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Predictive Patterns of Early Symptom Change in the Treatment of Depression

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Predictive Patterns of Early Symptom Change in the Treatment of Depression

By

Daniel Yoo

Advisor: W. Edward Craighead, Ph.D.

An abstract of
A dissertation submitted to the faculty of the
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Abstract

Predictive Patterns of Early Symptom Change in the Treatment of Depression
By Daniel Yoo

Major Depressive Disorder is a costly and recurrent illness affecting about 17% of adults in the United States throughout their lifetimes. In order to achieve the ambition of treatment tailored to an individual's needs, a better characterization of the process of symptom change is needed. Extant studies treat changes to a multi-dimensional construct in a unidimensional manner. The present study, therefore, uses two-level exploratory factor analysis to characterize four symptom change factors (SCF) in 338 treatment naïve patients with Major Depressive Disorder randomized to 12 weeks of treatment with either cognitive behavior therapy (CBT) or an antidepressant medication, escitalopram and duloxetine. A primary SCF capturing change in emotional and cognitive depressive symptoms and a secondary SCF capturing change in insomnia symptoms were differentially predictive of end-of-treatment outcomes at different times. In both the CBT and escitalopram groups, early improvements in insomnia symptoms predicted better end-of-treatment outcomes, however early improvements in insomnia were not a predictor of outcomes in the duloxetine group. In the CBT group, the predictive relationship was fully mediated by middle improvements in emotional and cognitive depressive symptoms. Specific early patterns of symptom change are differentially predictive of outcomes during treatment with CBT, escitalopram, and duloxetine. Further examinations of the temporal dynamics and structure of symptom change during the treatment of MDD are warranted.

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Introduction

About 16.6% of adults in the United States will suffer from Major Depressive Disorder (MDD) in their lifetimes (Kessler et al., 2005). Most who experience MDD will have recurrent episodes, and many will experience an episode that lasts for over a year (Kessler et al., 1997). In addition to the personal distress, individuals with MDD spend about 50-100% more on healthcare, depending on whether the cost of treating comorbid medical conditions is included (Simon, VonKorff, & Barlow 1995; Simon, Ormel, VonKorff & Barlow 1995).

The current first-line treatments for MDD are evidence-based psychotherapy or antidepressant medication, both with comparable rates of remission and response (DeRubeis et al., 2005). Many of those who receive treatment for MDD do not respond to treatment. Only about 30% of patients will show full remission after initial treatment with a first-line pharmacological treatment. About 17% show some response without remission (Gaynes et al., 2009). About 30% of non-remitters to an initial antidepressant treatment will attain remission if treatment is augmented with or switched to another antidepressant or cognitive behavior therapy. Some additional smaller gains can be made for those who do not respond if additional switches or augmentations are made; however, each stage of treatment can lengthen treatment by about 3 months (Thase et al., 2007; Gaynes et al., 2009).

Some who do not initially respond to treatment may discontinue treatment altogether. While estimating patient dropout and non-adherence to treatment presents methodological challenges, both are significant challenges to treatment in both pharmacological and psychotherapeutic approaches. Patient dropout rates for CBT (non-

specific to the treatment of depression) are estimated between 19-50% (Salmoiraghi & Sambhi, 2010). Rates of non-adherence for anti-depressant treatment are estimated to be over 50% (Cantrell et al., 2006). It is not clear the extent to which dropout and adherence may occur because of unresponsiveness to treatment, as published findings are partly obfuscated by patients dropping out when they have improved (Barkham et al., 2006). However, whether or not patients routinely dropout because they are not responding to the treatment, the high rates of patient dropout highlight the importance of choosing impactful treatments early on, in order to help patients before they discontinue treatment.

There has been a rising interest in better matching patients to treatment modalities, under the assumption that it may be possible to identify individuals who will respond better or worse to different treatments (Simon & Perlis, 2010). The aims of the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study are within this spirit of increasing efficacy by personalizing treatment. The study seeks to identify genetic, endocrine, immune, brain-imaging, and psychological predictors of remission to CBT, SSRI, or SNRI treatment of depression (Dunlop, Binder et al., 2012). The primary goal of this research is to better identify which treatments work for which people, based on individual characteristics. In addition to initially identifying the most effective treatments before treatment begins, it may also be important to identify more quickly when treatments are or are not working after treatments have begun. The sooner clinicians are able to identify the likelihood of a treatment working or not working, the sooner treatment modifications can be made. The present study uses data collected during the PReDICT study to determine predictors of

outcome based on early symptom changes over the course of cognitive behavior therapy (CBT) or antidepressant treatment (escitalopram or duloxetine).

Traditionally, clinical trials have focused on pre-treatment to post-treatment changes, often ignoring the dynamics of the changes that occur between the two time points. Some have theorized that the process of therapeutic change is discontinuous and nonlinear (see Hayes et al., 2007 for a review), and have argued for further research on the trajectory of therapeutic change as a way to better understand the process of therapy (e.g. Barkham, Stiles, & Shapiro, 1993; Laurenceau, Hayes & Feldman, 2007). Several studies have identified non-linear processes in therapy, for example about 60-70% of symptomatic change in CBT for depression occurs within the first few weeks of treatment, with change then leveling off (Ilardi & Craighead, 1994). Similar rapid early changes have been identified in CBT for bulimia nervosa, alcohol abuse, and panic disorder (Wilson, 1999). Others have identified that "sudden gains" (i.e. large reductions in symptoms that occur from session to session) may predict better long-term outcomes and may reflect a distinct type of symptom change (Tang & DeRubeis, 1999; Busch et al., 2006). However, more recently it has been demonstrated that these "sudden gains" could simply be the result of the measurement error in symptom measurement instruments (Thomas & Persons, 2013). Thomas and Persons also found that the power of "sudden gains" in predicting overall changes in depressive symptomatology might be accounted for by the predictive power of early rapid change during the initial 6 weeks of therapy. Rapid change also appears as a phenomenon in antidepressant treatment of depression, with about 25% of patients showing an initially rapid trajectory of change and 75% of patients showing a gradual trajectory of change. Similar to treatment with CBT,

those who show rapid initial change trajectories to antidepressant treatment appear to have better long-term outcomes (Uher et al., 2010).

In order for predictive patterns of change to be identified, ongoing monitoring of symptoms is needed. Several have advocated for increased adoption of continuous monitoring of outcome variables (e.g. Lambert et al., 2006; Kazdin, 2008). One effort to predict treatment outcomes through the ongoing monitoring of treatment progress is the Outcome Questionnaire-45 (OQ-45) (Lambert et al., 1996). The OQ-45 is a 45-item questionnaire administered at every session, and in addition to providing measures of symptomatology it offers feedback on the progress a patient is making based on the overall symptom change, number of sessions, and the relative to the initial level of symptoms at intake. The OQ-45 system has been shown to be predictive of treatment failures (Lambert et al., 2002). In addition to potentially identifying when treatment is not helpful, a worthwhile goal in and of itself (see Craighead & Craighead, 2003; and Lilienfeld, 2007 for discussions), providing feedback to clinicians about when a patient is at risk for a bad outcome has been found to reduce treatment failures (Lambert et al., 2003; Lambert et al., 2006). This highlights the potential for improved patient outcomes if longer-term outcomes can be predicted early in treatment.

Although researchers have moved beyond simple pre-treatment to post-treatment outcome measurement of change by adopting trajectory models using methods such as growth mixture modeling (Jung & Wickrama, 2008), most studies continue to examine change across a unitary dimension, such as an aggregate rating of depression symptom severity. This focus on change along a single dimension is somewhat surprising, as depression is generally characterized as a multi-dimensional construct, with many

different symptoms making up the diagnostic criteria in diagnostic instruments such as the DSM-V (5th ed.; *DSM–V*; American Psychiatric Association, 2013). Factor analyses have also identified a multi-dimensional structure to depressive symptoms as measured by depression questionnaires. In a meta-analysis of four commonly-used depression questionnaires, Beck Depression Inventory (BDI), the Center for Epidemiological Studies Depression Scale (CES-D), the Hamilton Rating Scale for Depression (HAM-D), and the Zung Self-Rating Depression Scale (SDS), Shafer (2006) found broad support for at least two factors, a general depression factor and a somatic symptoms factor. There was also some limited evidence for additional factors: anxiety, positive emotions, interpersonal functioning, and performance impairment. Shafer has argued that more specific factors could likely be identified if item pools were expanded. A pitfall of the typical method of developing instruments, in which factor structure parsimony and internal consistency measures are favored, is that interesting factors may be discarded if the initial item pool does not contain enough items to capture the latent variable. Shafer (2006) has pointed out that one potential solution is to conduct factor analyses across items across multiple measures, the approach adopted in the present study. The benefit to reanalyzing factors across multiple instruments is that factors with weak item support have a greater chance of surviving. It can also theoretically reduce the impact of the biases of the measurement instrument developers.

Yet another important nuance to capturing change in a multidimensional construct is that factor analyses typically analyze the covariation in scores between individuals rather than within individuals. The overwhelmingly common practice for creating a dataset for exploratory factor analyses is to measure a large number of individuals at one

point in time and to then characterize the variation between individuals. However, it cannot necessarily be assumed that the structure of how symptoms differ between individuals mirrors the structure of how symptoms change over time within individuals. Multi-level analysis of longitudinal data is one candidate method for disambiguating factors that underlie within-individual variation from the factors that underlie between-individual variation. Specifically, if multiple measures of symptoms are taken across time for multiple individuals, a two-level model can group the different measures across time within individuals, separating the between-individual variation from the within-individual variation across time. The present study uses this two-level approach.

Modeling change in a multi-dimensional space offers challenges that are not encountered when single aggregate measures of symptoms are used, particularly when the sample size is limited. Simple multivariate methods such as multiple regression run into quickly lengthening lists of predictor variables and interactions. This is accompanied by a risk of overfitting the data and creating a complex model that is difficult to interpret. Although the PReDICT study is one of the largest comparative clinical trials for the treatment of depression to date, with 338 study entrants, it is not large enough to reduce the risk of overfitting that comes with traditional multivariate methods. In order for change in depression to be treated as a multi-dimensional construct, methodological innovation is necessary. The current study uses a data analytic methodology that helps address the challenges of analyzing a multi-dimensional longitudinal dataset with a limited sample size, striking a balance between predictive power, treating depression as a multi-dimensional construct, the risk of over-fitting in a limited sample, and maximizing the interpretability of the data results.

