Distribution Agreement

In presenting this thesis as a partial fulfillment of the requirements for a degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter now, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Benjamin Furman March 23, 2020

Daily life stressors in the course of Major Depressive Disorder: Changes with treatment and potential predictor and moderator of treatment response

By

Benjamin Furman

Boadie W. Dunlop, MD, MSCR
Adviser

Neuroscience and Behavioral Biology

Boadie W. Dunlop, MD, MSCR
Adviser

Kristen Frenzel, PhD
Committee Member

Robert McCauley, PhD
Committee Member

2020

Daily life stressors in the course of Major Depressive Disorder: Changes with treatment and potential predictor and moderator of treatment response

By

Benjamin Furman

Boadie W. Dunlop, MD, MSCR
Adviser

An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2020

Abstract

Daily life stressors in the course of Major Depressive Disorder: Changes with treatment and potential predictor and moderator of treatment response

By Benjamin Furman

Background: Major Depressive Disorder (MDD) is one of the most prevalent and debilitating diseases worldwide. While the primary treatment options for MDD, evidence-based psychotherapy and pharmacotherapy, are equally effective for a population, for a given patient one treatment might provide significantly better results. Moreover, there have been few clinical or biological factors identified that predict differential response to these treatments and can thus guide optimal treatment selection

Objective: The Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study aimed to identify both clinical and biological factors that are predictive of treatment outcomes in MDD in treatment-naïve adults. This study evaluated whether scores on the Hassles and Uplifts Scale (HUPS) can serve as either general predictors of treatment outcome or moderators of the relationship between treatment type and treatment outcome.

Method: Treatment-naïve adults between the ages of 18 and 65 with MDD were randomly assigned with equal likelihood to 12 weeks of acute treatment in one of three treatment groups: escitalopram (selective serotonin reuptake inhibitor), duloxetine (serotonin norepinephrine reuptake inhibitor), or Cognitive Behavioral Therapy (CBT). Prior to treatment and following the end of acute treatment, participants responded to the HUPS. The primary outcome measure was change in the 17-item Hamilton Depression Rating Scale.

Results: Hassle scores generally significantly decreased and uplift scores generally increased following the conclusion of acute treatment. For the entire sample, the ratio of mean hassle intensity to mean uplift intensity scores (MHI:MUI) was a statistically significant predictor of treatment response and remission, and uplift frequency (UF) and the ratio of hassle frequency to uplift frequency (HF:UF) were significant, but weaker, predictors of remission. For patients in the CBT treatment arm, MHI:MUI was also a statistically significant predictor of response and remission while mean hassle intensity predicted response and UF and HF:UF predicted remission. However, HUPS scores did not predict response and remission for patients treated with medication. HUPS scores did not moderate the relationship between treatment method and treatment outcome.

Conclusion: Scores on the HUPS can predict treatment response and remission to CBT but not medication, yet they do not moderate differential remission rates.

Daily life stressors in the course of Major Depressive Disorder: Changes with treatment and potential predictor and moderator of treatment response

By

Benjamin Furman

Boadie W. Dunlop, MD, MSCR
Adviser

A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2020

Acknowledgements

I would like to thank Boadie Dunlop, MD, MSCR for his incredible mentorship and guidance throughout this process as well as then entire Mood and Anxiety Disorders Program at Emory University for fostering a welcoming and educational research environment. I would also like to thank Helen Mayberg, MD, W. Edward Craighead, PhD, Tanja Mletzko Crowe, MA, and Mary Kelley PhD for their assistance in acquiring and working with the data. Finally, I would like to thank Anika Wu for her support throughout this process. Without these people, none of this would have been possible.

Table of Contents

Introduction:

Major depressive disorder (MDD) is a highly prevalent and debilitating health issue. Approximately seven percent of the American population experiences an episode of MDD during a given year and just over sixteen percent experience MDD over the course of their lifetime (Kessler, 2003). A study published by the Harvard School of Public Health, the World Health Organization, and the World Bank concluded that in 1990, MDD was the fourth most disabling disease in the world and predicted that, by 2020, it would be the second most disabling disease, trailing only ischemic heart disease (Murray et al., 1996). MDD can also be the cause of immense financial pressure for patients with the disorder. Among primary care patients, the cost of healthcare for patients with MDD is approximately double that of individuals without MDD (Simon, Korff, and Barlow, 1995). The financial burden felt by individuals suffering from MDD can be attributed to a multitude of causes; however, the principal factor at hand is that patients suffering from MDD receive medical care at a rate four times greater than persons without MDD (Simon, Korff, and Barlow, 1995). Additionally, MDD correlates with an increased risk for other debilitating medical conditions such as diabetes mellitus, heart disease, and stroke (Whooley and Wong, 2013). MDD can also lead to suicidal ideations. Suicide is a prominent global health issue; 1.4% of all deaths worldwide in 2016 were suicides and it was the second leading cause of death in people aged 15-29 years old (WHO, 2019).

According to the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), a major depressive episode is diagnosed by the presence of a depressed mood or anhedonia, along with several associated symptoms (including reduced energy, changes in sleep, changes in appetite or weight, feelings of worthlessness or guilt, lowered abilities to concentrate or make decisions, psychomotor changes, and suicidal ideations) that are present most of the day, nearly

every day, over a minimum of a two-week period (American Psychiatric Association, 2013). These symptoms often first appear between the ages of 15 and 29 (Fergusson et al., 2005). For most people, major depressive episodes are not isolated incidents. MDD is a highly recurrent disorder; at least 50% of patients who recover from an initial depressive episode will have one or more additional episodes throughout their lives and nearly 80% of patients who have experienced two episodes will have at least one more recurrence (Burcusa and Iacono, 2008). The debilitating nature of both the symptomatology and recurrence of MDD make its effective treatment of upmost importance.

One of the premier challenges in effectively treating MDD is the choice of the initial intervention. The two primary initial treatment options for MDD are an evidence-based psychotherapy and pharmacotherapy (Otte et al., 2016). On average, both evidence-based psychotherapies and pharmacotherapies exhibit relatively equivalent efficacy (Amick et al, 2015 and Weitz et al, 2015). However, there is substantial inter-patient variability of response among different treatments. Thus, while both pharmacotherapy and psychotherapy are roughly equally effective treatments in general, for a given patient one treatment might provide significantly better results while another treatment might not work at all. It is therefore of great importance to create procedures to select the single best treatment available on an individual basis. Delivering a combination of medication and psychotherapy is not an efficient solution, as it is significantly more expensive, unattainable for many patients, and a wasteful use of healthcare resources. This goal is at the heart of a movement called personalized medicine (also known as precision medicine and personalized intervention), in which identifying individual-level indicators of treatment outcomes are emphasized over group-level, average outcomes (Simon and Perlis,

2010). In essence, personalized medicine is the search for "… the right pill [i.e., type of intervention] at the right time for the right patient" (Binder and Holsboer, 2006).

To identify such treatments, it is necessary to identify measurable attributes of patients that can serve as guides for the initial treatment selection. Such attributes may be found in a variety of domains including sociodemographic variables, clinical attributes, and biological markers (Simon and Perlis, 2010). These characteristics can be further classified as either predictors or moderators. A predictor is a patient characteristic, biological or clinical, of which either the presence or intensity influences the probability of a certain outcome during treatment (Papakostas and Fava, 2008). In contrast to a predictor, which predicts the likelihood of general treatment outcome, a moderator is a differential predictor; that is, a moderator is a clinical or biological patient characteristic, the presence or magnitude of which, at pre-treatment baseline, influences the relative likelihood of a given outcome occurring following treatment with one treatment versus another (Papokostas and Fava, 2008). Essentially, a characteristic would be deemed a moderator if patients with Characteristic X responded differently to Treatment A versus Treatment B (Simon and Perlis, 2010).

To this point, most studies investigating potential biological measures as predictors of treatment response have been limited to investigations of patient response to a single treatment modality (i.e., either psychotherapy or pharmacotherapy), and, thus, do not serve to elucidate whether a particular treatment is better suited to a particular patient (Kemp et al., 2008). Conversely, there have been a limited number of studies investigating clinical and socio-demographic factors as moderators for initial treatment choice. A few clinical variables have been identified from earlier studies as potential moderators for selecting between psychotherapy and pharmacotherapy. Two studies have reported that personality variables (i.e., the presence of

a personality disorder or higher levels of neuroticism) at pre-treatment baseline predicted better response to pharmacotherapy than psychotherapy (Fournier et al., 2008; Bagby et al., 2008). Another potential moderator is a history of childhood traumatic events; patients with a greater history of such events may respond better to psychotherapy than pharmacotherapy (Nemeroff et al, 2003).

Psychological stress has long been considered an important contributor to the development of PTSD, and the field of stress studies in depression is vast (Hammen, 2005). Given this history, it is surprising that so little work has examined stress levels as a moderator of treatment response in MDD. One study examining the effect of personal life factors, such as recent stressful life events, unemployment, and marital status, also predicted more favorable MDD treatment outcomes from psychotherapy as opposed to pharmacotherapy, but did not isolate current stressors specifically as a predictive variable. (Fournier et al., 2009).

Studies of psychological stress fall predominately within two broad categories: studies examining biological measures of stress, such as Hypothalamus-Pituitary-Adrenal (HPA) axis activity (Godoy et al., 2018), and studies which use patient-reported surveys or questionnaires to measure stress. The second category can be further divided into studies of stress caused by major life events and stress caused by chronic minor stressors, with the former comprising much of the research (DeLongis et al., 1982; Kanner et al., 1981; Salleh, 2008). However, there is a school of thought that chronic minor stressors, known as daily hassles, can predict future illness more accurately than major life events (DeLongis et al., 1982). In this conceptualization, major life events are distal measures of stress as they are merely representations of individual events and not the consequences they impose (DeLongis et al., 1982). Daily hassles, on the other hand, are a more proximal measure of stress as they represent an immediate stressor present in

everyday life and the individual's evaluation of the stressor (DeLongis et al., 1982). This belief is reflected in the chronic mild stress (CMS) model of depression, the predominant animal research model of MDD (Willner, 2017). In the CMS, rats or mice, are chronically stimulated with micro-stressors (Willner, 2017). This stimulation results in the animals developing behaviors that are analogous to depressive symptomatology in humans, such as a decreased response to rewards, and anhedonia (Willner, 2017).

To assess chronic minor stressors, the Daily Hassles and Uplifts Scale (HUPS), a questionnaire originally comprised of 117 potential day-to-day stressors in eight broad categories (work, family, social activities, environment, practical considerations, finances and health), was created by Anita DeLongis and colleagues. The scale also assesses uplifts, conceptualized as the inverse of daily hassles (i.e., minor positive day-to-day occurrences) (DeLongis et al., 1982).

Studies utilizing the HUPS have shown correlations between number of reported hassles (hassle frequency) and somatic health status (DeLongis et al., 1982) and negative affect (Kanner et al., 1981). Other studies indicate that hassle frequency, rather than life events, may be a better predictor of current psychological symptomatology (Kanner et al., 1981; Wagner et al., 1988). Additionally, significant positive relationships have been reported for symptomatology in schizophrenic patients and daily hassle frequency (Norman and Malla, 1994), depressive symptoms and daily hassles for mothers (Pascoe, 1990), depressive symptoms and increased hassle frequency in married, recent female Arabic immigrants (Aroian et al., 2016).

In patients with MDD, hassle frequency has been reported to be higher than in healthy controls (McIntosh et al., 2009). Other studies which have used a similar measure of stress to the HUPS, called the Everyday Problem Checklist (EPCL), found EPCL scores to be higher in participants with whiplash-associated disorder (WAD) than healthy controls and much of the

general distress of patients with WAD was statistically explained by scores on the EPCL (Blokhort et al., 2002). Additionally, increased daily hassles, as measured by the EPCL, were suggested as a risk factor for recurrence of depression, while major life events during adulthood had little to no impact on recurrence (Bockting et al., 2006). These data suggest that the HUPS used as a measure of day-to-day stressors may have utility as a predictor of treatment outcomes and potentially as a moderator for selecting specific treatments.

Studies evaluating potential moderators of treatment outcome are susceptible to confounding arising from past treatments participants have received. Exposure to and outcomes of previous treatments can impact the willingness of MDD patients to enroll in clinical trials, and may induce both enduring psychological (Weiner et al., 2013; Kraus et al., 2011) and biological (Bhagwagar and Cowen, 2007; Parsey et al., 2006) effects, which might impact an individual's response to study treatments. Thus, treatment-naïve patient samples are particularly valuable when investigating potential moderators for initial treatment selection.

The Emory Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study was conducted with the goal of identifying biological and psychological factors that could serve as predictors or moderators, at the individual-level, to psychotherapy or pharmacotherapy treatment. This randomized trial enrolled treatment-naïve patients and included administration of the HUPS questionnaire at baseline and after 12 weeks of treatment. Thus, the PReDICT study provides an ideal dataset to examine whether daily hassles, uplifts, or their combination demonstrate predictive or moderating effects on treatment outcomes in patients with MDD.

Methods:

Study Overview

A design paper detailing the rationale, methods, and protocol of the PReDICT study has been previously published (Dunlop et al., 2012). The PReDICT study was conducted by the Emory University Mood and Anxiety Disorders Program and involved two clinics: 1) the primary Mood and Anxiety Disorders Program Clinic at Emory University, with a satellite location in Stockbridge, Georgia, and 2) a solely Spanish-speaking clinic at Grady Memorial Hospital in Atlanta, Georgia. The study enrolled 344 treatment-naïve patients diagnosed with MDD who were randomly assigned to one of three possible treatments: a selective serotonin reuptake inhibitor (SSRI), escitalopram, a serotonin norepinephrine reuptake inhibitor (SNRI), duloxetine, or cognitive behavior therapy (CBT). The initial phase of the study was a 12-week course with one of these treatments. Patients that did not remit following the initial 12-week treatment were offered the combination of psychotherapy and medication for another 12-week treatment course. Data from this second phase are not included in the current analysis.

