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Research paper

Adding cognitive therapy to antidepressant medications decreases ssuicidal ideation

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ABSTRACT

Background: Psychotherapy for depression and antidepressant medications have both been associated with decreases in suicidal ideation. Studies have not examined whether adding psychotherapy to antidepressant medications further reduces suicidal ideation relative to medications alone in adults.
Methods: Participants ($N = 452$) were randomized to 7 months of treatment with antidepressant medications or combined treatment with both medications and cognitive therapy for depression. We examined change in the suicide items from the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) across treatment using Bayesian generalized linear mixed models for non-continuous outcomes.
Results: Suicidal ideation decreased across treatment. When measured with the BDI, participants receiving both cognitive therapy and antidepressant medications showed 17% greater reductions in suicidal ideation relative to those receiving medications alone; this effect remained significant when controlling for depression severity. While the same pattern was observed when suicidal ideation was measured with the HDRS, the effect was smaller (7%) and not statistically significant. When BDI and HDRS scores were combined, participants receiving both therapy and medications showed 9% greater reductions in suicidal ideation relative to those receiving medications alone; this effect was marginally significant when controlling for depression severity.
Limitations: This is a secondary analysis of a randomized clinical trial designed to treat depression, in which suicidal ideation was assessed using single-item measures.
Conclusions: Adding cognitive therapy to antidepressant medications may reduce suicidal ideation to a greater extent than medications alone. Pending replication, combination treatment may be preferred for individuals with suicidal ideation.
Trial registration: clinicaltrials.gov Identifier: NCT00057577

Suicide is a leading cause of death both globally and in the US, with over 48,000 Americans dying by suicide in 2018 (American Foundation for Suicide Prevention, 2020). Suicidal ideation, or thinking about, considering, or planning suicide, is a strong predictor of suicide attempts and deaths (Hubers et al., 2018; Klonsky et al., 2016), and depression is the disorder most strongly associated with suicidal outcomes (Hawton et al., 2013). Apart from its relation to suicide attempts, suicidal ideation is a concerning symptom in its own right given its associations with decreased quality of life, increased use of services, and poorer treatment outcomes (Goldney et al., 2001; Szanto et al., 2001).

Suicidal ideation can improve with psychotherapeutic or pharmacological therapy. Decreases in suicidal ideation have been observed during psychotherapy for suicidal outcomes (Brown & Jager-Hyman, 2014) and to some degree for depression (Cuijpers et al., 2013). Cognitive behavioral interventions specifically have been found to reduce suicidal ideation, perhaps because of the important role of maladaptive cognitions like hopelessness, helplessness, and intolerance of distress in increasing suicidal ideation (Calati et al., 2018; Leavey & Hawkins, 2017). Cognitive behavioral interventions for depression are particularly appropriate given the strong relationship between depression and suicide (Stewart et al., 2009). In addition to evidence for the efficacy of psychotherapy, studies have found that treatment with antidepressant medications is associated with reductions in suicidal ideation (Zalsman et al., 2016).

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Research comparing the efficacy of psychotherapy and antidepressant medications in decreasing suicidal ideation, however, is limited. One study found that both interpersonal therapy and antidepressant medications reduced suicidal ideation in adults to similar degrees (Weitz et al., 2014). Another study found that antidepressant medications led to greater reductions in cognitive and suicide symptoms relative to placebo by 4 weeks, and that both cognitive therapy and medications led to greater reductions in these symptoms relative to placebo by 8 weeks in adults; however, suicidal ideation was examined together with other cognitive symptoms like guilt and hopelessness (Fournier et al., 2013). Finally, a study found that adolescents treated with both cognitive behavior therapy and fluoxetine, an antidepressant medication, showed greater reductions in suicidal ideation compared to those treated with fluoxetine alone, cognitive therapy alone, or a placebo group after 12 weeks of treatment (March et al., 2004). After 36 weeks of treatment, patients treated with both cognitive behavior therapy and fluoxetine showed less clinically significant suicidal ideation compared to those treated with fluoxetine alone (March et al., 2007).

We are unaware of a randomized clinical trial in an adult sample that has compared decreases in suicidal ideation during treatment with both psychotherapy and antidepressant medications relative to treatment with medications alone. The combination of psychotherapy and medications tends to produce better outcomes for depression over medications alone (Cuijpers et al., 2009; Khan et al., 2012); however, the magnitude of the effect is modest and the extent to which it extends to suicidal ideation is unclear. Additionally, the greater cost of combined treatment indicates the need to understand for whom combined treatment is most advantageous. Previous studies, including analyses of the present data, found that combined treatment is more effective for individuals with severe depression (Hollon et al., 2014; Thase et al., 1997), as well as those with elevated distress and anhedonia at baseline (Khazanov et al., 2020).