The primary aim of the present study is to identify types of symptom changes in the initial sessions of treatment that are early predictors of remission and response to treatment. This approach departs from the aforementioned research, in that it tries to identify types of symptom change rather than simple rates of change on an aggregate measure. In order to treat changes in depressive symptoms as a multidimensional process while reducing the risk of Type I error, a two-step analytical pathway is used. The first step to this process is modeling the structure of symptom change in order to identify either continuous or discrete symptom change types. This initial step of modeling the structure of symptom change takes two approaches, a continuous approach and a categorical approach. The continuous approach employs two-level exploratory factor analysis to identify factors that underlie change at the intraindividual level under the hypothesis that these may be different from the factors typically detected at the interindividual level. The categorical approach treats change as being of several distinct types, and aims to identify whether different symptom changes can be classified into types using cluster analysis. This first data reduction step is critical, as it retains some degree of multi-dimensionality, but reduces the number of statistical tests considered, reducing the risk of drawing incorrect statistical conclusions. After the initial data reduction step, a second step examines the extent to which the identified types of symptom change predict outcomes at the end of 12 weeks of CBT or anti-depressant treatment. In addition to testing whether early types of change in symptoms are predictive of later outcomes, the present study conducts exploratory analysis of the dynamics of the symptom changes, in order to better understand the symptom change process.

Method

Study Overview

The PReDICT study is a randomized, double-blind clinical trial designed to identify baseline predictors of remission to 12 weeks of escitalopram, duloxetine, or CBT; followed by 12 weeks of combination treatment of pharmacotherapy and CBT for patients who do not remit after the initial 12 weeks. Although parts of the broader study are described below, the present study only involves data from the initial 12 weeks (16 sessions) of treatment. The study was conducted through Emory University's Mood and Anxiety Disorders Program starting January 2007 and the initial phase of 12 weeks of treatment was completed in July 2013. All patients provided written informed consent prior to participating in the study. The study was conducted in accordance with the Declaration of Helsinki and its amendments, and it was approved by Emory's Institutional Review Board. Further details about the broader study design and its aims are published (Dunlop, Binder et al., 2012), some of which is reproduced below.

Participants

Patients were recruited through a combination of advertising and clinical referral. Eligible participants were 338 adult outpatients between 18 and 65 years of age who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for a primary diagnosis of MDD without psychotic features. The Structured Clinical Interview for DSM-IV (SCID) was used to determine the presence of MDD and the absence of any exclusionary diagnoses. In addition, participating patients were required to have clinical agreement of an MDD diagnosis and the 17-item Hamilton

Depression Rating Scale (HAM-D) (Hamilton, 1960) total score ≥18 at the screening visit and ≥15 at the randomization visit.

Patients were excluded if they met lifetime DSM-IV criteria for bipolar disorder or a psychotic disorder, or currently met criteria for psychotic disorder, eating disorder, dissociative disorder, obsessive compulsive disorder, or dementia. Individuals with currently clinically important suicidal ideation requiring rapid initiation of treatment were also excluded. Substance abuse (excluding nicotine and caffeine) in the past 3 months prior to randomization, and substance dependence in the past year were also exclusionary criteria.

Patients were excluded if they had previously been treated for MDD or dysthymia, defined as four or more consecutive weeks of an antidepressant at a minimally effective dose or four or more sessions of an established structured psychotherapy for depression (i.e., CBT, behavior therapy, interpersonal therapy, or behavioral marital therapy). Additional exclusionary criteria included: any lifetime exposure to citalopram, escitalopram, or duloxetine; treatment with any dose of an antidepressant for any reason for four or more weeks during the current episode; use of any psychotropic medication (except hypnotics) within 1 week of the screening visit; any use of fluoxetine within 8 weeks of the screening visit; need for concurrent neuroleptic or mood stabilizer therapy; current medical disorder that would likely affect completion of the study; clinically important neurological, inflammatory, autoimmune, endocrine, or other medical illness that could interfere with the conduct of the study or interfere with interpretation of study results; contraindications for MRI; medical contraindications for escitalopram or duloxetine; currently pregnant or breast-feeding women; the presence of

factors that would likely prevent the patient from completing 12 weeks of the study; and being unlikely to comply with the study protocol, as judged by a study psychiatrist.

After being briefly interviewed on the phone, eligible and interested patients were seen initially for a screening visit. After signing the informed consent form, study participants met with a staff member for an initial psychiatric interview. The results of this initial interview were presented to a study psychiatrist who then conducted a 30-60 minute psychiatric diagnostic evaluation, including medical history and previous treatment history. Patients who remained eligible completed the SCID interview, administered by a trained clinical interviewer. The trained interviewer also administered the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), and Clinical Global Impression scale for Severity (CGI-S) (Guy, 1976).

Patients were then evaluated to ensure adequate physical health and to identify potential medical causes for a major depressive episode. This evaluation included: a medical review of systems, physical exam, electrocardiogram, and laboratory assessments. Demographic variables and family history of psychiatric illness were collected via self-report. Childhood trauma history was assessed via the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) and the Early Home Environment Interview (EHEI) (Lizardi et al., 1995). Patients who met all eligibility criteria underwent phlebotomy for measurement of inflammatory markers and extraction of mRNA and DNA. Next, patients completed the fMRI and a half-day CIN outpatient hospital stay during which a Dex/CRH test was performed.

At the randomization visit, patients completed the Quick Inventory of Depressive Symptoms (QIDS) (Rush et al., 2003), the Beck Depression Inventory (BDI) (Beck et al., 1961), the Qualitative Life Enjoyment Satisfaction Questionnaire (Q-LES-Q) (Endicott, Nee, Harrison & Blumenthal, 1993) and the Sheehan Disability Scale (SDS) (Sheehan, 2000). Patients also completed an abbreviated version of the Patient Attitudes and Beliefs Scale (PABS) (Dunlop, Kelly et. al., 2012), to indicate their treatment preference and their beliefs about the causes of their depression, and the Life Experiences Survey (Sarason, Johnson, Seigel, 1978) to assess important personal events over the previous 12 months. A blinded rater administered the HAM-D-24, HAM-A, MADRS, CGI-S, and CGI-Improvement (CGI-I).

Randomization and Treatments

Patients were randomized at a 1:1:1 ratio to receive 12 weeks of treatment with escitalopram, flexibly dosed from 10–20 mg/d; duloxetine, flexibly dosed from 30-60 mg/d; or 16 sessions of CBT. A permuted block randomization pattern with 6 participants in each block was generated prior to opening enrollment for the study. Randomized treatment assignments were individually printed and placed in sealed opaque envelopes by Emory employees uninvolved in the study. The randomization envelopes were stored in the research offices and opened sequentially at the time of each patient's randomization visit. The treatment assignment was generated using randomized permuted blocks, stratified by site.

The CBT provided followed a standardized protocol (Beck et al, 1979). The schedule for CBT delivery was 4 weeks of twice-weekly sessions, followed by weekly

sessions for the next 8 weeks, though twice weekly sessions could occur slightly later during the trial if earlier sessions were missed. Doctoral-level and masters-level providers trained in the specific CBT protocol for the study provided the therapy. Patients who completed at least 12 sessions of CBT and who were present for evaluation at weeks 10 and 12, were considered to have completed the course of CBT. Of 113 patients randomized to the CBT group, 72 patients completed the course of CBT and were included in the present analyses. All CBT-treated patients continuing in the study after week 12 receive three booster sessions at monthly intervals over the first 3 months and another three booster sessions, each separated by at least 1 month, during the second year of follow-up. There is also one additional crisis session available to patients during each year of follow-up. All therapy sessions were videotaped, and an independent off-site CBT expert at Beck's Institute of Cognitive Therapy rated selected sessions of all therapists' competence in Beck's type of CBT (Beck, Rush & Shaw,1979).

Antidepressant Medication (ADM) patients were seen by board certified psychiatrists or fourth-year psychiatry residents weekly for the first six weeks of treatment and then every other week for the final six weeks. All patients were started on one capsule per day of either escitalopram oxalate (equivalent to 10 mg of escitalopram free base) or duloxetine HCl (equivalent to 30 mg of duloxetine free base). If the patient did not demonstrate clinically meaningful improvement by week 4, the dose was raised to two capsules per day, though the treating psychiatrist, based on the severity of the patient's symptoms, could raise the dose earlier if deemed necessary. If there was a plateau in response, or if remission was not achieved by week 6, the dose was increased to two capsules per day. If adverse events were sufficiently distressing to the patient, the

dose could be lowered back to one capsule per day. Of 112 patients randomized to escitalopram, 92 completed the course of 12 weeks of treatment. Of 113 patients randomized to duloxetine, 86 completed the course of the 12 weeks of treatment. Only those who completed the 12 weeks of treatment are included in the present study.

All patients, in all three monotherapies, were assessed for symptom change weekly for the first 6 weeks and then every other week for the remaining 6 weeks. At assessment visits, experienced raters (blind to treatment preference and assignment) completed the HAM-D, MADRS, and HAM-A. The study physician, who was not blinded to treatment, met with the patient to assess safety and completed the Clinical Global Impression Severity and Change scales (Guy, 1979). Patients completed the QIDS and BDI at each assessment visit.

Symptom Measures

Depression and anxiety severity were assessed by both clinician interview (HAM-D, HAM-A, MADRS) and self-report forms (QIDS, BDI). The HAM-D is a rating scale designed for adults that is used to rate severity of depression and assesses symptoms of depressed mood, guilt, suicidality, insomnia, agitation or retardation, anxiety, difficulty functioning, and somatic symptoms. The MADRS is a depression rating scale designed to be particularly sensitive to changes during treatment (Montgomery & Asberg, 1979). The HAM-A is a rating scale intended to assess a broad range of anxiety symptoms. The QIDS is a self-report questionnaire designed to assess the nine symptom domains of DSM-IV Major Depressive Episodes. The BDI is a 21-item self-report measure of

depression severity originally developed from clinical observations of depressed patients (Beck et al., 1961).

Symptom measures were collected at unevenly spaced intervals. Ratings were administered weekly through the first six weeks and then at weeks 8, 10, and 12. Patients had biweekly CBT sessions during the first 4 weeks, than weekly sessions afterwards. Thus, during the first four weeks of treatment, the ratings were collected weekly and at every other session. During weeks 5 and 6, ratings were collected weekly and at every session. During weeks 7 through 12, ratings were collected bi-weekly and at every other session. The current study's analyses were based on a mixture of these three sets of ratings intervals.

