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Prevention of Depression in At-Risk Adolescents: Moderators of Long-term Response

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Abstract

In a randomized controlled trial, we found that a cognitive behavioral program (CBP) was significantly more effective than usual care (UC) in preventing the onset of depressive episodes, although not everyone benefitted from the CBP intervention. The present paper explored this heterogeneity of response. Participants were 316 adolescents ($M_{\text{age}}=14.8$, $SD=1.4$) at risk for depression due to having had a prior depressive episode or having current subsyndromal depressive symptoms, and having a parent with a history of depression. Using a recursive partitioning approach to baseline characteristics, we (Weersing et al., 2016) previously had identified distinct risk clusters within conditions that predicted depressive episodes through the end of the continuation phase (month 9). The present study used the same risk clusters that had been derived in the CBP group through month 9 to reclassify the UC group, and then to examine group differences in depression through month 33. We found that in this overall very high-risk sample, the CBP program was superior to UC among youth in the low risk cluster ($n=33$),

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Informed Consent: Voluntary assent was obtained from all participating youth. Institutional review boards at each site approved the study. Parents and adolescents provided written informed consent and assent, respectively.

characterized by higher functioning, lower anxiety, and parents not depressed at baseline, but not in the middle ($n=95$) and high-risk ($n=25$) clusters. Across conditions, significantly more depression-free days were found for youths in the low-risk cluster ($M=951.9$, $SD=138.8$) as compared to youths in the high-risk cluster ($M=800.5$, $SD=226.7$). Identification of moderators, based on purely prognostic indices, allows for more efficient use of resources and suggests possible prevention targets so as to increase the power of the intervention.

Keywords

depression; prevention; moderators; adolescents

Depression is a prevalent, disabling, and recurrent condition that often begins in adolescence (Avenevoli, Knight, Kessler, & Merikangas, 2008). Depressive disorders have profound effects on interpersonal relationships, academic and occupational achievement, and health (Jaycox et al., 2009), and are associated with other psychopathology such as anxiety (Garber & Weersing, 2010), substance use disorders (Rice, Lifford, Thomas, & Thapar, 2007), and suicide (e.g., Bridge, Goldstein, & Brent, 2006; Centers for Disease Control and Prevention [CDC], 2010). Moreover, depression during adolescence is a strong predictor of recurrence of depressive disorders in adulthood (Kovacs, 1996). Thus, the prevention of depression is a serious and pressing public health priority.

Evidence that depression can be prevented has been increasing in recent years (e.g., Merry et al., 2012; Munoz, Beardslee, & Leykin, 2012). In a meta-analytic review, Merry and colleagues concluded that there is evidence that targeted as well as some universal interventions prevent the onset of depressive disorders compared with no intervention. Despite these encouraging findings, however, preventive interventions have not worked the same way for all individuals, sometimes varying by age, gender, or initial depression level (Stice, Shaw, Bohon, Marti, & Rohde, 2009). Therefore, a critical task for the field is to determine what differentiates those who do versus do not benefit from these interventions. Detection of moderators can help make the provision of scarce resources more efficient, and can suggest ways to modify the preventive interventions to make them more effective.

In a randomized controlled trial of at-risk adolescents, we found that a cognitive behavioral program (CBP) was significantly more effective than usual care (UC) in preventing the onset of depressive episodes at 9 months (Garber et al., 2009) and 33 months post randomization (Beardslee et al., 2013). Nevertheless, some adolescents in the CBP condition still had depressive episodes. In particular, youth whose parents were depressed at baseline showed no differential benefit from CBP versus UC. To further examine this differential response to CBP, Weersing and colleagues (2016) used recursive partitioning of the survival function to define statistically homogenous clusters of adolescents with a similar risk of having a depression onset through the end of the continuation phase (month 9). Distinct risk clusters were identified using baseline characteristics of youths and parents from a pool of candidate variables, including current parental depression, parent history of hypomania, teens' depressive symptoms, anxiety symptoms, global functioning, and hopelessness. This process yielded three risk clusters within the CBP condition and two clusters within UC. The first

aim of the current study was to determine whether these same clusters continued to predict risk of a depression onset across the subsequent two-year follow-up. This first question is *prognostic* in nature and asks how different types of participants are likely to do within the same condition(s).

This second question is *prescriptive* and asks who will and will not benefit from the preventive intervention (Fournier et al., 2009). Building on our prior work, in the current study we applied the same cluster definitions, as derived previously in the CBP group, to youth in the UC condition to determine whether these risk clusters predicted different outcomes for different types of individuals across the two conditions (Kraemer et al., 2002); that is, whether the risk clusters operated as moderators.

