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Dysfunctional Attitudes as a Moderator of Pharmacotherapy and Psychotherapy for Chronic Depression

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Abstract

Objective—Individuals with chronic depression exhibit heterogeneous responses to treatment. Important individual differences may therefore exist within this particularly difficult to treat population that act as moderators of treatment response.

Method—The present study examined whether pretreatment levels of dysfunctional attitudes (DA) moderated treatment response in a large sample of chronically depressed individuals. Data were taken from the Research Evaluating the Value of Augmenting Medication with Psychotherapy (REVAMP) treatment study – a multi-site treatment and augmentation study of

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808 chronically depressed individuals. REVAMP comprised two phases: 1) a 12-week open-label antidepressant trial and 2), a subsequent phase, in which phase 1 non-remitters (N=491) were randomized to either receive an ongoing medication algorithm alone, medication plus cognitive behavioral analysis system of psychotherapy, or medication plus brief supportive psychotherapy.

Result—In phase 1, compared to the pharmacotherapy response of patients with lower DA scores, the response for patients with higher DA scores was steeper, but leveled off towards the end of the phase. In phase 2, DA predicted a differential response in the medication only arm, but not in the two psychotherapy+medication conditions. Specifically, in the phase 2 medication only condition, patients with higher DA improved while those with lower DA scores did not.

Conclusion—These results indicate that the relation between DA and treatment response in chronic depression is complex, but suggest that greater DA may be associated with a steeper reduction and/or better response to pharmacotherapy.

Keywords

dysfunctional attitudes; predictor; treatment; response; chronic depression

Chronic forms of depression, which encompass approximately 25–30% of cases of major depression (Kessler et al., 1993), are associated with greater functional impairment and disability than non-chronic major depression (Gilmer et al., 2005; Klein, Shankman & Rose, 2006; Satyanarayana et al., 2009). Although few studies have directly compared the treatment response of chronic and non-chronic depression, treatment response rates tend to be lower in chronic depression and may require modifications such as a longer duration of pharmacotherapy or combining pharmacotherapy with psychotherapy in order to achieve an adequate response (de Maat et al., 2007; Fournier et al., 2009; Keller et al., 2000; Klein, 2010).

Approximately half of chronically depressed individuals do not respond to an adequate treatment trial, suggesting significant heterogeneity in treatment efficacy (Keller et al., 1998; Thase et al., 1996). Thus, there may be important individual differences in patients with chronic depression that moderate treatment response. In recent years, researchers and clinicians have increasingly acknowledged the importance of identifying moderators of response and the National Institute of Mental Health (NIMH) listed this as a top objective in their recent strategic plan (Strategy 3.4; NIMH, 2008).

Researchers have used several definitions of the term “moderator.” Some have used the term to indicate a simple ‘predictor’ of treatment response (i.e., the variable has a ‘main effect’ on treatment response). An example may be the finding that compared to those with a later age of onset, those with an earlier onset have a worse response to medication A. However, recent studies argue that the term should only be used for a pretreatment or baseline variable that identifies *for whom* or under *what conditions* a particular treatment choice matters (i.e., the variable ‘interacts’ with the multilevel treatment arm variable; Kraemer et al., 2006; Kraemer et al., 2002; Simon & Perlis, 2010). An example may be the finding that patients with an earlier age of onset respond preferentially to treatment A compared to treatment B, whereas for those with a later onset, treatments A and B are equivalent. As an aim of this study is to examine both types of variables, we will use the term ‘predictor’ to describe the former and the term ‘moderator’ to describe the latter.

Pretreatment level of dysfunctional attitudes (DA; Dobson & Breiter, 1983) is a potential predictor and/or moderator of response to depression treatment. DA reflects maladaptive beliefs (or schemas) that are posited to identify individuals vulnerable to depression (Beck et al., 1979). DA levels are higher in individuals with depression compared to euthymic

controls (Hamilton & Abramson, 1983) and individuals with chronic depression have reported higher DA levels than those with nonchronic depression, even after adjusting for levels of depressive symptoms (Klein et al., 1988; Ley et al., 2011; Riso et al., 2003). Beck's cognitive-behavioral theory of depression hypothesizes that individual differences on DA may predict response to depression treatment (Beck et al., 1979) and numerous studies have found that individuals with higher levels of DA exhibit a poorer response to medication and psychotherapy (Hamilton & Dobson, 2002; Pedrelli et al., 2008; Peselow et al., 1990; Simons et al., 1995; Sotsky et al., 1991; Williams et al., 1990) although some have failed to find effects (Fava et al., 1994). Taken together, these studies suggest that DA may represent a predictor of treatment response.

Very few studies have examined whether DA represents a moderator of treatment response and the results of existing studies are quite mixed. Some studies have found that DA does not moderate treatment response (e.g., cognitive therapy vs. treatment-as-usual; Bockting et al., 2006). Other studies have yielded conflicting findings. Miller et al. (1990) randomized individuals to receive medication alone or medication plus cognitive-behavioral therapy (CBT; i.e., combination treatment). Individuals high on DA responded best to combination therapy and those low on DA had comparable response to both treatments. In the large NIMH Collaborative Treatment Study, which randomized patients to CBT, Interpersonal Psychotherapy (IPT), medication (imipramine), or pill placebo, DA was a moderator of treatment response (Sotsky et al., 1991). However, the effect was due to patients with *low* DA exhibiting a superior response to CBT and imipramine compared to placebo; those with high DA exhibited comparable responses to the different treatments (see Blatt et al., 1995).

There are several gaps in the literature regarding whether DA is a predictor and/or moderator of treatment for depression. First, moderator studies are typically underpowered and thus failures to find effects may reflect Type II errors (Hollon et al., 2002; Simon & Perlis, 2010). Second, many studies allocated patients to treatments based on clinical decision, rather than randomizing patients to particular treatments. Third, studies have typically examined moderation using ordinary least squares (OLS) regression instead of techniques such as random coefficient modeling, which allow for missing observations and examination of quadratic (as well as linear) treatment response. Finally, most previous studies were with admixture samples of chronic and nonchronic depressed individuals. As noted above, studies have shown that treatment response of chronic and non-chronic depression appears to differ (Klein, 2008) and chronically depressed individuals report higher levels of DA (Ley et al., 2011; Riso et al., 2003).