Outcome Measures

The primary outcome measures were remission status and end-of-treatment scores on the Hamilton Depression Rating Scale (HAM-D). Remission was defined as a HAM-D score of less than 8 at both weeks 10 and 12. Response was defined as a $\geq 50\%$ reduction in HAM-D item total score at week 12 as compared to baseline. A continuous measure of symptom improvement was estimated by averaging the total HAM-D score at weeks 10 and 12. Although other scales, such as the BDI, were available to be used as additional outcome measures, using the HAM-D as a single outcome measure was preferred because using fewer outcome measures helps to constrain the number of statistical tests conducted, reducing the risk of Type I error. Additionally, the HAM-D directly reflects clinician assessment and has very high reliability (Trajković, et al., 2011).

Data Analysis Overview

The primary goal of the present study was to better characterize the change processes during the first 12 weeks of CBT using symptom measures (HAM-D, MADRS, HAM-A, QIDS, & BDI), and to determine the extent to which they were predictive of outcomes. Conceptually, there were two steps to this process. The first step was to model the structure of symptom change by identifying discrete or continuous symptom change types. This step also served as a data reduction step, to reduce the dimensionality of the predictors. The second step was to examine the extent to which the change types or factors predicted remission and overall change at the end of 12 weeks of CBT.

STEP 1: Modeling Structure of Symptom Change

In the first analysis step, the changes in the symptom measures (HAM-D, MADRS, HAM-A, QIDS, & BDI) were reduced into a more concise representation by modeling the underlying structure of symptom change. This data reduction step attempted to identify underlying patterns of symptom change across all items in all five instruments. A secondary goal of the data reduction step was to generate variables that characterized change processes as a multi-dimensional process, rather than in the unidimensional way that is typically used when overall symptom change is evaluated. As noted above, however, a balance is needed between increasing the dimensionality of the predictors and an increased risk of overfitting to a specific sample as the number of dimensions is increased. The data reduction step aimed to find this balance. Additionally, it is important to highlight that the data reduction step was conducted without including information about end-of-treatment outcomes.

Two different approaches were used in this data reduction step, a continuous approach and a categorical approach. The first approach, the continuous approach, used two-level exploratory factor analysis (EFA) to identify factors that underlie changes in symptoms during treatment. Measurements at multiple time points were grouped within individuals, allowing the model to separate between-individual differences from within-individual changes over time. The within-individual factor solution can be considered symptom change factors, as they indicate the structure of how symptoms change over time. The two-level EFA was conducted in MPlus version 6.12 using the WLSMV algorithm, which has good estimation properties for ordinal items. An oblique Geomin rotation was used to allow the derived factors to have non-zero correlation. Twelve weeks of measures were used in the exploratory factor analysis. An initial attempt at estimating an EFA solution using only the first 6 weeks of scores for the factor analysis had poor stability and convergence, so additional data from all 12 weeks were used. A separate factor analysis was conducted for the CBT patients and the anti-depressant medication patients. The two medication groups were combined into a single factor analysis model, because there were some difficulties with the estimation algorithm converging when conducting a factor analysis in the Duloxetine group alone. There were no difficulties in the Escitalopram group. Combining the two medication treatment groups into a single group had better computational convergence.

There was not an unbiased way to compare the fit of the factor solutions between the CBT and anti-depressant medication (ADM) groups with a confirmatory factor analysis approach without a separate sample, therefore cosine similarity was used as a

descriptive measure of the similarity between the symptom change factors in the CBT and ADM groups..

Symptom change factor scores were calculated by summing the scores of all items with a factor loading of greater than .5. If an item had multiple factor loadings greater than .5, it was only included in the score with the highest factor loading, potentially reducing some of the correlation between the factor scores. Prior to summing, all item scores were normalized so that the range of the item was 1, with a minimum score was 0 and maximum score was 1. Normalization was necessary as different items had different ranges of possible values. This method of normalization has an advantage over normalization by standard deviation, in resulting in more stable and more easily replicated scores across different samples. Total change for each symptom change factor during the first three weeks was calculated as the total change in the symptom change factor from baseline to week three. Total change in the second three weeks was calculated as the total change from week three to week six. Missing data were imputed with the last observation carried forward (LOCF). LOCF imputation has the advantage of making few assumptions and being applicable to how clinical practitioners might impute missing data in real-world situations.

The second approach to modeling the underlying structure of symptom changes, a categorical approach, used cluster analysis to identify nominal types of change. Symptom change scores for each individual at each time point were calculated as a combination of both the current state and the change in the symptoms. For example, a symptom change might be characterized by a moderate reduction in a high score on a sad mood item and a

small reduction in a moderate score in a suicidality item. Including both state and change is necessary in order to allow for non-equivalent changes across the range of scores.

A Gaussian mixture model using the expectation maximization (EM) algorithm was used to identify clusters using Matlab 2013a. The optimal number clusters was estimated using the elbow method to identify a change in the slope of a plot of the variance explained by the clusters as the number of clusters increase. This is analogous to the scree test that is commonly used in deciding the number of factors in exploratory factor analysis, based on visually inspecting the contribution of the factors in explaining the variance in the data. A categorical symptom change type might be identified as the center of an identified cluster. In theory, these categorical symptom change types might represent archetypal symptom changes that occur during the treatment of depression.

However, the cluster analysis had significant modeling challenges, making identifying specific categorical symptom change types difficult. First, it was not clear how to determine the correct number of clusters. There was no clear elbow in a plot of the variance explained by the clusters, allowing a judgment of the optimal number of clusters. Adjusting the number of clusters also shifted the centers of all clusters, which is inconsistent with a model of archetypal discrete symptom change types. Second, the centers of the clusters were difficult to interpret. Third, the converged solution was very sensitive to the random initialization of the gaussians. Finally, the clusters seemed to better indicate the overall magnitude of symptom changes rather than a specific configuration of symptom changes. A second cluster analysis method, K-means clustering, was attempted, and yielded similar challenges. Overall, the difficulties were inconsistent with a model of categorical symptom change types and were more consistent

with a continuous model. As the categorical model did not yield an interpretable reduction of the data, additional analyses only investigated the continuous symptom change factors identified in the two-level exploratory factor analysis.

STEP 2: Treatment Outcome Prediction

Multiple regression models were used to examine whether early changes in the symptom change factors during the first three weeks of treatment indicated different end-of-treatment outcomes. Regression models examined whether early changes in the symptom change factors during the first three weeks predicted end-of-treatment HAM-D scores, controlling for baseline scores on the symptom change factors. All of the symptom change factors were entered in the same regression model, in order to control for the correlation between the symptom change factors. Logistic regression models examined whether the same early changes predicted end-of-treatment remission (HAM-D < 8 at both weeks 10 and 12). In order for the regression models to be comparable with the logistic regression using the dichotomous remission outcome measure, end-of-treatment HAM-D scores were calculated as the average of the week 10 and 12 HAM-D scores. Chi-squared deviance tests were used to test whether the early change prediction models had better fit than a baseline model including only baseline scores on the symptom change factors.

In addition to the predictive ability of early changes in the symptom change factors, the predictive ability of middle changes during the second three weeks of treatment were investigated. The middle change prediction models included change in the symptom change factors during the first three weeks of treatment and change during the

second three weeks of treatment along the same symptom change factors. Chi-squared deviance tests were used to evaluate whether the middle change prediction models had better fit than the early change prediction models. A Sobel test was used to test mediations identified in the middle change prediction model that indicated that early changes were mediated by middle changes in the symptom change factors.

It is important to emphasize that separate factor models were derived for the CBT and anti-depressant medication (ADM) groups. Although estimating a single factor model for all treatment groups was possible, doing so risked obfuscating differences between the groups. Therefore, the prediction models also had distinct symptom change factors as predictors for the CBT and anti-depressant groups. A disadvantage to this approach was that the predictors, i.e. changes in the symptom change factors, were different between the CBT and ADM groups. Separate predictive models were also examined for the Escitalopram and Duloxetine groups. Although the exploratory factor analysis combined the two groups for convergence and stability, the predictive models examined each anti-depressant medication treatment separately, in order to identify differences in the predictive relationships between the two groups.

Results

Two-Level Exploratory Factor Analysis

Scree-plots of the eigenvalues of the two-level exploratory factor analysis of the CBT group indicated that extracting four within-individual symptom change factors and five between-individual factors was reasonable. Inspection of the four symptom change factors suggested that the factors had reasonable interpretability. Five and three symptom

change factor solutions were also examined: however the four symptom change factors was determined to be both the most interpretable and best supported by a scree plot.

The four symptom change factors found in the CBT group were: 1. Cognitive and Emotional Features; 2. Anxiety, Tension, and Anhedonia; 3. Insomnia; and 4. Appetite and Weight Loss, and Agitation (table 1). The Cognitive and Emotional Features symptom change factor loaded highly of items that indicated sadness, pessimism, self-criticism, and depressed mood (table XX). This factor accounted for 53% of the sum of squared factor loadings. The Anxiety and Tension symptom change factor loaded highest on items that indicated feelings of anxiety and tension and accounted for 18% of the sum of squared factor loadings. The Insomnia symptom change factor loaded highly on early, middle, and late symptoms of insomnia and accounted for 15% of the sum of squared factor loadings. The Appetite and Weight Loss, and Agitation symptom change factor loaded highly on items that indicated decreased appetite, decreased weight, and increased agitation, and accounted for 14% of the sum of squared factor loadings.

There were differences between the symptom-change factors and individual-difference factors in the CBT group. The individual-difference factors separated the cognitive and emotional features of depression, however, a similar separation was not found in the symptom-change factors, where a single factor included both cognitive and non-cognitive depressive symptomatology. The cosine similarities of the symptom-change factors and the individual-difference factors (table 3) indicated strong similarity between the insomnia symptom change factor and the insomnia individual difference factor. There was weak similarity between the decreased weight and appetite individual-difference factor and the agitation and decreased weight and appetite symptom-change

factor. It should be emphasized that the symptom change factors are supported by much more data than the between-individual factors, as each individual is measured at multiple time points. The between-individual factors, on the other hand, are supported by relatively very little data, as there were only 338 subjects, split across the CBT and ADM groups. Because of the small amount of data underlying the between-individual factor solution, the between-individual factor solution has low stability and is not discussed further.