In the present study, we examined whether adding cognitive therapy to antidepressant medications resulted in greater reductions in suicidal ideation relative to medications alone in adults. In addition to focusing on adults versus adolescents, this study differs from March and colleagues' study (2004; 2007) in several important ways. First, the present study was more inclusive of individuals experiencing suicidal ideation – only participants at imminent suicidal risk (sufficient to require immediate hospitalization) were excluded. By contrast, the March study excluded participants with recent suicide attempts or hospitalizations for potential harm to self, intent or an active plan to commit suicide, and suicidal ideation in the context of a disorganized family. Second, the March study included all individuals with clinical levels of depression, whereas the present study included only individuals with recurrent or chronic depression, thereby focusing on a sample for whom suicidal outcomes are particularly relevant (Angst & Dobler-Mikola, 1985; Lewinsohn, et al., 1994). Third, the only medication offered in the March study was fluoxetine, whereas the present study had a goal of providing personalized antidepressant therapy using best clinical practice. This goal was met by using a principle-based algorithm to determine pharmacotherapy regimens, which involved up to four classes of antidepressants and augmenting agents typically used in clinical practice (Hollon et al., 2014), thereby increasing the generalizability of study results to real world settings.

We hypothesized that combined treatment would reduce suicidal ideation to a greater degree than medications alone. This finding would suggest that cognitive therapy improves treatment outcomes and should be recommended over and above antidepressant treatment for individuals with suicidal ideation. As we were interested in assessing decreases in suicidal ideation overall, as well as decreases in suicidal ideation when accounting for decreases in depression, we present results with and without controlling for overall depression severity. As the present study is a secondary analysis of a randomized clinical trial, we did not have access to multi-item measures of suicidal ideation. We therefore used single-item measures, following the lead of previous studies (Kellner et al., 2005; Kowal et al., 2014; Szanto et al., 2003; Weissman et al., 2018; Weitz et al., 2014), as well as studies showing the validity of this approach (Desseilles et al., 2012; Green et al., 2015). These items were derived from the Beck Depression Inventory (BDI; Beck et al., 1961) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), the most widely used self-reported and clinician-rated measures of depression, respectively.

1. Methods

1.1. Participants

Participants were treatment-seeking adults recruited from clinics at the University of Pennsylvania (Philadelphia), Rush Medical Center (Chicago, Illinois), and Vanderbilt University (Nashville, Tennessee). Inclusion criteria included experiencing recurrent (two or more episodes) or chronic (episode lasting more than two years) DSM-IV major depressive disorder (MDD) with a Hamilton Depression Rating Scale (HDRS) score of 14 or higher. Institutional Review Boards at all sites approved the study and participants provided informed consent.

All participants ($N = 452$) who began the study completed the HDRS at intake, while 445 participants completed the BDI at intake, so 452 and 445 participants were included in the HDRS and BDI analyses, respectively. About half of participants were assigned to the antidepressant-only (ADM) group (HDRS analyses: 225; BDI analyses: 219) and half were assigned to the combined group given both antidepressant medications and cognitive therapy (COM; HDRS analyses: 227; BDI analyses: 226). Analyses with a composite BDI and HDRS variable, which utilized only assessments during which participants completed both measures, included the same number of participants as the BDI analyses. Sensitivity analyses restricting to participants who endorsed suicidal ideation (a score above 0) at some point during treatment included 296 participants for the BDI analyses (ADM = 140; COM = 156) and 322 participants for the HDRS analyses (ADM = 158; COM = 164). Sensitivity analyses with the composite BDI and HDRS variable, restricted to participants who endorsed suicidal ideation at some point during treatment on either measure, included 352 participants (ADM = 171; COM = 181).

1.2. Design

Participants were randomly assigned to one of the two treatment groups, with randomization stratified by sex, marital status, symptom severity, recurrence, chronicity, and comorbid Axis II disorders. During the acute phase, participants were treated until they remitted (defined as experiencing 4 consecutive weeks of minimal symptoms) and during the continuation phase, they were treated until they recovered (defined as experiencing another 26 consecutive weeks without relapse)[1]. We examined change in the BDI and HDRS suicide items across the first 30 weeks (7 months) of treatment, as reassignment to different treatment groups [maintenance versus withdrawal from antidepressant medications in the second phase of the study; see DeRubeis et al. (2019) for details] could begin as early as month seven, when it was first possible to meet criteria for recovery. Systematic differences between treatments did not allow for longitudinal analyses of outcomes after this point of the study.

[1] Remission and recovery criteria (see Hollon et al., 2014 for details) were based on HDRS scores and scores on the Longitudinal Interval Follow-up Evaluation (LIFE; Keller et al., 1987). To meet criteria for remission, participants needed to have HDRS scores of 8 or less and LIFE ratings of 2 or less for 4 consecutive weeks. Participants relapsed when they had HDRS scores of 16 or more or LIFE scores of 5 or more for 2 consecutive weeks. When participants met criteria for remission and did not relapse for another 26 consecutive weeks, they achieved recovery.

As previously mentioned, all participants were provided with pharmacotherapy using a principle-based algorithm involving up to four classes of antidepressants and any augmenting agents typically used in clinical practice. Cognitive therapy followed the original treatment manual (Beck et al., 1979), enhanced when indicated for participants with comorbid Axis II disorders (Beck et al., 2003). A full study summary is provided in Hollon et al. (2014).

Participants with absent to severe suicidal ideation were allowed to participate in the study. However, those deemed as being at imminent suicidal risk (risk sufficient to require immediate hospitalization; 10 during screening and 1 during the diagnostic interview) were provided with alternative care. There were no completed suicides during the study, although two patients (one in each group) made suicide attempts.

