RUNNING HEAD: Dysfunctional attitudes as a moderator

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 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.

Key words: dysfunctional attitudes; predictor; treatment; response; chronic depression

Dysfunctional attitudes as a moderator of pharmacotherapy and psychotherapy for 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 a variable that

exhibits a main effect on treatment response and the term 'moderator' to describe a variable that interacts with a multilevel treatment arm variable (i.e., is associated with a differential treatment response).

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, 1992) 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).

Although DA was not a pre-defined moderator of response (e.g., individuals were not randomly assigned to conditions based on their DA scores), the REVAMP design was well-suited for examination of the moderating effects of DA for several reasons. 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.

<div align="center">Method</div>

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) $\geq$ 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

Institutional Review Board (IRB).

Treatments

Pharmacotherapy. The pharmacotherapy algorithm followed empirically derived algorithms (e.g., the Texas Medication Algorithm Project; 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., buproprion 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

HRSD (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, X^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.

<center>Results</center>

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. DAS scores prior to phase 1 were associated with an earlier age of onset of MDD, higher likelihood suicidal ideation/symptoms, and early childhood adversity (all *p*'s < .001; Klein et al., 2009). DAS scores were not associated with the Global Assessment of Functioning scale or any comorbid anxiety or substance use disorders.

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*time^2 *p-value*s<.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.[1]

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 (possibly due to their lower level of severity). 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.   Nevertheless, it may be possible that different psychotherapies not examined in this or other studies may yield differential efficacy for those with high or low DA (e.g., sequential or modular therapies that include components that specifically target DA, see Chu et al., 2012).

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). Hence, even though there is a moderately large supportive literature on DA as a moderator/predictor of response, the results need to be interpreted with caution. 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.

Acknowledgements

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Association, Toronto, Ontario, 1978.

Footnotes

1.   We also examined whether DAS administered at the beginning of phase 1 was associated with remission during phase 1, using the definition above. Interestingly, unlike the results of the IGC, DAS was not associated this dichotomous definition of remission (*p=.88*), highlighting the importance of examining depression as a variable that varies continuously over time in treatment studies.

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

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

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

Note. MEDS = medication switch/augmentation
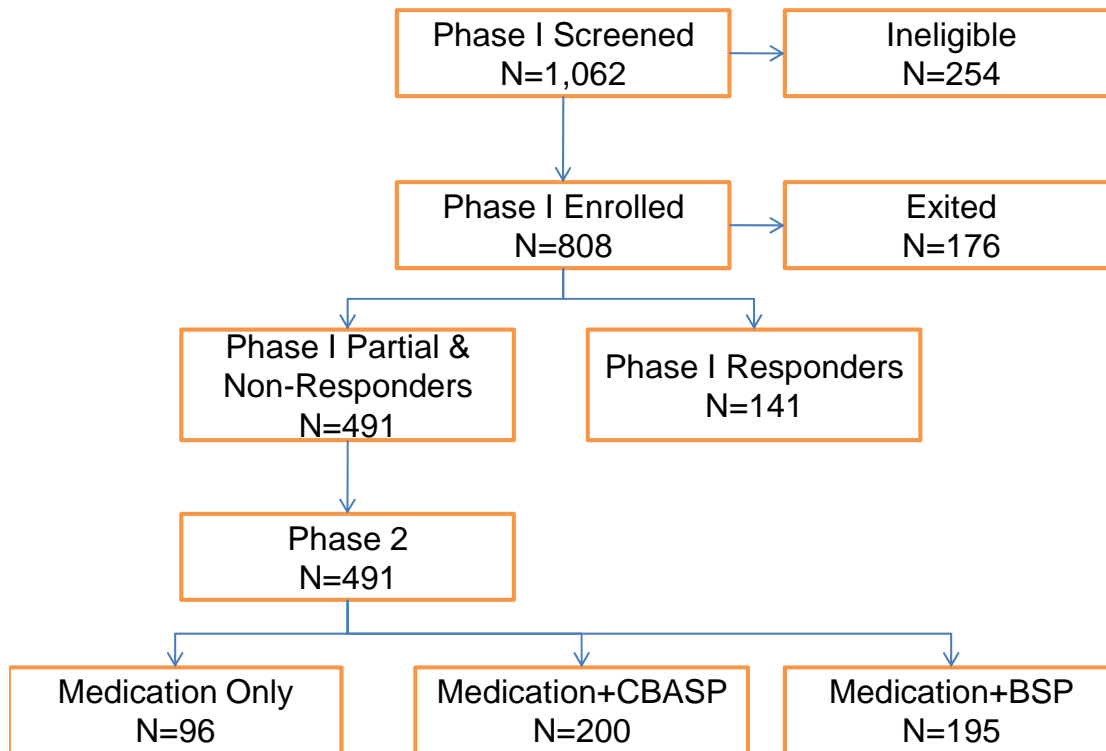
Figure 1. REVAMP Consort Chart

