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Benjamin Furman March 30, 2022

Don’t sweat the small stuff? Daily hassles, uplifts relationship with depression treatment.

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Abstract

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Background: Major Depressive Disorder (MDD) is one of the most prevalent and debilitating diseases worldwide. While the primary first-line 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 Daily 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). Remitting patients entered a 21-month follow-up phase. Non-remitting patients were eligible to enter a 12-week combination treatment phase. Patients who remitted from combination treatment entered an 18-month follow-up phase. Prior to treatment and every 12 weeks following, participants responded to the HUPS. The primary outcome measure was change in the 17-item Hamilton Depression Rating Scale.

Results: In patients treated with antidepressant medication, hassle scores generally significantly decreased and uplift scores generally increased following the conclusion of acute treatment regardless of treatment outcome. In patients treated with CBT, hassle scores generally decreased and uplift scores generally increased in patients that remitted but did not in patients that did not remit. HUPS scores did not predict remission or recurrence in the whole sample, sample treated with antidepressant medications, or sample treated with CBT. HUPS score did not moderate the relationship between initial treatment type and remission or recurrence.

Conclusion: Scores on the HUPS do not predict remission or recurrence and do not moderate the differential remission or recurrence rates. Reduction of negative affective biases are characteristic of treatment with antidepressant medications but not treatment with CBT.

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Chapter I: Introduction and Statement of the Problem and Purpose

Major depressive disorder (MDD) is a highly prevalent health issue in the United States. In 2017, over 17 million, or approximately seven percent, of American adults over the age of 18 experienced a major depressive episode (Center for Behavioral Health Statistics and Quality, 2018). In addition to being highly prevalent, MDD is highly debilitating, as nearly 64% of American adults were severely impaired by their major depressive episode (Center for Behavioral Health Statistics and Quality, 2018). 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 two most prominent treatment options for MDD are evidence-based psychotherapy and pharmacotherapy (Otte et al., 2016). At the population level, these two primary treatments have been shown to be equivalently efficacious (Amick et al., 2015 and Weitz et al., 2015). However, this population-level equivalence obscures substantial inter-patient response variability among different treatments. Identifying measurable attributes of patients that can guide healthcare providers to provide the treatment with the greatest likelihood of success for a given patient is an issue of great importance.

There is a long history of research suggesting that psychological stress is a key contributor to the development of psychiatric disorders and much research has been done examining the relationship between stress and MDD (Hammen, 2005). However, despite the prevalence of research relating to psychological stress and depression, very little work investigating the ability of psychological stress levels to predict differential treatment response and outcomes has been conducted.

The current study is predicated upon the theoretical groundwork laid out by Dr. Richard Lazurus and colleagues. In contrast to the prevailing ideologies of the time, which are still prevalent today, Lazurus posited that research relating to stress should focus on chronic minor stressors as opposed to major life events (Kanner et al., 1981). Lazarus's suggestion to study chronic minor stressors is rooted in concepts that he and Dr. Susan Folkman later crafted into the transactional model of stress and coping (Lazarus and Folkman, 1984). Given the ubiquity of stress-related research, the transactional model of stress and coping has been applied to studies with scopes ranging from coping with chronic disease to post-traumatic stress disorder (Sanaeinasab et al., 2017 and Sloan-Power et al., 2012).

This study aims to investigate whether scores calculated from a patient-reported survey measure of chronic minor stressors and pleasures, the Daily Hassles and Uplifts Scale (HUPS), can predict response to treatments for MDD and whether HUPS scores moderate the relationship between response to psychotherapeutic versus pharmacologic treatments. Additionally, HUPS scores were evaluated to determine if they predict MDD recurrence and moderate the relationship between initial treatment type and MDD recurrence. Additionally, the association of pre-treatment HUPS scores and patient preferences for treatment were investigated to determine if levels of chronic minor stressors or uplift responsiveness lead patients to prefer different treatments. Finally, the potential association between clinical measures of stress (e.g., HUPS scores) and biological measures of stress (adrenocorticotropin and cortisol concentrations assessed as part of the dexamethasone suppression test) were investigated to determine if the clinical and biological stress measures exhibit consistency.