1.3. Measures

1.3.1. HDRS

The 17-item HDRS (Hamilton, 1960) was used to measure depression severity. Trained interviewers blind to treatment condition administered the HDRS at intake, as well as at least biweekly through week 4, every 4 weeks through week 20 of the acute phase, and every 8 weeks thereafter. A subset of evaluations that were recorded and re-rated showed evidence of high interrater reliability (ICC = .96). We used the third item on the HDRS (HDRS_3) to examine extent of suicidal ideation. This item ranged from 0 (absent) to 3 (suicidal ideas or specific suicide plan; see Fig. 1). A fifth response option (attempts at suicide) was available, but this item was not endorsed at baseline. Analyses that controlled for depression severity used mean scores of the 16 HDRS items, excluding the suicide item. Participants in the COM group (M = 6.52; SD = 2.00, Mdn = 7) completed the same number of HDRSs as participants in the ADM group (M = 6.62; SD = 1.95, Mdn = 7, $X^2(13, N = 452) = 10.77$, p = .630).

1.3.2. BDI

The 21-item BDI was completed at each formal assessment along with the HRSD, according the schedule described above. We used the ninth item on the BDI (BDI_9) to examine extent of suicidal ideation; this item ranged from 0 (I don't have thoughts of killing myself) to 3 (I would kill myself if I had the chance; see Fig. 1). Analyses that controlled for depression severity used mean scores of the 20 BDI items, excluding the suicide item. Cognitive therapists also administered the BDIs prior to sessions in weeks during which there were no formal assessments; as a consequence, participants in the COM group completed more BDIs (M = 18.42; SD = 8.59, Mdn = 18) than participants in the ADM group (M = 11.16; SD = 4.82, Mdn = 11, $X^2(38, N = 445) = 135.34$, $p < .001$).

BDI and HDRS scores were imputed at the item level for participants with fewer than 25% of responses missing; we used random forest-based imputation implemented in R with the "missForest" package (Khazanov et al., 2020; Stekhoven, 2013). This method has been shown to outperform other imputation methods, and also generates a single imputed dataset to avoid the need to analyze multiple datasets (Shah et al., 2014). Scores missing more than 25% of responses (12 BDI and 2 HDRS assessments, fewer than .01% of assessments) or the suicide items (3 BDI and 1 HDRS assessment) were excluded. Additionally, the BDI and HDRS suicide items were non-normally distributed and contained a large proportion of 0 values. The scoring anchors also indicated that the intervals between values were not necessarily equivalent (see Fig. 1). We therefore chose to treat these variables as ordinal (Kappelmann et al., 2020).

1.3.3. Composite BDI and HDRS Variable

As the BDI and HDRS suicide items include different response options, and we were also interested in using all available assessments, we first analyzed these items separately. Given the close relationship between the BDI and HDRS suicide items in our sample (see Preliminary Results), we also constructed a composite variable representing suicidal ideation across both measures. To calculate this variable, we first limited our dataset to include only assessments in which both the BDI and HDRS were administered[2]. The frequency of these assessments did not differ across groups, (M = 5.31; SD = 2.14, Mdn = 5, $X^2(12, N = 445) = 8.97$, p = .706). The non-normal distributions of the BDI and HDRS suicide items precluded us from calculating a composite variable using standardized scores (Lavrakas, 2008). Using the same method as a previous study examining change in suicidal ideation across treatment with two single-item measures (Kowal et al., 2014), we summed participants' scores on the two items. The resulting variable ranged from 0 to 7 and, like the original BDI and HDRS suicide items, was treated as ordinal in analyses. Baseline scores on the composite variable were highly correlated with baseline scores on the BDI and HDRS suicide items (both $r_s >$ .88, both $p < .001$). To measure overall depression severity, we standardized and summed the BDI and HDRS mean scores that excluded the suicide items.

1.4. Analyses

1.4.1. Preliminary Analyses

All analyses were calculated in R version 4.0.2 (R Core Team, 2020) and were appropriate for ordinal variables. In preliminary analyses, we examined the relationships between BDI and HDRS suicide and non-suicide items at baseline and across treatment. First, we used Spearman's Rho to calculate the relationships between: (1) the BDI suicide item (BDI_9) and the remaining BDI items at baseline, (2) the HDRS suicide item (HDRS_3) and the remaining HDRS items at baseline, and (3) BDI_9 and HDRS_3 at baseline. Next, we computed standardized residual change scores from intake to 7 months of treatment and assessed the relationships between changes in: (1) BDI_9 and the remaining BDI items, (2) HDRS_3 and the remaining HDRS items, and (3) BDI_9 and HDRS_3.

1.4.2. Primary Analyses

To examine treatment outcome, we utilized Markov Chain Monte Carlo models (MCMC models; Hadfield, 2010), a Bayesian generalized linear mixed model designed for non-continuous outcomes. Analyses were run using the "MCMCglmm" package (Hadfield, 2019). MCMC models were run with time as a continuous variable and random intercepts and slopes for each participant so that the models accounted for attrition within the mixed model framework (Gallop & Tasca, 2009; Ram & Grimm, 2013). Plotting BDI and HDRS total scores, as well as the suicide items, over the 7-month period revealed a logarithmic pattern. Given these patterns, as well as prior evidence that growth models tend to have logarithmic distributions, we modeled the effects of time on the BDI and HDRS suicide items using a logarithmic distribution (Gallop & Tasca, 2009; Limpert et al., 2001; March et al., 2004). As tests for the assumption of proportional odds can incorrectly reject the null hypothesis with larger sample sizes, we followed Harrell's (2015, p. 287) recommendation for evaluating the proportional odds assumption by graphing and examining the vertical constancy of distances between logits.