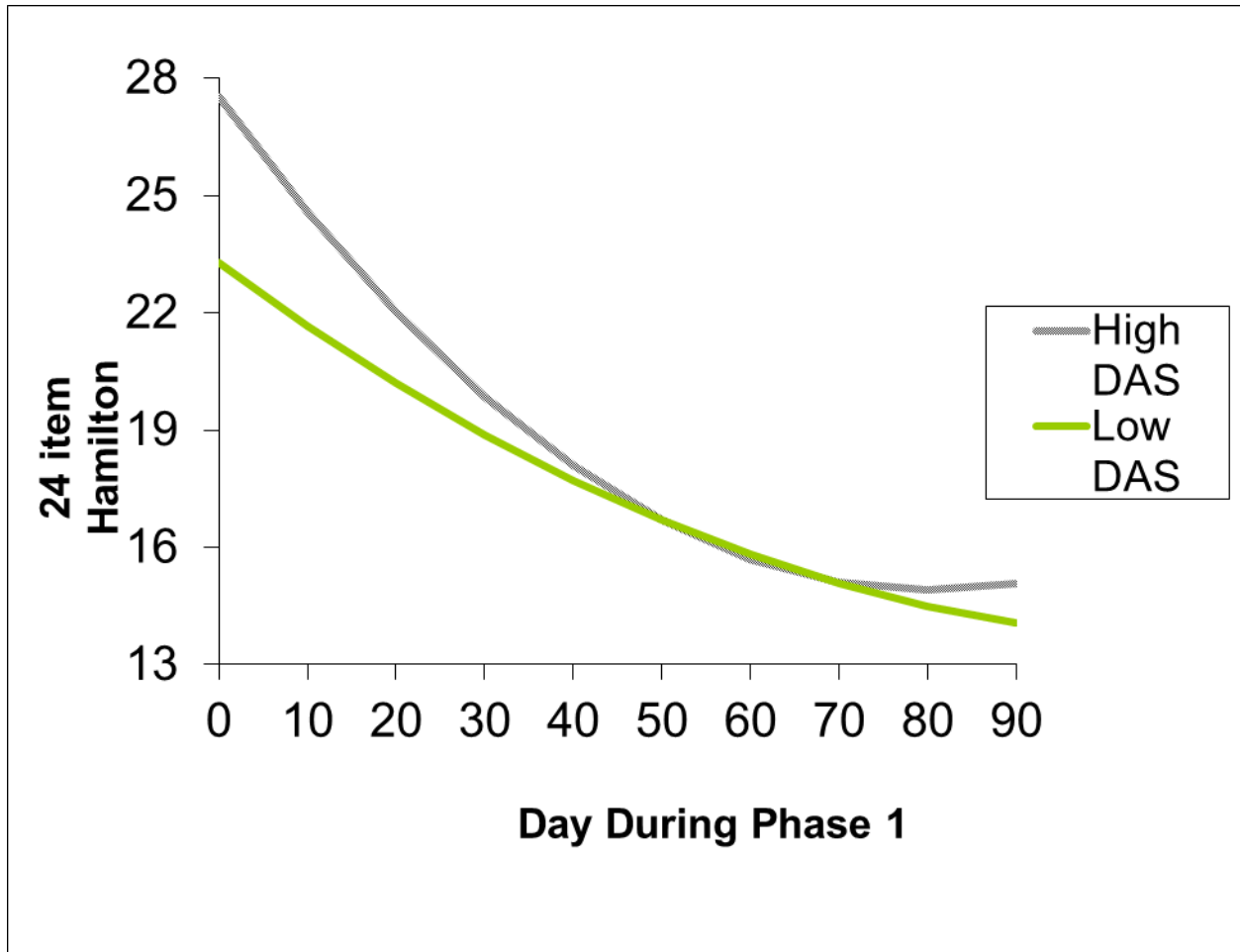Figure 2. DAS as moderator of change in depression severity with phase 1 treatment (pharmacotherapy)

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

CBASP + MEDS

BSP + MEDS

MEDS only