Scree plots of the eigenvalues for the Anti-depressant Medication (ADM) group indicated that four factors were reasonable for both the between-individual difference factors and the within-individual symptom change factors. The scree plot indicated fewer individual difference factors than the five indicated for the CBT group. As noted above, however, a relatively small amount of data supported the individual difference factors, likely resulting in instability in the between-individual factor extraction. The rotated factor solutions had reasonable interpretability, and four symptom change factors were retained (table 2). Three of the four symptom change factors in the ADM group had analogs in the CBT group. As in the CBT group, a factor capturing symptom changes in a broad range of cognitive and non-cognitive features of depression was identified. This factor had strong cosine similarity, .90, with its analog in the CBT group. An insomnia factor was also identified in the ADM group, with strong similarity with the insomnia factor in the CBT group, .88, indicated by early, middle, and late insomnia. The other two ADM symptom change factors had less clear analogs in the CBT group (table 4). The Appetite and Weight Loss, and Suicidality symptom change factor in the ADM group had weak cosine similarity, .70, with the Appetite and Weight Loss, and Agitation symptom

change factor in the CBT group. Finally a symptom change factor indicating changes in anxiety and agitation in the ADM group did not have a close analog in the CBT group.

Unlike in the CBT group, there was no separation of cognitive and emotional features of depression found in the individual difference factors in the ADM group. The General Depression symptom change factor had moderately strong cosine similarity, .87, with a similar General Depression individual difference factor. The Insomnia symptom change factor also had a similar individual difference factor with moderately strong cosine similarity, .84. The other two symptom change factors did not have clear analogs in the individual difference factors. As with the CBT group, although the factor loadings for the extracted individual difference factors are available in Appendix A, they should be interpreted with extreme conservatism and were not further analyzed because there is not enough data supporting the factor solution.

Treatment Outcome Prediction

The early change model in the CBT group (table 6) had better fit than a baseline model that only included the baseline scores in the symptom change factors ($\chi^2 = 1025.6$, $df = 4$, $p = 2.8 \times 10^{-8}$) in predicting end-of-treatment HAM-D scores. The only statistically significant early predictor of end-of-treatment outcomes was early changes in the Insomnia symptom change factor ($p = .005$). Improvements in the insomnia symptom change factor indicated better end-of-treatment HAM-D scores. Early changes in the Insomnia symptom change factor predicted remission status at weeks 10 and 12, however not at a statistically significant level ($p = .09$), consistent with the logistic regression

models losing some statistical power from the dichotomization of the continuous outcome.

The middle change model in the CBT group (table 7) had better fit than the early change model ($\chi^2 = 512.5$, df = 4, $p = 8.8 \times 10^{-6}$). Middle changes in the General Depression symptom change factor were a statistically significant predictor of end-of-treatment outcomes (p = .004). Interestingly, the addition of the middle changes in the symptom change factors had an impact on the early changes predictors. In the middle change model, early changes in insomnia were no longer a statistically significant predictor (p = .354). However, early changes in the General Depression symptom change factor were now a statistically significant predictor (p = .008). A chi-square deviance test indicated that the middle change model did not have significantly better fit than a reduced middle change model that only included middle changes in the General Depression symptom change factor ($\chi^2 = 49.0$, df = 3, p = .43), indicating that the reduced middle change model (table 8) was a better candidate model.

Including middle changes in the General Depression symptom change factor resulted in early changes in the Insomnia factor no longer having statistically significant predictive power, indicating a possible mediation pathway. Early changes in the Insomnia symptom change factor were a statistically significant predictor of middle changes in the General Depression symptom change factor, and a Sobel mediation test (z = 3.12, p = .0002) was consistent with a full mediation pathway from early improvements in Insomnia symptoms leading to middle improvements in General Depression symptoms leading to better end-of-treatment outcomes.

The early change model in the Escitalopram treatment group (table 9) had better fit than a baseline model that only included the baseline scores in the symptom change factors ($\chi^2 = 726$, df = 4, $p = 1.4 \times 10^{-6}$) in predicting end-of-treatment HAM-D scores. As in the CBT group, early changes in an Insomnia symptom change factor predicted better end-of-treatment outcomes (p = .004). Early improvement in the Agitation and Anxiety symptom change factor was also predictive of better end-of-treatment outcomes (p = .042). As in the CBT group, early changes in the general depression factor were not predictive of end-of-treatment outcomes (p = 0.127).

The middle change model in the Escitalopram group (table 10) had better fit than the early change model ($\chi^2 = 456.43$, df = 4, $p = 2.3 \times 10^{-5}$). Unlike the CBT group, there was no indication of a potential meditational pathway from early changes in insomnia to middle changes in the general depression factor to end-of-treatment outcomes. Early changes in the Insomnia symptom change factor remained a statistically significant predictor of end-of-treatment outcomes (p = .001), even with the inclusion of middle changes in the symptom change factors. In fact, the magnitude of the association strengthened between early change in Insomnia and end-of-treatmnet outcomes. Whereas in the CBT group, only middle change in the General Depression symptom change factor was predictive of outcomes, in the Escitalopram group, middle improvements in both the General Depression (p = .019) and Insomnia (p = .048) symptom change factors indicated better outcomes.

The early change model in the Duloxetine treatment group (table 11) also had better fit than a baseline model of only the baseline symptom change factor scores ($\chi^2 = 783.21$, df = 4, $p = 8.6 \times 10^{-8}$). Unlike the CBT and Escitalopram groups, in the

Duloxetine group, early change in the Insomnia symptom change factor did not predict better end-of-treatment outcomes ($p = .877$), and early changes in the General Depression symptom change factor were predictive of outcomes ($p = 1.5 \times 10^{-5}$). When middle changes in the symptom change factors were added (table 12), both early ($p = 4.3 \times 10^{-6}$) and middle changes ($p = .002$) in the General Depression symptom change factor were predictive of end-of-treatment outcomes. No other symptom change factors were statistically significant predictors of outcomes in the Duloxetine group, although it should be noted that in the middle change model, early change in the Agitation and Anxiety symptom change factor was nearly a statistically significant predictor of end-of-treatment outcomes ($p = .057$).

During the above analyses, it was apparent there might be negative autocorrelation in the change scores along the symptom change factors. All of the change scores in the symptom change factors had statistically significant strong negative autocorrelations. The negative autocorrelations were present when examining week-to-week change scores and when looking over longer periods (e.g. 3 weeks). The potential ramifications of the negative autocorrelations are discussed below.

Discussion

The present study identified symptom change factors that ascertain the pattern of how symptoms change during the treatment of depression. Early alterations in these symptom change factors were predictive of outcomes at the end of treatment. However the specific predictive pattern differed across the CBT, Escitalopram (ESC), and Duloxetine (DUL) treatments. Early changes in insomnia symptoms were predictive of

outcomes in both the CBT and ESC treatment groups, but not in the DUL group. In the CBT group, the predictive relationship between early change in insomnia symptoms and end-of-treatment outcomes was fully mediated by middle changes in more general symptoms of depression.

Different candidate models might explain the three different predictive patterns found in the three treatments. Only the CBT treatment group demonstrated a meditational relationship between early change, middle change, and treatment outcomes. The pattern of predictive findings in the CBT group is consistent with a causal mediation pathway, although non-causal models are also consistent with the data. One candidate causal mediation pathway is that early changes in Insomnia symptoms produce later changes in the General Depression symptom change factor, which results in a better end-of-treatment outcome. In this model, early changes in Insomnia only matter because they cause later changes in the broader General Depression symptom change factor. This could simply occur because the items in the General Depression factor are a close reflection of the outcome measure, the HAM-D. There are many candidate post-hoc explanations for why early changes in insomnia might indicate a causal impact on later changes in more general depressive symptoms. For example, CBT emphasizes developing skills, such as identifying the relationships between thoughts and feelings, and identifying and modifying cognitive errors. It may be that early improvements in sleep habits are indicative of good early skill building. Early changes in insomnia in the CBT group may be an indicator of the quality of the therapeutic relationship. However, with either of these explanations, it is difficult to account for why middle changes in insomnia are not predictive of outcomes in the CBT group. Another explanation for the

observed mediation in the CBT group may be that good sleep helps facilitate the learning of new skills. Reduced sleep has been linked with poorer encoding of new experiences (Walker & van der Helm, 2009). It may be that early improvements in insomnia matter because they improve the ability to learn CBT skills. Middle improvements in insomnia might not matter because any associated improvement in encoding new skills are occurring too late in the treatment to be impactful.

Many prior studies have linked insomnia symptoms to an increased risk for depression, and some have suggested research in directly treating insomnia to reduce the risk of depression (Baglioni et al., 2011; Reimann & Voderholzer, 2003). Baglioni and colleagues (2011) called for research into whether interventions targeting insomnia symptoms might also improve depressive symptoms. To the author's knowledge, the current study is the first to demonstrate evidence that the treatment of insomnia symptoms may lead to later improvements in more general depressive symptoms. However, further research is needed to test candidate causal models. It is clear, however, that the relationship between insomnia and more general depressive symptoms is not straightforward, as the relationships between insomnia and general depressive symptoms are very different across the three treatments. It should be emphasized that a causal pathway is not required to explain the statistical mediation found in the CBT group. It may be that when depression improves, different symptoms change at different times. Early improvements in Insomnia might simply be an early indicator for the beginning of a change process. In an early-indicator model, there would not need to be a direct causal link from insomnia to more general symptoms. An early-indicator model would be consistent with the pattern of findings found in both the CBT and ESC treatments.

However, if insomnia is merely an early indicator, is not immediately clear why the predictive effects of insomnia is fully mediated in the CBT group but not mediated at all in the ESC group, and not a predictor in the DUL group. Noise in the measurements complicates the ability to decipher whether a causal mediation pathway or an early-indicator model is more appropriate explanation for the predictive pattern in the CBT group. Further research investigating whether a targeted intervention to improve insomnia symptoms reduces later depression studies might better determine the more appropriate causal model.

Changes in Insomnia symptoms were important predictive features in both the CBT and ESC treatments, but had no predictive importance in the DUL group. Early and middle changes in insomnia were indicative of a good outcome in the ESC treatment, but not in the DUL treatment. It is not readily apparent why the ESC and DUL might have a different impact on insomnia symptoms, and further investigation is warranted. Sleep disturbances have been biologically linked to depression through the regulation of the serotinergic system, and the picture is further complicated by the potential short-term anti-depressive effect of short-term sleep-deprivation (Adrien 2002). Although the potential mechanisms of the differences between the ESC and DUL treatments are unclear, it is apparent that early changes in insomnia are likely to be a useful early indicator of successful treatment outcomes in the ESC group, but not the DUL group.