Patients:

The patient sample comprised of men and women between 18-65 years of age with MDD diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995) and confirmed by a study psychiatrist's interview. Patients had to have at least moderately severe depression, defined as a Hamilton Depression Rating Scale (HAM-D) scores ≥18 at the screening visit and ≥15 at the baseline visit. Patients were also required to be treatment-naïve for depression. Prior treatment was defined as patient-reported treatment for either MDD, dysthymia, or depressive disorder not otherwise specified with either an antidepressant at minimum effective dose for ≥4 weeks or ≥4 sessions of an evidence-based psychotherapy (i.e.,

CBT, interpersonal therapy or behavioral marital therapy) for depression. Exclusion criteria included a history of bipolar disorder, primary psychotic disorder, or dementia, or a diagnosis within the past year of obsessive-compulsive disorder, eating disorder, or dissociative disorder. Patients who met the DSM-IV criteria for substance abuse within the past 3 months and substance dependence within the last 12 months prior to the initial visit or those whose urine tested positive for drugs of abuse were also excluded. Any prior treatment with citalopram, escitalopram, or duloxetine was also exclusionary. Pregnant women, women who were breast-feeding, or women who were planning on becoming pregnant were excluded. Patients with significant uncontrolled medical conditions, or any potentially interfering medical condition, were also excluded.

Randomization

Patients were randomly assigned in a 1:1:1 ratio one of three possible treatments: 1) escitalopram 10-20 mg/day, 2) duloxetine 30-60 mg/day, or 3) CBT, 16 individual sessions. To ensure equal allocation across treatment groups the treatment assignment was created using randomized permuted blocks before opening the study to enrollment. Separate randomization lists were made for the English-speaking and Spanish-speaking clinics. An Emory University employee, unaffiliated with the study, placed treatment assignments into sealed, opaque envelopes. At a patient's baseline visit, following the study psychiatrist's confirmation that all eligibility requirements for randomization had been met, the study coordinator opened the envelope to identify whether the patient would receive medication or CBT. The specific medication was blinded to both the treatment team and the patient, with the unblinded medication list maintained by the Emory Investigational Drug Service.

Study Visits and Treatments

Following randomization, all patients returned to the study sites every week during weeks 1-6 and biweekly through week 12 for symptom assessment and safety monitoring, described below. To increase treatment and assessment consistency, Spanish-speaking raters and physicians also conducted assessments at the English-speaking site. Patients were given gift cards equal to $5.00 per visit attended to mitigate travel expenses.

Pharmacotherapy

Medications were compounded by the Emory Investigation Drug Service pharmacy into grey capsules containing either 10 mg of escitalopram or 30 mg of duloxetine. Patients randomized to pharmacotherapy were started on one capsule per day, which was scheduled to be increased to 2 capsules per day at week 4 if they had not improved. The study psychiatrist could also increase the dose at week 3 if deemed necessary for the patient. If the patient failed to achieve remission by week 6, an increase to 2 capsule per day was required, though the dose could be lowered if the patient experienced significant adverse effects. At week 12, serum concentrations of the medications were analyzed to ensure participant adherence to the medication. Additionally, this serum sample was tested in all participants for 10 other antidepressant medications to make sure participants were not taking other medications.

CBT

The CBT therapists were trained in Beck's standardized CBT protocol, widely used in clinical trials of CBT for MDD (Beck et al., 1979). Patients randomized to CBT met with their therapist twice a week for the first 4 weeks and then once a week for the following 8 weeks, though flexibility in this schedule was permitted as necessary. Therapist supervision occurred

weekly, and the videotaped therapy sessions were rated for CBT-protocol adherence via the Cognitive Therapy Scale from the Beck Institute for Cognitive Therapy and the Academy of Cognitive Therapy (Young and Beck, 1980). If a therapist's competency score fell below 40, the therapist received additional training.

Concomitant Medications

Medications used to mitigate chronic medical conditions were allowed. Non-study psychoactive medications were prohibited except for hypnotics, medications for insomnia, which could be used by all patients up to three times a week at the discretion of the study psychiatrist.

Assessments

Patients' demographic data was captured by a self-report form at the screening visit, as was their history of childhood abuse and neglect, using the Childhood Trauma Questionnaire (CTQ). The CTQ consists of a 28-item questionnaire which contains five subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein et al., 1997). Responses to each item are measured on a 5-point Likert scale with 1 corresponding to "never true" and 5 corresponding to "always true"; scores fall into four categories: none-to-low trauma exposure, low-to-moderate trauma exposure, moderate-to-severe trauma exposure, and severe-to-extreme trauma exposure (Bernstein et al., 1997).

The abbreviated version of the HUPS was used as the measure of daily stressors, administered at baseline and at week 12. The abbreviated HUPS consists of 53 items and is scored identically to the original version (DeLongis et al., 1988). The HUPS is a self-report measure in which the patient indicates the degree to which each of the 53 items (life activities or

relationships) had been an issue over a specific time frame; in PReDICT, the previous week was used for the time-period. Specifically, the scale asks, “How much of a HASSLE was this item for you over the past 7 days?”. Patients choose from one of four options for each item: “Not at all or not applicable” (=0), “Somewhat” (=1), “Quite a bit” (=2), or “A great deal” (=3). For these same 53 items, patients then respond to the question, “How much of an UPLIFT was this item for you over the past 7 days?” with the same scoring as for hassles. One HUPS summary metric is “frequency,” which is a simple count of the number of hassles endorsed as >0 or uplifts endorsed as >0. These scores were defined as Hassle Frequency (HF) and Uplift Frequency (UF), respectively. Another summary metric is “intensity,” with a summed total for all 53 hassles (Hassle Intensity, HI), and a summed total for all 53 uplifts (Uplift Intensity, UI). (DeLongis et al., 1982).

Six metrics derived from the HUPS questionnaire were used in the analyses. The frequency of hassles and uplifts (HF and UF) was defined above. The raw intensity scores (HI and UI) are dependent on the number of items the patient endorsed in the past week, which could vary across individuals based on static and dynamic life factors, and thus are highly dependent upon the HF and UF scores. Therefore, we calculated a Mean Hassle Intensity (MHI = HI/HF) and Mean Uplift Intensity (MUI = UI/UF) to better measure the degree of perceived feeling around the negative and positive events experienced. Finally, because HF and UF, and MHI and MUI, were significantly correlated at baseline ($r=0.56$, $p<.001$; $r=0.24$, $p<0.001$, respectively), we also calculated the ratios of HF:UF and MHI:MUI with the aim of controlling for the inter-individual variability in gauging the perceived thresholds for the terms used to measure intensity in the HUPS (e.g. “quite a bit” vs “a great deal”).

Symptom assessments were conducted at weeks 1-6, 8, 10, and 12 after the baseline visit. The primary clinical outcome was the 17-item HAM-D, administered by trained raters blinded to patient's treatment. The HAM-D's 17 items measure the severity of depressive symptoms and are scored between 0 and 4 points (Hamilton, 1967). Scores of 0-7 are considered normal, 8-16 indicate mild depression, 17-23 moderate, and above 24 severe depression (Hamilton, 1967). The maximum score is 52 (Hamilton, 1967). The blinded raters also assessed anxiety by administering the14-item Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) at each visit. Each of the 14 items on the HAM-A is defined by a series of symptoms scored on a scale of 0-4, with 4 being the most severe, for a total score range from 0-56 (Hamilton, 1959). A score of <17 indicates mild severity whereas scores between 18-24 and 25-30 indicate mild-to-moderate severity and moderate-to-severe severity respectively (Hamilton, 1959). To enhance assessment consistency across the study sites, Spanish-speaking raters and physicians also conducted assessments at the English-speaking site.

Patient-reported depressive symptoms were measured on the same visit schedule as the HAM-D and HAM-A using, the Beck Depression Inventory-I (BDI) (Beck et al., 1961) and the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) (Rush et al., 2003). The BDI is a 21-item survey that quantifies attitudes and symptoms characteristic of depression (Beck et al., 1961). Each item is scored on a scale of 0-3, such that 0 signifies the symptom is not present and 3 is most severe, for a maximum score of 63 (Beck et al., 1961). A score of less than 10 indicates minimal depression, while scores between 10-18, 19-29, and 30-63 indicate mild, moderate, and severe depression respectively (Beck et al., 1961). The QIDS-SR is a 16-item survey, also scored on a scale of 0-3 (Rush et al., 2003). However, not every item on the survey is included in scoring, so the maximum score is 27 (Rush et al., 2003). Scores between 6-

10 suggest mild depression, and scores between 11-15, 16-20, and 21-27 suggest moderate, severe, and very severe depression respectively (Rush et al., 2003). The Sheehan Disability Scale (SDS) was used to assess functional impairment (referred to as "functioning" in further analyses) (Rush et al., 2000). The SDS is a 3-item scale in which work/school, social life, and family life/home responsibilities are assessed in terms of how much a respondent's responsibilities are impaired by their symptoms on a scale from 0-10 with 0 representing no impairment and 10 representing extreme impairment (Rush et al., 2000). A combined score above ≥15, or any individuals score ≥5 are associated with significant functional impairment (Rush et al., 2000). The SDS was administered at the baseline visit and then every subsequent 4 weeks. Quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and administered on the same schedule as the SDS (Endicott, 1993). The Q-LES-Q is a 16-item self-report questionnaire in which respondents rate each item from 1-5 with 1 representing "very poor" satisfaction and 5 representing "very good" satisfaction (Endicott, 1993). Finally, recent important life events (referred to as life events) were evaluated with the Life Experiences Survey (LES) (Sarason et al., 1978). The LES is a 57 item measure that tasks respondents with rating the occurrence of life events (i.e., divorce, death of a loved one, etc.) in 1) the last 6 months and 2) the last 7 months to 1-year (Sarason et al., 1978). Each life event can be endorsed as either positive or negative, ranging from a scale from -3 (most negative) to +3 (most positive) (Sarason et al., 1978). The LES was administered at baseline and again at week 12.

Depression Outcomes

The primary continuous outcome measure for this study was the week 12 HAM-D score. For categorical analyses, two outcome measures were derived based on the week 12 HAM-D

score. *Response* was defined as a ≥50% reduction from the baseline HAM-D score at the week 12 visit. *Remission* was defined as a patient having a HAM-D score ≤ 7 at their week 12 visit. By these definitions, all remitters were also responders, but some responders failed to achieve remission.

Statistical Analysis

All data were analyzed with IBM SPSS statistics software version 26.

Missing Data

Due to a clerical error, on 73 of the 196 (37.2%) Hassle and Uplifts (HUPS) scales administered at baseline, HUPS item number 9 and 41 were duplicated such that they also occupied the slots for item 10 and 42 respectively. At week 12, the same duplication error was seen in 49 of the 153 (32.0%) of the HUPS scales administered. For the purposes of the statistical analyses, these items were treated as missing data points. In addition to the missing data due to the duplication error, there were missing values for 1.5% of the items on the correct version of HUPS scale across all patients and all visits. To handle the issue of missing data, multiple imputation, specifically the predictive mean matching method, was used to impute missing data points. Predictive mean matching, as opposed to linear regression based imputation, was used to ensure that all imputed data points fell within the parameters of possibility (i.e., only numbers within the observed data range can be generated) and because it is robust to transformations of the target variable (Van Buuren, 2018). One multiple imputation model was used, which generated data points for individual items that were missing from the HUPS questionnaire. The variables used as predictor variables in the imputation model were primary language (i.e., study site), age, marital status, gender, race, full-time employment status,

depression severity (QIDS-SR score) at baseline visit and week 12 , and the raw, untransformed HUPS scale data that were not being imputed in the model. The multiple imputation model generated 5 imputation iterations. The raw HUPS data were then transformed into the 6 analyzed HUPS scores: HF, MHI, UF, MUI, HF:UF, MHI:MUI. All transformed, raw HUPS scores (i.e., HUPS scores where missing data was deleted listwise, and thus the entire HUPS score was removed) and transformed, imputed HUPS scores were within 3.5% of each other at both baseline and week 12 (Table 1). Statistical analyses were carried out on the pooled set of the 5 imputation iterations except in cases where SPSS was unable to generate a pooled output for imputed data, such as for analyses of covariance and logistic regression. In these cases, because the difference between the raw and imputed data was so small, we determined it was appropriate to conduct the analyses using the raw scores.

Escitalopram vs Duloxetine

Independent-samples t-tests were conducted to compare the baseline HUPS scores between the escitalopram and duloxetine groups. There was no significant difference in baseline HF between the escitalopram (n= 64, M= 23.77, SD= 8.98) and duloxetine groups (n=66, M= 24.35, SD= 9.63; t (558656)= -.358, p= 0.72). The magnitude of the differences in the means (mean difference= -0.59, 95% CI: -3.79 to 2.62) was very small (eta squared= .001). There was also no significant difference in baseline MHI between the escitalopram (n=64, M= 1.71, SD = 0.40) and duloxetine groups (n=66, M=1.69, SD= 0.40; t (1572790) =-.291, p= 0.771), and the magnitude in the difference of the means (mean difference= 0.02, 95% CI= -0.12 to 0.16) was very small (eta squared= 0.001). As with baseline HF, there was no significant difference in baseline UF between the escitalopram (n=64, M= 18.76, SD= 9.46) and duloxetine groups (n= 66, M= 21.08, SD= 9.98; t (3548347) = -1.36, p= 0.18). The magnitude in the difference of the

means was (mean difference= -2.32, 95% CI: -5.66 to 1.03) was small (eta squared= 0.01). There was no significant difference between baseline MUI between the escitalopram (n= 64, M= 1.42, SD= 0.36) and duloxetine groups (n= 66, M= 1.44, SD= 0.30; t (42471) = -0.35, p= 0.727), and the magnitude in the difference of the means was (mean difference= -0.02, 95% CI= -0.13 to 0.09) was very small (eta squared= 0.001). As expected, the HF:UF ratio also demonstrated no significant difference at baseline between the escitalopram (n=64, M=1.74, SD= 1.64) and duloxetine groups (n= 66, M=1.36, SD= 0.82; t (3846.26) = 1.62, p= 0.11), and the magnitude of the mean difference (mean difference= 0.38, 95% CI= -0.08 to 0.84) small (eta squared= 0.02). Similarly, the MHI:MUI ratio did not significantly differ between the escitalopram groups (n= 64, M= 1.27, SD= 0.40) and the duloxetine groups (n= 66, M=1.21, SD= 0.32; t (104302) = 0.93, p= 0.35). The magnitude of the mean differences (mean difference= 0.06, 95% CI= -0.07 to 0.18) was small (eta squared= 0.01). Given this consistent lack of significant differences in any of the baseline HUPS scores between the two medication groups, for the remainder of the analyses, the escitalopram and duloxetine groups were combined into one "medication" group. Thus, the two treatment groups for the purposes of analyses were the medication group and the CBT group.

