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Differential change in specific depressive symptoms during antidepressant medication or cognitive therapy

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ABSTRACT

Cognitive therapy and antidepressant medications are effective treatments for depression, but little is known about their relative efficacy in reducing individual depressive symptoms. Using data from a recent clinical trial comparing cognitive therapy, antidepressant medication, and placebo in the treatment of moderate-to-severe depression, we examined whether there was a relative advantage of any treatment in reducing the severity of specific depressive symptom clusters. The sample consisted of 231 depressed outpatients randomly assigned to: cognitive therapy for 16 weeks ($n = 58$); paroxetine treatment for 16 weeks ($n = 116$); or pill placebo for 8 weeks ($n = 57$). Differential change in five subsets of depressive symptoms was examined: mood, cognitive/suicide, anxiety, typical-vegetative, and atypical-vegetative symptoms. Medication led to a greater reduction in cognitive/suicide symptoms relative to placebo by 4 weeks, and both active treatments reduced these symptoms more than did placebo by 8 weeks. Cognitive therapy reduced the atypical-vegetative symptoms more than placebo by 8 weeks and more than medications throughout the trial. These findings suggest that medications and cognitive therapy led to different patterns of response to specific symptoms of depression and that the general efficacy of these two well-validated treatments may be driven in large part by changes in cognitive or atypical-vegetative symptoms.

Introduction

The general efficacy of psychotherapeutic and somatic interventions for the treatment of adult depression has been well established (Hollon, Jarrett, et al., 2005). Relatively little published work, however, has examined whether one active treatment is superior to another in reducing the severity of specific symptoms or symptom clusters associated with depression. This would be particularly important if, for example, a given patient presented with symptoms that were experienced as distressing, such as insomnia; interfered with functioning, such as poor concentration or hypersomnia; or were considered to be potentially life threatening, such as suicidal ideation. Collecting a body of data that captures this information across different treatment modalities is crucial to the ultimate success of efforts to personalize interventions to meet the unique needs of individuals with depression. Furthermore, information about differential symptom reduction could inform research aimed at identifying the mechanisms through which a given treatment is exerting its therapeutic benefits.

The majority of the prior work examining change in specific symptoms during the treatment of depression has focused on response to one or more medications versus placebo (e.g., Farabaugh et al., 2010; Mallinckrodt et al., 2007). Only a small number of prior studies have compared medications and active psychotherapy regarding change on a wide array of depressive symptoms. DiMascio et al. (1979), for example, compared amitriptyline, interpersonal psychotherapy, combination treatment, and a nonscheduled treatment control, and found amitriptyline to produce an earlier response for symptoms of insomnia and a later response for mood and apathy symptoms. In contrast,

Abbreviations: ADM, Antidepressant medications; CT, Cognitive therapy; PBO, Placebo.

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patients who received interpersonal psychotherapy had an earlier response for apathy and mood symptoms. Rush, Kovacs, Beck, Weissenburger, and Hollon (1981) compared imipramine to cognitive behavioral therapy and found no differences between the treatments in reducing the severity of any of the depressive symptoms that were measured. The quality of the pharmacotherapy provided in the Rush et al. study, however, has been questioned (Meterissian & Bradwejn, 1989).

More recently, Stewart and Harkness (2012) re-analyzed data from the Treatment for Depression Collaborative Research Program (TDCRP). They observed that imipramine produced steeper, more accelerated symptom reductions for sleep symptoms compared to cognitive therapy, as well as steeper, more accelerated symptom reduction for cognitive-affective symptoms and somatic symptoms compared to psychotherapy (collapsing across cognitive therapy and interpersonal psychotherapy). Stewart and Harkness observed no significant differences, however, between imipramine and placebo in the reduction of any symptom factor. As the authors note, the adequacy of the implementation of cognitive therapy in the TDCRP has been questioned (Jacobson & Hollon, 1996).

In the current study, we examined data from a recent randomized, placebo-controlled, parallel group trial comparing cognitive therapy, antidepressant medications and placebo (DeRubeis et al., 2005; Hollon, DeRubeis, et al., 2005). In contrast to the data from the TDCRP, used in the Steward and Harkness report, the data used in the current study originated from a clinical trial of moderate-to-severely depressed patients in which the average magnitude of change in cognitive therapy was nearly the same as that observed in antidepressant medications following acute treatment (DeRubeis et al., 2005) and in which cognitive therapy evidenced a relapse-prevention effect during follow-up (Hollon, DeRubeis, et al., 2005). An additional advantage of the current study is that because of the number of measurement occasions in the trial from which we drew the data, we are able to examine predicted symptom levels both early in treatment (at 4 weeks) as well as at the termination of the placebo condition (at 8 weeks). The American Psychiatric Association's (2010) practice guidelines for the treatment of Major Depression suggest that the adequacy of initial treatment response should be assessed between weeks 4 and 6 of treatment. The choice to examine symptom improvement after 4 weeks corresponds to the beginning of this period. A separate study of data from this trial observed that the sequence of change in cognitive and vegetative symptoms did not differ between medications and cognitive therapy, however no differences in the magnitude of symptom reduction were examined (Bhar et al., 2008). Our aim in the current report was to build on previous findings and to explore differences between the active treatment conditions and placebo in the reduction of a broad range of depressive symptoms.