A third aim of this study was to test if these risk clusters predicted a complementary and important outcome – depression-free days (DFDs). The measure of DFDs often is utilized in studies of the cost-effectiveness of an intervention (e.g., Lave, Frank, Schulberg, & Kamlet, 1998; Lynch et al., 2011), but it also is useful clinically. DFDs are a count of the number of days within a particular time interval during which the individual did *not* have depressive symptoms.

Thus, DFDs take into consideration not only that an event (e.g., a depressive episode) occurred, but also the duration of the symptoms. The construct of depression-free days (DFDs) can incorporate multiple assessment points, reflects the person's experience of depressive symptoms over time, and provides a comprehensive view of the benefits of an intervention (Vannoy, Arean, & Unützer, 2010). Both study questions were applied to depression onsets (primary outcome) and depression-free days (secondary outcome).

Method

Participants

Participants were 316 adolescents ages 13 to 17 ($M_{\text{age}}=14.8$, $SD=1.4$) at risk for depression by presence of (a) current subsyndromal depressive symptoms (i.e., CES-D > 20; $n=63$), (b) a prior history of a DSM-IV depressive disorder ($n=175$), or (c) both ($n=78$); in addition, all adolescents had a parent with a past or current depressive disorder. The sample was 58.6% female and 80.4% Caucasian. To be consistent with the original sample from which the risk clusters were derived (Weersing et al., 2016), we excluded six children of non-biological target parents. Another six participants were missing all follow-up data. Thus, the final analytic sample was 304 youth, 153 in CBP and 151 in UC.

Exclusion criteria were bipolar I or schizophrenia in parents or children, a current DSM-IV mood disorder in the adolescent, current receipt of a therapeutic dose of an antidepressant medication (Brent et al., 2008), or having ever received more than eight sessions of CB therapy for depression. More than one sibling per family was allowed to participate; siblings were yoke randomized to ensure assignment to the same condition. There were 32 sets of siblings in the sample of 304 (one sibling set consisted of triplets).

The sample was recruited from August 2003 through February 2006 at four sites: Vanderbilt University, Nashville, TN; University of Pittsburgh, Pittsburgh, PA; Kaiser Permanente Center for Health Research, Portland, OR; and Judge Baker Children's Center/Children's Hospital Boston, Boston, MA. The detailed recruitment flow chart has been published previously (Garber et al., 2009). Retention of the sample at the month 33 evaluations was 84.8%, (N=282).

Procedures

Design—Adolescents were randomized to either CBP (n=159) or UC (n=157) using Begg and Iglewicz's (1980) modification of Efron's (1971) biased coin toss to ensure that the two cells were balanced on age [CBP: $M_{\text{age}}=14.8$ ($SD=1.5$); UC: $M_{\text{age}}=14.8$ ($SD=1.3$)], sex [females -- CBP: n=93 (58.5%); UC: n=92 (58.6%)], race [Caucasian – CBP: n=129 (82.7%); UC: n=125 (80.6%)], ethnicity [Latino/Hispanic – CBP: n=10 (6.3%); UC: n=11 (7.1%)], and inclusion criteria [CES-D entry qualifying score – CBP: $M=18.5$ ($SD=9.1$); UC: $M=18.8$ ($SD=9.6$)], [history of a depressive episode – CBP: n=130 (81.7%); UC: n=123 (78.3%)]. Most parents were employed [CBP: n=114 (82.0%); UC: n=117 (81.8%)], and had a high school education or higher [CBP: n=108 (77.7%); UC: n=110 (76.9%)]. No significant differences were found between conditions with regard to baseline demographic or clinical characteristics (Garber et al., 2009). The study used an intent-to-treat design; that is, all participants were considered part of the study from the point of randomization.

Intervention Conditions

The CBP program in the present RCT was a modified version of the intervention used by Clarke and colleagues (1995, 2001) and emphasized cognitive restructuring and problem solving. This CBP program consisted of 8 weekly (acute) plus six monthly (continuation) 90-minute sessions of mixed-sex groups of adolescents [$M=6.6$ ($SD=1.6$)]. The intervention was delivered with fidelity across sites by therapists who were at least Masters-level clinicians trained and supervised by Ph.D. clinicians.