The relationship between baseline HUPS scores and other clinical factors at baseline were evaluated using bivariate correlations. Statistical testing for group differences for each calculated HUPS score was done using independent t-tests. T-tests were two-tailed with a significance level of $p<0.05$. To evaluate the change in HUPS scores from baseline to week 12 by treatment group, a one-way analysis of covariance was performed with week 12 HUPS score as the dependent variable, treatment group as the independent variable, and baseline HUPS score as the covariate. These analyses were repeated in the subsamples of responders and non-

responders. SPSS does not generate a pooled output for imputed data when conducting analyses of covariance, so for this step, the original, un-imputed data was used.

For testing predictors of response and remission, simple logistic regressions were used. In each of the regression models, one baseline HUPS score (i.e., HF, UF, MHI, MUI, HF:UF, MHI:MUI) was used as the predictor variable and the treatment outcome (Response or Remission) was the dependent variable. Each HUPS score was assessed individually for its ability as a predictor, resulting in six regressions each for the two outcomes. Regressions were repeated within the medication group and the CBT group separately to examine for treatment-specific effects. Finally, to investigate the individual HUPS scores ability to act as a moderator for treatment outcome, two-way analyses of covariance were conducted. In the two-way analysis of covariance both treatment group and baseline HUPS score were the independent variables, week 12 HAM-D score was the dependent variable, and baseline HAM-D score was the covariate. An independent variable is acting as a moderator if there is a significant effect of the variable on the week 12 HAM-D score and there is also a significant interaction effect between the two independent variables in the model.

Results:

Baseline Demographics and Clinical Characteristics

The HUPS questionnaire was not part of the original PReDICT protocol; it was added part-way through the study. Consequently, of the 344 total patients enrolled into the study, 196 were administered HUPS scales at baseline and 153 at week 12. Clinical and demographic characteristics by treatment group at baseline are presented in Table 2 and Table 3, respectively. There were no significant differences between the CBT group and the Medication group in any of the clinical or demographic variables at baseline.

Baseline Correlates of HUPS Scale Scores

As shown in Tables 4 and 5, the direction and relative strength of the correlations between the HUPS variables at baseline were very similar to those observed at week 12. Notably, HF was not significantly correlated with MHI and UF was not significantly correlated with MUI demonstrating the utility of defining mean intensity scores rather than simply using the summed raw intensity scores. We also found high correlations between the two ratios of HF:UF and MHI:MUI. These results indicate that patients endorsing more hassles than uplifts tended to also endorse greater intensity to their hassles than to their uplifts.

Table 6 demonstrates the unique contribution of the HUPS questionnaire in characterizing depressed states. The depression rating scales, HAM-D and BDI, were positively, but only weakly, correlated with HF and MHI; conversely, those depression rating scales were negatively, but weakly, correlated with UF and MUI. These results support the construct validity of the HUPS and that it is not simply reflecting the same concept as a depression questionnaire. Generally, the ratio measures (HF:UF and MHI:MUI) showed stronger correlations to the

clinical measures of depression and anxiety, as well as self-reported quality of life, than did the individual HUPS scale scores. Other notable findings from the baseline analyses are the very weak correlations between the number of stressful life events in the past year and any of the HUPS scale scores, indicating that the HUPS is clearly capturing a different variable than major life events. As shown in Table 7, at week 12, HF and MHI were moderately positively correlated with the depression rating scales, while UF and MUI exhibited weakly negative and moderately negative correlations with the ratings scales. Both ratio measures had strong positive correlations with both depression rating scales.

The association at baseline between the HUPS scale scores and demographic variables are presented in Tables 8-13. At baseline, the only demographic group which displayed a significant difference in HF scores was employment status. Participants who were employed had a significantly greater HF than those who were unemployed ($p=0.005$). MHI was significantly greater in participants who were not married or cohabitating with another person than those who were ($p=0.04$), and in those with lifetime substance abuse than those without ($p=0.02$). Notably, Hispanics endorsed substantially greater frequency of uplifts ($p=.01$) and had a lower HF:UF ratio ($p=.01$) than non-Hispanics. MUI did not differ significantly across any demographic groups. MHI:MUI was significantly greater in participants with a history of a substance use disorder than those without($p=0.02$).

Change in HUPS Scores over the 12 Week Acute Treatment Phase

Paired t-tests were conducted to evaluate the change in HUPS scores from baseline to week 12, the end of the acute treatment phase. As shown in Figure 1, there was a significant decrease in HF ($p<0.01$) and MHI ($p<0.01$) from baseline to week 12, while UF ($p<0.01$) and

MUI ($p<0.01$) both significantly increased. The HF:UF ratio significantly decreased from baseline to week 12 ($p< 0.01$), and the MHI:MUI ratio significantly decreased from baseline to week 12 ($p< 0.01$). These results present a consistent picture that treatment of depression results in both reductions in perceived hassles and increases in perceived uplifts.

Change in HUPS Scores over 12 Week Acute Treatment Phase by Treatment Group

As displayed in Table 2, HUPS scores did not significantly vary by treatment arm at baseline, and Figure 2 shows HUPS scores changing with the same pattern across treatment groups from baseline to week 12, with the exception of UF. The increase in UF was statistically significant for the medication group ($p<0.001$) but not the CBT group ($p=0.11$), though the both groups increased and the difference between the groups was relatively small (mean difference at week 12= 3.76). To evaluate whether changes in HUPS scores at the end of acute treatment differed between patients who received medication versus those who received CBT, a one-way analysis of covariance was performed (Table 14). The independent variable was the treatment group and the dependent variable was the week 12 HUPS score, with baseline HUPS score as the covariate. Preliminary measures to ensure there were no violations of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate were conducted. After adjusting for baseline HUPS scores, there was a significant difference between treatment groups on week 12 UF and the HF:UF ratio. Despite the significant differences across treatment groups, the effect size of the treatment group was small in both cases indicating that only a small percentage of variance in week 12 UF and HF:UF was explained by the different treatments. Strong relationships between baseline HUPS scores and week 12 HUPS scores were seen in all measures except for HF:UF.

These analyses were repeated in the subsamples of non-responders (Table 15) and responders (Table 16). In the non-responders, after adjusting for baseline HUPS scores, the non-responders in the medication group showed a significantly higher MUI and lower HF:UF ratio at week 12 compared to the CBT non-responders. The effect of treatment group on these HUPS scale scores was large (η^2= 0.21 and η^2= 0.17, respectively), indicating that the medication improved patients' experience of minor positive events, even in patients who did not demonstrate substantial clinical improvement in overall depression severity. In contrast, among the responders to each treatment, there were no significant differences on any of the week 12 HUPS scores.

Baseline HUPS Scores as Predictors of Treatment Response

Rates of treatment response and remission are tabulated in Table 17. There were no significant differences in response (χ^2= 3.79, df=1, p=0.052) or remission (χ^2=2.03, df=1, p=0.11) rates across treatment groups. Figure 3 depicts the change in HAM-D scores from baseline to week 12 by treatment group. HAM-D Scores significantly decreased in both the medication and CBT groups.

Two simple logistic regression models were used to assess the impact of baseline HUPS scores on the likelihood that participants would respond to treatment. One model used response as the dependent variable and one model used remission as the dependent variable. Six models were run, one with each baseline HUPS score as the independent variable.

For predicting response among the entire sample, only the MHI:MUI ratio emerged as a significant (p=0.02) predictor with an odds ratio of 0.15, meaning that having a higher MHI:MUI was associated with a lower likelihood of response (Table 18). Given that the standard deviation

(SD) of the MHI:MUI ratio is 0.36, this means that for every SD increase in the MHI:MUI ratio, the odds of responding decrease by 0.42 (i.e., reduce the probability of response by more than half). The MHI:MUI ratio was also the strongest significant predictor of remission (p=0.02, OR=0.15). UF, and the HF:UF ratio were also statistically significant, but weaker predictors of remission (p=0.03, OR=1.06; p=0.04, OR=0.47, respectively) (Table 19). Given the SDs of UF and HF:UF are 10.02 and 1.26 respectively, the odds of remission increase by 0.11-fold for each SD increase in UF and decrease by a factor of 0.37 for every SD increase in the HF:UF ratio.

The response and remission analyses were run again separately within each treatment arm. Within the CBT group, MHI and the MHI:MUI were significant predictors for response (p=0.04, OR=0.07; p=0.02, OR=0.02); given the SDs of MHI and MHI:MUI in the CBT group are 0.39 and 0.36 respectively, the odds of response decrease by 0.18 and 0.06 respectively (Table 20). As in the overall sample, UF, and the HF:UF, and MHI:MUI ratios were significant predictors for remission (p=0.02, OR=1.25; p=0.01, OR=0.01, p=0.04, OR=0.03) (Table 21). Thus, for each SD increase in UF the likelihood of remission increases 0.13-fold and for each increase in SD for HF:UF and MHI:MUI, the likelihood of remission decreases by 0.01 and 0.08 respectively. Remarkably, none of the baseline HUPS measures were significant predictors of response or remission in the medication group (Table 22, 23). These data suggest that the ability to benefit from CBT depends substantially on a patient's capacity to experience an increase in mood with good events, which does not appear to be a meaningful predictor for patients treated with antidepressants.

Baseline HUPS Scores as Moderators of Outcome by Treatment Group

The differences in the predictive capacity of HUPS scale scores on outcomes for the CBT- and medication-treated patients suggest that these scores, particularly the MHI:MUI ratio could serve as moderators to guide treatment selection for individual patients. We assessed he potential moderating effect by conducting a two-way analysis of covariance assessing the effects of baseline HUPS scores and treatment group on week 12 HAM-D scores, while controlling for baseline HAM-D scores. For this analysis, we divided the HUPS scale scores using a median split (high/low). Table 24 displays the means, adjusted means, standard deviations, and standard errors for week 12 HAM-D scores for each treatment group by high or low baseline HUPS Score. Preliminary checks were done to ensure the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate were not violated. After adjusting for HAM-D score at baseline, there was not a significant interaction effect for any of the HUPS scores. These results indicate that despite the power of HUPS scale scores to predict overall treatment outcomes, they do not function as moderators to guide treatment selection at the individual level.

Discussion:

This research was a *post-hoc* analysis of data from the largest randomized clinical trial conducted by a single institution in patients with MDD**.** Of the 207 total participants analyzed in this sample set, the average benefits from 12 weeks of acute treatment with either CBT or medication did not significantly differ in terms of mean change in symptom severity scales or proportion of participants who responded to treatment or remitted. Overall, these results align with other studies of MDD which have suggested roughly equivalent efficacy of psychotherapy and pharmacotherapy (Amick et al, 2015 and Weitz et al, 2015).

Additionally, to our knowledge, this study was the first to evaluate scores on the Hassles and Uplifts Scale as either predictors of treatment outcome or moderators of treatment efficacy in individuals diagnosed with MDD. Hassles scores (HF, and MHI), significantly decreased from baseline to the conclusion of the acute treatment phase, while uplift scores (UF, MUI) significantly increased over that time frame. Moreover the ratio of hassles to uplifts, both in terms of frequency (HF:UF) and intensity (MHI:MUI) also showed decreases from baseline to week 12. This observation is consistent with and expands upon prior research which has suggested that higher levels of HF are associated with greater negative affect in an adult, community sample (Kanner et al., 1981) and patients with depression have increased HF when compared to healthy controls (McIntosh et al., 2009). Additionally, across treatment groups, individuals with hassle scores above the median tended to have higher HAM-D scores than those below the median.

We found few differences in HUPS scores at the end of the acute treatment phase between the treatment groups. One exception was that UF significantly increased in the medication group from baseline to week 12, though the effect size of the treatment group was

small; the increase in UF in the CBT group was smaller and not statistically significant. Among the sample of non-responding patients however, uplift scores at week 12 (UF and MUI) were significantly higher among the medication group than the CBT group while the HF:UF ratio was significantly lower in medication group than the CBT group at week 12. For all three of these differences there was a large effect size of the treatment. In responding patients, there were no significant differences across treatment arms. These findings are consistent with findings on the effects of antidepressant medications on negative affective biases. Depressed patients tend to focus on and remember negative social information, while disregarding positive information (Harmer, 2017). These negative affective biases are likely not only a result of depressed mood but also factors in a depressed patient's appraisal of everyday social and emotional situations, like chronic stressors (Harmer, 2017). Antidepressant medications increase the relative processing of positive versus negative affective information upon administration to both depressed patients and healthy controls (Harmer et al., 2009). Antidepressants' reduction of negative bias has been associated with improvement in depression severity (Godlewska et al., 2016). Our findings, that uplift measures generally significantly increased and hassle measures generally significantly decreased from baseline to week 12, parallel these previous studies. The finding that uplift measures increased regardless of treatment outcome in the medication group not only reflects the theory that antidepressant medications reduce negative affective biases but also suggests that this effect is seen regardless of treatment outcome. In summary, there were no differences in HUPS schore changes among responders to CBT or medication, but the effects among non-responders did differ by treatment. Specifically, non-responders to CBT had lower uplift scores and higher hassles scores than non-responders to medication groups, indicating that reductions in negativity bias can occur with antidepressant treatment regardless of the drug's

overall benefit for depression, but in CBT such improvements occur only if the depression itself improves.

The finding that certain HUPS scores acted as predictors when analyzing the entire sample was promising. Interestingly, HF was not a significant predictor despite this HUPS score being reported most often as related to both somatic and mental health in previous research (DeLongis et al., 1982; Kanner et al., 1981; Wagner et al., 1988, Norman and Malla, 1994; Pascoe, 1990; Aroian et al., 2016; McIntosh et al., 2009). However, the HF:UF ratio did significantly predict remission for the entire sample. In addition, an intensity score, the MHI:MUI ratio, was a significant predictor of both response and remission among the entire sample. Taken together, these findings suggest that when evaluating the impact of daily stressors on outcomes in MDD, the stressors or hassles are less informative when considered in isolation than when they are considered in conjunction with positive experiences, such as uplifts. The utility of the hassle to uplift ratios derives from their ability to normalize the inter-individual variability in determining what should "count" as a hassle or uplift, as well as the individual's internal calibration for interpreting qualitative metrics of intensity.