Materials and methods

A full description of the participant characteristics and treatment protocols, along with the main treatment outcome findings, has been reported elsewhere (DeRubeis et al., 2005; Hollon, DeRubeis, et al., 2005). Briefly, the original sample consisted of 240 depressed outpatients (diagnosed using the Structured Clinical Interview for DSM-IV Diagnosis; First, Spitzer, Gibbon, & Williams, 2001) who achieved scores of 20 or higher over two consecutive weeks on a modified 17-item version of the HRSD (Hamilton, 1960). Patients were excluded if they evidenced a history of psychosis or bipolar disorder, active substance abuse, the presence of another Axis I disorder that was judged to be primary, or previous non-response to study medications. Also excluded were patients who met criteria for antisocial, borderline, or schizotypal personality disorders (personality disorder diagnoses were made at intake using the Structured Clinical Interview for DSM-III_R Personality Disorders, SCID-II; Spitzer, Williams, Gibbon, & First, 1990) as well as patients judged to be at such a high risk for suicide that immediate hospitalization was deemed necessary. The study was conducted in accordance with the Declaration of Helsinki, study protocols were approved by the institutional review boards at each of the two study sites (the University of Pennsylvania and Vanderbilt University), and all patients provided written informed consent after study procedures were fully explained.

Treatments

Patients entering the trial were randomly assigned to receive cognitive therapy (CT, $n = 60$) antidepressant medication (ADM, $n = 120$), or pill-placebo (PBO, $n = 60$). The medication used was paroxetine, augmented with lithium or desipramine after Week 8 if response to paroxetine alone was not adequate. Twice the number of subjects were randomized to the ADM condition to allow responders to be randomized a second time to continuation medication versus medication withdrawal as part of a follow-up study of relapse (Hollon, DeRubeis, et al., 2005). The two active treatments, CT and ADM, were provided for 16 weeks. By design, participants were kept on pill-placebo for only 8 weeks due to ethical considerations before being offered active medications.

Measurement

The measures used in the current analyses were derived from a modified 24-item version of the HRSD, which allows for collection of both typical and atypical vegetative symptoms of depression (Reimherr et al., 1998; Thase, Frank, Mallinger, Hamer, & Kupfer, 1992). Previous studies have utilized a variety of methods to divide the HRSD into component symptoms, ranging from the use of each individual item (Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010), to the formation of symptom clusters based on prior theory and research (Serretti, Mandelli, Lattuada, Cusin, & Smeraldi, 2002), to the use of formal factor analytic procedures (Stewart & Harkness, 2012). Although factor analyses of several versions of the HRSD have been published (Cole et al., 2004; Shafer, 2005), we are aware of no published analysis of the version used in this study. We used a combination of strategies to divide the HRSD for the current analyses. Because typical and atypical symptoms historically have been conceptualized as distinct entities associated with different subtypes of depression, we created one depressive symptom set to represent the atypical-vegetative symptoms of depression, including hypersomnia and weight gain/increased appetite (the only atypical symptoms of depression that are measured by the HRSD), and one to represent typical-vegetative symptoms. The remaining HRSD symptoms were factor analyzed as follows: the average score for each item was calculated across two separate intake assessments for each participant, and the resulting dataset was subjected to common factor analysis (Gorsuch, 1983). Factor loadings of >0.30 were considered to be salient. The scree test suggested that 3 factors could be extracted. The three factors were, Cognitive/Suicide Symptoms (suicidal ideation, guilt, helplessness, hopelessness, and worthlessness), Mood Symptoms (depressed mood, anhedonia, and loss of energy), and Anxious-Somatic Symptoms (psychomotor agitation, psychic anxiety, somatic anxiety, and hypochondriasis). See Supplemental Material for additional detail regarding these analyses.

Statistical analyses

In order to assess whether particular depressive symptoms changed differentially over time in the two treatments, separate

hierarchical linear models (HLM) were performed examining symptom levels across time for each of the five symptom sets. Using this approach, each subject's growth curve and outcome score at the end of treatment is estimated from a collection of patient-specific parameters (slopes and intercepts). These are treated as having been randomly sampled from a population of individuals. For all models, an unstructured covariance structure was assumed in order to model the correlation between intercepts and slopes. Because we are interested in drawing inferences about the effects of treatments on symptoms only for those patients who received at least one dose of the treatment, patients were included in the models if they received at least one assessment after treatment was initiated ($N = 116$ in the ADM condition, $N = 58$ in the CT condition; $N = 57$ in the PBO condition). In the original publication of the treatment outcome data, the authors reported a significant site-by-treatment interaction (DeRubeis et al., 2005). Consequently, site and the site-by-treatment interaction terms were added to all models described below. For each model, scores at intake on the relevant symptom set were added to the model as a covariate. In addition, each model included, as a covariate, a variable that represented the sum of the patient's scores on all of the remaining items of the HRSD to account for global baseline depression severity.