Primary models were run with all available BDI_9 and HRSD_3 scores. For all analyses, we examined change in suicidal ideation across 7 months of treatment by modeling: 1) Overall change; 2) Differential change depending on assignment to condition (COM versus ADM); 3) Differential change, controlling for change in depression severity.

1.4.3. Sensitivity Analyses

As sensitivity analyses, we reran all models including only participants who endorsed suicidal ideation (a score above 0) at some point during the 7 months of treatment. For models using the individual BDI

[2] As assessments were not always completed on the same day, we included BDI and HDRS scores that were completed within two days of one another.

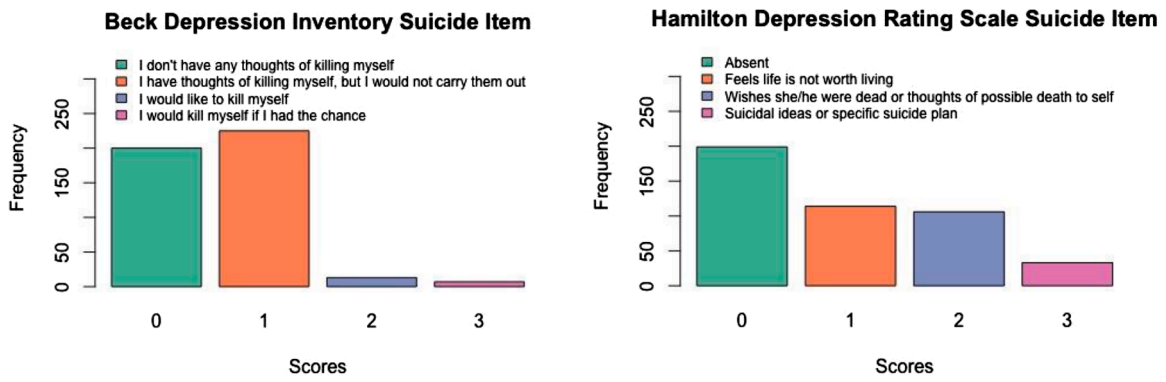

Fig. 1. Baseline scores for the Beck Depression Inventory (BDI) suicide item and the Hamilton Depression Rating Scale (HDRS) suicide item.

and HRSD variables, we ran additional sensitivity analyses to account for the COM group completing more BDIs than the ADM group. For these analyses, we selected the HDRS or BDI completed closest to the end of each month of treatment such that each participant had only one score per month. For these analyses, the number of HDRS assessments across groups did not differ ($M = 5.41$; $SD = 1.50$, $Mdn = 6$; $X^2(7, N = 452) = 5.93$, $p = .549$). The number of BDI assessments was still significantly higher for the COM group ($M = 6.72$; $SD = 1.75$, $Mdn = 7$) than the ADM group ($M = 6.18$; $SD = 1.82$, $Mdn = 7$, $X^2(7, N = 445) = 25.45$, $p < .001$) because participants in the COM group were more likely to have at least one score per month than participants in the ADM group. However, the median number of assessments across groups was the same (7) and the difference in means was much smaller than in the primary analyses (original difference = 7.26; difference in sensitivity analyses = 0.54).

Given prior evidence that antidepressant treatment can increase suicidality in some individuals (Möller et al., 2008), we ran a final set of sensitivity analyses examining differences in elevations in suicidal ideation by group. We first identified individuals who reported no suicidal ideation at baseline on either the BDI_9 or HDRS_3 ($n = 147$). Of these individuals, we identified those who reported any suicidal ideation on either the BDI_9 or HDRS_3 at any point during the 7 months of treatment ($n = 54$; ADM = 29; COM = 25). Lastly, we ran a chi-square test to evaluate whether there was a significant difference between conditions in the number of individuals showing increases in suicidal ideation during treatment.

2. Results

2.1. Preliminary Results

At baseline, BDI_9 and the remaining BDI items were moderately related ($r_s = .42$, $p < .001$), whereas HDRS_3 and the remaining HDRS items were weakly related ($r_s = .10$, $p = .026$). BDI9 and HDRS3 were strongly related at baseline ($r_s = .71$, $p < .001$). Changes in BDI_9 and the remaining BDI items over the first 7 months of treatment were moderately related ($r_s = .41$, $p < .001$), while changes in HDRS_3 and the remaining HDRS items over these 7 months were weakly related ($r_s = .11$, $p = .021$). Finally, changes in BDI_9 and HDRS_3 over the 7 months of treatment were strongly related ($r_s = .56$, $p < .001$).