Adolescents attended an average of 6.5 acute sessions ($Median=8.0$; range, 0-8) and an average of 3.8 continuation sessions ($Median=5.0$; range, 0-6). During continuation sessions, cognitive and problem-solving strategies were reviewed and additional skills (e.g., behavioral activation, relaxation, or assertiveness) were taught. Meetings to inform parents about the skills their children were learning were conducted in weeks 1 and 8. Parents of 76.4% of the youth in CBP attended session 1, and 70.9% attended session 8.

Usual Care—Participants in both intervention conditions were permitted to seek outside services. When episodes of depression were identified at a follow-up for youths in either condition, appropriate clinical referrals were provided.

Assessments—Data for this report were drawn from evaluations conducted at baseline, 9 months ($Median=42.1$ weeks post-baseline), and 33 months ($Median=150$ weeks post-baseline). Independent evaluators, unaware of experimental condition, conducted the assessments. Evaluators completed extensive training, participated in ongoing supervision,

and demonstrated a minimum inter-rater reliability level of $\kappa = 0.80$ on diagnostic variables in two practice interviews before conducting actual study assessments.

Measures

Candidate Moderators—Parents and adolescents were assessed at baseline with a comprehensive battery of questionnaires and interviews including the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; First et al., 1997), *Schedule for Affective Disorders and Schizophrenia for School-aged Children - Present and Lifetime Version* (K-SADS; Kaufman et al., 1997), *Center for Epidemiological Studies – Depression Scale for Adolescents* (CESD-A; Radloff, 1991), *Hopelessness Scale* (HS; Beck, Weissman, Lester, & Trexler, 1974), *Screen for Anxiety Related Emotional Disorders* (SCARED; Birmaher et al., 1997), *Aggression Questionnaire* (Buss & Perry, 1992), *Disruptive Behavior Disorder Scale-Adolescent Report* (DBDA, Silva et al., 2005), *Children's Global Adjustment Scale* (CGAS; Shaffer et al., 1983), *Conflict Behavior Questionnaire* (CBQ; Robin & Weiss, 1980), *Children's Report of Parent Behavior Inventory* (CRPBI; Schludermann & Schludermann, 1970), *Life Events Checklist* (LEC, Johnson & McCutcheon, 1980), *trauma exposure* (from the PTSD section of the K-SADS), and the *Self-Rating Scale for Pubertal Development* (PDS; Carskadon & Acebo, 1993). Demographic information about the family was obtained from parents; race/ethnicity was collected via self-report from parents and adolescents.

Risk clusters—Previously, we identified significant moderators of the month-9 outcome (i.e., onset of a depressive episode) from the pool of candidate variables (see Weersing et al., 2016). Cox regression models were conducted that included a candidate variable, the intervention (CBP vs. UC), and their interaction, which was the test of moderation (Kraemer, Wilson, Fairburn, & Agras, 2002). Six baseline clinical characteristics of youths and parents that met this criterion were: current parental depression (SCID), parent history of hypomania (SCID), lower teen functioning (CGAS), higher teen depressive symptoms (CESD-A), higher teen anxiety symptoms (SCARED), and higher teen hopelessness (HS). Clinically *worse* values on these variables were associated with a greater risk of onset through month 9 in CBP.

To clarify and organize relations among these characteristics rather than trying to test and interpret a seven variable interaction term, Weersing et al. (2016) used the six moderators identified through the univariate analyses as classification factors to partition the sample *within* each condition. Recursive partitioning of the survival function (Zhang & Singer, 1999) was used to define statistically homogenous clusters of adolescents with similar risk of a depression onset through the end of continuation phase (month 9). This process yielded three risk clusters within the CBP group and two clusters within the UC group.

Within CBP, the three risk clusters were defined by the combination of adolescent's general level of functioning (CGAS), anxiety (SCARED), hopelessness (HS), and whether the parent was in a depressive episode at baseline. As seen in Table 1, the *low* risk CBP cluster was characterized by higher teen functioning, the absence of current parental depression, and lower teen anxiety. The *medium* risk CBP group also was defined by higher teen functioning, but adolescents in this group had *either* (a) a parent who was not currently

depressed, but the teen had high levels of anxiety, *or* (b) a parent who was depressed at baseline, but the teen had lower hopelessness. The *high* risk CBP group was characterized by *either* (a) lower adolescent functioning, *or* (b) the combination of higher adolescent functioning, current parental depression, and higher adolescent hopelessness. Within UC, only adolescent functioning (on the CGAS) defined the risk clusters, with a high- and a low-functioning group.