To address these concerns, the present study sought to examine the moderating and/or predictive effects of DA using data from a large randomized controlled study of chronically depressed individuals, the Research Evaluating the Value of Augmenting Medication with Psychotherapy (REVAMP) treatment study (Kocsis et al., 2009). This study enrolled 808 chronically depressed individuals into a 12-week open-label antidepressant trial (phase 1). Patients not achieving remission in phase 1 were enrolled in phase 2 and randomized to one of three conditions; 1) medication switch or augmentation (MEDS) alone, 2) MEDS plus cognitive behavioral analysis system of psychotherapy (CBASP), an interpersonally oriented variant of CBT specifically designed for individuals with chronic depression (Keller et al., 2000; McCullough et al., 2000), or 3) MEDS plus brief supportive psychotherapy (BSP; Markowitz et al., 2008). Of patients completing phase 1, 22.3% remitted. In phase 2, 15.0% of patients remitted although neither adjunctive psychotherapy (CBASP or BSP) significantly improved outcome over and above MEDS alone (Kocsis et al., 2009).

For several reasons, the REVAMP design was well-suited for examination of the moderating effects of DA. First, the two treatment phases allowed for a test of whether DA is a predictor

of medication response (phase 1) and a differential predictor (or moderator) of three treatment strategies (phase 2). Second, the comparison of MED+CBASP and MED+BSP controlled for nonspecific psychotherapeutic factors that most psychotherapies share (e.g., empathy, understanding). If DA moderated MED+CBASP outcome, we would be able to examine whether this effect was specific to CBASP or applied to psychotherapies more generally. Third, the frequent (biweekly) depressive symptom assessments during each phase permitted examination of moderation using random coefficients modeling, a more advanced statistical method than OLS regression. Fourth, the study of chronically depressed patients could inform treatment recommendations for this less treatment responsive subtype of depression. A final advantage of the REVAMP dataset was that it focused on patients with a history of failed treatment, a population that has not been examined extensively in the literature (Anderson & Tomenson, 1995). Identifying moderators within treatment non-responders could inform treatment enhancement, thus minimizing risks of dropout and clinical deterioration associated with continued treatment failures (Leykin et al., 2007).

Based on the aforementioned findings of elevated DA as a predictor of treatment response (e.g., Pedrelli et al., 2008; Simons et al., 1995) we hypothesized that individuals with higher DA would respond more poorly to medication in phase 1. Hypotheses for DA as a moderator in phase 2 were unclear as the literature provided little guidance about DA as a moderator of differential treatment response in chronically depressed individuals who have previously not responded to medication. Thus, the phase 2 analyses were considered exploratory.

Method

Overview of Design

Kocsis et al. (2009) provide a more detailed description of the REVAMP design and methods (see Figure 1 for consort chart). Conducted between 2002 and 2006, REVAMP consisted of two 12-week phases. During phase one, 808 chronically depressed individuals were assigned to receive an antidepressant medication according to a pharmacotherapy algorithm (Thase & Rush, 1997) that closely paralleled the one used in the STAR*D study (Fava et al., 2003). Patients who did not achieve remission were randomized into phase 2. Remission was defined as a) = 60% reduction in the 24-item Hamilton Depression Scale [HAM-D], b) a HAM-D score less than 8, and c) no longer meeting DSM-IV criteria for MDD for two consecutive visits during weeks 6 through 12.

In phase 2, participants who did not respond or only partially responded to phase 1 treatment (N=491) were randomly assigned to one of three treatment cells in a 2:2:1 ratio – CBASP + MEDS : BSP + MEDS : MEDS alone. In all three cells, nonresponders received the next step medication in the pharmacotherapy algorithm, whereas partial responders remained on their phase 1 medication augmented with another medication (e.g., lithium) as per the algorithm.

Participants

Recruitment involved outreach to clinicians and advertising at eight academic sites. All patients had a current DSM-IV major depressive episode for at least 4 weeks and unremitted depressive symptoms for more than 2 years, as assessed by the Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 1995). Patients met criteria for major depression with antecedent dysthymic disorder (double-depression), chronic major depression, or recurrent major depression with incomplete recovery – three forms of chronic depression shown to be comparable on nearly every meaningful clinical variable (McCullough et al., 2003). Patients were between 18 and 75 and scored at least 20 on the HAM-D at baseline.

Exclusion criteria were pregnancy; previous CBASP treatment; failure of at least 4 of the treatment steps in the pharmacotherapy algorithm; a serious, unstable, or terminal medical illness that would compromise study participation; current diagnosis of any psychotic disorder; history of bipolar disorder; dementia; principal diagnosis of posttraumatic stress disorder, anorexia, bulimia, or obsessive-compulsive disorder; antisocial, schizotypal or severe borderline personality disorder; and current alcohol or other substance-related dependence disorder (except nicotine dependence) requiring detoxification. Patients with substance use disorders were enrolled if they agreed to participate in Alcoholics Anonymous or chemical dependence counseling and to implement a sobriety plan in conjunction with study treatment. Each participant gave informed consent and the study was conducted in compliance with each site's IRB.

Treatments

Pharmacotherapy

The pharmacotherapy algorithm followed empirically derived algorithms (e.g., the Texas Medication Algorithm Project; Beevers et al., 2007; Crimson et al., 1999) and comprised a sequence including two selective serotonin reuptake inhibitors (SSRIs; sertraline hydrochloride and escitalopram oxalate) and newer alternatives (e.g., bupropion hydrochloride, venlafaxine hydrochloride). Protocol specified minimum and maximum doses, speed of dosage escalation, and trial lengths. Patients were evaluated every 2 weeks. To minimize attrition, a patient intolerant to a medication during the first 4 weeks could move to the next level of the sequence (e.g., from sertraline to escitalopram). Pharmacotherapists provided minimal psychotherapeutic intervention and were supervised bimonthly by senior pharmacotherapists to ensure adherence to procedures. During phase 2, pharmacotherapy sessions were audiotaped and reviewed for adherence to guidelines.

CBASP—CBASP is a highly structured therapy in the family of cognitive and behavioral therapies. It differs from CBT in its focus on a structured interpersonal problem-solving algorithm and by viewing maladaptive cognitions more in the context of their contribution (or lack of contribution) to desired interpersonal outcomes than in terms of their validity. Although similar to interpersonal psychotherapy in its focus on interpersonal problems, it is more structured, emphasizes teaching a specific approach to interpersonal problem-solving (i.e., Situational Analysis), assigns homework, makes extensive use of structured problem-solving, and includes transferential elements (McCullough, 2000; 2002). Patients randomized to CBASP+MEDS in phase 2 received CBASP twice weekly during weeks 1 through 4 and weekly during weeks 5–12, with the option for a second session in weeks 5–8 if they had not mastered situational analysis. Therapists and supervisors were trained and certified by the developer of CBASP, James McCullough, Ph.D. Therapists were required to have at least 2 years of clinical experience after their psychiatric residency or completing a PhD program, or to have had 5 years of experience after completing a masters in social work degree. Therapists met with site supervisors weekly. Therapy sessions were videotaped, and McCullough and the site supervisors monitored protocol adherence and performance using a CBASP Therapist Adherence Rating Scale based on the manual (McCullough, 2001).