Standard assumptions of HLMs require model residuals to be normally distributed (Raudenbush & Bryk, 2002). The plausibility that our data met this assumption was considered by a visual examination of the histograms of the outcome variables at several assessment points, and was verified by inspection of model residuals. Three of the five symptom sets, Typical-v, Atypical-v, and Cognitive/Suicide Symptoms, failed to meet this assumption. Their distributions conformed more closely to a Poisson distribution; consequently, these three symptom sets were examined using mixed effects Poisson regression models (Hedeker & Gibbons, 2006). In order to model the trajectory of symptom levels over time properly, several specifications of the temporal variable were examined: the standard linear representation of time, the log transformation of time (shifted to account for time = 0), the square root transformation of time, and the addition of a quadratic time variable. The best fitting model was chosen for each symptom set by examining the Aikake Information Criteria, a measure of model fit. Standard HLM analyses (for normally distributed data) were performed using SAS Version 9.1 PROC MIXED. Analyses of mixed effects Poisson models were performed using SAS Version 9.1 PROC NLMIXED (SAS Institute Inc, Cary, NC).

Primary outcomes

Differential changes in symptoms were assessed with models of data up to two time points: a) Week 4, representing early rapid change in symptoms; and b) Week 8, representing the magnitude of change up to the point at which the placebo condition was terminated. We opted to estimate two separate models because we did not want data collected after Week 4 to influence the estimates of symptoms at this time point. Exploratory analyses were conducted to examine change in ADM and CT through 16 weeks for those symptom clusters for which a significant treatment effect was observed at Weeks 4 or 8. Differences between treatments were assessed for each symptom set using model-estimated symptom scores at the time-point of interest (Week 4 and Week 8 for the primary analyses, and Week 16 for the exploratory analyses). To correct the type-I error rate for the multiple symptom sets under examination, the alpha level was set to 0.01 for all analyses (representing $p = 0.05/5$ symptom clusters).

Results

Primary analyses

Outcomes Through 4 Weeks. We assessed whether antidepressant medication, cognitive therapy, or pill-placebo treatments differed from each other in early rapid symptom reduction (represented by estimated scores at 4 weeks) for each of the five symptom sets. Each symptom set was estimated in a separate statistical model. Table 1 displays the results of these analyses, along with information regarding the manner in which the variable representing time was modeled, and the distributional assumptions that were implemented in the respective models. The Cognitive/Suicide ($F(2, 229) = 8.79$, $p < 0.001$) and the Atypical-v ($F(2, 229) = 8.29$, $p < 0.001$) symptom sets were the only two sets for which the three treatments differed at 4 weeks. Post-hoc comparisons of the Cognitive/Suicide symptoms revealed that ADM was superior to PBO by Week 4, $t(229) = 4.19$, $p < 0.001$, $d = 0.68$, 99%CI[0.25, 1.10]. Using the pre-specified threshold, neither the CT vs. PBO, $t(229) = 2.38$, $p = 0.02$, $d = 0.44$, 99%CI

Table 1
Differential change in symptoms between cognitive therapy, medications, and placebo.

Predictor symptom set	Time[a]	Distribution[b]	$F/(DF)$	p	d: ADM-PBO[c] (99%CI)	d: CT-PBO[c] (99%CI)	d: ADM-CT[c] (99%CI)
Week 4:							
Mood	Square root	Normal	0.75 (2, 216)	0.47	0.08 (−0.34, 0.49)	0.22 (−0.26, 0.70)	−0.15 (−0.56, 0.27)
Cognitive/suicide	Square root	Poisson	8.79 (2, 229)	<0.001**	0.68** (0.25, 1.10)	0.44 (−0.04, 0.93)	0.22 (−0.20, 0.63)
Anxiety	Log	Normal	0.87 (2, 222)	0.42	0.21 (−0.21, 0.63)	0.11 (−0.37, 0.59)	0.10 (−0.32, 0.51)
Typical-v	Linear	Poisson	0.81 (2, 229)	0.44	0.16 (−0.26, 0.58)	0.23 (−0.25, 0.71)	−0.07 (−0.49, 0.34)
Atypical-v	Linear	Poisson	8.29 (2, 229)	<0.001**	−0.42** (−0.84, 0.00)	0.21 (−0.27, 0.69)	−0.61** (−1.03, −0.18)
Week 8:							
Mood	Quadratic	Normal	3.29 (2, 218)	0.04	0.37 (−0.05, 0.79)	0.06 (−0.42, 0.54)	0.31 (−0.11, 0.72)
Cognitive/suicide	Square root	Poisson	10.71 (2, 229)	<0.001**	0.75** (0.32, 1.18)	0.50** (0.01, 0.99)	0.23 (−0.19, 0.64)
Anxiety	Quadratic	Normal	1.47 (2, 215)	0.23	0.23 (−0.19, 0.65)	0.01 (−0.47, 0.49)	0.22 (−0.19, 0.64)
Typical-v	Square root	Poisson	0.33 (2, 229)	0.72	0.08 (−0.34, 0.50)	−0.04 (−0.53, 0.44)	0.12 (−0.29, 0.54)
Atypical-v	Square root	Poisson	6.45 (2, 229)	0.002**	−0.09 (−0.50, 0.33)	0.50** (0.01, 0.99)	−0.57** (−0.99, −0.15)

