (7.34)	32.48 (11.07)	35.80 (15.97)
	%	%	%
MDD Wk12	5.3	14.0	24.0

CBT Cognitive behavioral therapy; COMB CBT + fluoxetine; CDRS-R, Children's Depression Rating Scale – Revised; MDD, Major Depressive Disorder

however, measures of the biological, behavioral, and cognitive underpinnings of a given psychological process can provide additional perspectives that may enrich the picture. As such, future use of multi-modal assessments may allow for better identification of subgroups of depressed adolescents and better understanding of how a particular construct is implicated in treatment outcome and may facilitate the identification of key treatment targets (Berenbaum 2013; Cuthbert and Kozak 2013).

This study has several limitations. One limitation is the composition of the sample, which included clinically depressed adolescents with episodes of long duration and of moderate to marked severity and very few mildly depressed adolescents. Thus, we do not know whether the results generalize to adolescents with milder depression. Another limitation is the narrow range of interpersonally-focused measures. TADS included several measures of family relationship quality, but did not assess adolescents' peer or romantic relationships, or relationships with other adults (e.g. teachers). It is possible that the results could differ if other types of interpersonal relationships were examined. In addition, although the sample was the largest in any treatment study for adolescent depression, it is difficult to detect moderator effects without large samples. The present results must be considered exploratory rather than definitive. Furthermore, this study did not include IPT-A condition and it is not clear whether similar or different results would have been observed in a study specifically examining IPT-A or comparing IPT-A with CBT. Future studies should further assess these research questions in a study with an IPT-A condition. The current study focused on the acute phase of treatment in TADS. TADS did assess outcomes up to 12 months post-treatment; however, the study design was less optimal for examining predictors of treatment response past 12 weeks. At the end of the acute phase of treatment, patients were assigned to different dosages of their randomized treatment depending on their CGI improvement score at 12 weeks. In addition, after 36 weeks, treatment was completely uncontrolled. The lack of systematic treatment provided after week 12 would make it difficult to interpret any findings regarding long-term treatment outcomes. These limitations suggest strategies through which future research may better identify subgroups of depressed adolescents based on their cognitions and interpersonal relationships and how to use these constructs to guide intervention selection with the goal of improving adolescent depression treatment outcome.

In summary, we assessed whether we could identify subgroups of depressed adolescents with different levels of difficulty with unrealistic negative cognitions and interpersonal relationships, and whether these subgroups predicted or moderated treatment outcome. We found that depressed adolescents had either high or low levels in both domains and not only in one, with most adolescents having moderate levels of difficulties in both domains. We also found that treatment effects on outcomes did not differ by group membership. This poses challenges to the personalized approach to treatment, emphasized by the Precision Medicine Initiative® led by NIH and by NIMH Strategic Plan, and suggests that strategies other than risk factor-based personalization may be needed.

Compliance with Ethical Standards

Conflict of Interest There are no conflicts of interest to report.

Ethical Approval The coordinating center at Duke University Medical Center and the Institutional Review Board at each site approved and monitored the study. The Data and Safety Monitoring Board of the National Institute of Mental Health performed quarterly review.

Informed Consent Adolescents and at least one parent/caregiver provided written informed consent and assent.

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