2.2. Primary Results

Suicidal ideation decreased across the first 7 months of treatment by 21% for BDI_9 (see Table 1, top; OR = .79, $p < .001$) and 25% for HDRS_3 (OR = 0.75, $p < .001$). Suicidal ideation as measured by BDI_9 interacted with condition such that the COM group showed 17% greater reductions during treatment than the ADM group (OR = 0.83, $p < .001$; See Fig. 2). This interaction was significant when controlling for the effect of time (OR = 0.75, $p < .001$), indicating that suicidal ideation decreased across treatment, and controlling for the effect of condition (OR = 1.65, $p = .008$), indicating that individuals randomly assigned to the COM group had higher baseline scores on the BDI_9 than those

Table 1
Markov Chain Monte Carlo (MCMC) models examining change in suicidal ideation across 7 months of treatment.

Outcomes using all available measures	Beck Depression Inventory Item 9					Hamilton Depression Rating Scale Item 3				
	n	Log odd	Odds ratio	95% CI	*p* value	*n*	Log odd	Odds ratio	95% CI	*p* value
Overall change	445	-0.24	0.79**	0.74, 0.83	<.001	452	-0.29	0.75**	0.68, 0.80	<.001
Differential change depending on condition	445	-0.18	0.83**	0.75, 0.91	<.001	452	-0.07	0.93	0.84, 1.04	.184
Differential change, controlling for change in depression severity	445	-0.12	0.88**	0.81, 0.97	.002	452	-0.03	0.97	0.88, 1.09	.520
Outcomes including only participants with suicidal ideation during treatment										
Overall change	296	-0.26	0.77**	0.75, 0.80	<.001	322	-0.36	0.70**	0.63, 0.78	<.001
Differential change depending on condition	296	-0.14	0.87**	0.81, 0.92	<.001	322	-0.05	0.95	0.87, 1.03	.262
Differential change, controlling for change in depression severity	296	-0.13	0.88*	0.79, 0.98	.014	322	-0.03	0.97	0.84, 1.11	.680
Outcomes using one score per month										
Overall change	445	-0.54	0.58**	0.50, 0.68	<.001	452	-0.93	0.39**	0.33, 0.48	<.001
Differential change depending on condition	445	-0.37	0.69**	0.55, .84	<.001	452	-0.77	0.46*	0.19, 0.95	.034
Differential change, controlling for change in depression severity	445	-0.34	0.71*	0.52, 0.96	.018	452	-0.15	0.86	0.63, 1.14	.282

Note. CI = Confidence Interval.
* $p < .05$.
** $p < .01$.

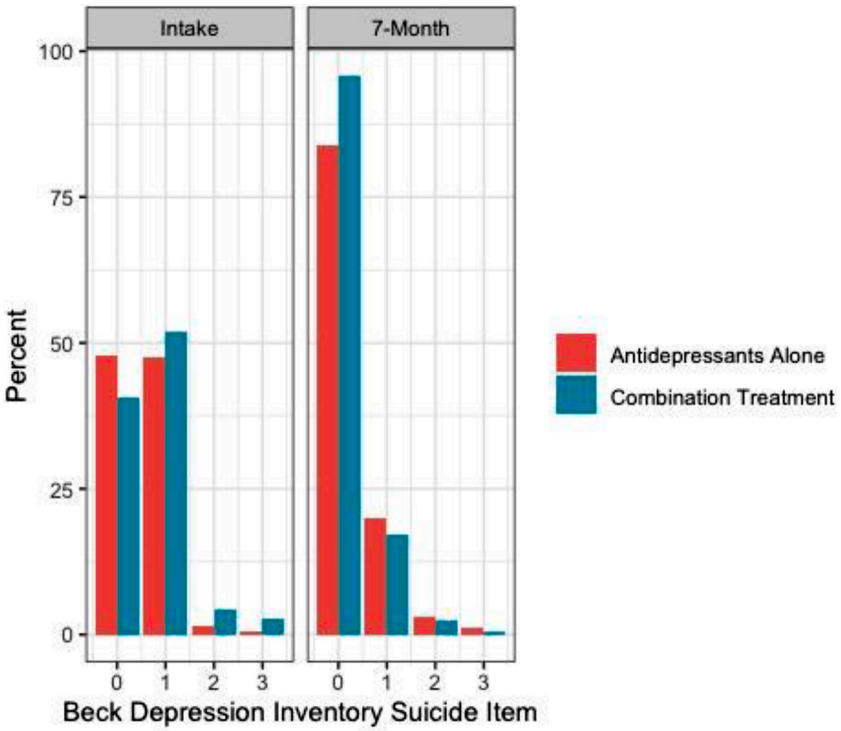

Fig. 2. Percentages of Beck Depression Inventory suicide item scores at baseline and after 7 months of treatment.

randomly assigned to the ADM group. The pattern of results was similar for HDRS_3, but the effect was smaller (the COM group showed 7% greater reductions than the ADM group) and not statistically significant (OR = 0.93, $p = .184$; See Fig. 3).

Suicidal ideation as measured by BDI_9 continued to interact with condition such that the COM group showed 12% greater reductions than the ADM group over and above changes in depression severity across treatment (OR = 0.88, $p = .002$). This interaction was significant when controlling for the effect of time (OR = 0.86, $p = .008$), condition (OR = 1.52, $p = .012$), the remaining BDI items at baseline (OR = 1.10, $p < .001$), and the interaction between the remaining BDI items and time (OR = 1.00, $p = .066$). The pattern of results was similar for HDRS, but the effect was smaller (the COM group showed 3% greater reductions than the ADM group) and not statistically significant (OR = 0.97, $p = .520$).