Note. Values represent the treatment effect estimated from separate HLM models predicting symptom scores either at Week 4 or Week 8. Estimates at Week 4 were derived from models that included data through Week 4 only.

** Crosses the a-priori defined threshold $p < 0.01$.

[a] Values represent the manner in which the time variable was modeled in the analyses.

[b] Values represent the nature of the distributional assumptions of the multilevel models that were performed: Normal = normally distributed data (standard HLM techniques); Poisson = Poisson distributed data (hierarchical Poisson models).

[c] Values represent Cohen's d effect size estimates of the difference in symptoms between treatments modeled at the time point of interest. Positive values indicate that the treatment on the left lowered the symptoms more than did the treatment on the right. Negative values indicate the opposite (the treatment on the right lowered symptoms more than did the treatment on the left). 99% Confidence Intervals are displayed in parentheses and reflect the corrected alpha threshold of 0.01.

[−0.04, 0.93], nor the ADM vs. CT, $t(229) = 1.34$, $p = 0.18$, $d = 0.22$, 99%CI[−0.20, 0.63] contrasts were significant.

Regarding the Atypical-v findings, contrasts revealed that both CT and PBO were superior to ADM in the treatment of Atypical-v symptoms through four weeks ($t(229) = -3.76$, $p < 0.001$, $d = -0.61$, 99%CI[−1.03, −0.18] for ADM vs. CT; $t(229) = -2.60$, $p = 0.01$, $d = -0.42$, 99%CI [−0.84, 0.00,] for ADM vs. PBO). No difference was observed between CT and PBO ($t(229) = 1.14$, $p = 0.25$, $d = 0.21$, 99%CI[−0.27, 0.69]) during this period. In order to understand this effect further, the Atypical-v symptom domain was decomposed into its two components, items reflecting hypersomnia and items assessing weight gain/increased appetite, and each was modeled separately. There was a significant effect of treatment on the reduction of hypersomnia symptoms, $F(2, 229) = 14.27$ $p < 0.001$. Both CT and PBO were superior to ADM in the reduction of hypersomnia by 4 weeks ($t(229) = -4.92$, $p < 0.001$; $d = -0.79$, 99%CI[−1.22, −0.36] for CT vs. ADM; and $t(229) = -3.31$, $p = 0.001$; $d = -0.53$, 99%CI[−0.96, −0.11] for PBO vs. ADM. The CT and PBO conditions did not differ from each other, $t(229) = 1.63$, $p = 0.10$; $d = 0.30$, 99%CI[−0.18, 0.79]. The difference between the treatments on weight gain/increased appetite was not significant, $F(2, 229) = 0.17$, $p = 0.85$.

Outcomes Through 8 Weeks. We assessed whether antidepressant medication, cognitive therapy, or pill-placebo treatments differed from each other in the magnitude of symptom reduction (represented by estimated scores at 8 weeks) for each of the five symptom sets. The results of these analyses are also presented in Table 1. Again, the Cognitive/Suicide ($F(2, 229) = 10.71$, $p < 0.001$) and the Atypical-v ($F(2, 229) = 6.45$, $p = 0.002$) symptom sets were the only two sets for which the three treatments differed. Post-hoc comparisons of the Cognitive/Suicide symptoms revealed that at 8 weeks, both active treatments were superior to placebo in reducing these symptoms ($t(229) = 4.62$, $p < 0.001$, $d = 0.75$, 99%CI[0.32, 1.18] for the ADM vs. PBO comparison; $t(229) = 2.70$, $p = 0.008$, $d = 0.50$, 99%CI[0.01, 0.99] for the CT vs. PBO comparison). ADM and CT did not differ significantly from each other ($t(229) = 1.41$, $p = 0.16$, $d = 0.23$, 99%CI[−0.19, 0.64]). The levels of Cognitive/Suicide symptoms over time in each treatment are displayed in Fig. 1. Fig. 2 displays the model-estimated symptoms at Weeks 4 and 8.