Although baseline level of functioning appeared within both the CBP and UC groups as an important classification variable, the cut-points on the CGAS were different. In the UC condition, “high functioning” was defined by a CGAS score ≥ 72.5 , which corresponds to no more than slight impairment and transient difficulties in functioning. In contrast, the cut-point for higher functioning in CBP was ≥ 65.5 , which corresponds to “some difficulties in functioning in a single area.” Thus, the relation between functioning and outcome varied by condition.

Depression Outcomes—At each follow-up evaluation, parents and adolescents were interviewed with the *Longitudinal Interval Follow-up Evaluation* (LIFE; Keller et al., 1987) to obtain a continuous measure of the teens' symptoms and onset/offset of disorders since the last assessment. A score of 1 through 6 on the Depression Symptom Rating (DSR) scale was given for each week of the follow-up period based on the number of symptoms and extent of impairment. The primary outcome variable in the current trial was time to onset of a probable or definite episode of major depression (MDE: DSR ≥ 4) for at least two consecutive weeks. Inter-rater reliability of the DSR scale was high (97.5% agreement).

Depression-free days (DFDs) were calculated using the DSR from the LIFE data. Participants' weekly ratings were converted to depression weights ranging from 0 to 1, with 0 being no depressive symptoms and 1 representing a depressive episode, for each week from baseline through the 33-month evaluation. Depression weights of 0.00, 0.33, 0.66, and 1.00 were assigned to DSR ratings of 1, 2, 3, and 4, respectively. Weekly depression weights were multiplied by 7 (days in a week) and summed to the individual-level. DFDs were calculated by subtracting the total of the depression weights from the total days of the follow-up, thus representing the total number of days a youth was depression-free.

Health Service Utilization—At each assessment, adolescents and parents completed the Child and Adolescent Services Assessment (Ascher, Farmer, Burns, & Angold, 1996; Farmer, Angold, Burns, & Costello, 1994) about the adolescent's mental health service use over the follow-up period. Youths in both conditions were permitted to obtain non-study mental health services. Youth in CBP versus UC did not differ significantly in either outpatient mental health services (49.0% vs. 45.7%) or medication use (16.3% vs. 13.25%). The rates of service use also did not differ significantly across the three CBP risk clusters ($p's > .70$) or between the two UC clusters ($p's > .33$). The 2 conditions (CBP, UC) by 3 risk clusters (low, medium, high) analyses of service utilization yielded neither significant main effects of condition or risk clusters ($p's > .39$) nor their interactions ($p's > .57$). Thus, differential health service utilization did not account for observed differences between conditions or within the risk clusters.

Data Analysis Plan

We first examined time to onset of depressive episodes to determine whether membership in the risk clusters associated with differences in depression onset at month 9 continued to predict adolescents' outcomes over the following two years (i.e., through month 33). Second, to test for moderation, we classified youths in UC according to the more fully differentiated CBP risk clusters and examined whether differences between the conditions were larger in some risk clusters than in others. Finally, we repeated both sets of these prognostic and prescriptive tests with respect to the other index of depression -- depression-free days.

For episode data, we utilized a random-effects survival analysis framework (i.e., a gamma frailty model) to account for subject-to-subject heterogeneity in event times (Clark, Bradburn, Love, & Altman, 2003). As in our previous report of long-term outcomes in this sample (Beardslee et al., 2013), including sibling clusters did not alter clinical results and provided poorer overall model fit. For depression-free-days, we examined intra-class correlation coefficients for site ($ICC=0.04$) and sibling clusters ($ICC=0.16$), and fit general estimating equations (GEE) to account for sibling effects.

Results

Onsets of Depressive Episodes through Month 33 (Prognostic)

We modeled *time-to-onset* through month 33 separately for CBP and UC using a random-effects survival analysis framework and included the previously derived month-9 risk clusters. Within CBP, the gamma frailty model converged; risk cluster was a significant predictor of time to onset [$F(2, 152)=10.37, p<.001$] (see Table 2a). Youth in both the low risk ($t=-4.38, df=152, p<.001$) and medium risk CBP clusters ($t=-3.63, df=152, p<.001$) had significantly longer times to a depression onset as compared to youth in the CBP high risk cluster (see Figure 1a); the difference between low and medium risk CBP clusters was not significant ($t=3.31, df=152, p=.07$). Within UC, youths in the high functioning cluster had a significantly longer time to onset than youth in the low functioning UC cluster, $t=-6.21, df=150, p<.001$ (see Table 2b, Figure 1b). Thus, the risk clusters derived from baseline data and generated on the 9-month depression outcomes continued to predict cumulative risk across the 33-month follow-up.