BSP—Defined in an unpublished treatment manual (John C. Markowitz and Michael H. Sacks, 2002), BSP emphasizes the nonspecific or “common” factors assumed to be important ingredients across psychotherapies, including reflective listening, empathy, evoking affect, therapeutic optimism, and acknowledgment of patients' assets (Frank, 1971; Rogers, 1951). To differentiate BSP from CBASP and other psychotherapies, specific interpersonal, cognitive, behavioral, and psychodynamic interventions were strictly proscribed. Paralleling the CBASP condition, patients received 16 to 20 BSP sessions during the 12 weeks of treatment. BSP therapists' professional degrees, clinical experience,

training, and supervision were comparable to those of the CBASP therapists. The certification and training procedures were led by John C. Markowitz, M.D. (Markowitz et al., 2008).

Adherence Monitoring and Phase 2 Attendance—Adherence monitoring procedures are described in Kocsis et al., (2009). Phase 2 adherence ratings were conducted on 84 BSP, 68 CBASP, and 52 pharmacotherapy sessions. Only one CBASP session was rated as inadequately adherent to protocol. Patients assigned to BSP and CBASP attended a mean (SD) of 13.1 (7.0) and 12.5 (6.6) therapy sessions, respectively. The mean (SD) numbers of pharmacotherapy visits in phase 2 were 5.4 (1.4), 5.3 (1.5), and 5.2 (1.5) in the CBASP +MEDS, BSP+MEDS, and MEDS-only groups, respectively.

Measures

Dysfunctional Attitudes—DA was assessed using the Dysfunctional Attitude Scale (DAS; Weissman & Beck, 1978). The DAS is a self-report questionnaire in which respondents rate on a 7-point Likert scale which self-evaluative statements best describe their thinking. The current study used the 40-item short form of the DAS (Form A), which has been shown to correlate with the full DAS ($r=.84$; Nelson et al., 1992). The DAS includes items reflecting such attitudes as need for approval, perfectionism, and avoidance of appearing weak.

The DAS was administered at the phase 1 baseline and the beginning of phase 2. Both administrations demonstrated high internal consistencies (Cronbach's alpha = .94 at both time points) and were highly correlated ($r=.71$, $p < .001$), suggesting high rank order stability. However, because DAS scores were significantly lower at the beginning of phase 2 compared to phase 1, 144.0 vs 129.2, $t(570)=12.35$, $p < .001$, we used the DAS at the beginning of phase 1 for the phase 1 analyses and the DAS at the beginning of phase 2 for the phase 2 analyses (i.e., the more proximal DAS assessment was used for each phase's analysis). Table 1 includes the means and SDs for DAS in phase 1 and 2.

Hamilton Depression Rating Scale—The primary outcome measure was the 24-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967). We chose the 24-item version of the HAM-D because it contains symptoms (e.g., helplessness, hopelessness) particularly prevalent in chronic depression (Klein et al., 1996). Analyses restricted to the 17-item HAM-D yielded nearly identical results. HAM-D's were administered biweekly during both phase 1 and phase 2 by experienced, reliable raters blind to treatment condition. Our group has previously demonstrated high inter-rater reliability on the HRS-D (Manber et al., 2008).

Data Analysis

All tests of moderation were conducted using mixed effects linear regression (Raudenbush & Bryk, 2002) using the software package SAS (version 9.2; SAS Institute, Cary, NC). Our approach hypothesized a growth trajectory for each patient. Individual growth curve (IGC) analysis has several advantages over other repeated measures data analytic strategies. It can: a) account for the hierarchical structure of data (e.g., observations nested within person), b) examine the within person stability or change over multiple assessments rather than being limited to comparisons between pairs of assessments; and c) model each person's slope (i.e., rate of within-person change) and intercept (i.e., estimated 'beginning' of trajectory when the subject entered the study) even if lacking data for all assessment points (Singer & Willett, 2003). Each model included two random effects (intercept and time) and fixed effects for the main effect of DAS (centered based on the mean of subjects in the particular analysis) and the DAS by time interaction. As participants varied in the exact day they came

in for the HAM-D assessment (i.e., the week 2 HAM-D was not always on day 14), we used the days from baseline as our time variable rather than assessment week. The DAS was correlated with baseline HAM-D ($r = .20$, $p < .001$ for phase 1 and $r = .25$, $p < .001$ for phase 2) and age ($r = -.26$, $p < .001$ for phase 1 and $r = -.22$, $p < .001$ for phase 2). We therefore entered age and each phase's respective baseline HAM-D as additional fixed effects covariates (both centered). An identical pattern of results emerged from models not including these covariates.

For the phase 1 analyses, a quadratic effect for time added significantly to a model that only included a linear term because it significantly improved the fit of the phase 1 model (-2 log likelihood difference test, $\chi^2(1) = 77.2$, $p < .001$). The quadratic term for time did not improve the phase 2 model, suggesting only a linear effect in phase 2.

Results

Phase 1: Response to medication

In phase 1, 42 of 808 patients who were enrolled in phase 1 were missing a baseline DAS. Patients with and without a DAS did not differ significantly on any demographic or clinical characteristics. Table 1 shows the demographic and clinical characteristics of the 766 patients in the phase 1 analyses.

The phase 1 IGC model revealed significant main effects for DAS ($b = .06$, $t(1777) = 4.37$, $p < .001$), and time ($b = -.24$, $t(564) = -13.82$, $p < .001$ for linear effect; $b = .001$, $t(564) = 8.82$, $p < .001$ for quadratic effect) suggesting that a higher DAS was associated with higher HAM-D scores throughout phase 1 and that on average, patients' depression improved. Additionally, there were DAS*time interactions (both DAS*time and DAS*time² p -values $< .001$). To follow up this interaction, we conducted simple slopes analyses by recoding the moderator variable (DAS) into two separate conditional moderators representing high and low levels of DAS (Aiken & West, 1991; Holmbeck, 2002). So as not to arbitrarily dichotomize a continuous variable, these analyses create separate 'high DAS' and 'low DAS' conditional moderators where '0' represented 1 SD (35.56 on DAS) above and below the mean on DAS, respectively. Thus, high DAS and low DAS did not represent groups but relative levels on the moderator. Results are presented in Figure 2. The lines for high and low DAS patients had significant linear and quadratic effects, however these effects were stronger for high DAS patients (high DAS: linear – $b = -.31$, $p < .0001$, quadratic – $b = .002$, $p < .001$; low DAS: $b = -.17$, $p < .0001$, quadratic – $b = .0007$, $p < .01$). Figure 2 shows the estimated HAM-D scores for these IGC models. Even though these models corrected for baseline HAM-D, those with high DAS appeared to begin treatment with higher HAM-D scores than those with low DAS, but eventually converged with the low DAS individuals approximately halfway through treatment. By end of phase 1, those with low DAS appeared to continue to improve while those with high DAS leveled off.