Regarding the Atypical-v symptoms, post-hoc contrasts revealed that by Week 8, CT was superior both to PBO, $t(229) = 2.68$, $p = 0.008$, $d = 0.50$, 99%CI[0.01, 0.99], and to ADM, $t(229) = -3.54$, $p < 0.001$, $d = -0.57$, 99%CI[−0.99, −0.15]. There was no difference observed between ADM and PBO regarding

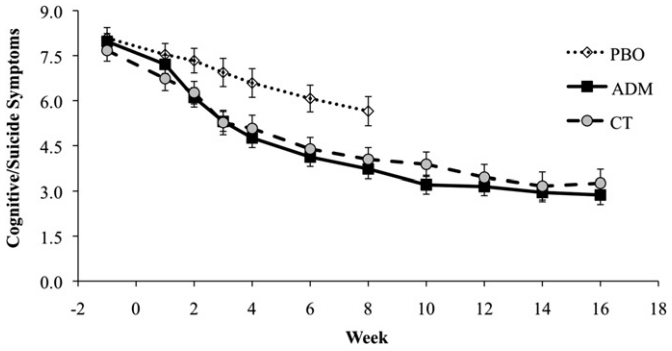

Fig. 1. Values represent cognitive/suicide symptoms at each assessment point. For display purposes only, and to ensure equal Ns at each time-point, missing values were interpolated when possible. In the case of attrition, last observations were carried forward. A total of 12% of data points were missing: 8% from PBO, 12% from ADM, 15% from CT. Error bars represent ±1 standard error. I=Intake, PBO = placebo; ADM = antidepressant medication; CT = cognitive therapy.

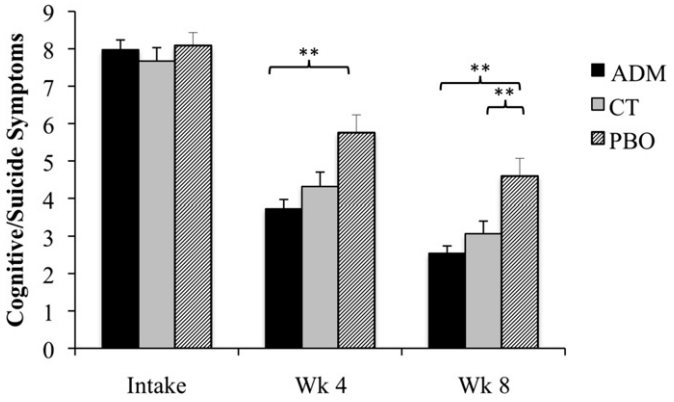

Fig. 2. Bars represent scores for the cognitive/suicide symptom set at intake, and model-estimated scores at Week 4 and Week 8 for the cognitive therapy, medication, and placebo conditions. Error bars represent 1 standard error. CT = cognitive therapy, ADM = antidepressant medication, PBO = placebo, Wk = Week. ** Indicates statistical significance at the a-priori threshold, $p < 0.01$.

Atypical-v symptoms at Week 8, $t(229) = -0.54$, $p = 0.59$, $d = -0.09$, 99%CI[−0.50, 0.33]. Examining this effect further, there was a significant effect of treatment on the reduction of hypersomnia symptoms, $F(2, 229) = 12.00$ $p < 0.001$. CT was superior to ADM ($t(229) = -4.90$, $p < 0.001$; $d = -0.79$, 99%CI[−1.22, −0.36] and PBO ($t(229) = 3.27$, $p = 0.001$; $d = 0.61$, 99%CI[0.12, 1.10] in the reduction of hypersomnia symptoms. ADM and PBO did not differ, $t(229) = -1.34$, $p = 0.18$; $d = -0.22$, 99%CI[−0.64, 0.20]. The difference between the treatments on weight gain/increased appetite was not significant, $F(2, 229) = 0.01$, $p = 0.99$. The levels of Atypical-v and atypical sleep symptoms over the course of the trial are displayed in Fig. 3a and b, respectively. Fig. 4 displays the model-estimated atypical symptoms at Weeks 4 and 8.