Chapter II: Review of the Literature

MDD is a pervasive health issue in the United States, with over seven percent of the adult American population experiencing a major depressive episode in 2017, and just over sixteen percent of the adult American population having experienced MDD over the course of their lifetime (Center for Behavioral Health Statistics and Quality, 2018 and Kessler et al., 2003). MDD is also the leading cause of global health loss in terms of disability-adjusted life years among mental disorders and one of the top ten causes of global health loss across all health issues (GBD 2019 Diseases and Injuries Collaborators, 2019). Furthermore, a diagnosis of MDD has been shown to be correlated with an increased risk for numerous other debilitating medical conditions such as diabetes mellitus, heart disease, and stroke (Whooley and Wong, 2013). Individuals with mental disorders, including but not limited to MDD, exhibit an elevated risk for all-cause mortality and suicide mortality, with individuals with MDD displaying some of the highest suicide risks of all individuals living with mental disorders (Chesney et al., 2014). Suicide is a prominent global health issue, as 1.3 percent of total deaths were death by suicide, and suicide was the fourth-leading cause of death among people aged 15-29 in 2019 (World Health Organization, 2021). Moreover, patients with MDD can face great financial pressure as a result of their condition. Primary care patients diagnosed with MDD have nearly double the cost of healthcare when compared to primary care patients without MDD (Simon, Korff, and Barlow, 1995). The discrepancy in healthcare-associated financial burden experienced by individuals with MDD can be attributed to numerous factors, but the likely principal cause is that individuals diagnosed with MDD receive medical care at a rate four times higher than individuals without MDD (Simon, Korff, and Barlow, 1995).

The *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5) defines a major depressive episode as the presence of a depressed mood or anhedonia, along with several associated symptoms (e.g., reduced energy, changes in sleep, appetite, or weight, feelings of worthlessness or guilt, diminished concentration or decision making abilities, psychomotor changes, and recurrent suicidal ideation or thoughts of death) that are present most of the day, nearly every day, over a minimum of a two-week period and cause clinically significant distress or impairment in social, occupational, or other areas of functioning (American Psychiatric Association, 2013). Typically, symptoms first appear when individuals are between 15 and 29 years old (Fergusson et al., 2005). A further concerning issue is the highly recurrent nature of MDD. More than half of patients who remit from a major depressive episode will experience one or more additional episodes over the course of their life, and close to 80 percent of patients with two prior episodes will have at least one more recurrence (Burusca and Iacono, 2008). MDD's debilitating nature in terms of symptomatology and recurrence as well as its association with other negative health and financial outcomes makes its effective treatment of paramount importance.

Choosing an initial intervention for MDD is one of the primary challenges clinicians face in treating MDD. Two general classes of treatment, evidence-based psychotherapy and pharmacotherapy, are the first-line options for initial MDD treatment (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

may not work at all. Given the adverse health outcomes associated with MDD, it is imperative that methods to identify the single best treatment available for a given individual are created. While a seemingly effective solution, delivering combined psychotherapy and pharmacotherapy is neither a feasible nor efficient solution, as it is significantly more expensive than delivering a single treatment, unattainable for many patients, and a misapplication of limited healthcare resources. The goal of providing individually-tailored treatments is the central ideology of the personalized medicine movement (also known as precision medicine or personalized intervention), in which identifying individual-level indicators of treatment outcomes are emphasized over larger group-level, average outcomes (Simon and Perlis, 2010). Essentially, 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).

In the search to identify methods to determine the treatment best suited for a given patient, it is necessary to also identify measurable patient attributes that can guide initial treatment selection. These attributes can range from biological markers to clinical attributes to sociodemographic variables (Simon and Perlis, 2010). Among potential variables for guiding treatment selection, two further classifications emerge: those characteristics that predict response regardless of the form of treatment provided, and those characteristics that moderate the relationship between specific treatment types and treatment outcome. A treatment predictor can be defined as any patient characteristic of which either the presence or intensity influences the probability of a certain outcome (Papakostas and Fava, 2008). In contrast to a predictor, which predicts the likelihood of outcome to any form of treatment, a moderator is a *differential* predictor; that is, a moderator is a 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 (Papakostas and Fava, 2008). More simply, a patient characteristic would be deemed a moderator if patients with Characteristic X responded differently to Treatment A versus Treatment B (Simon and Perlis, 2010).