Phase 2: Response to psychotherapy plus MEDS vs. MEDS alone

At the beginning of phase 2, ANOVAs comparing patients in the three arms revealed that patients had comparable HAM-D scores, gender, DAS, ethnicity, marital status, education, and employment status (all p 's $> .10$). Those in the MEDS only condition were slightly younger than those in BSP+MEDS (43.7 vs. 47.0; $p < .05$).

To examine whether DAS differentially predicted response, separate models each compared two arms (CBASP+MEDS vs. MEDS only; BSP+MEDS vs. MEDS only; CBASP+MEDS vs. BSP+MEDS). All models included age and HAM-D at the beginning of phase 2 as covariates. In all three models there were significant main effects for DAS and time. Additionally, for the CBASP vs. MEDS only and BSP vs. MEDS only models, there was a

DAS*time*treatment arm interaction (both p -values $<.05$). For the CBASP+MEDS vs. BSP+MEDS model, the DAS*time*treatment arm interaction was not significant ($p=.71$).

To follow-up the three way interactions, we looked at each treatment arm separately (see Table 2 and Figure 3). The BSP+MEDS and CBASP+MEDS arms yielded no DAS*time interactions, but there was a DAS*time interaction in the MEDS only condition. Simple slopes analyses revealed that this was due to high DAS patients improving significantly in the MEDS only condition (i.e., significant negative slope), whereas low DAS patients did not (i.e., non-significant slope). In other words, the DAS*time*treatment arm interactions were driven by the DAS effect in the MEDS only condition.

Discussion

Individuals with chronic depression have heterogeneous responses to antidepressant treatment (Fournier et al., 2009; Harrison & Stewart, 1995; Keller et al., 1998; Klein, 2010). Thus, identifying moderators of treatment for chronically depressed individuals is essential for better patient/treatment matching (Hollon & Ponniah, 2010; Simon & Perlis, 2010). This was the first study to examine whether DA constitutes a predictor and/or moderator of treatment in a large sample of patients with chronic depression. There were several noteworthy findings.

In phase 1 (acute, open label antidepressant treatment), individual differences on baseline DA predicted different patterns of response to pharmacotherapy. Unlike most studies examining DA as a predictor of treatment, we used IGC analyses, allowing more fine grained analysis of the pattern of treatment response. Compared to patients with lower DAS scores, patients with higher DAS scores had a higher level of depressive symptoms at the start of treatment (even though the analyses covaried baseline HRSD), and exhibited a much steeper reduction in depressive symptoms over time. As a result, the two DAS groups converged approximately mid-way through phase 1. Higher DAS patients' responses then appeared to asymptote during the final weeks of phase 1, while patients with lower DAS scores continued to improve. Importantly, this latter observation indicates that the more dramatic gains of the higher DAS patients are not due to a floor effect in the lower DAS group.

These findings provide a more nuanced picture of the relation between DA and treatment response than is evident in the literature. In line with previous studies suggesting that DA predicted poor response (e.g., Hamilton & Dobson, 2002; Pedrelli et al., 2008; Simons et al., 1995), we found that higher DAS scores were associated with higher levels of depressive symptoms over the course of the acute phase (i.e., main effect of DAS). However, it would be misleading to characterize DA simply as a poor prognostic factor, as patients with higher DAS scores exhibited a steeper rate of improvement and finished the phase with depression scores that were only marginally greater than patients with lower DAS scores.

During phase 2 (the randomization phase for patients who did not remit in phase 1), patients improved in all treatment arms: i.e., all three arms had significant negative slopes overall (Kocsis et al., 2009). However, DA appeared to moderate treatment response in this phase, specifically predicting response in the MEDS only arm, but not in the two MEDS + psychotherapy conditions. Somewhat surprisingly, in the MEDS only condition, patients with higher DAS scores improved while those with lower DAS scores did not. However, these results are at least partially consistent with our phase 1 results, where patients with higher DAS scores exhibited a markedly steeper reduction in depressive symptoms than patients with lower DAS scores.

The phase 2 results have clear treatment implications for chronically depressed individuals who fail a prior trial of medication. If the patient has high dysfunctional attitudes, these results suggest that the patient should have their medication switched or augmented, and psychotherapy may not be necessary, at least acutely. If the patient has low dysfunctional attitudes, the present results suggest that, in addition to a pharmacotherapy change, psychotherapy is also indicated. Regarding this last implication, because there was no psychotherapy *without* medication arm in phase 2, we are unable to determine whether the low DAS patients benefited from the combination of medication and psychotherapy or psychotherapy on its own.

There are several possible explanations as to why higher DA scores predicted a better response in the medication only condition in phase 2. One possibility is that the finding may be due to a 'differential sieve' effect (D.F. Klein, 1996; Driessen & Hollon, 2010; Hollon et al., 1991), in that phase 2 differentially retained (or *sieved*) a subgroup of low DAS patients who were particularly medication resistant. Another possibility is that psychosocial factors may play a relatively more important role in the depression of those with low DA, compared to those with high DA (for whom biological factors may play a relatively more important role; Meyer et al., 2004). Assuming that these psychosocial factors are preferentially responsive to psychotherapy as opposed to medication, the lack of psychotherapy in the meds only condition may have led the low DA patients to have a worse response in this arm (and the high DA patients to have comparable response to all three arms).

In phase 2, DAS did not moderate the efficacy of CBASP+MEDS vs. BSP+MEDS. It may be surprising that CBASP had no greater efficacy than BSP for high DAS patients inasmuch as CBASP has its roots in CBT, and DA plays a prominent role in the cognitive model of depression (Beck et al., 1979). However, few data support the idea that individuals with high DA are particularly good candidates for CBT-based therapies relative to other psychotherapies. In the NIMH collaborative depression study, *low* dysfunctional attitudes predicted a better response to CBT compared to placebo-case management and those with high dysfunctional attitudes exhibited comparable responses across all treatment arms (Sotsky et al., 1991). Additionally, Watson et al. (2003) found that CBT and process-experiential therapy were equivalent at reducing dysfunctional attitudes.