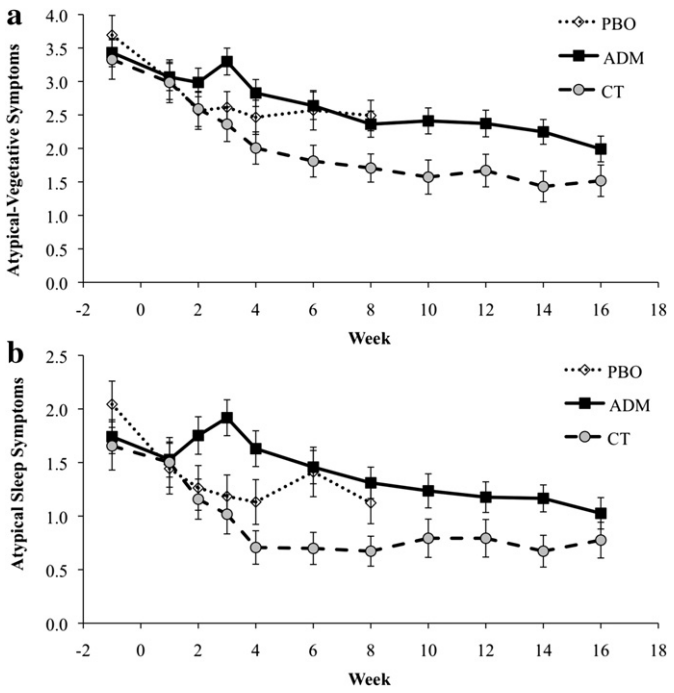

Fig. 3. Values represent atypical-vegetative (3a) and atypical sleep (3b) symptoms at each assessment point. For display purposes only, and to ensure equal Ns at each time-point, missing values were interpolated when possible. In the case of attrition, last observations were carried forward. A total of 12% of data points were missing: 8% from PBO, 12% from ADM, 15% from CT). Error bars represent ±1 standard error. I=Intake, PBO = placebo; ADM = antidepressant medication; CT = cognitive therapy.

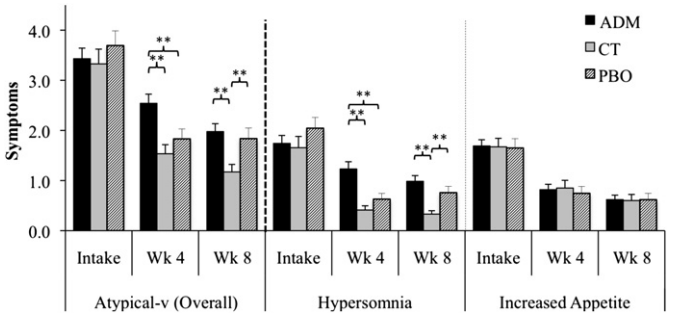

Fig. 4. Bars represent scores for the atypical-vegetative symptom set at intake and model-estimated scores at Week 4 and Week 8 for the cognitive therapy, medication, and placebo conditions. Intake scores and estimated Week 4 and Week 8 scores for the two components of the Atypical-v symptom set, hypersomnia and increased appetite/weight gain, are also displayed. Error bars represent 1 standard error. CT = cognitive therapy, ADM = antidepressant medication, PBO = placebo, Wk = Week. ** Indicates statistical significance at the a-priori threshold $p < 0.01$.

Secondary analyses

In order to examine potential differences in symptom change by the end of the acute treatment phase (16 weeks), estimated treatment (CT and ADM) scores were evaluated up to Week 16 for both the Cognitive/Suicide and Atypical-v symptoms sets. For both symptom sets, the patterns observed at Week 8 were maintained through Week 16. That is, the two active treatments did not differ with respect to the Cognitive/suicide symptom sets at Week 16, $t(172) = 1.33$, $p = 0.18$, *Cohen's* $d = 0.21$, 99%CI[−0.20, 0.63]. Also like the analyses at Week 8, CT was superior to ADM in reducing Atypical-v symptoms at Week 16, $t(172) = -3.44$, $p < 0.001$; *Cohen's* $d = -0.55$, 99%CI[−0.97, −0.13]. CT was again superior to ADM in the reduction of hypersomnia symptoms ($t(172) = -3.23$, $p = 0.002$; $d = -0.52$, 99%CI[−0.94, −0.10]. The difference between the two treatments on weight gain/increased appetite did not cross the pre-specified significance threshold ($t(172) = -2.10$, $p = 0.04$; $d = -0.34$, 99%CI[−0.75, 0.08].

In order to determine whether the superiority of CT over ADM for Atypical-v symptoms might be explained by possible iatrogenic effects of the medication (i.e., a worsening of symptoms compared to what might be expected from a control intervention), change scores were calculated from subject specific Week 4, Week 8, and Week 16 symptom estimates (from separate models; intake scores were not covaried). For each of the three treatments, the percentage of patients who experienced a worsening of Atypical-v symptoms was calculated. A higher proportion of patients in the medication condition (41.4%) evidenced a worsening of Atypical-v symptoms relative to cognitive therapy (22.4%) and placebo (22.8%) at Week 4 ($\chi^2(1, N = 173) = 5.78$, $p = 0.02$ for ADM vs. PBO; $\chi^2(1, N = 174) = 6.11$, $p = 0.01$ for ADM vs. CT). The medication condition (30.2%) also evidenced a worsening of Atypical-v symptoms relative to the CT condition (15.5%) at Week 8 ($\chi^2(1, N = 174) = 4.40$, $p = 0.04$). At Week 8, the medication and placebo (22.8%) conditions no longer differed in the percentages of patients who experienced a worsening of symptoms ($\chi^2(1, N = 173) = 1.03$, $p = 0.31$).