An important potential limitation of the current study is that the HUPS is a retrospective questionnaire, which asks whether particular issues were either hassles or uplifts within the past seven days. As described in the methods, the intensity of each item was scored on a 0-3 Likert scale. Retrospective measures of the relative intensity of experiences suffer from potentially important biases. In a pain stimulation study, Daniel Kahneman found that a person's self-reported retrospective pain intensity ratings for the total amount of pain experienced during the procedure was not equal to the total amount of pain reported contemporaneously during the experiment. Rather, the retrospective total pain intensity rating was closer to the average of: 1)

the level of pain endorsed at the experiment's most painful moment and, 2) the level of pain at the experiment's end, a phenomenon which he coined the "peak-end rule" (Kahneman, 2011). Moreover, the duration of the pain had no effect on the rating of total pain rating, which he termed "duration neglect." Kahneman attributes the "peak-end rule" and "duration neglect" to a conflict between two-selves: the "remembering self" and the "experiencing self" (Kahneman, 2011). The "experiencing self" thinks in terms of the present, whereas the "remembering self" evaluates the experience as a whole (Kahneman, 2011). People's thoughts generally align with the "remembering self," as memories are products of experience and are actually what people think of when thinking about an experience (Kahneman, 2011). The HUPS scores, particularly the measures of intensity, are *de facto* measures of the "remembering self"; they comprise retrospectively recalled characteristics of recent life events. For many, the remembered version of events eventually overtakes the contemporaneously experienced version in their minds (Kahneman, 2011). Kahneman's work suggests that the predictive effects of the HUPS on treatment outcomes may not be due to the *actually experienced* frequency and intensity of reported uplifts and hassles, but rather from the *retrospectively constructed* version of life events. It is worth noting, however, that Kahneman's caveats apply to nearly all rating scales used in psychiatry and psychology which assess a past timeframe, including the widely used HAM-D and BDI measures of depression intensity.

Another important finding from this work is that the predictors of response and remission were not consistent across both treatment groups. While the MHI:MUI ratio was a significant predictor for both response and remission and the HF:UF ratio was a significant predictor of response in the CBT group, neither ratio significantly predicted these outcomes in the medication group. The finding that the predictive effects of these HUPS ratio measures differed

by treatment group is intriguing, but ultimately our moderator analysis failed to prove a statistically significant effect of these measures to justify their use as variables to guide treatment selection for patients with MDD presenting for care. This result is consistent with other data from the original PReDICT study which found that no clinical or sociodemographic variables moderated differential remission rates (Dunlop et al., 2017).

Correlations between HUPS scores and other clinical measures support the HUPS' construct validity. The lack of significant correlations at baseline between any of the HUPS scores and the CTQ and LES reinforce the distinction between daily hassles and uplifts and major life events. Weak, positive correlations were observed between hassle scores and depression rating scales and anxiety rating scales, while weak, negative correlations were observed between uplift scores and the depression rating scales and anxiety rating scales. The fact that the HUPS scores were only weakly correlated with depression and anxiety rating scales shows that the HUPS is not just reflective of depression severity but its own discrete measure. The HF:UF ratio result may reflect the biased attention (and memory) for negative events previously demonstrated in MDD patients. The MHI:MUI ratio result may reflect anhedonia, which would be expected to diminish the MUI score. At week 12, the correlations between HUPS scores and depression scales were all stronger than at baseline which is consistent with studies which have suggested change in emotional outlook to be associated with improvement in depression severity (Godlewska et al., 2016).

Strengths of this study include the robust participant sample and the fact that all participants were randomized within a single institution. Additionally, due to the diverse demographics of study participants, the study's generalizability to the public would appear to be

strong. Another strength was the use of multiple imputation for missing data where possible, which increased statistical power to avoid type II error.

There are a few potential limitations to the study beyond the issue of the retrospective nature of the HUPS described above. First, the maximum dose of duloxetine was 60 mg/day, which is lower than is often used in in clinical practice. This dosage discrepancy leads to the possibility that the full efficacy of the medication may not have been achieved. Additionally, multiple statistical comparisons were conducted in this study. The more statistical comparisons that are conducted, the higher the probability of type I error becomes. This research was the first analysis of the HUPS in predicting outcomes from depression treatments; given this exploratory approach, methods to control for multiple comparisons, such as the Bonferroni correction, were not applied. Another limitation for this study is the lack of treatment blinding at the patient level, which is inevitable in studies examining differential treatment outcomes between psychotherapy and pharmacotherapy. Another limitation pertaining to generalizability is the fact that patients with only mild depressive symptoms or concomitant substance use disorders were excluded from the study.

This study lays the foundations for a variety of future investigations of the impact minor daily stressors and uplifts on mental health. A first, necessary, step is to validate the current findings using data from the subsequent phases of the PReDICT study. In Phase II, patients who did not achieve remission were eligible to enter a 12-week combined treatment phase, during which they received both psychotherapy and medication. The HUPS scores for these patients could validate the current results by evaluating if HUPS scores deemed to be predictors of treatment outcome in this analysis of Phase I also served as predictors in Phase II. Additionally, external validation in a separate dataset would strengthen confidence in the conclusion that

HUPS scores can act as predictive variables and could be considered in making clinical recommendations. Thus, future investigations of MDD should incorporate the HUPS, so that similar analyses of the HUPS scores' change with treatment, predictor capabilities, and moderator capabilities can be conducted. The finding of different post-treatment HUPS scores across treatment groups warrants further investigation as well. A potential direction in which to take this would be to utilize the emotional categorization and emotional memory tasks Catherine Harmer developed to evaluate negative affective biases in patients with MDD (Harmer, 2009). Patients could undergo these tasks and complete the HUPS both before and after acute treatment with either psychotherapy or medication. Then, analyses of correlations between the HUPS score and emotion tasks could be conducted and compared across treatment groups.

An increased number of chronic minor stressors as measured by the EPCL has been associated with an increased risk of MDD recurrence (Bockting, 2006). Thus, it would be pertinent to examine whether HUPS scores, especially the MHI:MUI, given it was the strongest predictor of acute outcomes, could also be a predictor of recurrence and a moderator of the relationship between treatment group and recurrence. This analysis can be conducted on the data from Phase III of PReDICT, the long-term follow-up stage of the study where patients were seen every 3 months for 18-21 months. Finally, further assessment of Dr. Kahneman's "peak-end rule" for retrospective questionnaires is another interesting direction in which to take this work. One potential study design would have patients use as a mobile app or a physical journal to record the occurrence and intensity of both hassles and uplifts in real time as they occurred, and then complete the HUPS measure at the end of the period during which the real-time reporting was performed. Comparisons of patients' real-time versus retrospective scores could be conducted to provide further evidence for Dr. Kahneman's postulations. These ideas showcase

the array of clinical and research questions that could be explored by expanding upon the foundation laid by the current study.

Tables and Figures:

Table 1: Raw HUPS scores versus Imputed HUPS Scores at Baseline and Week 12

HUPS Measure	Raw	Imputed	Absolute Mean Difference	Percent Difference
Baseline	N=121	N=196		
HF (n=121, 196)	23.66	23.91	0.25	1.05
MHI (n=119, 194)	1.69	1.70	0.01	0.59
UF (n= 120, 195)	18.92	19.35	0.43	2.25
MUI (n=118, 193)	1.39	1.41	0.02	1.43
HF:UF (n=117, 192)	1.57	1.55	0.02	1.28
MHI:MUI (n=116, n=191)	1.25	1.26	0.01	0.80
Week 12	N= 104	N= 153		
HF (n= 104, 153)	19.17	18.52	0.65	3.45
MHI (n= 102, 151)	1.42	1.44	0.02	1.40
UF (n= 104, 153)	24.90	24.45	0.45	1.82
MUI (n=104, 153)	1.57	1.52	0.05	3.24
HF:UF (n= 104, 153)	0.87	0.87	0.00	0.00
MHI:MUI (n=102, 151)	0.96	0.94	0.02	2.10

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. At baseline 1 patient did not complete uplift data. For 2 patients, baseline HI was 0, which resulted in a divide by 0 error when computing MHI. For 4 patients, either baseline HF or UF was 0, so SPSS eliminated the responses when computing the ratio. For 5 patients either baseline HI or UI was 0 resulting in undefined MHI and MUI, resulting in SPSS eliminating these responses when computing the ratio. At week 12, 2 patients had hassle intensities of 0 resulting in 2 lost MHI and MHI:MUI values.

Table 2: Clinical Characteristics at Baseline

Characteristic	All Patients (n=207)		CBT (n=69)		Medication (n=138)		Analysis		
	Mean	SD	Mean	SD	Mean	SD	t	df	p
Age (years)	39.18	11.75	39.45	11.76	39.04	11.78	-0.23	205	0.82
HAM-D 17	19.88	3.81	20.36	3.88	19.64	3.76	-1.23	205	0.20
BDI	23.14	7.02	23.20	7.11	23.11	7.00	-0.09	205	0.93
HAM-A	16.12	5.23	16.70	5.00	15.83	5.34	-1.12	205	0.26
HF	23.90	9.45	23.61	9.84	24.06	9.28	0.32	1061701	0.75
MHI	1.70	0.39	1.71	0.38	1.70	0.40	-0.24	222766	0.81
UF	19.35	10.02	18.20	10.50	19.94	9.76	1.15	590001	0.25
MUI	1.41	0.33	1.36	0.32	1.43	0.33	1.35	72677	0.18
HF:UF	1.55	1.26	1.55	1.17	1.55	1.31	-0.02	4055	0.98
MHI:MUI	1.26	0.36	1.30	0.43	1.24	0.36	-1.23	59356	0.22

CBT=Cognitive Behavioral Therapy. SD= Standard Deviation. df= Degrees of Freedom. HAM-D 17= Hamilton Depression Rating Scale. BDI= Beck Depression Inventory. HAM-A= Hamilton Anxiety Rating Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Rati

Table 3: Demographic Characteristics at Baseline

Characteristic		All Patients (n=207)		CBT (n=69)		Medication (n=138)		Analysis		
		N	%	N	%	N	%	χ^2	df	p
Sex								0.30	1	0.58
	Male	83	40.1	30	43.5	53	38.4			
	Female	124	59.9	39	56.5	85	61.6			
Race								5.76	3	0.12
	White	80	38.6	32	46.4	48	34.8			
	Black	40	19.3	8	11.6	32	23.2			
	Other	87	42.0	29	42.0	58	42.0			
Ethnicity								0.13	1	0.72
	Hispanic	71	34.3	22	31.9	49	35.5			
	Non-Hispanic	136	65.7	47	68.1	89	64.5			
Married or cohabitating								0.41	1	0.52
	Yes	104	50.2	32	46.4	72	52.2			
	No	103	49.8	37	53.6	66	47.8			
Full-time Employment								0.04	1	0.85
	Yes	87	42.0	30	43.5	57	41.6			
	No	118	57.0	38	55.1	80	58.4			

CBT= Cognitive Behavioral Therapy. df= Degrees of Freedom

Table 4: Pearson's r Correlations between HUPS Scores at Baseline

HUPS Scores	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HF	_	0.24	0.56 **	0.08	0.18 *	0.31 **
MHI	_	_	-0.22 **	0.24 **	0.25 **	0.66 **
UF	_	_	_	0.11	-0.51 **	-0.29 **
MUI	_	_	_	_	-0.31 **	-0.54 **
HF:UF	_	_	_	_	_	0.50 **
MHI:MUI	_	_	_	_	_	_

HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

* $p < 0.05$
** $p < 0.01$

Table 5: Pearson's r Correlations between HUPS scores at Week 12

HUPS Scores	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HF	_	0.03	0.43 **	-0.32 **	-0.07	0.17 *
MHI	_	_	-0.20 *	0.13	0.25 **	0.68 **
UF	_	_	_	0.30 **	-0.40 **	-0.40 **
MUI	_	_	_	_	-0.46 **	-0.60 **
HF:UF	_	_	_	_	_	0.57 **
MHI:MUI	_	_	_	_	_	_

HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

* $p < 0.05$
** $p < 0.01$

Table 6: Pearson's r Correlations between Baseline HUPS Scores and Other Clinical Measures at Baseline

	HF	MHI	UF	MUI	HF:UF	MHI:MUI
Childhood Trauma Questionnaire	0.09	0.01	-0.06	-0.12	0.05	0.10
Age of Onset	-0.02	0.00	-0.15	0.02	0.15 *	-0.01
HAM-D 17	0.12	0.15 *	-0.20 *	-0.21 **	0.36 **	0.30 **
BDI	0.27 **	0.24 **	-0.11	-0.20 **	0.24 **	0.34 **
HAM-A	0.17 **	0.05	0.05	-0.21 **	0.20 **	0.22 **
Weight	0.09	0.16 *	-0.09	0.10	0.10	0.03
Number of Life Events	0.06	0.13	0.16	0.01	-0.04	0.13
Quality of Life	-0.03	-0.34 **	0.28 **	0.14	-0.35 **	-0.41 **
Functioning	0.13	0.23 **	-0.04	-0.12	0.12	0.35 **

HAM-D 17= Hamilton Depression Rating Scale. BDI= Beck Depression Inventory. HAM-A= Hamilton Anxiety Rating Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

* $p < 0.05$
** $p < 0.01$

Table 7: Pearson's r Correlations between Week 12 HUPS Scores and Other Clinical Measures at Week 12

	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HAM-D 17	0.34 **	0.22 **	-0.22 **	-0.47**	0.52 **	0.54 **
BDI	0.35 **	0.31 **	-0.23 **	-0.45**	0.57 **	0.60 **
Weight	-0.02	0.02	-0.07	0.04	0.01	-0.01

HAM-D 17= Hamilton Depression Rating Scale. BDI= Beck Depression Inventory. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio.