Early improvement in the Agitation and Anxiety symptom change factor was also predictive of better end-of-treatment outcomes in the ESC group as versus the DUL group. The divergence between the two medications is somewhat surprising since both are used in the treatment of anxiety disorders. Although the current study is not able to

provide clear explanations as to why the predictive patterns might differ between the two antidepressant medications, it does show the potential for using patterns of symptom change as a way of describing treatment mechanisms in a richer way than a gross aggregate measure of depressive symptomatology. To the author's knowledge, this is the first study to identify different predictive patterns of anxiety symptom change between an SSRI (ESC) and an SNRI (DUL).

It is quite puzzling that early changes in core depressive symptoms were only predictive of end-of-treatment outcomes in the Duloxetine group. One would expect that any improvements in the core depressive symptomatology over the course of treatment would be predictive of better outcomes. Understanding the dynamics of the symptom change factors is complicated by a strong negative autocorrelation found across all the symptom change factors, likely reflecting a strong regression to the mean effect for the change scores. A negative autocorrelation induced by regression to the mean could make it difficult for symptom change to be a good predictor over a short time period. Across all three groups, adding middle changes in the symptom change factors to the predictive models enhanced the level of statistical significance of early change in the general depression symptom change factor. This pattern is consistent with a regression to the mean effect, as the addition of the middle changes helps control for regression to the mean effects that might confound the impact of early changes. Unfortunately, there are no clear methods to fully account for the impact of regression to the mean in the present study. Regression to the mean effects may also make it challenging to use early prediction models in clinical settings. It is important to emphasize that a strong regression to the mean effect makes it challenging to study symptom changes longitudinally. It may

be that the development of symptom measures that are focused on measuring change rather than current state might be more resistant to regression to the mean effects. Better measures of symptom change could significantly aid future research into the dynamics of symptom changes. For example, current measures of symptomatology focus on measuring the current state of symptoms at a single period of time. Alternatively, measures might focus on measuring change over a period of time, by asking whether symptoms have improved or worsened this week relative to the prior week. Measuring change in such a direct fashion could remove the regression to the mean effect and aid future research in the dynamics of symptom change.

A continuous symptom change factor approach was chosen over a discrete symptom change type model, primarily because the discrete cluster analysis did not lead to an interpretable solution. Although an interpretable discrete cluster analysis solution was not found in the present study, that does not necessarily mean that discrete types of symptom change do not exist. It may simply be that the clustering problem was too high dimensional for discrete types to be identified with the amount of data available. The discrete cluster analysis attempted to identify clusters at the item level, therefore, the 77 included items corresponded to a 77-dimensional space. Further exploration of categorical patterns of symptom change at the item level will likely require much larger datasets for interpretable findings. Larger datasets might also have the statistical power to examine the predictive utility of discrete symptom change types even if they are difficult to interpret.

The factor structure of symptom changes identified in the present study will need further replication. Due to sample-size limitations, the current study was not able to

conduct a confirmatory factor analysis of the factor structure in order to compare the fits of the factor models identified for the CBT group and the Medication groups in an unbiased way. A confirmatory factor analysis might also examine invariance in the factor structure between treatment groups, using a three-level factor analysis, with ratings over time grouped within individuals grouped with treatment groups. A larger dataset will likely be required for such an analysis.

It is interesting that although separable factors loaded onto cognitive and emotional symptoms of depression when examining between-individual differences, the within-individual differences did not support separable factors. This is consistent with differences in cognitive and emotional features of depression being a between-individual trait. In terms of how symptoms change within an individual over time during treatment, it appears that the cognitive and emotional symptoms change at the same time, at least as measured at the time-scale of the current study. Further investigations into separating within-individual variation from between-individual variation may lead to a better understanding of the trait-like and state-like features depressive symptoms. Unfortunately, the present study did not have enough subjects for a thorough exploration of the between-level latent variable structure; however, these preliminary findings suggest that further investigation may yield a more nuanced understanding of the latent structure of depressive symptoms.

The present study did not address patient attrition, an important feature of the treatment of depression. An intent-to-treat analysis was not used, because the analyses depended on observing symptom change over time and predicting end-of-treatment

outcomes, Further analyses may examine whether the early patterns in the identified symptom change factors predict patient dropout.

In the treatment of depression, it is common to complete a course of treatment before switching to or augmenting with a different treatment. A full course of treatment might take 12 weeks. The present study suggests that for some patients, it may be possible to determine whether a treatment is working or not working early on in treatment. Further replication of the symptom change factors and their predictive utility might help clinicians move toward earlier detection of treatment failures and successes. The present study also suggests that the early indicators are likely to be treatment dependent, reflecting the different mechanisms of different treatments. It should be noted that although the PReDICT study was a large-scale study, many of the analyses were computationally and statistically constrained by the size of the dataset.

The present study demonstrates the rich potential of using two-level factor analysis to describe the patterns of symptom changes during the treatment of psychological disorders. In treating change in depressive symptomatology as a multi-dimensional construct, distinct predictive patterns of symptom progression were identified between treatment with CBT, ESC, and DUL. In particular, the relationship between insomnia and more general depressive symptoms in predicting end-of-treatment outcomes appears to be an important feature indicating different mechanisms between the three treatments. Although theoretical explanations of the mechanisms underlying the different predictive patterns are unclear, the current research is an important first step towards better models of symptom change processes. A rich dynamic process can be found in the multi-dimensional analysis of patterns of symptom change. The current

study is the first to identify the importance of multi-dimensional symptom change factors for investigating treatment mechanisms and the early prediction of treatment outcomes.

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Table 1
CBT Symptom Change Factor Loadings

		1	2	3	4
		General Depression	Anxiety & Tension	Insomnia	Appetite and Weight Loss, and Agitation
BDI-1	Sadness	**0.64**	0.19	0.04	-0.01
BDI-2	Pessimism	**0.67**	-0.04	0.10	-0.07
BDI-3	Sense of Failure	**0.83**	-0.13	0.02	0.02
BDI-4	Lack of Satisfaction	**0.80**	0.04	0.00	-0.11
BDI-5	Guilt	**0.72**	-0.01	0.00	-0.04
BDI-6	Expectations of Punishment	**0.76**	-0.20	0.17	0.04
BDI-7	Self-dislike	**0.81**	-0.09	-0.05	-0.05
BDI-8	Self-accusations	**0.76**	-0.13	0.09	0.00
BDI-9	Suicidal Ideas	**0.82**	-0.12	0.03	0.13
BDI-10	Crying	**0.58**	0.10	0.10	0.04
BDI-11	Irritability	**0.58**	0.08	0.06	-0.26
BDI-12	Social Withdrawal	**0.70**	0.01	-0.04	-0.25
BDI-13	Indecisiveness	**0.71**	-0.05	0.05	-0.16
BDI-14	Body Image Change	**0.66**	-0.18	0.15	-0.05
BDI-15	Work Difficulty	**0.70**	0.05	0.04	-0.14
BDI-16	Insomnia	0.27	-0.01	**0.53**	0.02
BDI-17	Fatigability	**0.72**	-0.02	0.11	-0.12
BDI-18	Loss of Appetite	0.45	0.02	0.18	0.43
BDI-19	Weight Loss	0.40	-0.11	0.14	0.40
BDI-20	Somatic Preoccupation	0.47	0.03	0.16	-0.06
BDI-21	Loss of Libido	**0.57**	0.11	0.02	-0.31
QIDS-1	Trouble Falling Asleep	0.25	0.09	0.48	-0.13
QIDS-2	Interrupted Sleep	0.16	-0.09	0.46	-0.08
QIDS-3	Waking Early	0.15	-0.01	**0.52**	-0.03
QIDS-4	Sleeping too much	0.38	0.16	-0.02	-0.07
QIDS-5	Sadness	**0.68**	0.22	0.07	0.06
QIDS-6	Decreased Appetite	0.43	-0.04	0.30	**0.53**
QIDS-7	Increased Appetite	0.28	0.24	-0.12	-0.32
QIDS-8	Decreased Weight	0.38	-0.14	0.15	**0.59**
QIDS-9	Increased Weight	0.04	0.16	-0.06	-0.38
QIDS-10	Concentration/Indecisiveness	**0.55**	0.12	0.11	-0.16
QIDS-11	Self-criticism	**0.76**	-0.01	-0.08	-0.07
QIDS-12	Suicidality	**0.79**	-0.13	-0.03	0.22
QIDS-13	Lack of interest	**0.71**	0.10	-0.07	-0.21
QIDS-14	Energy Level	**0.58**	0.11	0.18	-0.12
QIDS-15	Slowed down	**0.62**	0.09	0.04	-0.17
QIDS-16	Restless	0.40	0.13	0.20	-0.12

Table 1 continued

		General Depression	Anxiety & Tension	Insomnia	Appetite and Weight Loss, and Agitation
MADRS-1	Apparent Sadness	**0.55**	0.35	0.01	0.18
MADRS-2	Reported Sadness	**0.57**	0.50	-0.05	0.25
MADRS-3	Inner Tension	0.06	**0.67**	0.19	-0.18
MADRS-4	Reduced Sleep	0.06	0.02	**0.89**	0.12
MADRS-5	Reduced Appetite	-0.04	0.35	0.42	**0.70**
MADRS-6	Concentration Difficulties	0.35	0.27	0.14	-0.05
MADRS-7	Lassitude	0.50	0.32	0.09	0.04
MADRS-8	Inability to feel	**0.56**	0.48	-0.16	0.00
MADRS-9	Pessimistic Thoughts	**0.53**	0.24	-0.02	0.06
MADRS-10	Suicidal Thoughts	**0.81**	0.03	-0.19	0.47
HRSD-1	Depressed Mood	**0.58**	0.41	0.05	0.16
HRSD-2	Guilt	**0.54**	0.23	0.02	0.11
HRSD-3	Suicidality	**0.91**	0.01	-0.23	**0.54**
HRSD-4	Insomnia Early	0.12	0.13	**0.64**	-0.01
HRSD-5	Insomnia Middle	0.12	0.01	**0.70**	0.05
HRSD-6	Insomnia Late	0.06	-0.05	**0.58**	0.03
HRSD-7	Work and Activities Functioning	**0.58**	**0.52**	-0.12	0.01
HRSD-8	Psychomotor Retardation	0.13	0.42	-0.03	0.05
HRSD-9	Agitation	0.07	0.47	0.01	**0.68**
HRSD-10	Psychological Anxiety	0.02	**0.74**	0.18	-0.26
HRSD-11	Somatic Anxiety	0.10	0.39	0.18	-0.03
HRSD-12	Loss of Appetite	-0.10	0.38	0.45	**0.74**
HRSD-13	General Somatic Symptoms	0.49	0.39	0.07	-0.03
HRSD-14	Genital Symptoms	**0.50**	0.19	0.00	-0.17
HRSD-15	Hypochondriasis	0.15	0.43	-0.02	0.07
HRSD-16	Loss of Weight	0.22	0.17	0.25	0.24
HRSA-1	Anxious Mood	0.00	**0.78**	0.22	-0.22
HRSA-2	Tension	0.13	**0.58**	0.14	-0.05
HRSA-3	Fears	-0.04	0.39	0.14	0.05
HRSA-4	Insomnia	0.05	0.04	**0.93**	0.06
HRSA-5	Intellectual	0.36	0.27	0.15	-0.13
HRSA-6	Depressed Mood	**0.59**	0.49	-0.06	0.27
HRSA-7	Somatic (Muscular)	0.19	0.22	0.09	-0.06
HRSA-8	Somatic (Sensory)	0.16	0.41	0.05	-0.01
HRSA-9	Cardiovascular Symptoms	0.22	0.21	0.11	0.01
HRSA-10	Respiratory Symptoms	0.09	0.35	0.06	0.11
HRSA-11	Gastrointenstinal Symptoms	-0.06	0.34	0.13	-0.05
HRSA-12	Genitourinary symptoms	0.34	0.20	0.08	-0.05
HRSA-13	Autonomic symptoms	0.05	0.38	0.20	-0.04
HRSA-14	Behavior at interview	0.02	**0.60**	-0.04	**0.74**