For the composite BDI and HDRS variable, suicidal ideation

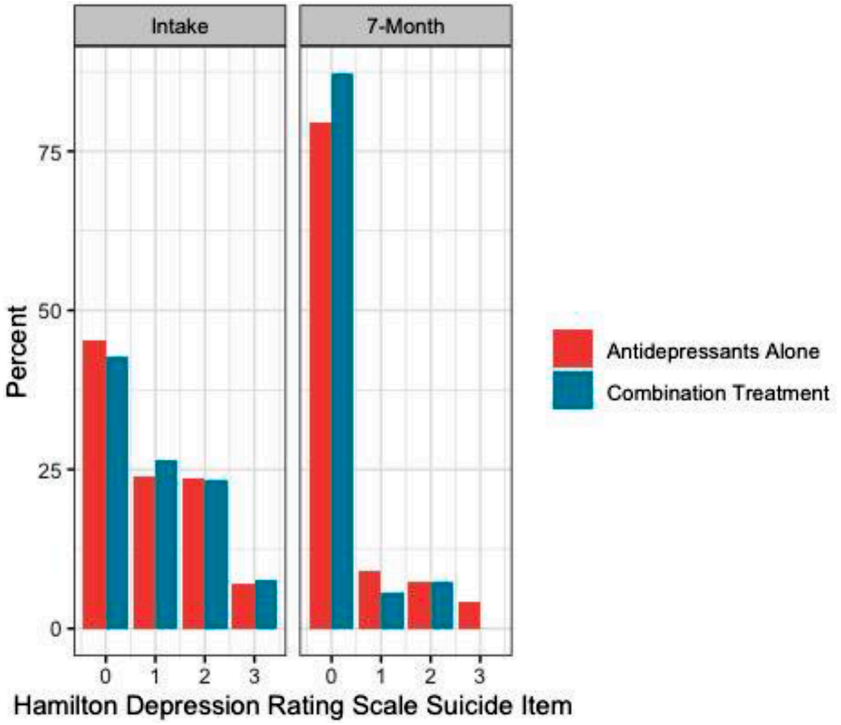

Fig. 3. Percentages of Hamilton Depression Rating Scale suicide item scores at baseline and after 7 months of treatment.

decreased across treatment by 31% (OR = 0.69, $p < .001$). Suicidal ideation interacted with condition such that the COM group showed 9% greater reductions during treatment than the ADM group (OR = 0.91, $p = .008$; See Fig. 4). When controlling for changes in depression severity across treatment, this effect became marginally significant (OR = 0.97, $p = .082$). This analysis controlled for the effect of time (OR = 0.91, $p < .001$), condition (OR = 1.11, $p = .022$), depression severity as measured by a composite score of the remaining BDI and HDRS items at baseline (OR = 1.72, $p < .001$), and the interaction between this depression severity composite score and time (OR = 1.09, $p < .001$).

2.3. Results of Sensitivity Analyses

The results described above replicated when including only participants who endorsed suicidal ideation at some point during treatment. For this group, suicidal ideation decreased across treatment by 23-30% (see Table 1, middle, and Table 2, bottom; all ORs < 0.78, all $p < .001$). For BDI_9, the COM group showed 13% greater reductions than the ADM group without controlling for depression severity, and 12% greater reductions than the ADM group over and above changes in depression severity (both ORs < 0.89, both $p < .015$). For HDRS_3, the pattern of results was similar, but the effect was not significant (both ORs > 0.94, both $p < .681$). For the composite BDI and HDRS variable, the COM group showed 9% greater reductions than the ADM group both with and without controlling for depression severity (both ORs = 0.91, both $p < .037$).

These results were similar when including only one BDI or HDRS score per participant per month. Suicidal ideation decreased across treatment by 42-61% (see Table 1, bottom; both ORs < 0.59, both $p < .001$). For both the BDI_9 and HDRS_3, the COM group showed 41% and 54% greater reductions than the ADM group, respectively (both ORs < 0.70, both $p < .035$). This interaction remained significant for the BDI_9 when controlling for depression severity (OR = .71, $p = .018$), but declined to non-significance for the HDRS_3 (OR = .86, p = .282). These analyses were not conducted for the composite variable, as frequencies of this variable did not differ across groups. Finally, we determined that the number of individuals reporting increases in suicidal ideation during treatment did not differ by group (ADM = 29, COM = 25; $X^2(1, N = 452) = 0.22$, $p = .639$).

Table 2
Markov Chain Monte Carlo (MCMC) models examining change in suicidal ideation across 7 months of treatment.