* $p < 0.05$
** $p < 0.01$

Table 8: Baseline Hassle Frequency Scores by Demographic Groups

		N	HF		Analysis		
			Mean	SD	t	df	p
Sex					1.62	7011378	0.11
	Female	117	24.81	9.32			
	Male	79	22.58	9.54			
Ethnicity					1.35	11919588	0.18
	Non-Hispanic	128	24.57	9.30			
	Hispanic	68	22.66	9.67			
Race					-0.11	12784107	0.91
	White	77	24.30	8.99			
	Black	36	24.51	10.52			
Age†					-0.36	1062907	0.72
	<38 yrs	100	23.67	9.43			
	≥38 yrs	96	24.16	9.51			
Married/cohabiting					-0.51	677752	0.61
	No	96	23.56	9.79			
	Yes	100	24.24	9.14			
Employment Status					-2.82	185418	0.005 **
	No	110	22.22	9.16			
	Yes	84	26.01	9.42			
Number of Children					-1.10	4838806	0.27
	0	60	22.78	9.38			
	1+	120	24.46	9. 86			
Comorbid Anxiety Disorder					-1.74	550761	0.08
	No	121	22.99	9.63			
	Yes	75	25.40	9.02			
Chronic Episode (2+ years)					-0.38	850253	0.71
	No	142	23.76	9.31			
	Yes	48	24.35	9.84			
Previous Suicide Attempt					-0.35	10437689	0.72
	No	178	23.84	9.69			
	Yes	14	24.77	7.46			
Lifetime Substance Use					-0.55	384962	0.59
	No	139	23.98	9.60			
	Yes	29	25.05	9.46			

HF= Hassle Frequency. SD= Standard Deviation. Df= Degrees of Freedom

†A median split (38 years) was applied to age,
* p <0.05
** p <0.01

Table 9: Baseline Mean Hassle Intensity Scores by Demographic Groups

		N	MHI		Analysis		
			Mean	SD	t	df	p
Sex					1.04	173631	0.30
	Female	116	1.73	0.41			
	Male	78	1.67	0.37			
Ethnicity					1.57	1142755	0.12
	Non-Hispanic	127	1.74	0.38			
	Hispanic	67	1.64	0.40			
Race					-1.15	2910040	0.25
	White	77	1.71	0.36			
	Black	35	1.79	0.40			
Age †					-0.52	949543	0.60
	<38 yrs	99	1.69	0.38			
	≥38 yrs	95	1.72	0.40			
Married/cohabiting					2.03	2791064	0.04 *
	No	95	1.76	0.40			
	Yes	99	1.65	0.38			
Employment Status					0.176	143502	0.86
	No	108	1.71	0.42			
	Yes	84	1.70	0.36			
Number of Children					-0.26	5203037	0.80
	0	59	1.69	0.35			
	1+	119	1.70	0.41			
Comorbid Anxiety Disorder					-0.17	626901	0.87
	No	119	1.70	0.40			
	Yes	75	1.71	0.37			
Chronic Episode (2+ years)					-1.58	17198587	0.114
	No	142	1.67	0.38			
	Yes	46	1.78	0.41			
Previous Suicide Attempt					-0.92	183096	0.36
	No	176	1.70	0.39			
	Yes	14	1.80	0.35			
Lifetime Substance Use					-2.42	662743	0.02 *
	No	138	1.68	0.40			
	Yes	28	1.88	0.38			

MHI= Mean Hassle Intensity. SD= Standard Deviation. Df= Degrees of Freedom

†A median split (38 years) was applied to age,
* p <0.05
** p <0.01

Table 10: Baseline Uplift Frequency Scores by Demographic Groups

		N	UF		Analysis		
			Mean	SD	t	df	p
Sex					0.88	496843	0.38
	Female	117	19.87	9.89			
	Male	79	18.58	10.23			
Ethnicity					-2.77	11503981	0.01 **
	Non-Hispanic	128	17.93	9.18			
	Hispanic	68	22.02	11.03			
Race					0.71	6470812	0.478
	White	77	18.66	9.18			
	Black	36	17.33	9.55			
Age †					-0.01	11220585	0.993
	<38 yrs	100	19.35	10.12			
	≥38 yrs	96	19.36	9.98			
Married/cohabiting					-1.46	530154	0.145
	No	96	18.29	10.46			
	Yes	100	20.37	9.52			
Employment Status					-1.72	1050490	0.09
	No	96	18.21	9.61			
	Yes	100	20.70	10.46			
Number of Children					-0.28	7423413	0.78
	0	60	19.17	8.76			
	1+	120	19.62	10.61			
Comorbid Anxiety Disorder					0.003	2452229	0.99
	No	121	19.35	9.68			
	Yes	75	19.35	10.61			
Chronic Episode (2+ years)					0.62	979500	0.53
	No	142	19.87	9.86			
	Yes	48	18.84	10.10			
Previous Suicide Attempt					-1.01	714723	0.31
	No	178	19.25	10.12			
	Yes	14	22.10	9.28			
Lifetime Substance Use					0.45	6065700	0.65
	No	139	19.57	10.24			
	Yes	29	18.63	10.30			

UF= Uplift Frequency. SD= Standard Deviation. Df= Degrees of Freedom

†A median split (38 years) was applied to age,
* p <0.05
** p <0.01

Table 11: Baseline Mean Uplift Intensity Scores by Demographic Groups

		N	MUI		Analysis		
			Mean	SD	t	df	p
Sex					-0.71	16456	0.45
	Female	116	1.39	0.32			
	Male	78	1.43	0.34			
Ethnicity					-0.75	119948	0.45
	Non-Hispanic	126	1.39	0.32			
	Hispanic	68	1.43	0.34			
Race					-1.61	61840	0.11
	White	77	1.36	0.29			
	Black	35	1.46	0.33			
Age †					-0.30	1370438	0.77
	<38 yrs	99	1.40	0.30			
	≥38 yrs	95	1.41	0.35			
Married/cohabiting					-0.50	16733	0.62
	No	94	1.39	0.29			
	Yes	100	1.42	0.36			
Employment Status					1.57	241911	0.12
	No	109	1.44	0.36			
	Yes	83	1.36	0.27			
Number of Children					0.43	110303	0.67
	0	59	1.43	0.31			
	1+	119	1.41	0.34			
Comorbid Anxiety Disorder					1.30	201192	0.19
	No	120	1.43	0.36			
	Yes	74	1.37	0.26			
Chronic Episode (2+ years)					-0.09	56611	0.93
	No	142	1.41	0.32			
	Yes	47	1.41	0.32			
Previous Suicide Attempt					-0.20	380318	0.84
	No	176	1.41	0.33			
	Yes	14	1.43	0.28			
Lifetime Substance Use					0.98	2118557	0.33
	No	138	1.43	0.35			
	Yes	28	1.36	0.24			

MUI= Mean Uplift Intensity. SD= Standard Deviation. Df= Degrees of Freedom

†A median split (38 years) was applied to age,
* $p < 0.05$
** $p < 0.01$

Table 12: Baseline Hassle Frequency to Uplift Frequency Ratios by Demographic Groups

		N	HF:UF		Analysis		
			Mean	SD	t	df	p
Sex					-0.11	2834	0.91
	Female	116	1.54	1.32			
	Male	78	1.56	1.18			
Ethnicity					2.50	1796	0.01 *
	Non-Hispanic	126	1.72	1.39			
	Hispanic	68	1.24	0.85			
Race					-0.96	9963621	0.34
	White	77	1.60	1.10			
	Black	35	1.87	1.87			
Age †					-0.52	29165	0.60
	<38 yrs	99	1.50	1.27			
	≥38 yrs	95	1.60	1.25			
Married/cohabiting					1.38	7197	0.17
	No	94	1.68	1.50			
	Yes	100	1.43	1.00			
Employment Status					0.37	17624	0.71
	No	109	1.59	1.42			
	Yes	83	1.52	1.04			
Number of Children					-1.94	102307	0.053
	0	59	1.27	0.56			
	1+	119	1.64	1.43			
Comorbid Anxiety Disorder					-1.11	10252	0.27
	No	120	1.47	1.08			
	Yes	74	1.68	1.51			
Chronic Episode (2+ years)					-1.35	68851	0.18
	No	142	1.46	1.04			
	Yes	47	1.74	1.73			
Previous Suicide Attempt					0.88	2291157	0.38
	No	176	1.56	1.30			
	Yes	14	1.25	0.59			
Lifetime Substance Use					0.26	49223	0.80
	No	138	1.60	1.43			
	Yes	28	1.53	0.69			

HF:UF= Hassle Frequency to Uplift Frequency Ratio. SD= Standard Deviation. Df= Degrees of Freedom

†A median split (38 years) was applied to age,
* $p < 0.05$
** $p < 0.01$

Table 13: Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratios by Demographic Groups

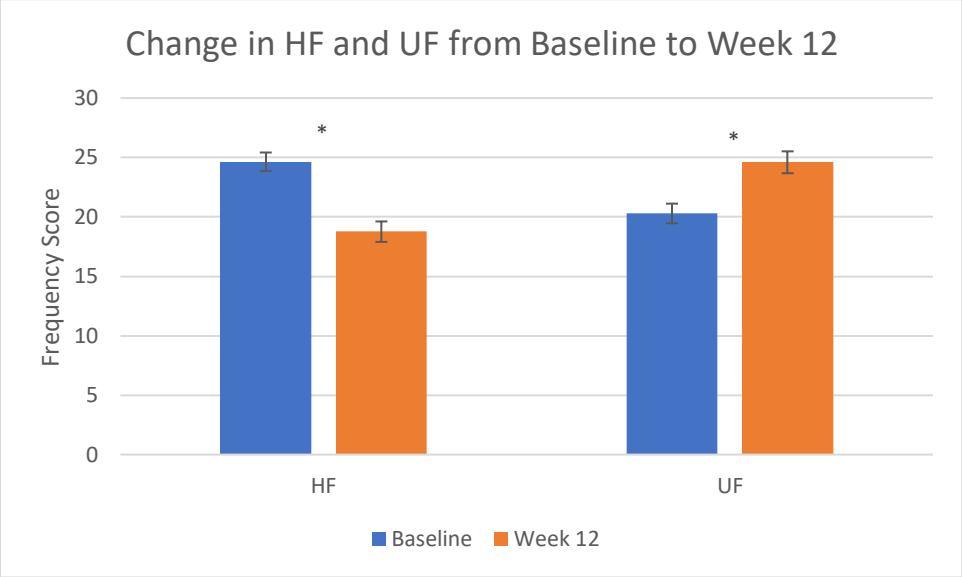
		N	MHI:MUI		Analysis		
			Mean	SD	t	df	p
Sex					1.61	19559	0.11
	Female	115	1.29	0.39			
	Male	78	1.21	0.30			
Ethnicity					1.53	169807	0.13
	Non-Hispanic	126	1.29	0.35			
	Hispanic	67	1.20	0.36			
Race					0.16	278586	0.88
	White	77	1.28	0.31			
	Black	35	1.27	0.40			
Age †					-0.36	1294661	0.72
	<38 yrs	98	1.25	0.36			
	≥38 yrs	95	1.27	0.35			
Married/cohabiting					1.57	41051	0.12
	No	94	1.30	0.35			
	Yes	99	1.22	0.36			
Employment Status					-0.80	57148279	0.42
	No	108	1.24	0.37			
	Yes	83	1.28	0.35			
Number of Children					-0.73	126924	0.46
	0	58	1.21	0.27			
	1+	119	1.25	0.36			
Comorbid Anxiety Disorder					-0.91	198759	0.37
	No	119	1.24	0.35			
	Yes	74	1.29	0.37			
Chronic Episode (2+ years)					-1.31	149406	0.19
	No	142	1.23	0.35			
	Yes	46	1.31	0.39			
Previous Suicide Attempt					-0.42	215678	0.67
	No	175	1.26	0.36			
	Yes	14	1.30	0.32			
Lifetime Substance Use					-2.31	9844629	0.02 *
	No	137	1.23	0.37			
	Yes	28	1.40	0.3			

MHI:MUI= Hassle Frequency to Uplift Frequency Ratio. SD= Standard Deviation. Df= Degrees of Freedom

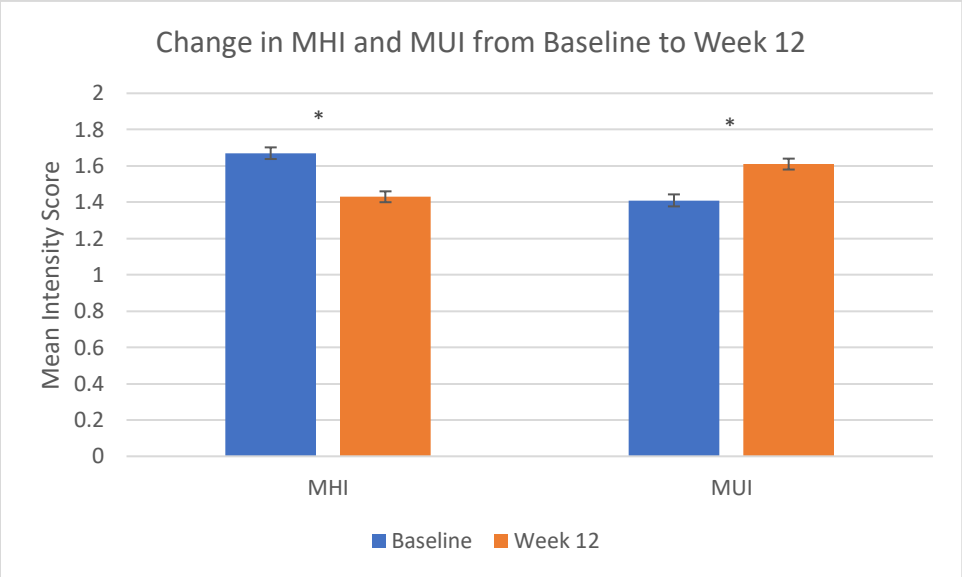
†A median split (38 years) was applied to age,
* $p < 0.05$
** $p < 0.01$