Table 2
Anti-Depressant Medication (ADM) Symptom Change Factor Loadings

		1	2	3	4
		General Depression	Insomnia	Appetite and Weight Loss, and Suicidality	Agitation and Anxiety
BDI-1	Sadness	**0.83**	-0.06	0.16	-0.04
BDI-2	Pessimism	**0.71**	-0.02	0.08	0.01
BDI-3	Sense of Failure	**0.75**	-0.01	0.04	-0.03
BDI-4	Lack of Satisfaction	**0.83**	-0.01	0.04	-0.06
BDI-5	Guilt	**0.77**	-0.04	0.11	0.00
BDI-6	Expectations of Punishment	**0.68**	-0.06	0.07	0.00
BDI-7	Self-dislike	**0.73**	0.03	0.03	-0.06
BDI-8	Self-accusations	**0.77**	0.04	0.02	-0.09
BDI-9	Suicidal Ideas	**0.80**	-0.15	0.24	0.10
BDI-10	Crying	**0.62**	0.10	0.13	-0.04
BDI-11	Irritability	**0.59**	0.02	0.07	0.02
BDI-12	Social Withdrawal	**0.79**	-0.02	-0.03	-0.11
BDI-13	Indecisiveness	**0.82**	-0.01	-0.03	-0.08
BDI-14	Body Image Change	**0.66**	0.02	-0.04	-0.07
BDI-15	Work Difficulty	**0.79**	0.04	-0.01	-0.12
BDI-16	Insomnia	0.30	0.50	-0.01	-0.02
BDI-17	Fatigability	**0.62**	0.16	-0.05	-0.13
BDI-18	Loss of Appetite	0.19	0.49	0.41	-0.14
BDI-19	Weight Loss	0.01	0.48	**0.56**	-0.04
BDI-20	Somatic Preoccupation	**0.54**	0.18	0.03	-0.04
BDI-21	Loss of Libido	**0.55**	0.13	-0.11	-0.20
QIDS-1	Trouble Falling Asleep	0.27	**0.56**	0.01	-0.02
QIDS-2	Interrupted Sleep	0.19	0.37	-0.01	0.00
QIDS-3	Waking Early	0.12	**0.51**	-0.06	0.00
QIDS-4	Sleeping too much	0.33	-0.01	0.02	-0.07
QIDS-5	Sadness	**0.84**	-0.04	0.14	-0.02
QIDS-6	Decreased Appetite	0.08	**0.55**	**0.51**	-0.16
QIDS-7	Increased Appetite	**0.66**	-0.26	-0.45	-0.05
QIDS-8	Decreased Weight	-0.10	0.42	**0.57**	-0.08
QIDS-9	Increased Weight	**0.51**	-0.36	-0.44	-0.06
QIDS-10	Concentration/Indecisiveness	**0.74**	0.08	-0.05	-0.10
QIDS-11	Self-criticism	**0.78**	-0.08	0.04	-0.03
QIDS-12	Suicidality	**0.69**	-0.14	0.30	0.11
QIDS-13	Lack of interest	**0.75**	0.01	-0.01	-0.09
QIDS-14	Energy Level	**0.67**	0.13	-0.05	-0.14
QIDS-15	Slowed down	**0.70**	0.13	-0.05	-0.14
QIDS-16	Restless	**0.50**	0.14	0.03	-0.01

Table 2 continued

		General Depression	Insomnia	Appetite and Weight Loss, and Suicidality	Agitation and Anxiety
MADRS-1	Apparent Sadness	**0.69**	0.09	0.17	0.12
MADRS-2	Reported Sadness	**0.76**	-0.05	0.37	0.11
MADRS-3	Inner Tension	**0.71**	-0.02	0.00	0.47
MADRS-4	Reduced Sleep	0.00	**0.92**	0.00	0.14
MADRS-5	Reduced Appetite	0.24	0.35	0.33	-0.04
MADRS-6	Concentration Difficulties	**0.90**	0.07	**-0.55**	0.05
MADRS-7	Lassitude	**0.67**	0.15	-0.03	-0.01
MADRS-8	Inability to feel	**0.75**	0.12	0.07	-0.16
MADRS-9	Pessimistic Thoughts	**0.66**	0.05	0.07	0.15
MADRS-10	Suicidal Thoughts	0.49	0.03	**0.52**	0.40
HRSD-1	Depressed Mood	**0.79**	0.10	-0.04	0.06
HRSD-2	Guilt	**0.69**	0.06	0.05	0.14
HRSD-3	Suicidality	0.50	0.01	**0.57**	0.44
HRSD-4	Insomnia Early	0.09	**0.75**	0.03	0.06
HRSD-5	Insomnia Middle	0.06	**0.73**	-0.04	0.11
HRSD-6	Insomnia Late	0.00	**0.62**	-0.02	0.01
HRSD-7	Work and Activities Functioning	**0.79**	0.16	0.07	-0.14
HRSD-8	Psychomotor Retardation	0.42	0.07	0.10	0.12
HRSD-9	Agitation	-0.01	0.23	-0.01	**0.83**
HRSD-10	Psychological Anxiety	**0.75**	-0.06	-0.04	**0.53**
HRSD-11	Somatic Anxiety	0.39	0.16	0.03	0.12
HRSD-12	Loss of Appetite	0.19	0.41	0.33	-0.04
HRSD-13	General Somatic Symptoms	**0.64**	0.18	-0.02	0.03
HRSD-14	Genital Symptoms	**0.52**	0.19	-0.05	-0.10
HRSD-15	Hypochondriasis	0.40	0.17	-0.02	0.13
HRSD-16	Loss of Weight	0.18	0.28	0.38	0.01
HRSA-1	Anxious Mood	**0.76**	-0.07	-0.06	**0.55**
HRSA-2	Tension	**0.64**	0.03	-0.01	0.41
HRSA-3	Fears	0.41	0.16	0.07	0.07
HRSA-4	Insomnia	-0.01	**0.96**	-0.04	0.17
HRSA-5	Intellectual	**0.91**	0.05	**-0.60**	0.05
HRSA-6	Depressed Mood	**0.76**	-0.06	0.38	0.11
HRSA-7	Somatic (Muscular)	0.34	0.12	-0.04	0.15
HRSA-8	Somatic (Sensory)	0.34	0.20	-0.10	0.09
HRSA-9	Cardiovascular Symptoms	0.27	0.13	0.03	0.12
HRSA-10	Respiratory Symptoms	0.35	0.10	0.07	0.16
HRSA-11	Gastrointenstinal Symptoms	0.20	0.20	0.00	0.05
HRSA-12	Genitourinary symptoms	0.39	0.17	-0.08	-0.06
HRSA-13	Autonomic symptoms	0.28	0.18	0.01	0.13
HRSA-14	Behavior at interview	-0.06	0.27	0.01	**0.85**

Table 3
CBT Symptom Change Factor and Individual Difference Factor Cosine Similarity

	Individual Differences Factors				
Symptom Change Factors	Cognitive Depressive Symptoms	Emotional, Anhedonia, Somatic Depressive Symptoms	Appetite and Weight Loss	Somatic Anxiety	Insomnia
General Depression	0.65	0.75	0.26	0.33	0.11
Anxiety & Tension	-0.12	0.58	0.17	0.51	0.06
Insomnia	0.03	0.16	0.24	0.24	0.85
Appetite and Weight Loss, and Agitation	0.15	-0.02	0.68	-0.26	-0.05

Table 4
ADM Symptom Change Factor and Individual Difference Factor Cosine Similarity

	Individual Differences Factors			
Symptom Change Factors	General Depression	Anhedonia, Reduced Functioning, Appetite Loss	Insomnia	Somatic Anxiety
General Depression	0.87	0.57	0.10	0.40
Insomnia	0.05	0.39	0.84	0.15
Appetite and Weight Loss, and Suicidality	0.20	0.25	0.19	-0.13
Agitation and Anxiety	0.18	-0.15	0.18	0.08

Table 5
CBT and ADM Symptom Change Factor Cosine Similarity

	ADM Symptom Change Factors			
CBT Symptom Change Factors	General Depression	Insomnia	Appetite and Weight Loss, and Suicidality	Agitation and Anxiety
General Depression	0.90	0.23	0.32	0.02
Anxiety & Tension	0.57	0.22	0.02	0.57
Insomnia	0.21	0.88	0.07	0.12
Appetite and Weight Loss, and Agitation	-0.08	0.37	0.70	0.36

Table 6
CBT Early Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	0.01	3.64	0.00	0.998	
Baseline Level						
General Depression	0.03	0.06	0.21	0.29	0.777	
Anxiety & Tension	0.18	1.87	1.20	1.56	0.125	
Insomnia	0.38	1.78	0.51	3.46	0.001	***
Appetite and Weight Loss, and Agitation	0.32	2.27	1.01	2.24	0.028	*
Early Change (First 3 Weeks)						
General Depression	0.15	0.27	0.22	1.27	0.210	
Anxiety & Tension	0.23	1.65	0.91	1.82	0.075	†
Insomnia	0.36	1.98	0.68	2.90	0.005	**
Appetite and Weight Loss, and Agitation	0.15	1.41	1.28	1.10	0.275	