Moderation Hypothesis: Comparison of the Same Three Risk Clusters across CBP and UC

To test the moderation hypothesis, we cross-classified UC youth with respect to the same risk clusters that predicted differential onset of depression in the CBP youth through month 9. Thus, youth in UC were divided into the three risk clusters, using the same baseline variables and cut-offs that defined low, medium, and high risk within the CBP condition. We then examined the interaction of condition (CBP vs. UC) by risk cluster (low, medium, high) to predict time to onset of a depressive episode. These analyses allowed us to compare sets of youths as follows [low risk: (Cluster A_{CBP} vs. Cluster A_{UC}); medium risk: (Cluster B_{CBP} vs. Cluster B_{UC}); and high risk: (Cluster C_{CBP} vs. Cluster C_{UC})] “matched” with regard to the baseline variables that defined each of the three clusters.

Results of these analyses are presented in Table 3 and Figure 2. We modeled *time-to-onset* through month 33 in a survival analysis framework. In this analysis, the gamma frailty model again converged; the condition by risk interaction significantly predicted time to onset [$F(2,303)=5.29$, $p=.01$]. Analyses to unpack this interaction indicated that the effect of condition was significant in the low risk group ($p<.001$), but not in the medium ($p=.18$) or high risk ($p=0.50$) comparisons. Thus, among youth characterized as low risk (in this overall high-risk sample), those randomized to CBP had significantly better outcomes (i.e., later onset of depressive episodes) than youth assigned to UC.

Depression-free Days

We next examined number of depression-free days. Within the CBP condition, adolescents in the low- and medium-risk clusters had significantly more depression-free days than those in the high-risk cluster ($\chi^2_2=12.08$, $p=.002$; see Table 4). Youth in the low- and medium-risk CBP clusters had approximately 6 and 4 more months, respectively, of depression-free days compared to youth in the high risk CBP cluster. In the UC condition, higher functioning youth had significantly more depression-free days than lower functioning youth ($z=-3.66$, $p < 0.001$; see Table 4).

Next, to test for moderation, we again cross-classified participants in the UC condition with respect to the risk clusters developed for the CBP participants. The analysis comparing the three CBP-defined risk groups across the two conditions regarding the number of depression-free days yielded an overall significant main effect of risk, $\chi^2_2=11.76$, $p=.003$. Across conditions, low-risk youth ($M=951.9$, $SD=138.8$) had significantly more depression-free days than high-risk youth ($M=800.5$, $SD=226.7$) ($\beta = -108.17$, 95% CI: -193.78 to -22.55; $z = -2.48$; $p=0.01$). The main effect for condition ($B=73.37$, 95% CI: -12.02, 158.76, $z=1.68$, $p=.09$), and the condition by risk interaction were not significant ($\chi^2_2=2.16$, $p=0.34$). The means and standard deviations for each risk group by condition were as follows: low risk [CBP: $M = 987.3$ ($SD=82.2$), UC: $M = 910.2.3$ ($SD=177.5$)], medium risk [CBP: $M = 928.3$ ($SD=159.1$), UC: $M = 919.4$ ($SD=157.2$)], and high risk [CBP: $M = 799.4$ ($SD=247.1$), UC: $M = 801.4$ ($SD=213.5$)].

Discussion

Three important findings emerged from the present study. First, membership in risk categories defined using baseline characteristics that predicted onsets of depressive episodes by the end of the continuation phase of the intervention (month 9) remained a potent predictor of cumulative depression onsets two years later (i.e., through month 33). As can be seen in Figure 1, the risk clusters within CBP and within UC, respectively, separated early and essentially maintained these trajectories across the follow-up. That is, we observed neither a major spreading nor a substantial decrease in the differences in depressive episodes among the three CBT clusters or between the two UC clusters across the two years. These results support the long-term predictive validity of the risk categories derived from baseline characteristics that had predicted short-term risk. Thus, the effects of the intervention on depressive episodes appear to have occurred early and were generally maintained over two years.