Figure 1: Change in HUPS Scores from Baseline to Week 12

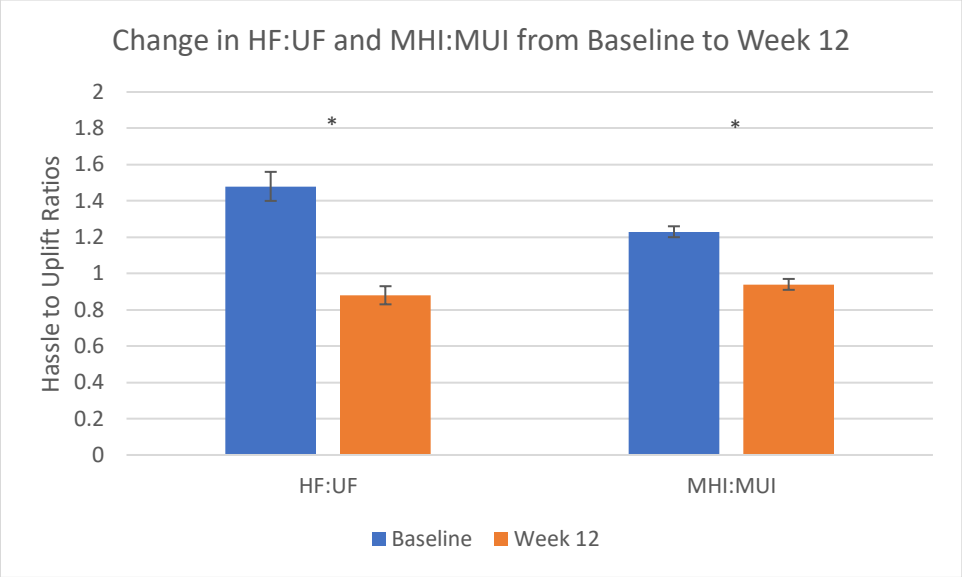
1a.) Change in HF and UF from Baseline to Week 12



1b.) Change in MHI and MUI from Baseline to Week 12



1c.) Change in HF:UF and MHI:MUI from Baseline to Week 12



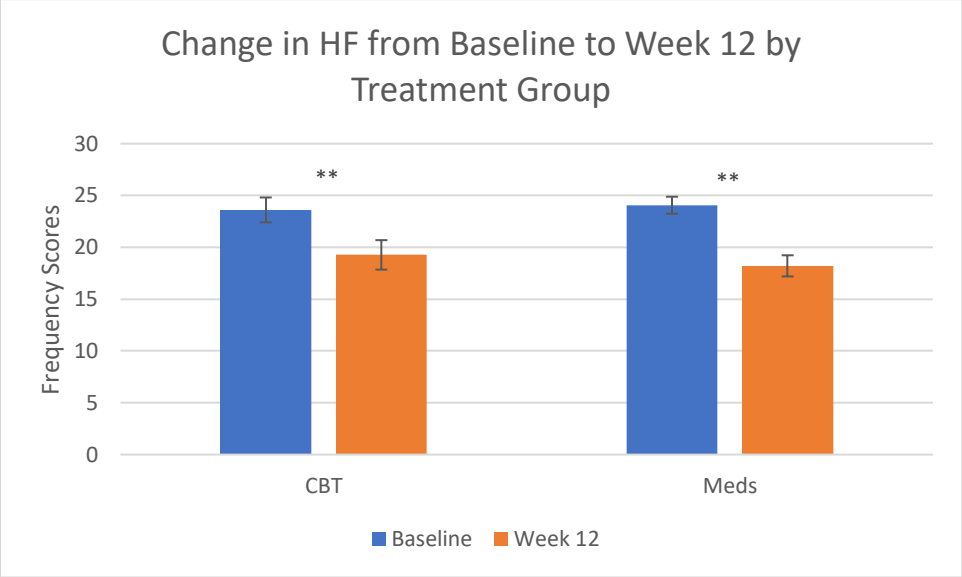
HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

* $p < 0.01$

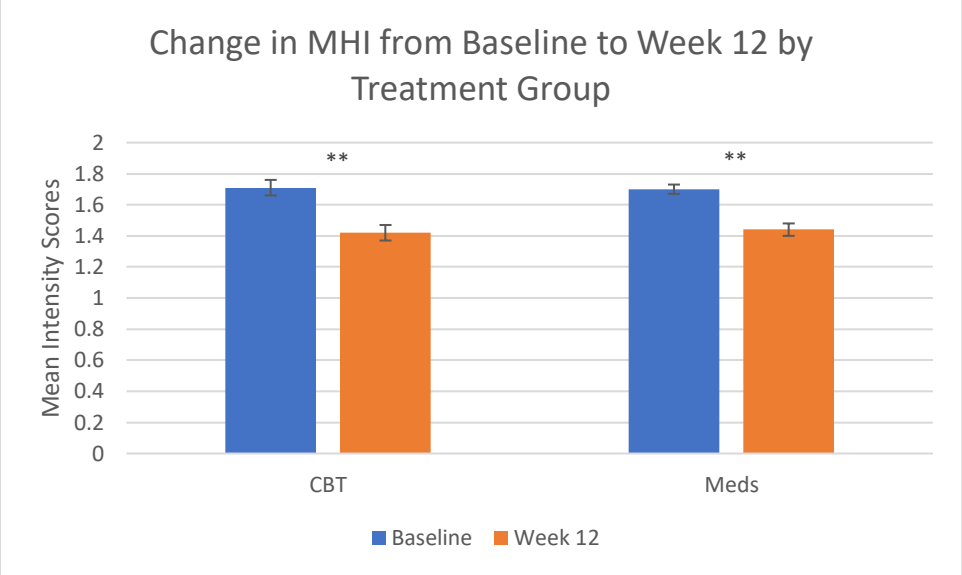
Figure 1) Change in HUPS Scores from baseline to week 12. 1a) There was a significant decrease in hassle frequency from baseline (m= 24.64) to week 12 (m= 18.76, $p < 0.01$) and a significant increase in uplift frequency from baseline (m= 20.29) to week 12 (m= 24.6, $p < 0.01$). 1b). Mean hassle intensity significantly decreased from baseline (m= 1.67) to week 12 (m=1.43, $p < 0.01$) and mean uplift intensity significantly increased from baseline (m=1.41) to week 12 (m= 1.61, $p < 0.01$). 1c) Hassle frequency to uplift frequency ratios significantly decreased from baseline (m=1.48) to week 12 (m=0.88, $p < 0.01$), and hassle intensity to uplift intensity ratios significantly decreased from baseline (m= 1.23) to week 12 (m= 0.94, $p < 0.01$). Error bars represent the standard error of the mean.

Figure 2: Change in HUPS Scores from Baseline to Week 12 by Treatment Group

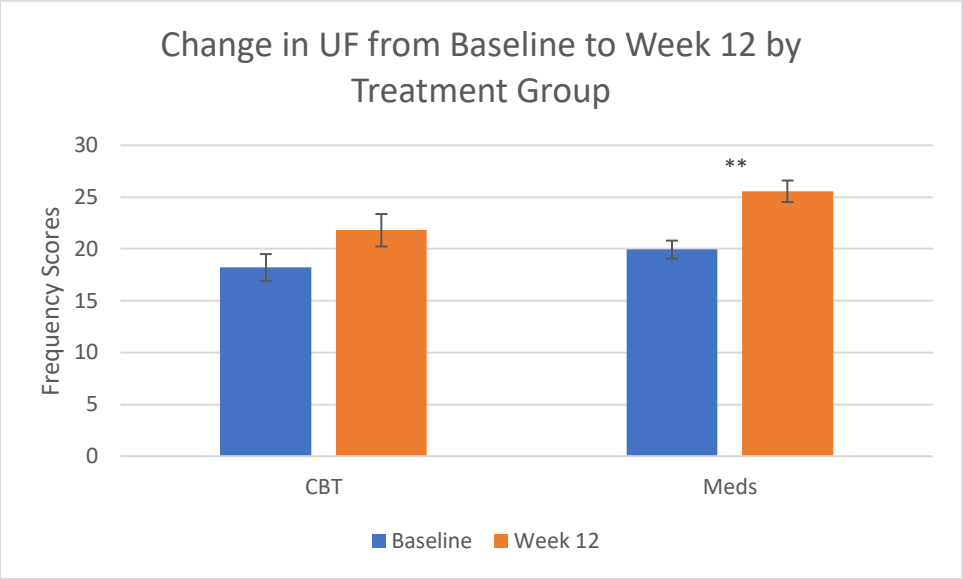
2a)



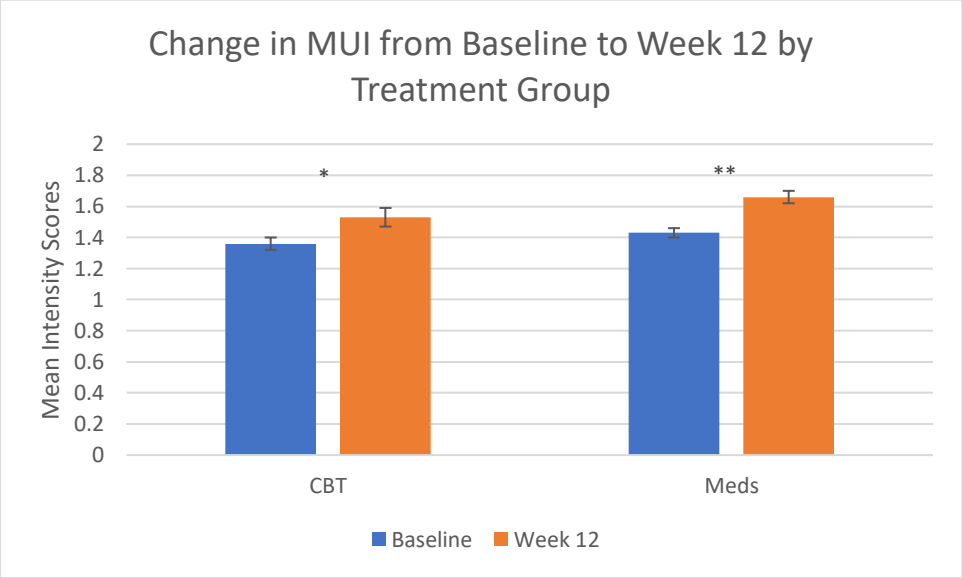
2b)



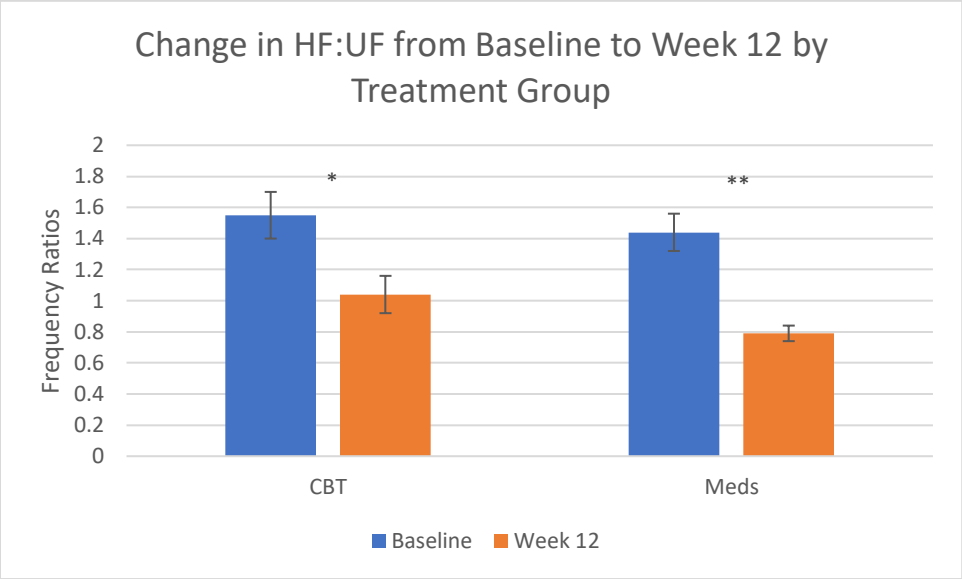
2c)


Change in UF from Baseline to Week 12 by Treatment Group
Frequency Scores
30
25
20
15
10
5
0
**
CBT
Meds
Baseline
Week 12

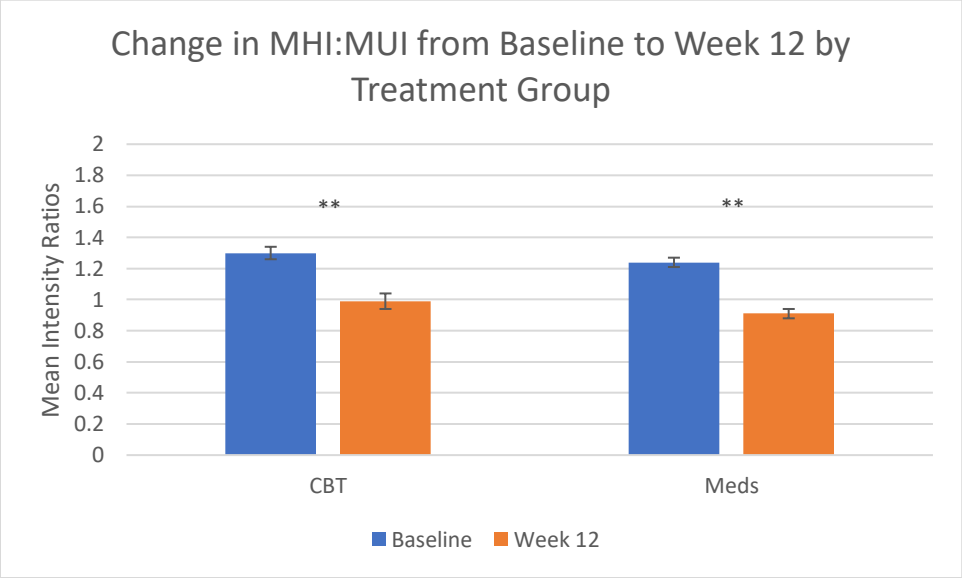
2d)


Change in MUI from Baseline to Week 12 by Treatment Group
Mean Intensity Scores
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
**
CBT
Meds
Baseline
Week 12

2e)



2f)



HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. CBT= Cognitive Behavioral Therapy.