Discussion

We investigated differences among cognitive therapy, antidepressant medication, and placebo in the reduction of specific symptoms of depression during the acute treatment of outpatients with moderate to severe depression. Of the five subsets of depressive symptoms examined in this report, differential treatment effects relative to placebo were observed for only two of the symptom clusters, cognitive/suicide and atypical-vegetative symptoms. This suggests that the general efficacy of medications and cognitive therapy for the treatment of depression may be driven in large part by changes in one or both of these particular symptoms. By contrast, the active treatments did not differ from placebo in the reduction of the other symptom clusters, one of which, mood symptoms, included the two symptoms of depression that are given primacy in the DSM-IV system: depressed mood and loss of interest.

Although much disagreement exists in the literature regarding the structure of symptom inventories for depression (see, e.g., Bagby, Ryder, Schuller, & Marshall, 2004; Cole et al., 2004), the five clusters of depressive symptoms examined in the current report are similar in nature to those that have been identified in past examinations (Bagby et al., 2004; Cole et al., 2004; Shafer, 2005). Moreover, several of the symptom constellations identified in the current work have important clinical and theoretical implications. For example, high levels of anxiety, captured herein by the Anxiety cluster, have recently emerged as a potentially important predictor of response to pharmacotherapy for depression (Domschke, Deckert, Arolt, & Baune, 2010; Fava et al., 2008). By contrast, the cognitive symptom set taps elements important to the cognitive theory of depression, from which cognitive therapy was derived (Beck, Rush, Shaw, & Emery, 1979). That is, change in negative cognitions, such as excessive guilt, helplessness, hopelessness, and worthlessness, is hypothesized to be a potentially important causal mechanism through which full symptom recovery is produced (DeRubeis et al., 1990; Garratt, Ingram, Rand, & Sawalani, 2007). Finally, the typical- and atypical-vegetative symptom sets were formed a-priori specifically to retain the important theoretical distinction between the typical and atypical symptoms of depression. The typical-vegetative symptoms have long been associated with melancholic depression whereas the atypical-vegetative symptoms are a part of the atypical classification (Aarons, Frances, & Mann, 1985; Fink, Bolwig, Parker, & Shorter, 2007). Although individuals with melancholic depression tend to share several symptoms in common with those diagnosed with atypical depression, the typical- and atypical-vegetative symptoms are among the symptoms that most clearly differentiate between the two sub-classifications (Angst, Gamma, Benazzi, Ajdacic, & Rössler, 2007). By examining whether and to what degree medications, cognitive therapy, and placebo differ in the reduction in each of the five symptom sets, we aim not only to inform treatment decisions but also to identify possible mechanisms of action that might differ among the three treatment conditions.

The results of the current study indicated that paroxetine, the medication used in this study, had specific efficacy for cognitive and suicidal symptoms early in treatment. By the end of eight weeks of treatment, both active treatments had evidenced specific benefit for these symptoms, relative to placebo. As Hollon, Stewart, & Strunk (2006)'s note, previous comparative trials of medications and active psychotherapies (DeRubeis et al., 1990; Imber et al., 1990; Rector, Bagby, Segal, Joffe, & Levitt, 2000) have typically concluded that the two treatment modalities lead to similar reductions in negative and/or dysfunctional cognitions during acute treatment. The findings in the current study are consistent with this prior work, and together they suggest that changes in the cognitive symptoms of depression are not unique to cognitive therapy. One explanation for this pattern is that these symptoms do not represent mechanisms of action that differ between medications and cognitive therapy. Indeed, some suggest that changes in the cognitive processing of affective information is a critical mechanism through which antidepressant medications operate (Harmer, Goodwin, & Cowen, 2009). Our findings do not rule out the

possibility, however, that the cognitive symptoms act as mechanisms in one treatment, and are a consequence of change in symptoms in the other (DeRubeis et al., 1990; Hollon, DeRubeis, & Evans, 1987). Regardless, these findings clearly point to a potentially important difference between active treatments and placebo treatments for depression. Future work should attempt to determine how each of the active treatments was able to alter the cognitive symptoms of the illness whereas placebo treatment was not, despite comparable reductions in many of the other symptoms. Such work could provide valuable insight into the mechanisms that differ between active and sham treatments for depression.