Second, we found evidence of moderation that went beyond the previously reported moderator of baseline parental depression (Beardslee et al., 2013; Garber et al., 2009). Within this very high-risk sample, we classified youth in both the CBP and UC conditions according to the same three risk clusters identified earlier in Weersing et al. (2016) as differentiating outcomes within the CBP group. When so doing, the preventive effect of CBP versus UC was evident for youths in the low risk cluster, which was characterized by higher levels of functioning (i.e., a CGAS > 65), lower anxiety, and no current parental depression. Thus, among the 22% of the sample that fell into this “low-risk” group, CBP had a truly preventative effect, whereas for youths in the medium- or high-risk clusters, CBP was not more effective than UC.

Hence, knowing if a parent is depression-free at baseline does not appear to be sufficient to fully predict youths' response to CBP. Rather, also knowing the teen's levels of functioning and anxiety will improve the prediction of intervention response. Nonetheless, even relatively low-risk youths, within this very high-risk sample, characterized by high functioning, low anxiety, and a parent currently free of depression were at elevated risk if they did not receive CBP. Thus, the CBP program was effective in extending the time to onsets of depressive episodes for youths experiencing relative “wellness” in both themselves and their parents.

Third, in addition to assessing time to onset of depressive episodes, the current study examined the number of days during the interval between baseline and month 33 that adolescents were without depressive symptoms – depression-free days (DFDs). This metric is frequently used in studies of the cost-effectiveness of interventions (e.g., Lave et al., 1998; Lynch et al., 2011), but also has clinical utility. Within the CBP condition, youths in the high-risk cluster had depressive symptoms for 4 and 6 months more than did teens in the medium- and low-risk clusters, respectively. Similarly, within the UC condition, youths in the lower functioning cluster had about four months more days of depression than higher functioning youth. Thus, for approximately a semester or more of school, youths most at-risk for depression likely were not performing at their best academically or socially, which in turn, could affect their future scholastic achievements and interpersonal relationships. Reducing the number of days during which an adolescent experiences depressive symptoms could substantially impact important domains of functioning, and therefore should be targeted as an outcome of preventive interventions, in addition to decreasing onsets of depressive episodes.

Finally, no significant differences were found in health care utilization between the intervention conditions or among the different risk clusters within conditions. Almost half of the youth within each risk cluster in both CBP and UC received some kind of mental health services during the 33 months post baseline, further confirming the high level of risk in this sample. Nevertheless, the differences observed in depression outcomes for youth in CBP versus UC cannot be plausibly attributed to differential utilization of mental health services. Because such interventions were not randomized, we are unable to determine the impact of such treatment on the observed results.

Limitations and Future Directions

Limitations of the study provide directions for future research. First, because the sample was at very high risk for developing depression based on both their familial and personal history of depressive disorders or current subsyndromal symptoms, the results might not generalize to a sample at lower or no risk. Second, although this was a relatively large targeted sample compared to other depression prevention trials, an even larger sample might be needed to have sufficient power to detect multivariate moderators of the intervention effect, particularly among youth with several interacting risk factors. Third, given the complexity of the lives of many of the participants, more sessions over a longer period of time may be needed to significantly impact the numerous challenges with which these at-risk youth were dealing. Finally, although we were able to identify several combinations of variables that predicted increased risk of a depression onset, the precise mechanisms through which these factors either exacerbate or reduce vulnerability needs to be investigated.

Although the findings of the current study strengthen the previously reported results (Weersing et al., 2016) regarding the stability of the clusters derived with regard to the 9-month outcomes, additional questions remain. Other baseline variables also might predict stability within condition over time. Thus, future analyses should explore whether other combinations of baseline variables predict the 33-month outcome as well as or better than those used here. It also will be important to examine whether the same lack of differentiation in the UC group (only baseline functioning) continues to hold in predicting outcomes at 33 months.

Implications

These results have several implications for public health and clinical practice. First, mental health service providers planning to implement the CBP program might want to assess the various constructs that comprised the risk clusters identified here (e.g., adolescents' global functioning, anxiety, and hopelessness, and parents' current depression). Such information would have prognostic value in that clinicians could estimate the likelihood of an onset of a depressive episode for youth receiving CBP given a particular risk profile.

Second, assessing these risk factors might help guide clinicians in terms of what needs to be added to the current CBP program to more explicitly target these vulnerabilities. Of note, all of the risk factors identified in this report were potentially modifiable (in contrast to demographic or fixed/historical). For example, clinicians could supplement the program with modules that specifically aim to reduce anxiety or hopelessness, or improve functioning. Low functioning, however, is multi-faceted and therefore the particular factors contributing to the adolescent's impairment (e.g., learning difficulties, other psychopathology) would need to be assessed as well. The extent to which supplementing the current CBP program improves its efficacy for youths with various risk profiles needs to be systematically tested in an RCT.