Figure 2) Change in HUPS Scores from baseline to week 12 by treatment group. 2a) There was a significant decrease in HF from baseline to week 12 in both the CBT (m_{BL}= 23.61, m_{w12}= 19.27, $p<0.01$) and medication (m_{BL}= 24.06, m_{w12}= 18.21, $p<0.01$) groups. 2b) There was a significant decrease in MHI from baseline to week 12 in both the CBT (m_{BL}= 1.71, m_{w12}= 1.42, $p<0.01$) and medication (m_{BL}= 1.70, m_{w12}= 1.44, $p<0.01$) groups. 2c) There was a significant increase in UF from baseline to week 12 in the medication (m_{BL}= 19.94, m_{w12}= 25.56, $p<0.01$) but no the CBT (m_{BL}= 18.20, m_{w12}= 21.80, $p=0.11$) groups. 2d) There was a significant increase

in MUI from baseline to week 12 in both the CBT (m_{BL}= 1.36, m_{w12}= 1.53, $p<0.05$) and medication (m_{BL}= 1.43, m_{w12}= 1.66, $p<0.01$) groups. 2e) There was a significant decrease in HF:UF from baseline to week 12 in both the CBT (m_{BL}= 1.55, m_{w12}= 1.04, $p<0.01$) and medication (m_{BL}= 1.55, m_{w12}= 0.79, $p<0.01$) groups. 2f) There was a significant decrease in MHI:MUI from baseline to week 12 in both the CBT (m_{BL}= 1.30, m_{w12}= 0.99, $p<0.01$) and medication (m_{BL}= 1.24, m_{w12}= 0.91, $p<0.01$) groups Error bars represent standard error of the mean.

* $p <0.05$
** $p <0.01$

Table 14: Effect of Treatment Group on Change in HUPS Scores from Baseline to Week 12 for the Whole Sample

HUPS Score		CBT	MEDS	Analysis						
				df	$F_{treatment}$	$P_{treatment}$	$\eta_{p2treatment}$	$F_{covariate}$	$P_{covarriate}$	$\eta_{p2covariate}$
HF	N	27	60	(1, 86)	0.29	0.59	0.003	29.76	0.00 **	0.024
	BL	23.61	24.06							
	W12	19.27	18.21							
MHI	N	26	59	(1, 84)	0.02	.88	0.00	30.2	0.00 **	0.27
	BL	1.71	1.70							
	W12	1.42	1.44							
UF	N	27	61	(1, 87)	3.95	.05 *	0.04	38.16	0.00 **	0.31
	BL	18.20	19.94							
	W12	21.8	25.56							
MUI	N	27	61	(1, 87)	1.33	0.25	0.02	31.19	0.00 **	0.27
	BL	1.36	1.43							
	W12	1.53	1.66							
HF:UF	N	27	60	(1, 86)	4.47	0.04 *	0.05	0.29	0.59	0.003
	BL	1.55	1.44							
	W12	1.04	0.79							
MHI:MUI	N	26	59	(1, 84)	1.36	0.25	0.02	8.84	0.004 **	0.10
	BL	1.33	1.24							
	W12	0.99	0.91							

HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. CBT= Cognitive Behavioral Therapy. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 15: Effect of Treatment Group on Change in HUPS Scores from Baseline to Week 12 for Non-Responding Patients

HUPS Score		CBT	MEDS	Analysis						
				df	$F_{treatment}$	$P_{treatment}$	$\eta_{p2treatment}$	$F_{covariate}$	$P_{covarriate}$	$\eta_{p2covariate}$
HF	N	11	17	(1, 27)	0.25	0.62	0.01	9.02	0.01 **	0.27
	BL	25.64	24.61							
	W12	24.25	24.18							
MHI	N	11	17	(1, 27)	0.02	0.89	0.001	9.76	0.004 **	0.28
	BL	1.86	1.63							
	W12	1.52	1.51							
UF	N	11	17	(1, 27)	6.82	0.02 *	0.21	39.07	0.00 **	0.61
	BL	17.64	19.78							
	W12	18.67	26.05							
MUI	N	11	17	(1, 27)	6.90	0.02 *	0.22	23.35	0.00 **	0.48
	BL	1.31	1.30							
	W12	1.25	1.49							
HF:UF	N	11	17	(1, 27)	5.17	0.03 *	0.17	1.45	0.24	0.06
	BL	1.50	1.57							
	W12	1.68	1.00							
MHI:MUI	N	11	17	(1, 27)	2.18	0.15	0.08	5.41	0.03 *	0.18
	BL	1.43	1.29							
	W12	1.24	1.06							

HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. CBT= Cognitive Behavioral Therapy. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 16: Effect of Treatment Group on Change in HUPS Scores from Baseline to Week 12 for Responding Patients

HUPS Score		CBT	MEDS	Analysis						
				df	$F_{treatment}$	$P_{treatment}$	$\eta_{p2treatment}$	$F_{covariate}$	$P_{covarriate}$	$\eta_{p2covariate}$
HF	N	16	43	(1, 58)	0.19	0.67	0.003	23.89	0.00 **	0.30
	BL	22.25	24.61							
	W12	15.67	17.10							
MHI	N	15	42	(1, 56)	0.00	0.99	0.00	18.90	0.00 **	0.26
	BL	1.53	1.66							
	W12	1.34	1.34							
UF	N	16	44	(1, 59)	0.43	0.51	0.01	14.51	0.00 **	0.20
	BL	20.13	19.93							
	W12	23.56	26.33							
MUI	N	16	44	(1, 59)	0.04	0.85	0.001	15.91	0.00 **	0.22
	BL	1.34	1.44							
	W12	1.62	1.66							
HF:UF	N	16	43	(1, 58)	0.04	0.85	0.001	0.01	0.93	0.00
	BL	1.60	1.46							
	W12	0.68	0.70							
MHI:MUI	N	15	42	(1, 56)	0.07	0.79	0.001	0.42	0.52	0.01
	BL	1.16	1.18							
	W12	0.87	0.87							

HUPS= Hassles and Uplifts Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. CBT= Cognitive Behavioral Therapy. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

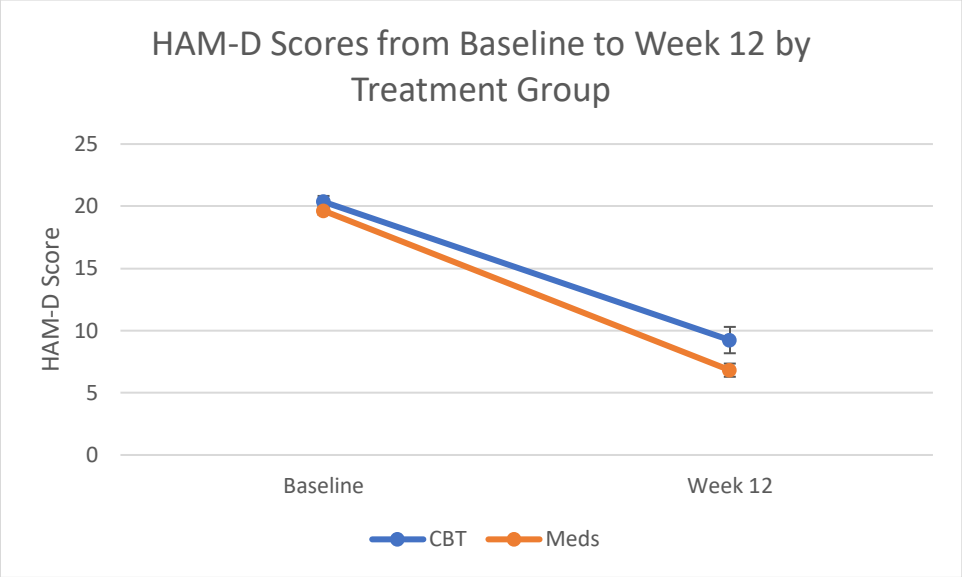
Table 17: Response and Remission Rates by Treatment Group

	CBT (n=46)		Medication (n=111)		Total Sample (n=157)	
Outcome	N	%	N	%	N	%
Response						
No	20	43.5	29	26.1	49	31.2
Yes	26	56.6	82	73.9	108	68.8
Remission						
No	28	60.9	52	46.8	80	51.0
Yes	18	39.1	59	53.2	77	49.0

CBT= Cognitive Behavior Therapy

There were no significant differences in response (χ_2= 3.79, df=1, p=0.052) or remission (χ_2=2.03, df=1, p=0.11) rates across treatment groups.

Figure 3: HAM-D Scores from Baseline to Week 12 by Treatment Group



HAM-D= Hamilton Depression Scale. CBT= Cognitive Behavioral Therapy
Error bars represent standard error of the mean.

Figure 3) HAM-D Scores significantly decreased in both the medication (m_{BL}=19.16, m_{W12}= 6.82, $p<0.01$) and CBT (m_{BL}=19.46, m_{W12}=9.24, $p<0.01$).

Table 18: Simple Logistic Regressions Predicting Likelihood of Treatment Response for the Whole Sample

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	-0.01	0.03	0.25	1	0.62	0.99	0.94	1.04
Constant	1.03	0.66	2.46	1	0.12	2.81		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	-0.65	0.59	1.21	1	0.27	0.52	0.17	1.67
Constant	1.81	1.02	3.15	1	0.08	6.09		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.01	0.03	0.25	1	0.62	1.01	0.96	1.07
Constant	0.50	0.54	0.84	1	0.36	1.64		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	1.34	0.85	2.47	1	0.12	3.80	0.72	20.12
Constant	-1.07	1.16	0.85	1	0.36	0.34		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	-0.03	0.20	0.02	1	0.89	0.97	0.65	1.45
Constant	0.77	0.39	4.01	1	0.05 *	2.16		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-1.92	0.79	5.96	1	0.02 *	0.15	0.03	0.69
Constant	3.14	1.03	9.25	1	0.002 **	23.14		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 19: Simple Logistic Regressions Predicting Likelihood of Remission for the Whole Sample

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	-0.01	0.02	0.06	1	0.81	0.99	0.95	1.04
Constant	0.03	0.61	0.002	1	0.97			

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	-0.66	0.57	1.36	1	0.24	0.52	0.17	1.57
Constant	0.98	0.96	1.04	1	0.31	2.65		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.05	0.03	4.59	1	0.03 *	1.06	1.01	1.11
Constant	-1.15	0.54	4.56	1	0.03 *	0.32		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	1.13	0.74	2.36	1	0.12	3.09	0.73	13.05
Constant	-1.65	1.03	2.54	1	0.11	0.19		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	-0.75	0.35	4.46	1	0.04 *	0.47	0.24	0.95
Constant	0.95	0.52	3.35	1	0.07	2.59		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-1.91	0.78	5.94	1	0.02 *	0.15	0.03	0.69
Constant	2.22	0.97	5.20	1	0.02 *	9.18		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 20: Simple Logistic Regressions Predicting Likelihood of Treatment Response within the CBT Group

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	-0.05	0.05	1.11	1	0.29	0.95	0.86	1.05
Constant	1.67	1.23	1.65	1	0.20	5.30		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	-2.73	1.30	4.38	1	0.04 *	0.07	0.005	0.84
Constant	4.97	2.25	4.88	1	0.03 *	144.04		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.04	0.05	0.57	1	0.45	1.04	0.94	1.14
Constant	-0.33	1.00	0.11	1	0.74	0.72		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	0.59	1.78	0.11	1	0.74	1.80	0.06	59.56
Constant	-0.41	2.40	0.03	1	0.87	0.66		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	0.06	0.31	0.04	1	0.84	1.06	0.58	1.95
Constant	0.28	0.62	0.21	1	0.65	1.32		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-3.91	1.74	5.09	1	0.02 *	0.02	0.001	0.60
Constant	5.42	2.31	5.53	1	0.02 *	226.76		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 21: Simple Logistic Regressions Predicting Likelihood of Remission within the CBT Group

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	0.01	0.05	0.04	1	0.84	1.01	0.92	1.11
Constant	-0.61	1.22	0.24	1	0.62	0.55		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	-1.81	1.22	2.21	1	0.14	0.16	0.02	1.78
Constant	2.59	2.00	1.67	1	0.20	13.33		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.22	0.09	5.87	1	0.02 *	1.25	1.04	1.49
Constant	-4.76	1.90	6.30	1	0.01 *	0.01		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	1.75	1.85	0.90	1	0.34	5.77	0.16	215.88
Constant	-2.72	2.52	1.17	1	0.28	0.07		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	-5.40	2.04	7.03	1	0.01 **	0.01	0.00	0.25
Constant	6.55	2.60	6.35	1	0.01 *	701.95		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-3.58	1.74	4.25	1	0.04 *	0.03	0.001	0.84
Constant	4.06	2.14	3.60	1	0.06	58.09		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 22: Simple Logistic Regressions Predicting Likelihood of Treatment Response within the Medication Group

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	0.00	0.03	0.00	1	0.99	1.00	0.94	1.06
Constant	0.89	0.79	1.29	1	0.26	0.24		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	0.16	0.72	0.05	1	0.83	1.17	0.28	4.83
Constant	0.64	1.22	0.27	1	0.60	1.89		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.002	003	0.004	1	0.95	1.00	0.94	1.06
Constant	0.88	0.66	1.78	1	0.18	2.41		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	1.52	1.02	2.22	1	0.14	4.55	0.62	33.46
Constant	-1.15	1.38	0.69	1	0.41	0.32		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	-0.10	0.28	0.12	1	0.72	0.91	0.53	1.56
Constant	1.04	0.51	4.18	1	0.04 *	2.84		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-1.18	0.90	1.71	1	0.19	0.31	0.05	1.80
Constant	2.35	1.17	4.07	1	0.04	10.49		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 23: Simple Logistic Regressions Predicting Likelihood of Remission within the Medication Group

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF	-0.01	0.03	0.19	1	0.66	0.99	0.94	1.04
Constant	0.29	0.72	0,17	1	0.69	1.34		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI	-0.27	0.66	0.17	1	0.68	0.76	0.21	2.76
Constant	0.44	1.11	0.16	1	0.69	1.56		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
UF	0.02	0.03	0.64	1	0.42	1.02	0.97	1.08
Constant	-0.41	0.60	0.46	1	0.50	0.67		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MUI	0.95	0.81	1.39	1	0.24	2.59	0.53	12.56
Constant	-1.30	1.15	1.27	1	0.26	0.27		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
HF:UF	-0.45	0.31	2.14	1	0.14	0.64	0.35	1.16
Constant	0.66	0.51	1.69	1	0.19	1.93		

	B	SE	Wald	df	p	Odds Ratio	95% CI	
							Lower	Upper
MHI:MUI	-1.33	0.87	2.32	1	0.13	0.26	0.05	1.45
Constant	1.61	1.09	2.20	1	0.14	5.00		

HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio. SE= Standard Error. CI= Confidence Interval. Df= Degrees of Freedom.