This study had numerous strengths including a large, carefully characterized sample; an active psychotherapy comparison condition (BSP) in phase 2 (instead of, for example, a waitlist control; Kendall, et al., 2004); and the ability to examine whether DA predicts acute phase medication treatment and differential treatment in those who did not respond to pharmacotherapy. However, the study findings require interpretation in the light of several limitations. First, REVAMP was not designed to examine whether DA moderates treatment response. Thus, patients in phase 1 were not randomized. Moreover, randomization in phase 2 was not based on DAS scores (although patients in the three treatment arms did not differ on the DAS). Second, the duration of psychotherapy may have been too brief for this sample of chronically depressed individuals. Third, we lacked data on therapist effects. Fourth, phase 2 lacked a psychotherapy only condition, which might have produced a different pattern of results. Fifth, the design of REVAMP was sequential. Thus, entry into phase 2 (and thus the results of phase 2) was dependent on phase 1. Given these limitations, future replications are necessary.

In summary, few studies have identified general predictors or differential moderators of antidepressant treatment response (Simon & Perlis, 2010), and even fewer provide relevant data for patients with chronic depression. The results of this study provide preliminary evidence that for chronically depressed patients, individual differences on DA may predict different patterns of acute phase antidepressant treatment response and differentially

moderate response to subsequent treatments for acute phase non-responders. As large numbers of chronically depressed individuals do not respond to treatment (Keller et al., 1998; 2000; Kocsis et al., 1988), this study contributes to the goal of developing individualized, prescriptive approaches to intervention.

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References

- Aiken, LS.; West, SG. Multiple regression: Testing and interpreting interactions. Thousand Oaks, Ca: Sage Publications, Inc; 1991.
- Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *British Medical Journal*. 1995; 310:1433–38. [PubMed: 7613276]
- Beck, AT.; Rush, AJ.; Shaw, BF.; Emery, G. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.
- Beevers CG, Wells TT, Miller IW. Predicting response to depression treatment: The role of negative cognition. *Journal of Consulting and Clinical Psychology*. 2007; 75:422–31.10.1037/0022-006X.75.3.422 [PubMed: 17563159]
- Blatt SJ, Quinlan DM, Pilkonis PA, Shea MT. Impact of perfectionism and need for approval on the brief treatment of depression: The National Institute of Mental Health Treatment of Depression Collaborative Research Program revisited. *Journal of Consulting and Clinical Psychology*. 1995; 63:125–32. [PubMed: 7896977]
- Bockting CLH, Spinhoven P, Koeter MWJ, Wouters LF, Visser L, Schene AH. Differential predictors of response to preventative cognitive therapy in recurrent depression: a 2-year prospective study. *Psychotherapy and Psychosomatics*. 2006; 75:229–36.10.1159/000092893 [PubMed: 16785772]
- Crismon ML, Trivedi M, Pigott TA, Rush AJ, Hirschfeld RMA, Kahn DA, et al. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on medication treatment of major depressive disorder. *Journal of Clinical Psychiatry*. 1999:142–56.10.1097/00004583-200007000-00021 [PubMed: 10192589]
- de Maat SM, Dekker J, Schoevers RA, de Jonghe F. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: A meta-analysis. *European Psychiatry*. 2007; 22:1–8.10.1016/j.eurpsy.2006.10.008 [PubMed: 17194571]
- Dobson KS, Breiter HJ. Cognitive assessment of depression: Reliability and validity of three measures. *Journal of Abnormal Psychology*. 1983; 92:107–09.10.1037/0021-843X.92.1.107 [PubMed: 6833629]

- Driessen E, Hollon SD. Cognitive behavioral therapy for mood disorders: Efficacy, moderators, and mediators. *Psychiatric Clinics of North America*. 2010; 33:537– 55. [PubMed: 20599132]
- Fava M, Bless E, Otto MW, Pava JA, Rosenbaum JF. Dysfunctional attitudes in major depression. *The Journal of Nervous and Mental Disease*. 1994; 182:45–9. [PubMed: 8277301]
- Fava M, Rush JA, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, et al. Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. *Psychiatric Clinics of North America*. 2003; 26:457–94. [PubMed: 12778843]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis-1 Disorders, Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1995.
- Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R. Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. *Journal of Consulting and Clinical Psychology*. 2009; 77:775–87.10.1037/a0015401 [PubMed: 19634969]
- Frank J. Therapeutic factors in psychotherapy. *American Journal of Psychotherapy*. 1971; 25:350–61. [PubMed: 4936109]
- Gilmer WS, Trivedi MH, Rush AJ, Wisniewski SR, Luther J, Howland RH, et al. Factors associated with chronic depressive episodes: A preliminary report from the STAR-D project. *Acta Psychiatrica Scandinavica*. 2005; 112:425–33.10.1111/j.1600-0047.2005.00633.x [PubMed: 16279871]
- Hamilton EW, Abramson LY. Cognitive patterns and major depressive disorder: a longitudinal study in a hospital setting. *Journal of Abnormal Psychology*. 1983; 92:173–84.10.1037/0021-843X.92.2.173 [PubMed: 6863732]
- Hamilton KE, Dobson KS. Cognitive therapy of depression: Pretreatment patient predictors of outcome. *Clinical Psychology Review*. 2002; 22:875–94.10.1016/S0272-7358(02)00106-X. [PubMed: 12214329]
- Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social Clinical Psychology*. 1967; 6:278–96.
- Harrison, WM.; Stewart, JW. Pharmacotherapy of dysthymic disorder. In: Kocsis, JH.; Klein, DN., editors. *Diagnosis and treatment of chronic depression*. New York, NY: Guilford Press; 1995. p. 124-145.
- Hollon SD, Thase ME, Markowitz JC. Treatment and prevention of depression. *Psychological Science in the Public Interest*. 2002; 3:39–77.10.1111/1529-1006.00008.
- Hollon SD, Shelton RC, Loosen PT. Cognitive therapy and pharmacotherapy for depression. *Journal of Consulting and Clinical Psychology*. 1991; 59:88– 9. [PubMed: 2002147]
- Hollon SD, Ponniah K. A review of empirically supported psychological therapies for mood disorders in adults. *Depression and Anxiety*. 2010; 27:891–932.10.1002/da.20741 [PubMed: 20830696]
- Holmbeck GN. Post-hoc probing of significant moderational and mediational effects in studies of pediatric populations. *Journal of Pediatric Psychology*. 2002; 27:87–96.10.1093/jpepsy/27.1.87 [PubMed: 11726683]
- Keller MB, Gelenberg AJ, Hirschfeld RMA, Rush AJ, Thase ME, Kocsis JH, et al. The treatment of chronic depression. Part 2: A double-blind, randomized trial of sertraline and imipramine. *Journal of Clinical Psychiatry*. 1998; 59:598–607. [PubMed: 9862606]
- Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine*. 2000; 342:1462–1470. [PubMed: 10816183]
- Kendall, PC.; Holmbeck, GN.; Verduin, T. Methodology, design, and evaluation in psychotherapy research. In: Lambert, MJ., editor. *Handbook of psychotherapy and behavior change*. 5. New York, NY: Wiley; 2004. p. 16-43.
- Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity, and recurrence. *Journal of Affective Disorders*. 1993; 29:85–96.10.1016/0165-0327(93)90026-G [PubMed: 8300981]
- Klein DF. Preventing hung juries about therapy studies. *Journal of Consulting and Clinical Psychology*. 1996; 64:81–7. [PubMed: 8907087]