Another strategy might be to target specific risk factors prior to implementing CBP. For example, current parental depression was associated with reduced efficacy of CBP; therefore, clinicians might treat the parents' depression prior to implementing the CBP

program with the teen, or treat the parents' depression while simultaneously providing the preventive intervention to the children. If having a depressed parent plays a causal role (and is not simply a marker of greater familial risk), then reducing depression in the parent may enhance the efficacy of the prevention program with the teen. The relative efficacy of sequential versus concurrent interventions for depressed parents and their children should be investigated.

It also is possible, however, that the CBP program in its current form may not be sufficient for adolescents who have certain clinical vulnerabilities, particularly ones that are relatively stable. If so, then it may be necessary, albeit challenging, to modify or supplement the existing program with interventions that specifically target such risk factors. Finally, even some of the lower-risk youth in the CBP program had onsets of depressive episodes, although they occurred later than onsets in the higher-risk group. Thus, the CBP program clearly can prevent or at least delay depression in at-risk adolescents, particularly when implemented at moments of relative wellness in youths and their parents. Further modifications of the program, however, may be needed to specifically address risk factors not currently targeted in the intervention.

In summary, we identified risk clusters that predicted the onset and persistence of depression in youth at high risk for depressive disorders; that is, how a given individual can be expected to do *within* either CBP or UC. Although such information is purely *prognostic*, it does provide a basis for predicting subsequent course. We then used these risk clusters to identify which youths were most likely to benefit from CBP versus UC, and which youths were likely not to show differential effects. Such information is *prescriptive* in that it can be used to determine whether a given teen is likely to benefit from this particular preventive intervention.

These findings highlight two important conclusions. First, among adolescents who are offspring of depressed parents and who also have their own history of mood disorders or current subsyndromal depressive symptoms, CBP was effective for those with low anxiety, relatively high functioning, and no current parental depression. In contrast, the effects for some other prevention programs have been most pronounced in the highest risk groups (see Merry et al., 2012). Perhaps the “low” high risk youth in the current very high-risk sample were at a similar level of vulnerability as those considered to be “high” risk in universal samples.

Second, the factors that comprise vulnerabilities to depression are quite heterogeneous. The current study focused on only a subset of possible risk factors. Nevertheless, modifying the CBP program to address the variables that were associated with an attenuated response (e.g., current parental depression, adolescent hopelessness) may be one productive pathway to boosting the efficacy of CBP, particularly for youths at greatest risk for developing depressive disorders.

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Figure 1.

(a) Youths in both the low-risk CBP Cluster (red line) and the medium-risk CBP Cluster (green line) had significantly longer time to depression onset as compared to youth in the CBP high-risk Cluster (blue line). Youths in the low- and medium-risk CBP Clusters were not significantly different from each other. (b) Youths in the lower risk UC Cluster (orange line; CGAS ≥ 72.5) had significantly longer time to onset compared to youths in the higher risk UC Cluster (black line; CGAS < 72.5). The 9-month assessment was conducted at about week 41.

Figure 2.

CBP youth in the low risk CBP-defined Cluster (solid line) had significantly longer time to onset compared to UC youth in the low risk CBP defined UC Cluster (dashed line). Within either the medium or high CBP-defined risk clusters, time to depression onset was not significantly different for youth in CBP (solid lines) versus UC (dashed lines). The 9-month assessment had been conducted at about week 41.

The risk clusters derived from baseline characteristics (current parental depression; adolescents' functioning, anxiety, and hopelessness) that had predicted onsets of depression at the post continuation evaluation (month 9) were tested as predictors of depression onsets two years post continuation (month 33)

Table 1

Cluster	Moderators						9 months		33 months	
	Lower functioning [†]	Parent depressed at baseline	Higher anxiety [‡]	Higher hopelessness [§]	N ^a	N	Onset rate	N	Onset rate	
<i>CBP</i>										
A. Low risk	No	No	No	---	-	33	0%	33	27%	
B. Medium risk	No	No	Yes	---	37	94	19%	95 ^b	37%	
	No	Yes	---	No	57					
C. High risk	No	Yes	---	Yes	18	25	56%	25	56%	
	Yes	---	---	---	7					
<i>Usual Care</i>										
Higher functioning	No	---	---	---	-	96	24%	96	46%	
Lower functioning	Yes	---	---	---	-	53	49%	55 ^b	60%	

[†] Although functioning appeared within both CBP and UC as a cluster classification variable, the cut-points on the CGAS were different in the two conditions (CBP: CGAS < 65.5; UC: CGAS < 72.5). Thus, the relation between level of functioning at baseline and the subsequent onset of depression varied by condition.