* $p < 0.05$
** $p < 0.01$

Table 24: Means, Adjusted Means, Standard Deviations and Standard Errors for Week 12 HAM-D Scores for the Treatment Groups

Treatment Group					Analysis	
	CBT		MEDS		$P_{HF*Trtmnt}$	$\eta_{p2HF*Trtmnt}$
HAM-D Score	Low HF	High HF	Low HF	High HF	0.43	0.01
M	8.27	20.3	7.48	7.45		
(SD)	6.55	7.86	5.88	5.82		
M_{adj}	8.28	10.16	7.69	7.25		
(SE)	1.81	1.62	1.17	1.10		

Treatment Group					Analysis	
	CBT		MEDS		$P_{MHI*Trtmnt}$	$\eta_{p2MHI*Trtmnt}$
HAM-D Score	Low MHI	High MHI	Low MHI	High MHI	0.09	0.03
M	6.21	12.62	7.09	7.87		
(SD)	5.82	7.34	5.66	6.02		
M_{adj}	6.48	12.38	6.95	7.99		
(SE)	1.63	1.69	1.08	1.11		

Treatment Group					Analysis	
	CBT		MEDS		$P_{UF*Trtmnt}$	$\eta_{p2UF*Trtmnt}$
HAM-D Score	Low UF	High UF	Low UF	High UF	0.11	0.03
M	13.00	6.33	8.35	6.5		
(SD)	5.77	7.08	5.92	5.56		
M_{adj}	12.77	6.54	8.26	6.59		
(SE)	1.77	1.58	1.09	1.07		

Treatment Group					Analysis	
	CBT		MEDS		$P_{MUI*Trtmnt}$	$\eta_{p2MUI*Trtmnt}$
HAM-D Score	Low MUI	High MUI	Low MUI	High MUI	0.51	0.01
M	10.67	8.20	9.30	5.33		
(SD)	7.70	6.92	6.34	4.28		
M_{adj}	10.41	8.45	9.21	5.41		
(SE)	1.75	1.57	1.05	1.10		

Treatment Group					Analysis	
	CBT		MEDS		$P_{HF:UF*Trtmnt}$	$\eta_{p2HF:UF*Trtmnt}$
HAM-D Score	Low HF:UF	High HF:UF	Low HF:UF	High HF:UF	0.17	0.02
M	5.91	11.63	6.74	8.19		
(SD)	5.19	7.67	5.76	5.84		
M_{adj}	6.24	11.43	6.85	8.07		
(SE)	1.88	1.54	1.10	1.10		

Treatment Group					Analysis	
	CBT		MEDS		$P_{MHI:MUI*Trtmnt}$	$\eta_{p2MHI:MUI*Trtmnt}$
HAM-D Score	Low MHI:MUI	High MHI:MUI	Low MHI:MUI	High MHI:MUI	0.19	0.02
M	5.92	12.00	6.51	8.70		
(SD)	4.58	7.96	5.39	6.18		
M_{adj}	6.13	11.87	6.56	8.63		
(SE)	1.75	1.56	1.02	1.16		

Trtmnt= Treatment. HAM-D= Hamilton Depression Rating Scale. HF= Hassle Frequency. MHI= Mean Hassle Intensity. UF= Uplift Frequency. MUI= Mean Uplift Intensity. HF:UF= Hassle Frequency to Uplift Frequency Ratio. MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio.

"Low" and "High" HUPS Scores were defined by applying a median split to each respective HUPS Score

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub.

Amick, H. R., Gartlehner, G., Gaynes, B. N., Forneris, C., Asher, G. N., Morgan, L. C., Coker-Schwimmer, E., Boland, E., Lux, L. J., Gaylord, S., Bann, C., Pierl, C. B., & Lohr, K. N. (2015). Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. *BMJ*, h6019. https://doi.org/10.1136/bmj.h6019

Aroian, K., Uddin, N., & Blbas, H. (2016). Longitudinal study of stress, social support, and depression in married Arab immigrant women. *Health Care for Women International*, *38*(2), 100-117. https://doi.org/10.1080/07399332.2016.1253698

Bagby, R. M., Quilty, L. C., Segal, Z. V., McBride, C. C., Kennedy, S. H., & Costa, P. T. (2008). Personality and Differential Treatment Response in Major Depression: A Randomized Controlled Trial Comparing Cognitive-Behavioural Therapy and Pharmacotherapy. *The Canadian Journal of Psychiatry*, *53*(6), 361-370. https://doi.org/10.1177/070674370805300605

Beck, A. T., Ward, C. H., & Mendelson, M. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561. https://doi.org/10.1001/archpsyc.1961.01710120031004

Bernstein, D. P., ahluvaliaHLUVALIA, T., Pogge, D., & Handelsman, L. (1997). Validity of the childhood trauma questionnaire in an adolescent psychiatric population. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(3), 340-348. https://doi.org/10.1097/00004583-199703000-00012

Bhagwagar, Z., & Cowen, P. (2007). 'It's not over when it's over': persistent neurobiological abnormalities in recovered depressed patients. *Psychological Medicine*, *38*(3), 307-313. https://doi.org/10.1017/s0033291707001250

Binder, E. B., & Holsboer, F. (2006). Pharmacogenomics and antidepressant drugs. *Annals of Medicine*, *38*(2), 82-94. https://doi.org/10.1080/07853890600551045

Blokhorst, M., Lousberg, R., Vingerhoets, A., Winter, F., & Zilvold, G. (2002). Daily hassles and stress vulnerability in patients with a whiplash-associated disorder. *International Journal of Rehabilitation Research*, *25*(3), 173-179. https://doi.org/10.1097/00004356-200209000-00002

Bockting, C. L., Spinhoven, P., Koeter, M. W., Wouters, L. F., & Schene, A. H. (2006). Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: A 2-year prospective study. *The Journal of Clinical Psychiatry*, *67*(05), 747-755. https://doi.org/10.4088/jcp.v67n0508

Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. *Clinical Psychology Review*, *27*(8), 959-985. https://doi.org/10.1016/j.cpr.2007.02.005

Buuren, S. V. (2018). *Flexible imputation of missing data* (2nd ed.). CRC Press.

DeLongis, A., Coyne, J. C., Dakof, G., Folkman, S., & Lazarus, R. S. (1982). Relationship of daily hassles, uplifts, and major life events to health status. *Health Psychology*, *1*(2), 119-136. https://doi.org/10.1037/0278-6133.1.2.119

DeLongis, A., Folkman, S., & Lazarus, R. S. (1988). The impact of daily stress on health and mood: Psychological and social resources as mediators. *Journal of Personality and Social Psychology*, *54*(3), 486-495. https://doi.org/10.1037/0022-3514.54.3.486

Dunlop, B. W., Binder, E. B., Cubells, J. F., Goodman, M. M., Kelley, M. E., Kinkead, B., Kutner, M., Nemeroff, C. B., Newport, D. J., Owens, M. J., Pace, T. W., Ritchie, J. C., Rivera, V. A., Westen, D., Craighead, W. E., & Mayberg, H. S. (2012). Predictors of remission in depression to individual and combined treatments (PReDICT): study protocol for a randomized controlled trial. *Trials*, *13*(1). https://doi.org/10.1186/1745-6215-13-106

Dunlop, B. W., Kelley, M. E., Aponte-Rivera, V., Mletzko-Crowe, T., Kinkead, B., Ritchie, J. C., Nemeroff, C. B., Craighead, W. E., & Mayberg, H. S. (2017). Effects of Patient Preferences on Outcomes in the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) Study. *American Journal of Psychiatry*, *174*(6), 546-556. https://doi.org/10.1176/appi.ajp.2016.16050517

Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Suicidal behaviour in adolescence and subsequent mental health outcomes in young adulthood. *Psychological Medicine*, *35*(7), 983-993. https://doi.org/10.1017/s0033291704004167

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1995). Structured clinical interview for DSM-IV axis disorders, patient version (SCID-I/P, Version 2.0). *New York, Biometrics Research Department, New York State Psychiatric Research Institute*.

Fournier, J. C., DeRubeis, R. J., Shelton, R. C., Gallop, R., Amsterdam, J. D., & Hollon, S. D. (2008). Antidepressant medications v. cognitive therapy in people with depression with or without personality disorder. *British Journal of Psychiatry*, *192*(2), 124-129. https://doi.org/10.1192/bjp.bp.107.037234

Fournier, J. C., DeRubeis, R. J., Shelton, R. C., Hollon, S. D., Amsterdam, J. D., & Gallop, R. (2009). Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. *Journal of Consulting and Clinical Psychology*, *77*(4), 775-787. https://doi.org/10.1037/a0015401

Godlewska, B. R., Browning, M., Norbury, R., Cowen, P. J., & Harmer, C. J. (2016). Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational Psychiatry*, *6*(11), 957. https://doi.org/10.1038/tp.2016.130

Godoy, L. D., Rossingoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & Henrique de Lima Umeoka, E. (2018). A comprehensive overview on stress neurobiology: Basic concepts and clinical implications. *Frontiers in Behavioral Neuroscience*, *12*, 127. https://doi.org/10.3389/fnbeh.2018.00127

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, *32*(1), 50-55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*, *6*, 278-296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*, 293-319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry*, *4*(5), 409-418. https://doi.org/10.1016/s2215-0366(17)30015-9

Harmer, C. J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G. M., & Cowen, P. J. (2009). Effect of Acute Antidepressant Administration on Negative Affective Bias in Depressed Patients. *American Journal of Psychiatry*, *166*(10), 1178-1184. https://doi.org/10.1176/appi.ajp.2009.09020149

Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, *4*(1), 1-39. https://doi.org/10.1007/bf00844845

Kahneman, D. (2011). *Thinking, fast and slow*. Doubleday Canada.

Kemp, A. H., Gordon, E., Rush, A. J., & Williams, L. M. (2008). Improving the prediction of treatment response in depression: Integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. *CNS Spectrums*, *13*(12), 1066-1086. https://doi.org/10.1017/s1092852900017120

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E., & Wang, P. S. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, *289*(23), 3095. https://doi.org/10.1001/jama.289.23.3095

Kraus, D. R., Castonguay, L., Boswell, J. F., Nordberg, S. S., & Hayes, J. A. (2011). Therapist effectiveness: Implications for accountability and patient care. *Psychotherapy Research*, *21*(3), 267-276. https://doi.org/10.1080/10503307.2011.563249

McIntosh, E., Gillanders, D., & Rodgers, S. (2009). Rumination, goal linking, daily hassles and life events in major depression. *Clinical Psychology & Psychotherapy*, n/a-n/a. https://doi.org/10.1002/cpp.611

Murray, C. J., Lopez, A. D., World Health Organization, World Bank, & Harvard School of Public Health. (1996). *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Hardvard University Press.

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, A. J., Schatzberg, A. F., Ninan, P. T., McCullough, J. P., Weiss, P. M., Dunner, D. L., Rothbaum, B. O., Kornstein, S., Keitner, G., & Keller, M. B. (2005). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *FOCUS*, *3*(1), 131-135. https://doi.org/10.1176/foc.3.1.131

Norman, R. M., & Malla, A. K. (1994). A prospective study of daily stressors and symptomatology in schizophrenic patients. *Social Psychiatry and Psychiatric Epidemiology*, *29*(6), 244-249. https://doi.org/10.1007/bf00802047

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature review disease primers*, *2*. https://doi.org/10.1038/nrdp.2016.65

Papakostas, G. I., & Fava, M. (2008). Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. *Dialogues in clinical neuroscience*, *10*(4), 439-451.

Parsey, R. V., Oquendo, M. A., Ogden, R. T., Olvet, D. M., Simpson, N., Huang, Y., Van Heertum, R. L., Arango, V., & Mann, J. J. (2006). Altered Serotonin 1A Binding in Major Depression: A [carbonyl-C-11]WAY100635 Positron Emission Tomography Study. *Biological Psychiatry*, *59*(2), 106-113. https://doi.org/10.1016/j.biopsych.2005.06.016

Pascoe, J. M. (1990). Maternal stress and depressive symptoms. *American Journal of Public Health*, *80*(11), 1397. https://doi.org/10.2105/ajph.80.11.1397

Rush, A., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., &

Keller, M. B. (2003). The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*(5), 573-583. https://doi.org/10.1016/s0006-3223(02)01866-8

Salleh, M. R. (2008). Life events, stress and illness. *The Malaysian Journal of Medical Sciences, 15*(4), 9-18.

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology, 46*(5), 932-946. https://doi.org/10.1037/0022-006x.46.5.932

Simon, G. E., Korff, M., & Barlow, W. (1995). Health care costs of primary care patients with recognized depression. *Archives of General Psychiatry, 52*(10), 850. https://doi.org/10.1001/archpsyc.1995.03950220060012

Simon, G. E., & Perlis, R. H. (2010). Personalized medicine for depression: Can we match patients with treatments? *American Journal of Psychiatry, 167*(12), 1445-1455. https://doi.org/10.1176/appi.ajp.2010.09111680

Wagner, B. M., Compas, B. E., & Howell, D. C. (1988). Daily and major life events: A test of an integrative model of psychosocial stress. *American Journal of Community Psychology, 16*(2), 189-205. https://doi.org/10.1007/bf00912522

Weiner, I. B., Stricker, G., & Widiger, T. A. (2012). Behavior therapy and cognitive behavioral therapy. In *Handbook of psychology, clinical psychology* (2nd ed., pp. 291-319). John Wiley & Sons.

Weitz, E. S., Hollon, S. D., Twisk, J., Van Straten, A., Huibers, M. J., David, D., DeRubeis, R. J., Dimidjian, S., Dunlop, B. W., Cristea, I. A., Faramarzi, M., Hegerl, U., Jarrett, R. B., Kheirkhah, F., Kennedy, S. H., Mergl, R., Miranda, J., Mohr, D. C., Rush, A. J., … Cuijpers, P. (2015). Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy. *JAMA Psychiatry, 72*(11), 1102. https://doi.org/10.1001/jamapsychiatry.2015.1516

Whooley, M. A., & Wong, J. M. (2013). Depression and cardiovascular disorders. *Annual Review of Clinical Psychology, 9*, 327-354. https://doi.org/10.1146/annurev-clinpsy-050212-185526

Willner, P. (2017). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress, 6*, 78-93. https://doi.org/10.1016/j.ynstr.2016.08.002

World Health Organization. (n.d.). *Suicide data*. Retrieved July 8, 2019, from https://www.who.int/mental_health/prevention/suicide/suicideprevent/en/