- Klein DN. Classification of depressive disorders in the DSM-V: Proposal for a two-dimension system. *Journal of Abnormal Psychology*. 2008; 117:552–60.10.1037/0021-843X.117.3.552 [PubMed: 18729608]
- Klein DN. Chronic depression: Diagnosis and classification. *Current Directions in Psychological Science*. 2010; 19:96–100.10.1177/0963721410366007
- Klein DN, Kocsis JH, McCullough JP, Holzer CP III, Hirschfeld RMA, Keller MB. Symptomatology in Dysthymic and Major Depressive Disorder. *Psychiatric Clinics of North America*. 1996; 19:41–55.10.1016/S0193-953X(05)70272-0 [PubMed: 8677219]
- Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. *The American Journal of Psychiatry*. 2006; 163:872–80.10.1176/appi.ajp.163.5.872 [PubMed: 16648329]
- Klein DN, Taylor EB, Harding K, Dickstein S. Double depression: Comparison with episodic major depression on demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. *American Journal of Psychiatry*. 1988; 145:1226–31. [PubMed: 3421343]
- Kocsis JH, Frances AJ, Voss C, Mann JJ, Mason BJ, Sweeney J. Imipramine treatment for chronic depression. *Archives of General Psychiatry*. 1988; 45:253–57. [PubMed: 3277579]
- Kocsis JH, Gelenberg AJ, Rothbaum BO, Klein DN, Trivedi MH, Manber R, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: The REVAMP trial. *Archives of General Psychiatry*. 2009; 66:1178–88. [PubMed: 19884606]
- Kraemer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. *Journal of the American Medical Association*. 2006; 296:1286–89.10.1001/jama.296.10.1286 [PubMed: 16968853]
- Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*. 2002; 59:877–83.10.1001/archpsych.59.10.877 [PubMed: 12365874]
- Ley P, Helbig-Lang S, Czilwik S, Lang T, Worlitz A, Brucher K, et al. Phenomenological differences between acute and chronic forms of major depression in inpatients. *Nordic Journal of Psychiatry*. 2011; 65:330–337. [PubMed: 21271948]
- Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *Journal of Consulting and Clinical Psychology*. 2007; 75:267–76. [PubMed: 17469884]
- Manber R, Kraemer HC, Arnow BA, Trivedi M, Rush AJ, Thase ME, et al. Faster remission of chronic depression with combined psychotherapy and medication than with each therapy alone. *Journal of Consulting and Clinical Psychology*. 2008; 76:459–67. [PubMed: 18540739]
- Markowitz J, Sacks M. Manual for brief supportive psychotherapy. Unpublished manuscript. 2002
- Markowitz JC, Manber R, Rosen P. Therapists' responses to training in brief supportive psychotherapy. *American Journal of Psychotherapy*. 2008; 62:67–81. [PubMed: 18461844]
- McCullough, JP. Treatment for chronic depression: cognitive behavioral analysis system of psychotherapy. New York, NY: Guilford Press; 2000.
- McCullough, JP. Skills training manual for diagnosing and treating chronic depression: Cognitive behavioral analysis system of psychotherapy. New York, NY: Guilford Press; 2001.
- McCullough, JP. Patient manual for the cognitive behavioral analysis system of psychotherapy. New York, NY: Guilford Press; 2002.
- McCullough JP. Treatment for chronic depression using cognitive behavioral analysis system of psychotherapy (CBASP). *Journal of Clinical Psychology*. 2003; 59:833–46.10.1002/jclp.10176 [PubMed: 12858425]
- Meyer JH, Houle S, Sagrati S, Carella A, Hussey DF, Ginovart N, et al. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: Effects of major depressive episodes and severity of dysfunctional attitudes. *Archives of General Psychiatry*. 2004; 61:1271–79.10.1001/archpsyc.61.12.1271 [PubMed: 15583118]

- Miller IW, Norman WH, Keitner GI. Treatment response of high cognitive dysfunction depressed inpatients. *Comprehensive Psychiatry*. 1990; 30:62–71.10.1016/0010-440X(90)90055-W [PubMed: 2404660]
- Nelson LD, Stern SL, Cicchetti DV. The dysfunctional attitude scale: how well can it measure depressive thinking? *Journal of Psychopathology and Behavioral Assessment*. 1992; 14:217–23.10.1007/BF00962629
- NIMH. The National Institute of Mental Health Strategic Plan. Rockville, MD: National Institute of Mental Health; 2008. Retrieved from <http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml>
- Pedrelli P, Feldman GC, Vorono S, Maurizio F, Petersen T. Dysfunctional attitudes and perceived stress predict depressive symptoms severity following antidepressant treatment in patients with chronic depression. *Psychiatry Research*. 2008; 161:302–8.10.1016/j.psychres.2007.08.004 [PubMed: 18976817]
- Peselow ED, Robins CJ, Block P, Barouche F, Fieve RR. Dysfunctional attitudes in depressed patients during depression and following clinical treatment: Comparison with control subjects. *American Journal of Psychiatry*. 1990; 147:439–44. [PubMed: 2180328]
- Raudenbush, SW.; Bryk, AS. Hierarchical linear models: Applications and data analysis methods. Newberry Park, CA: Sage Publications; 2002.
- Riso LP, du Toit PL, Blandino JA, Penna S, Dacey S, Duin JS, et al. Cognitive aspects of chronic depression. *Journal of Abnormal Psychology*. 2003; 112:72–80. [PubMed: 12653415]
- Rogers, CR. Client-centered therapy. Boston, MA: Houghton Mifflin; 1951.
- Simon GE, Perlis RH. Personalized Medicine for Depression: Can we match patients with treatments? *American Journal of Psychiatry*. 2010; 167:1445– 55. [PubMed: 20843873]
- Simons AD, Gordon JS, Monroe SM, Thase ME. Toward an integration of psychologic, social, and biologic factors in depression: Effects on outcome and course of cognitive therapy. *Journal of Consulting and Clinical Psychology*. 1995; 63:363–77.
- Thase ME, Fava M, Halbreich U, Kocsis JH, Koran L, Davidson J, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Archives of General Psychiatry*. 1996; 53:777–784. [PubMed: 8792754]
- Thase, ME.; Rush, AJ. Treatment-resistant depression. In: Bloom, FE.; Kupfer, DJ., editors. *Psychopharmacology The Fourth Generation of Progress*. New York, NY: Raven Press; 1995. p. 1081-1097.
- Thase ME, Rush AJ. When at first you don't succeed: Sequential strategies for antidepressant nonresponders. *The Journal of Clinical Psychiatry*. 1997; 58:23–29. [PubMed: 9402916]
- Satyanarayana S, Enns MW, Cox BJ, Sareen J. Prevalence and correlates of chronic depression in the Canadian Community Health Survey: Mental health and well-being. *The Canadian Journal of Psychiatry*. 2009; 54:389–98.
- Singer, JD.; Willett, JB. *Applied longitudinal data analysis: Modeling change and event occurrence*. New York, NY: Oxford University Press; 2003.
- Sotsky SM, Glass DR, Shea MT, Pilkonis PA, Collins JF, Elkin I, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. *The American Journal of Psychiatry*. 1991; 148:997–1008. [PubMed: 1853989]
- Watson JC, Gordon LB, Stermac L, Kalogerakos F, Steckley P. Comparing the effectiveness of process-experiential with cognitive-behavioral psychotherapy in the treatment of depression. *Journal of Consulting and Clinical Psychology*. 2003; 71:773–81.10.1037/0022-006X.71.4.773 [PubMed: 12924682]
- Williams JMG, Healy D, Teasdale JD, White W, Paykel ES. Dysfunctional attitudes and vulnerability to persistent depression. *Psychological Medicine*. 1990; 20:375–81. [PubMed: 2356263]
- Weissman, AN.; Beck, AT. Development and validation of the dysfunctional attitude scale: A preliminary investigation. Paper presented at the Annual Meeting of the American Educational Research Association; Toronto, Ontario. 1978;