^a Number of participants within each subgroup for medium and high risk in the CBP condition

^b These numbers are higher because some participants who had not completed the assessment at month 9, completed it at month 33.

[‡] SCARED 20

[§] Hopelessness Scale (HS) 9.5

Table 2a
Comparison of risk clusters in the Cognitive Behavioral Prevention (CBP) program using a random-effects survival analysis (i.e., gamma frailty model)

	Estimate	SE	95% CI	DF	test	p
Intercept	4.33	0.41	(3.51, 5.15)	152	t=10.47	<0.001
Risk Clusters						
				2, 152	F=10.37	<0.001
CBP Low risk ~	-2.64	0.60	(-3.83, -1.45)	152	t=-4.38	<0.001
CBP Medium risk ~	-1.74	0.48	(-2.69, -0.79)	152	t=-3.63	<0.001
Frailty (gamma)						
	1.48	0.34	(0.80, 2.16)	152	4.32	<0.001
Random effect (logsig)	0.69	0.11	(0.48, 0.91)	152	t=6.34	<0.001

~ Dummy variable for risk cluster, with CB High risk cluster as the reference category

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Table 2b
Comparison of risk clusters in the Usual Care (UC) condition using a random-effects survival analysis (i.e., gamma frailty model)

	Estimate	SE	95% CI	DF	test	p
Intercept	4.23	0.15	(3.93, 4.53)	150	t=28.14	<0.001
Risk Clusters ~	-1.37	0.22	(-1.81, -0.93)	150	t=-6.21	<0.001
Frailty (gamma)	2.67	0.54	(1.60, 3.74)	150	t=4.94	<0.001
Random effect (logsig)	0.75	0.04	(0.66, 0.84)	150	t=16.46	<0.001

~ Comparison between higher versus lower functioning clusters in Usual Care (UC)

Table 3

Comparison of the three risk clusters derived for the Cognitive Behavioral Prevention (CBP) program applied to youth in the Usual Care (UC) condition using a random-effects survival analysis (i.e., a gamma frailty model) to test the condition by risk interaction.

	Estimate	SE	95% CI	df	test	p
Intercept	4.68	0.44	(3.81, 5.56)	303	t=10.54	<0.001
Condition	-2.24	0.59	(-3.4, -1.07)	303	t=-3.78	<0.001
Risk Cluster				2, 303	F=2.39	0.09
Medium risk ~	-0.87	0.51	(-1.88, 0.13)	303	t=-1.71	0.09
High risk ~	-0.02	0.60	(-1.21, 1.17)	303	t=-0.03	0.98
Condition by Risk Cluster				2, 303	F=5.29	0.01
Condition by Medium risk	1.76	0.70	(0.39, 3.13)	303	t=2.53	0.01
Condition by High risk	2.62	0.82	(1.00, 4.24)	303	t=3.19	<0.001
Frailty (gamma)	1.54	0.29	(0.97, 2.11)	303	t=5.32	<0.001
Random effect (logsig)	0.67	0.07	(0.53, 0.81)	303	t=9.41	<0.001

~ Dummy variables for risk. Low risk cluster is the reference category.

Table 4

Total number of depression-free days (DFDs) was compared among the three clusters within the CBP condition (i.e., low, medium, and high); youths in the high-risk cluster had significantly fewer DFDs than youths in both the low and medium risk clusters. A separate analysis of youths in the usual care condition revealed that high functioning UC youth had significantly more DFDs as compared to low functioning UC youth.

Clusters	N (%)	Depression-free Days Mean (SD)	Test	p
<i>Cognitive Behavioral Prevention</i>			$\chi^2_{2}=12.08$	< 0.002
Low risk	33 (22%)	987.3 (82.2) ^a		
Medium risk	95 (62%)	928.3 (159.1) ^a		
High risk	25 (16%)	799.4 (247.1) ^b		
<i>Usual Care</i>			MW z = 3.66	< 0.001
Higher functioning	96 (64%)	934.3 (141.0)		
Lower functioning	55 (36%)	820.2 (214.4)		

^{a,b} Cognitive behavioral prevention program (CBP) clusters with different superscripts were significantly different from each other at $p < .017$

SD = Standard Deviation; MW = Mann-Whitney test