Outcomes using all available measures	Composite Beck Depression Inventory & Hamilton Depression Rating Scale Suicide Variable				
	n	Log odd	Odds ratio	95% CI	*p* value
Overall change	445	-0.37	0.69**	0.66, 0.73	<.001
Differential change depending on condition	445	-0.09	0.91**	0.85, 0.98	.008
Differential change, controlling for change in depression severity	445	-0.03	0.97	0.94, 1.03	.082
Outcomes including only participants with suicidal ideation during treatment					
Overall change	352	-0.34	0.71**	0.65, 0.78	<.001
Differential change depending on condition	352	-0.10	0.91**	0.85, 0.97	.004
Differential change, controlling for change in depression severity	352	-0.10	0.91*	0.86, 0.97	.036

Note. CI = Confidence Interval.
* $p < .01$.
** $p < .01$.

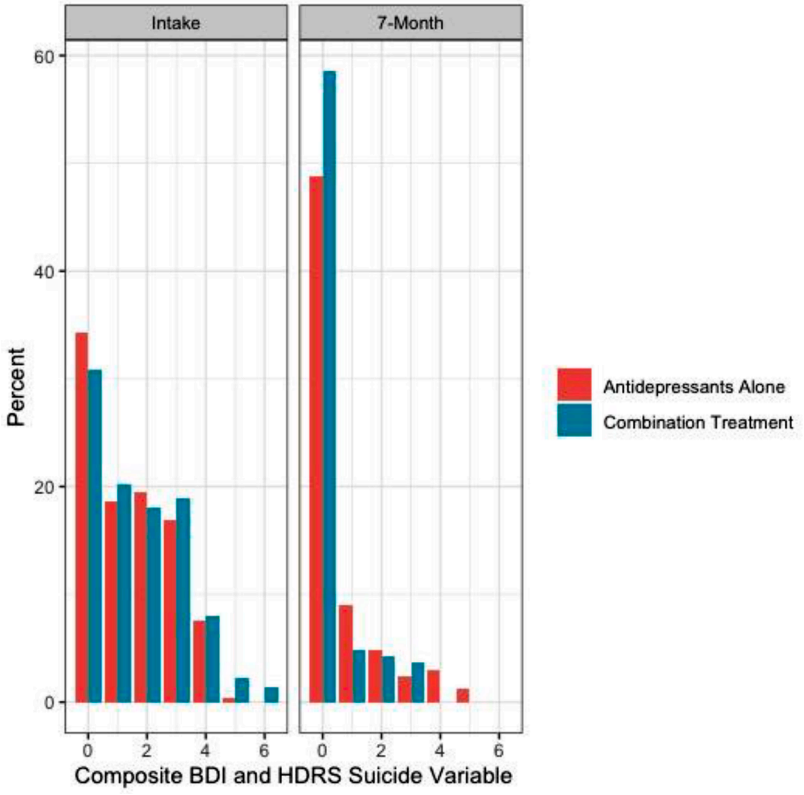

Fig. 4. Percentages of the composite Beck Depression Inventory and Hamilton Depression Rating Scale suicide variable at baseline and after 7 months of treatment.

3. Discussion

We examined whether adding cognitive therapy to antidepressant medications led to greater reductions in suicidal ideation relative to medications alone in a secondary analysis of a randomized clinical trial of adults with depression. Suicidal ideation decreased for all participants across 7 months of treatment. When suicidal ideation was measured with the BDI or a composite score based on the BDI and HDRS, participants receiving both cognitive therapy and medications showed 9-17% greater reductions in suicidal ideation relative to those receiving only medications. When controlling for changes in depression severity, this effect remained significant for the BDI and became marginally significant for the composite score based on the BDI and HDRS. When suicidal ideation was measured by the HDRS, the pattern was similar, but the effect was smaller and not statistically significant. These effects held when restricting to only those participants who reported suicidal ideation during treatment and when adjusting the number of assessments across groups to be more similar. When restricting to only participants who reported suicidal ideation during treatment, the suicidal ideation composite score continued to significantly interact with study condition even when controlling for changes in depression severity.

Our findings suggest that combined treatment with both cognitive therapy and antidepressant medications may improve suicidal ideation to a greater extent than medications alone. These results extend those of March and colleagues (2004; 2007) by showing that combined treatment resulted in greater reductions in suicidal ideation than medications alone in adults as well as adolescents. These results held even though multiple antidepressants were prescribed and augmented using best clinical practice, and participants included only those with recurrent or chronic depression. While combined treatment produces only slightly better outcomes for depressed individuals overall (Khan et al., 2012), this effect may be more pronounced for individuals with higher suicidal ideation, as well as individuals with more severe depression and elevated distress and anhedonia (Hollon et al., 2014; Khazanov et al., 2020; Thase et al., 1997). Pending further replication, combined treatment may be recommended to individuals pursuing treatment for depression who report suicidal ideation.

Finally, we determined that the number of individuals reporting no suicidal ideation at baseline, but increases in suicidal ideation during treatment, did not differ by group. This finding suggests that adding cognitive therapy to antidepressant medication treatment does not appear to change rates of elevated suicidal ideation during treatment. Our finding differs from March and colleagues (2007), who reported higher rates of treatment-emergent suicidal events in adolescents treated with antidepressant medications only compared with combined treatment. Their definition of suicidal events differed substantially from ours, however, and included suicide attempts and preparatory action toward suicidal behavior in addition to suicidal ideation. This difference may also be explained by the much higher rates of treatment-emergent suicidal ideation in adolescents compared to adults (Stone et al., 2009).