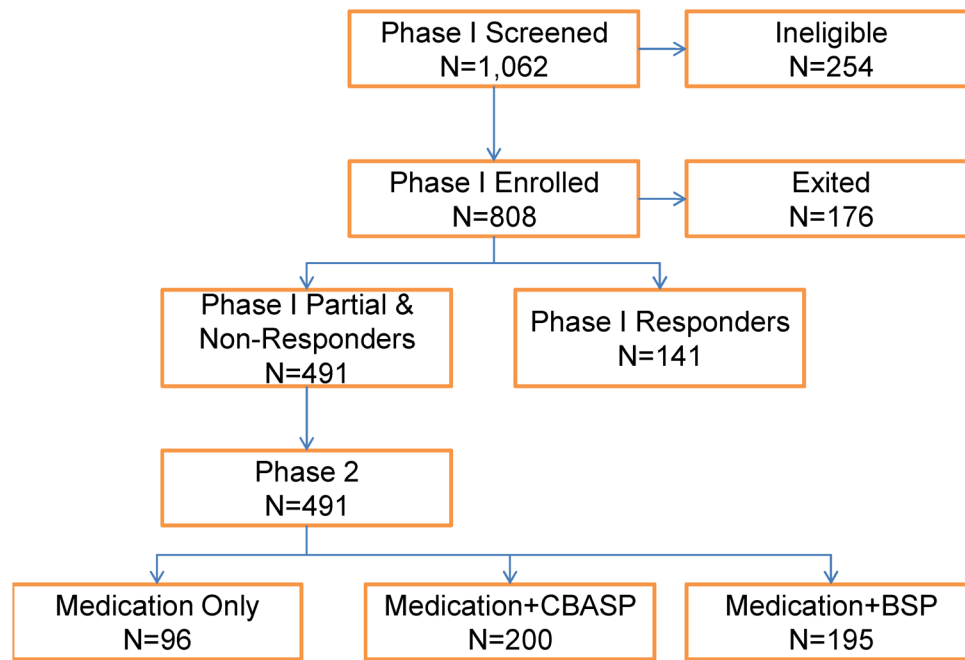


Figure 1.
REVAMP Consort Chart

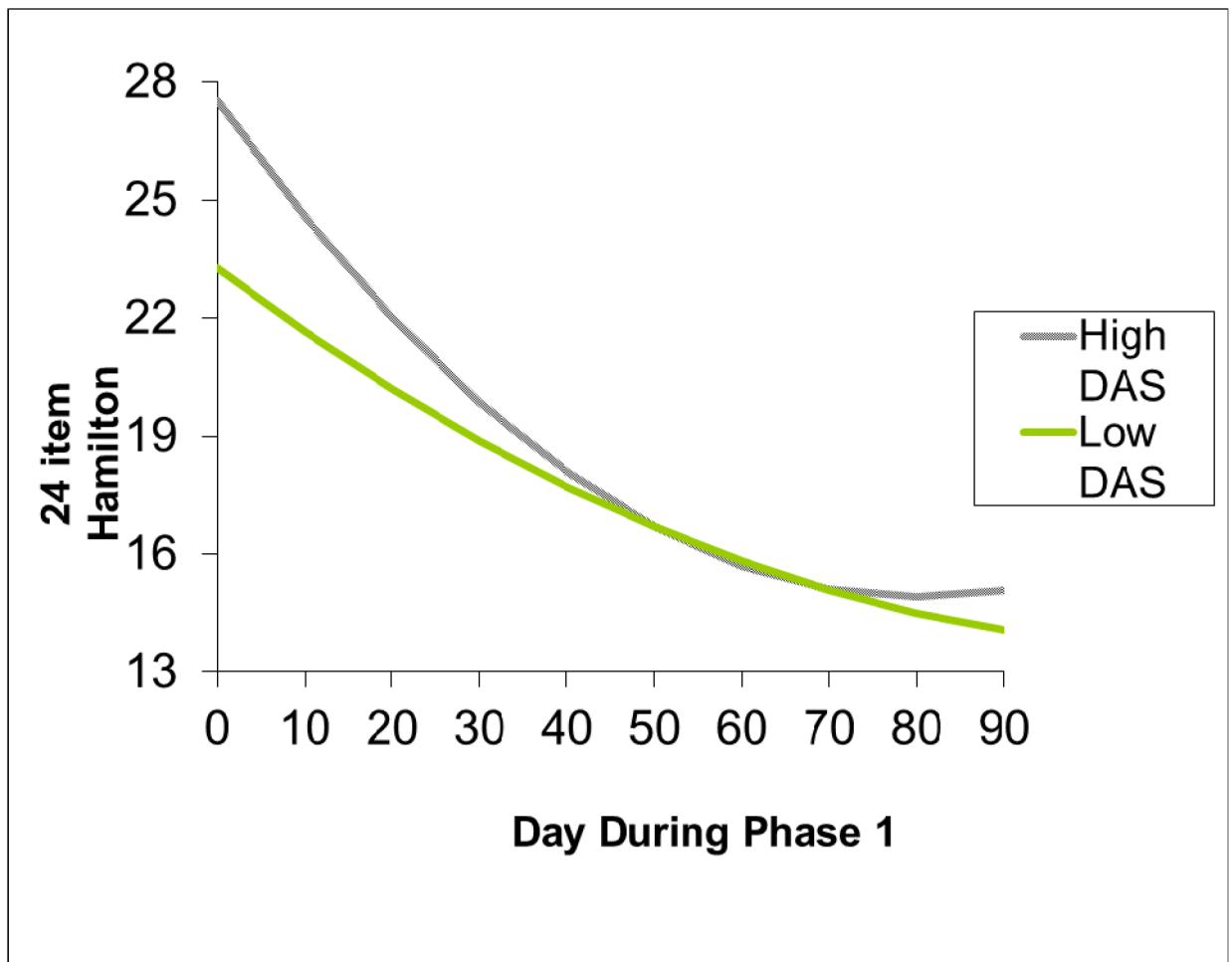


Figure 2.
DAS as moderator of change in depression severity with phase 1 treatment
(pharmacotherapy)

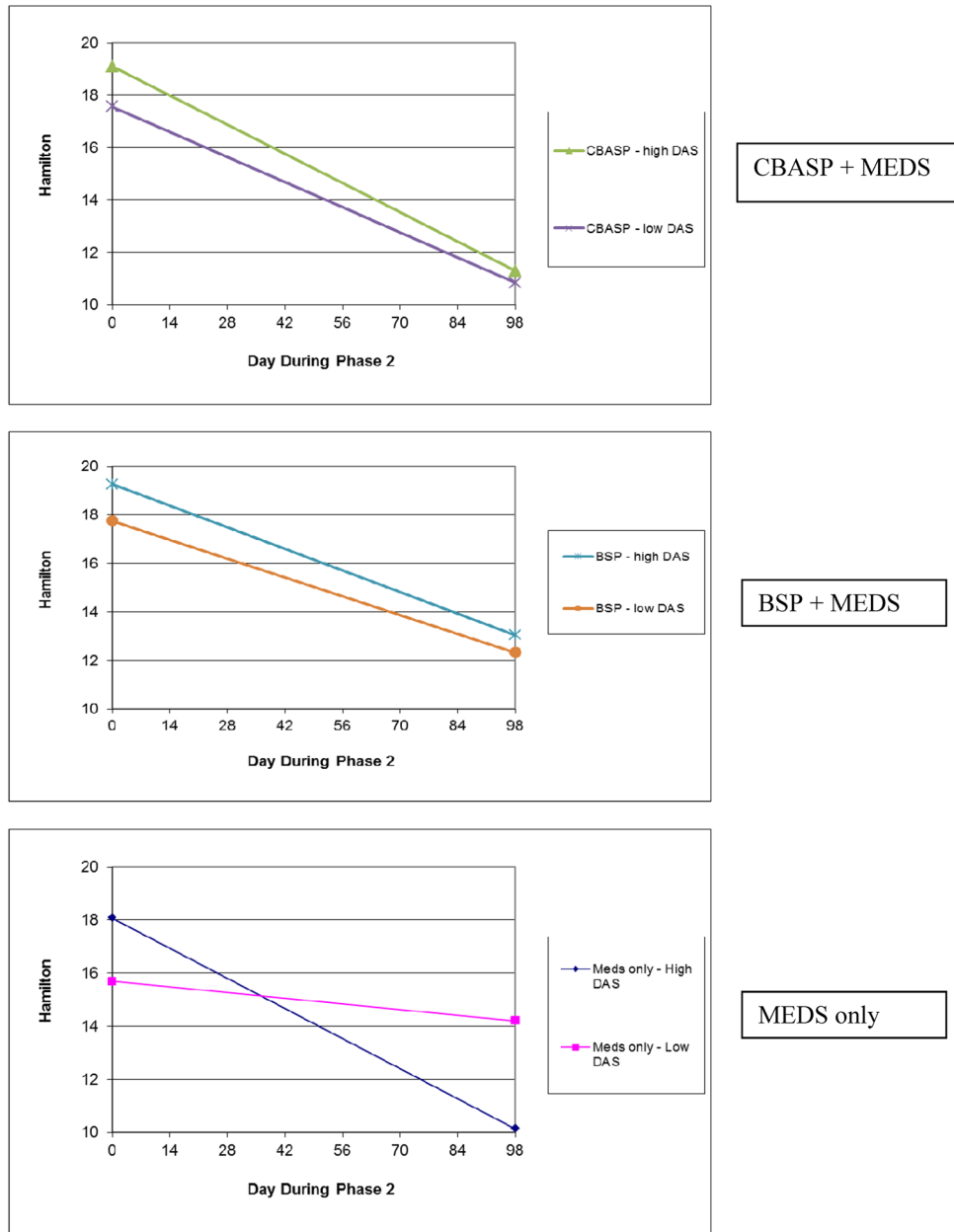


Figure 3. DAS as a Moderator of Change in Depression Severity with Treatments in Phase 2

Table 1

Demographic and clinical characteristics of sample

Age (M, SD)	44.2 (1.2)
Gender (% female)	56%
Education	
< High School	2.5%
High school graduate	37.5%
> high school	59.7%
Employment	
Employed	62.5%
Unemployed	30.9%
Retired	6.6%
Marital Status	
Married	35.5%
Never married	35.6%
Divorced	26.4%
Widowed	2.6%
Race	
White	88.3%
Black	7.6%
Other	4.2%
Hispanic Ethnicity	
Yes	7.6%
No	92.4%
Age of onset (M; SD)	23.8 (13.6)
Baseline HAM-D (M; SD)	26.6 (6.6)
Duration of index episode of MDD in months (M; SD)	84.2 (105.3)
Phase 1 DAS (M; SD)	144.0 (35.5)
Phase 2 DAS (M; SD)	129.2 (36.1)

Table 2

Effects of Time, DAS, and DAS*Time for Each of the Three Arms in Phase 2

	<i>Time</i>	<i>DAS</i>	<i>DAS*time</i>
BSP+MEDS arm			
Overall model	*** b= -.059 t (164) = -8.46	+ b=.021 t (580) = 1.69	ns
CBASP+MEDS arm			
Overall model	*** b= -.074 t (171) = -9.43	b=.023 t (613) = 1.55	ns
MEDS only arm			
Overall model	*** b= -.048 t (79) = -4.73	+ b=.032 t (285) = -1.71	** b=-.0009 t (285) = -3.19
High DAS (simple slope)	*** b= -.081 t (79) = -5.43	----	----
Low DAS (simple slope)	ns (p=.29)	----	----

*
p< .05;**
p<.01,***
p<.001,+
p<.10.

Note. MEDS = medication switch/augmentation