The results of several analyses in the current study also converged to indicate that the atypical vegetative symptoms, primarily hypersomnia, were differentially responsive to the two active treatment modalities. The mechanism underlying this effect, however, appears to have changed over time in the trial. That is, atypical symptoms appeared to be somewhat placebo-responsive during the first four weeks of treatment. During this period, paroxetine was inferior both to placebo and to cognitive therapy, suggesting a possible iatrogenic effect regarding the atypical symptoms early in treatment for this medication. Beyond this period, cognitive therapy yielded specific benefits in regard to atypical symptoms, as evidenced by superior improvement on these symptoms relative to medication and to placebo at Week 8. Cognitive therapy maintained its advantage relative to paroxetine for these symptoms through the end of acute treatment.

Changes in the atypical symptoms of depression have received little attention in prior studies (see, e.g., Vaishnavi et al., 2006 for an exception) despite the fact that atypical depression was originally identified on the basis of differential response to specific pharmacological treatments (Aarons et al., 1985) and is one of the two officially recognized sub-classifications of depression in the DSM (American Psychiatric Association, 2000). In the current study, the superiority of cognitive therapy relative to paroxetine and placebo for the treatment of atypical vegetative symptoms of depression may have resulted from specific components of cognitive therapy. That is, the close monitoring by the patient of his or her activity and the use of specific cognitive and behavioral interventions that are aimed at combating inactivity, may have resulted in a reduction of sedentary activity and a reduction of time spent in bed. Such findings are consistent with the conclusions of Barber & DeRubeis (1989) who suggest that the primary mechanism of action for cognitive therapy might be the provision of compensatory skills with which patients can combat and cope with negative automatic thoughts and maladaptive behaviors. By contrast, somnolence is one of the known side effects of paroxetine, the primary antidepressant medication used in this study (Caley & Weber, 1993). This could account for our finding that patients in the medication group experienced a worsening of the atypical vegetative symptoms relative to placebo in the first few weeks of treatment. However, as cognitive therapy was superior not only to medications but also to placebo by the 8th week of treatment, our findings cannot be explained entirely by iatrogenic effects of medication on atypical vegetative symptoms.

Limitations

There are several considerations that may limit the conclusions that can be drawn from the current study. First, measurements of the symptom sets were not ideal; the internal consistency of three of the sets (Mood symptoms, Anxiety symptoms, and Typical-vegetative symptoms) fell below widely accepted standards, although most fell within the ranges that have been reported previously for the 17-item HDRS total score (Supplemental Information). These symptom sets were retained in the current analyses for exploratory purposes; however, the low internal consistencies likely limited the sensitivities of the tests of differences between the two treatments. Future investigations of these symptoms, with more psychometrically sound instruments and larger sample sizes, would be in order before more definitive conclusions about the lack of difference between the two treatments in the reduction of these symptoms can be made. Second, two of the symptom sets, Typical-vegetative symptoms and Atypical-vegetative symptoms, were formed prior to conducting the factor analysis. This decision was made in order to allow for the examination of changes in these symptoms separately over the course of the trial - an examination that, to our knowledge, is the first of its kind. Third, due to the design of the study from which we drew the data, twice the number of participants received medications compared with those who received cognitive therapy or placebo. As such, contrasts between cognitive therapy and placebo had less power than contrasts that included patients who received medications. Finally, the results reported from this study can be expected to generalize only to outpatients diagnosed with moderate to severe depression treated for 16 weeks with the specific therapeutic modalities employed in this study. Paroxetine, along with other similar selective serotonin reuptake inhibitors, frequently produces side effects that mimic atypical symptoms of depression (e.g., hypersomnolence, daytime tiredness, carbohydrate craving, weight gain, etc). It is possible, indeed likely, that different antidepressant medications with different side-effect profiles, such as buproprion, would produce a different pattern of findings. It is our hope that future studies will be conducted that compare different combinations of active treatments for the degree to which they can reduce specific depressive symptoms. Only when such a knowledge base exists will the field be able to recommend with confidence a specific treatment in order to target a specific patient complaint.

Conclusions

These findings, if replicated or sustained when combined with similar efforts through meta-analysis, suggest that paroxetine shows specific benefit in reducing cognitive symptoms of depression (including suicidal ideation) by the 4th week of treatment and that both cognitive therapy and paroxetine show specific efficacy in reducing these symptoms by the 8th week. That both active treatments outperformed placebo for these symptoms suggests that important differences exist in the mechanisms of response between active and placebo treatments for depression. The mechanisms of the active treatments may lead individuals to think differently about themselves and their situations. The mechanisms of the placebo response do not appear to do so to the same extent. In addition, cognitive therapy may be particularly effective at reducing atypical vegetative symptoms of depression. For patients for whom these symptoms are interfering with life functioning, cognitive therapy might be considered a first line treatment. For those patients who experience an increase in these symptoms while taking medications, it is possible that cognitive therapeutic techniques might be helpful in addressing these symptoms.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brat.2013.03.010.

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