3.1. Explanation of Results

There are several possible explanations for our findings. First, it may be that adding any type of psychotherapy to medication treatment reduces suicidal ideation for depressed individuals due to common factors addressed in psychotherapy that are associated with reduced suicidal ideation, like increased social support, greater hope for the future, or decreased depression severity (Calati et al., 2019; Hawton et al., 2013). Second, cognitive therapy may be specifically helpful for reducing suicidal ideation when added to treatment with medications because of its focus on negative cognitions relevant to suicidal ideation, like hopelessness and intolerance of distress (Leavey & Hawkins, 2017). Third, as the present study did not include an attention-control condition, differences between groups may be due to the additional therapeutic contact provided to participants who received psychotherapy instead of the psychotherapy itself.

While we found that suicidal ideation improved more with combined treatment than with medications alone when measured by the BDI and a composite score based on the BDI and HDRS, analyses of the HDRS alone were not significant. These findings may be attributed to differences between these two measures. It is possible that the self-reported BDI captured changes in suicidal ideation to a greater degree than the clinician-rated HDRS because participants were more willing to report their recent suicidal thoughts when rating items on their own than when discussing them with a clinician (Kaplan et al., 1994). It is also possible that the BDI suicide item prompts, which are more straightforward and specifically describe different intensities of suicidal thoughts, captured suicidal ideation more accurately than the HDRS (Green et al., 2015). Much research has described the shortcomings of the HDRS, even though it is the most widely used clinician-rated depression measure (Bagby et al., 2004; Gibbons et al., 1993). The HDRS suicide item is a good example of these limitations – the clearest being that two of the prompts are double-barreled (e.g., "suicidal ideas or specific suicide plan"). On the other hand, participants may have perceived and reported a decrease in suicidal ideation on the BDI that was not noticeable or reliable enough to be captured on the HDRS.

Finally, the differences in suicidal ideation that we observed between treatment groups may be artifactual. For example, the group receiving both cognitive therapy and medications may have shown greater reductions in suicidal ideation on the BDI because they completed more BDIs than the medication only group, whereas both groups completed the same number of HDRSs. While our results held when adjusting the number of assessments across groups to be more similar and when controlling for depression severity using the other BDI items (which did not differ across groups at baseline), minor group differences in the number of assessments completed remained significant in these analyses. Additionally, we were unable to account for the possibility that the act of completing more BDIs decreased reports of suicidal ideation over time. Lastly, higher baseline scores on the BDI suicide item in the group receiving both cognitive therapy and medications relative to the medications only group may have led to the greater changes in this group over time; importantly, we controlled for this difference in all analyses.

3.2. Strengths and Limitations

This present study has multiple strengths. Ours is the first analysis of a randomized clinical trial comparing combined treatment with both cognitive therapy and medications to treatment with medications alone in an adult sample. Unlike many depression treatment trials, participants with high levels of suicidal ideation were included; only participants who required immediate hospitalization were excluded. We used robust statistical analyses appropriate for ordinal variables and replicated our results after restricting them to only participants who endorsed suicidal ideation during the study and adjusting the number of assessments across groups.

The study also had several limitations. First, we conducted a secondary analysis of a randomized clinical trial designed to examine depression outcomes and relied on single-item measures of suicidal ideation. About a third of participants did not report suicidal ideation at any point in the study, and the majority of participants reported only mild levels of suicidal ideation. Second, while we found significant differences in treatment groups when suicidal ideation was measured with the BDI and the composite score based on the BDI and HDRS, these differences did not reach significance when suicidal ideation was measured with the HDRS. Third, the combined group receiving both cognitive therapy and antidepressant medications completed more BDIs, and also had higher scores on the BDI suicide item at baseline, than the medication only group. Although we adjusted for these differences in analyses, they remain limitations of the data. Finally, the study did not include therapy-only, pill placebo, or attention control conditions. Therefore, we cannot be certain that treatment itself, versus the effect of

time, reduced suicidal ideation. Additionally, we do not know whether adding cognitive therapy to medications reduced suicidal ideation versus greater therapeutic contact time, any exposure to cognitive therapy, or the addition of any intervention. Despite these limitations, this study is the first to test whether combined treatment reduces suicidal ideation to a greater degree than medications alone in adults, and suggests that recommending combined treatment to individuals with suicidal ideation may result in better outcomes.

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CRediT authorship contribution statement

Gabriela K Khazanov: Conceptualization, Writing - original draft, Writing - review & editing. **Colin Xu:** Data curation, Writing - review & editing. **Steven D Hollon:** Project administration, Supervision, Writing - review & editing. **Robert J DeRubeis:** Project administration, Supervision. **Michael E Thase:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors report no conflicts of interest directly related to this work.

Michael E Thase reports the following relationships over the past three years:

Consultant—Acadia, Akili, Alkermes, Allergan, Clexio, Gerson Lehrman Group, Guidepoint Global, Janssen Pharmaceuticals, Jazz Pharmaceuticals, H. Lundbeck A/S, Otsuka Pharmaceutical Co., Pfizer, Sage Pharmaceuticals, Seelos Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company

Employment—His spouse, Dr. Diane Sloan, is Senior Medical Director of Peloton Advantage, which does business with several pharmaceutical companies

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