Model R^2: 0.48
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 7
CBT Middle Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	-3.04	3.19	-0.95	0.344	
Baseline Level						
General Depression	0.21	0.40	0.23	1.80	0.078	†
Anxiety & Tension	0.23	2.39	1.16	2.06	0.044	*
Insomnia	0.36	1.71	0.57	3.02	0.004	**
Appetite and Weight Loss, and Agitation	0.32	2.27	0.96	2.35	0.022	*
Early Change (First 3 Weeks)						
General Depression	0.35	0.62	0.23	2.73	0.008	**
Anxiety & Tension	0.26	1.88	0.95	1.98	0.053	†
Insomnia	0.13	0.74	0.79	0.94	0.354	
Appetite and Weight Loss, and Agitation	0.12	1.06	1.19	0.89	0.375	
Middle Change (Second 3 Weeks)						
General Depression	0.43	0.75	0.25	2.99	0.004	**
Anxiety & Tension	0.16	1.25	0.89	1.40	0.166	
Insomnia	0.06	0.30	0.59	0.51	0.612	
Appetite and Weight Loss, and Agitation	-0.12	-1.27	1.14	-1.12	0.268	

Model R^2: 0.65
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 8
CBT Reduced Middle Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	-2.36	3.10	-0.76	0.449	
Baseline Level						
General Depression	0.26	0.49	0.19	2.52	0.014	*
Anxiety & Tension	0.15	1.59	1.02	1.57	0.123	
Insomnia	0.33	1.56	0.43	3.60	0.001	***
Appetite and Weight Loss, and Agitation	0.38	2.73	0.86	3.19	0.002	**
Early Change (First 3 Weeks)						
General Depression	0.41	0.72	0.20	3.58	0.001	***
Anxiety & Tension	0.17	1.18	0.77	1.53	0.132	
Insomnia	0.09	0.50	0.64	0.77	0.442	
Appetite and Weight Loss, and Agitation	0.18	1.64	1.08	1.53	0.132	
Middle Change (Second 3 Weeks)						
General Depression	0.50	0.87	0.17	5.11	0.000	***

Model R^2: 0.64
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 9
Escitalopram Early Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	-1.28	3.33	-0.38	0.702	
Baseline Level						
General Depression	0.39	0.55	0.14	3.97	0.000	***
Insomnia	0.08	0.37	0.53	0.70	0.485	
Appetite and Weight Loss, and Suicidality	-0.05	-0.35	1.26	-0.28	0.781	
Agitation and Anxiety	0.14	1.81	1.52	1.19	0.238	
Early Change (First 3 Weeks)						
General Depression	0.18	0.21	0.14	1.54	0.127	
Insomnia	0.30	1.20	0.40	3.00	0.004	**
Appetite and Weight Loss, and Suicidality	0.13	0.98	1.28	0.77	0.446	
Agitation and Anxiety	0.25	2.30	1.11	2.07	0.042	*

Model R^2: 0.41
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 10
Escitalopram Middle Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	-1.64	2.93	-0.56	0.577	
Baseline Level						
General Depression	0.45	0.64	0.13	4.86	0.000	***
Insomnia	0.09	0.42	0.50	0.84	0.403	
Appetite and Weight Loss, and Suicidality	0.26	1.88	1.57	1.20	0.236	
Agitation and Anxiety	0.14	1.78	1.49	1.19	0.237	
Early Change (First 3 Weeks)						
General Depression	0.22	0.25	0.13	1.96	0.054	†
Insomnia	0.35	1.41	0.39	3.61	0.001	***
Appetite and Weight Loss, and Suicidality	0.40	3.03	1.64	1.85	0.069	†
Agitation and Anxiety	0.24	2.21	1.15	1.91	0.060	†
Middle Change (Second 3 Weeks)						
General Depression	0.24	0.32	0.13	2.40	0.019	*
Insomnia	0.20	0.92	0.46	2.01	0.048	*
Appetite and Weight Loss, and Suicidality	0.21	2.46	1.54	1.60	0.114	
Agitation and Anxiety	-0.01	-0.06	1.07	-0.06	0.952	

Model R^2: 0.57
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 11
Duloxetine Early Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	0.36	2.83	0.13	0.898	
Baseline Level						
General Depression	0.38	0.56	0.17	3.38	0.001	**
Insomnia	0.26	1.01	0.40	2.54	0.013	*
Appetite and Weight Loss, and Suicidality	0.01	0.11	1.18	0.09	0.926	
Agitation and Anxiety	-0.05	-0.66	1.64	-0.40	0.690	
Early Change (First 3 Weeks)						
General Depression	0.50	0.59	0.13	4.62	0.000	***
Insomnia	0.02	0.07	0.46	0.16	0.877	
Appetite and Weight Loss, and Suicidality	0.12	0.91	1.19	0.77	0.445	
Agitation and Anxiety	0.08	0.71	1.12	0.64	0.525	

Model R^2: 0.44
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Table 12
Duloxetine Middle Change Prediction Model

	Standardized Coefficient	Coefficient	Standard Error	t Statistic	Prob(>|t|)	
Intercept	0.00	0.76	2.52	0.30	0.764	
Baseline Level						
General Depression	0.42	0.63	0.15	4.11	0.000	***
Insomnia	0.18	0.69	0.37	1.88	0.063	†
Appetite and Weight Loss, and Suicidality	0.00	-0.02	1.19	-0.02	0.986	
Agitation and Anxiety	0.05	0.65	1.53	0.43	0.672	
Early Change (First 3 Weeks)						
General Depression	0.53	0.64	0.13	4.96	0.000	***
Insomnia	0.04	0.16	0.42	0.38	0.706	
Appetite and Weight Loss, and Suicidality	0.11	0.87	1.21	0.72	0.472	
Agitation and Anxiety	0.26	2.38	1.23	1.93	0.057	.
Middle Change (Second 3 Weeks)						
General Depression	0.31	0.41	0.13	3.13	0.002	**
Insomnia	0.06	0.36	0.46	0.79	0.432	
Appetite and Weight Loss, and Suicidality	-0.05	-0.65	1.08	-0.60	0.553	
Agitation and Anxiety	0.18	1.58	1.00	1.57	0.121	

Model R^2: 0.59
† Probability(>|t|) < .10, * Probability(>|t|) < .05, ** Probability(>|t|) < .01, *** Probability(>|t|) < .001

Appendix A

Table A1
CBT Between-Individual Factor Loadings

		Cognitive Depressive Symptoms	Emotional, Anhedonia, Somatic Depressive Symptoms	Decreased Appetite and Weight	Somatic Anxiety	Insomnia
BDI-1	Sadness	0.37	**0.54**	-0.01	-0.01	0.11
BDI-2	Pessimism	**0.58**	**0.52**	0.00	-0.12	-0.03
BDI-3	Sense of Failure	**0.74**	0.35	0.03	-0.02	-0.04
BDI-4	Lack of Satisfaction	0.26	**0.59**	0.14	0.06	0.05
BDI-5	Guilt	**0.75**	0.36	0.00	-0.04	0.01
BDI-6	Expectations of Punishment	**0.64**	0.34	0.16	0.00	0.06
BDI-7	Self-dislike	**0.69**	0.42	-0.15	-0.09	0.05
BDI-8	Self-accusations	**0.70**	0.44	-0.01	-0.05	0.00
BDI-9	Suicidal Ideas	**0.82**	-0.02	0.14	0.15	-0.03
BDI-10	Crying	0.12	0.38	0.01	0.28	0.14
BDI-11	Irritability	0.18	**0.53**	-0.10	0.22	0.03
BDI-12	Social Withdrawal	0.25	**0.55**	0.08	0.10	0.08
BDI-13	Indecisiveness	0.21	0.45	0.07	0.27	-0.15
BDI-14	Body Image Change	0.42	0.21	-0.31	0.26	-0.01
BDI-15	Work Difficulty	0.05	**0.79**	-0.12	-0.07	0.06
BDI-16	Insomnia	0.13	0.04	0.06	0.21	**0.68**
BDI-17	Fatigability	0.15	**0.59**	-0.11	0.18	0.13
BDI-18	Loss of Appetite	0.13	0.03	**0.71**	0.25	-0.20
BDI-19	Weight Loss	0.32	-0.16	**0.61**	0.02	-0.03
BDI-20	Somatic Preoccupation	0.04	0.16	0.08	0.43	0.01
BDI-21	Loss of Libido	0.00	0.12	0.15	0.40	0.01
QIDS-1	Trouble Falling Asleep	-0.01	0.15	0.01	0.10	**0.51**
QIDS-2	Interrupted Sleep	0.11	0.14	-0.10	-0.05	**0.74**
QIDS-3	Waking Early	0.04	-0.23	0.09	0.32	**0.72**
QIDS-4	Sleeping too much	-0.03	0.23	-0.07	-0.07	-0.32
QIDS-5	Sadness	0.28	**0.58**	0.04	0.02	0.21
QIDS-6	Decreased Appetite	0.03	0.00	**0.77**	0.11	0.06
QIDS-7	Increased Appetite	0.07	-0.08	**-0.70**	**0.66**	-0.10
QIDS-8	Decreased Weight	0.21	-0.19	**0.55**	-0.02	0.04
QIDS-9	Increased Weight	0.14	-0.07	-0.44	**0.53**	-0.22
QIDS-10	Concentration/Indecisiveness	-0.01	**0.58**	0.02	0.27	-0.01
QIDS-11	Self-criticism	**0.75**	0.32	-0.04	0.03	-0.06
QIDS-12	Suicidality	**0.82**	0.03	0.14	0.07	-0.09
QIDS-13	Lack of interest	0.22	**0.58**	0.12	0.23	0.01
QIDS-14	Energy Level	0.00	**0.64**	-0.14	0.07	0.17
QIDS-15	Slowed down	-0.30	0.34	0.07	0.47	0.02
QIDS-16	Restless	0.16	0.18	0.05	0.24	0.17

Table A1 continued

		Cognitive Depressive Symptoms	Emotional, Functioning, Somatic Depressive Symptoms	Loss of Appetite and Weight Loss	Somatic Anxiety	Insomnia
MADRS-1	Apparent Sadness	0.00	**0.74**	0.24	-0.13	0.03
MADRS-2	Reported Sadness	0.02	**0.73**	0.24	0.15	0.08
MADRS-3	Inner Tension	0.14	0.45	-0.04	0.38	0.17
MADRS-4	Reduced Sleep	0.00	0.13	0.02	-0.05	**0.93**
MADRS-5	Reduced Appetite	0.06	0.05	**0.83**	-0.05	0.01
MADRS-6	Concentration Difficulties	-0.29	**0.53**	0.07	0.40	-0.03
MADRS-7	Lassitude	-0.21	**0.88**	-0.01	-0.02	-0.08
MADRS-8	Inability to feel	-0.14	**0.65**	0.31	0.16	-0.06
MADRS-9	Pessimistic Thoughts	0.26	**0.58**	0.05	-0.21	0.07
MADRS-10	Suicidal Thoughts	**0.59**	0.04	0.38	0.03	-0.01
HRSD-1	Depressed Mood	0.03	**0.74**	0.16	0.15	0.08
HRSD-2	Guilt	**0.51**	0.42	0.07	-0.02	0.06
HRSD-3	Suicidality	**0.68**	-0.02	0.39	0.07	-0.01
HRSD-4	Insomnia Early	-0.04	0.19	-0.03	0.02	**0.59**
HRSD-5	Insomnia Middle	-0.03	0.19	-0.05	-0.14	**0.85**
HRSD-6	Insomnia Late	-0.01	-0.14	0.09	0.12	**0.75**
HRSD-7	Work and Activities Functioning	-0.14	**0.82**	0.25	0.01	-0.07
HRSD-8	Psychomotor Retardation	-0.31	0.35	0.36	-0.09	-0.06
HRSD-9	Agitation	0.03	0.36	-0.20	-0.26	-0.31
HRSD-10	Psychological Anxiety	0.09	0.44	-0.08	0.34	0.15
HRSD-11	Somatic Anxiety	-0.07	0.09	0.03	**0.75**	0.08
HRSD-12	Loss of Appetite	0.00	0.10	**0.85**	-0.04	0.00
HRSD-13	General Somatic Symptoms	-0.19	**0.79**	-0.02	0.04	0.02
HRSD-14	Genital Symptoms	-0.13	0.06	0.15	0.34	-0.09
HRSD-15	Hypochondriasis	0.01	-0.22	-0.02	0.45	0.04
HRSD-16	Loss of Weight	0.15	-0.23	**0.73**	0.05	0.13
HRSA-1	Anxious Mood	0.23	0.42	-0.14	0.37	0.15
HRSA-2	Tension	0.14	0.32	-0.06	**0.56**	0.09
HRSA-3	Fears	-0.03	-0.23	0.24	0.49	0.13
HRSA-4	Insomnia	-0.04	0.09	0.02	0.01	**0.97**
HRSA-5	Intellectual	-0.25	0.49	0.00	0.44	-0.06
HRSA-6	Depressed Mood	0.05	**0.77**	0.11	0.15	0.05
HRSA-7	Somatic (Muscular)	-0.01	0.15	-0.07	**0.67**	-0.18
HRSA-8	Somatic (Sensory)	-0.18	-0.05	0.11	**0.73**	0.06
HRSA-9	Cardiovascular Symptoms	-0.17	0.01	-0.21	**0.67**	0.16
HRSA-10	Respiratory Symptoms	-0.30	0.11	0.16	**0.64**	-0.01
HRSA-11	Gastrointenstinal Symptoms	-0.24	0.06	0.05	**0.88**	-0.01
HRSA-12	Genitourinary symptoms	-0.07	0.06	0.07	0.46	-0.12
HRSA-13	Autonomic symptoms	-0.09	0.08	-0.05	**0.50**	0.23
HRSA-14	Behavior at interview	-0.11	0.49	0.01	-0.46	-0.23

Table A2
Anti-Depressant Medication (ADM) Between-Individual Factor Loadings

		Cognitive and Emotional Depressive Symptoms	Anhedonia, Decreased Functioning and Appetite.	Insomnia	Somatic Anxiety
BDI-1	Sadness	**0.70**	0.18	0.03	0.02
BDI-2	Pessimism	**0.88**	0.07	0.08	-0.22
BDI-3	Sense of Failure	**0.89**	-0.02	-0.09	-0.07
BDI-4	Lack of Satisfaction	**0.71**	0.32	0.05	0.03
BDI-5	Guilt	**0.85**	0.03	-0.08	0.01
BDI-6	Expectations of Punishment	**0.72**	-0.12	-0.04	0.14
BDI-7	Self-dislike	**0.91**	-0.06	-0.01	-0.18
BDI-8	Self-accusations	**0.85**	-0.12	-0.02	0.03
BDI-9	Suicidal Ideas	**0.55**	0.14	0.11	-0.06
BDI-10	Crying	0.35	0.12	0.02	0.14
BDI-11	Irritability	0.40	0.15	0.10	0.27
BDI-12	Social Withdrawal	0.45	**0.52**	-0.10	-0.03
BDI-13	Indecisiveness	0.49	0.50	-0.17	0.01
BDI-14	Body Image Change	**0.64**	-0.30	-0.02	0.24
BDI-15	Work Difficulty	0.48	**0.50**	-0.03	-0.07
BDI-16	Insomnia	0.10	0.13	**0.78**	0.01
BDI-17	Fatigability	0.31	0.39	0.11	0.20
BDI-18	Loss of Appetite	0.02	**0.66**	0.17	-0.09
BDI-19	Weight Loss	-0.11	0.25	0.20	0.09
BDI-20	Somatic Preoccupation	0.18	0.06	0.06	**0.56**
BDI-21	Loss of Libido	0.05	0.44	0.12	0.13
QIDS-1	Trouble Falling Asleep	0.10	-0.04	**0.62**	-0.01
QIDS-2	Interrupted Sleep	-0.06	0.12	**0.68**	0.09
QIDS-3	Waking Early	0.10	0.08	**0.66**	0.04
QIDS-4	Sleeping too much	0.20	0.18	-0.27	-0.10
QIDS-5	Sadness	**0.70**	0.17	0.00	0.13
QIDS-6	Decreased Appetite	-0.02	**0.59**	0.22	-0.03
QIDS-7	Increased Appetite	0.19	-0.30	-0.19	0.49
QIDS-8	Decreased Weight	-0.21	0.30	0.11	0.21
QIDS-9	Increased Weight	0.18	-0.23	-0.22	0.40
QIDS-10	Concentration/Indecisiveness	0.35	**0.56**	-0.13	0.11
QIDS-11	Self-criticism	**0.86**	-0.01	-0.03	-0.04
QIDS-12	Suicidality	**0.54**	0.09	0.12	-0.14
QIDS-13	Lack of interest	0.45	**0.63**	-0.02	-0.03
QIDS-14	Energy Level	0.45	0.49	0.06	0.10
QIDS-15	Slowed down	0.27	0.47	-0.23	0.40
QIDS-16	Restless	0.26	0.09	0.19	0.14

Table A2 continued

		Cognitive and Emotional Depressive Symptoms	Anhedonia, Decreased Functioning and Appetite.	Insomnia	Somatic Anxiety
MADRS-1	Apparent Sadness	**0.51**	0.18	0.17	0.04
MADRS-2	Reported Sadness	**0.57**	0.28	0.08	0.18
MADRS-3	Inner Tension	0.37	-0.10	0.19	0.42
MADRS-4	Reduced Sleep	0.08	-0.03	**0.95**	0.02
MADRS-5	Reduced Appetite	-0.03	**0.65**	0.22	-0.09
MADRS-6	Concentration Difficulties	0.19	**0.59**	-0.11	0.17
MADRS-7	Lassitude	0.36	**0.58**	-0.01	0.01
MADRS-8	Inability to feel	0.35	**0.59**	-0.02	0.15
MADRS-9	Pessimistic Thoughts	**0.81**	0.01	0.11	-0.25
MADRS-10	Suicidal Thoughts	**0.56**	0.01	0.13	-0.12
HRSD-1	Depressed Mood	**0.52**	0.28	0.04	0.21
HRSD-2	Guilt	**0.84**	-0.04	-0.01	-0.04
HRSD-3	Suicidality	**0.61**	-0.02	0.13	-0.15
HRSD-4	Insomnia Early	0.06	-0.06	**0.61**	0.02
HRSD-5	Insomnia Middle	-0.01	0.05	**0.79**	0.02
HRSD-6	Insomnia Late	0.15	-0.06	**0.77**	0.00
HRSD-7	Work and Activities Functioning	**0.51**	**0.57**	-0.03	-0.03
HRSD-8	Psychomotor Retardation	0.22	0.23	-0.01	-0.04
HRSD-9	Agitation	0.06	0.07	-0.03	-0.32
HRSD-10	Psychological Anxiety	0.49	-0.04	0.13	0.20
HRSD-11	Somatic Anxiety	-0.20	0.03	0.02	**0.85**
HRSD-12	Loss of Appetite	-0.03	**0.65**	0.25	-0.11
HRSD-13	General Somatic Symptoms	0.27	0.41	0.10	0.18
HRSD-14	Genital Symptoms	-0.05	0.43	0.14	0.16
HRSD-15	Hypochondriasis	0.05	0.03	0.00	**0.51**
HRSD-16	Loss of Weight	-0.12	**0.56**	-0.02	-0.07
HRSA-1	Anxious Mood	0.48	-0.07	0.08	0.15
HRSA-2	Tension	0.23	-0.01	0.22	**0.57**
HRSA-3	Fears	0.13	0.11	-0.22	0.46
HRSA-4	Insomnia	0.15	0.01	**0.91**	0.00
HRSA-5	Intellectual	0.18	**0.57**	-0.07	0.18
HRSA-6	Depressed Mood	**0.53**	0.29	0.08	0.18
HRSA-7	Somatic (Muscular)	0.10	0.01	0.09	**0.51**
HRSA-8	Somatic (Sensory)	-0.08	0.21	0.06	**0.66**
HRSA-9	Cardiovascular Symptoms	-0.01	0.02	-0.01	**0.76**
HRSA-10	Respiratory Symptoms	0.02	-0.01	-0.06	**0.78**
HRSA-11	Gastrointenstinal Symptoms	-0.07	0.06	0.02	**0.78**
HRSA-12	Genitourinary symptoms	-0.09	0.43	0.08	0.26
HRSA-13	Autonomic symptoms	-0.10	0.09	0.09	**0.72**
HRSA-14	Behavior at interview	0.13	0.06	0.03	-0.35