Currently, the psychiatric literature predominately is comprised of studies investigating potential *biological* measures as predictors of treatment response to a *single* treatment modality (i.e., either psychotherapy or pharmacotherapy), and can thus not determine whether a given characteristic can moderate the relationship between treatment type and treatment outcome (Kemp et al., 2008). Furthermore, very few studies have been conducted investigating clinical and socio-demographic factors as potential moderators of the relationship between treatment type and outcome. Currently, a small number of clinical variables have been suggested as potential moderators for selecting between psychotherapy and pharmacotherapy. Two studies have reported that certain personality characteristics (i.e., the presence of a personality disorder or elevated levels of neuroticism) at pre-treatment baseline predicted better treatment response to pharmacotherapy as opposed to psychotherapy (Fournier et al., 2008; Bagby et al., 2008) and one study has indicated that patients with a greater history of childhood traumatic events may respond better to psychotherapy than pharmacotherapy (Nemeroff et al., 2003). Similar to the research regarding potential predictors and moderators of treatment response, the current literature surrounding MDD recurrence is weighted heavily towards identifying predictive characteristics (i.e., studies employ only a single treatment method) rather than moderators of the relationship between treatment option and relapse status (Buckman et al., 2018).

The history of investigating the relationship between psychological stress and mental disorders is rich, especially in terms of studies examining stress's role in MDD (Hammen, 2005). Despite this history, there has been little work examining stress as a potential moderator for

treatment response and outcome in MDD. A study investigating the effects of components of participant's personal lives, such as recent major stressful life events, unemployment status, and marital status, indicated more successful MDD treatment outcomes from psychotherapy as opposed to pharmacotherapy; however, this study did not specifically analyze current minor stressors or uplifts as predictive variables (Fournier et al., 2009).

Studies regarding psychological stress can be broadly classified as falling within two categories: those examining biological stress measures (e.g., hypothalamus-pituitary-adrenal (HPA) axis activity) and those that use patient-reported surveys or questionnaires to assess stress levels (Godoy et al., 2018). Studies utilizing patient-report measures can be further subdivided into studies of stress induced by major life events and stress caused by chronic minor stressors; the bulk of current research is based upon the former (DeLongis et al., 1982; Kanner et al., 1981; Salleh, 2008). However, the theory that chronic minor stressors, known as daily hassles, predict future physical and mental health more accurately than life events has support (DeLongis et al., 1982). According to this hypothesis, major life events are distal measures of stress, as they are solely representations of individual events rather than the consequences they impose (DeLongis et al., 1982). Conversely, daily hassles are a proximal stress measure, as they represent an immediate stressor present in everyday life and an individual's evaluation of the stressor (DeLongis et al., 1982). This belief is built upon Lazarus and Folkman's transactional model of stress and coping. In this model, rather than be conceptualized as a unilateral phenomenon (i.e., it is neither the individual nor their environment that is entirely responsible for stress), stress is a potential result of the bidirectional transaction between a person and presented stimuli in their environment (Lazarus and Folkman, 1984). Two central tenets of the transactional model of stress and coping are cognitive appraisal and coping (Lazarus and Folkman, 1984). Lazarus and

Folkman further break down cognitive appraisal into primary and secondary appraisal (Lazarus and Folkman, 1984). Primary appraisal determines the impact of a particular individual-environment transaction on their well-being and can be classified on a range from negative to positive (Lazarus and Folkman, 1984). Transactions can be deemed stressful when they challenge a person's coping mechanisms (Lazarus and Folkman, 1984). Secondary appraisal is a subsequent cognitive process in which an individual evaluates their potential coping strategies (Lazarus and Folkman, 1984). An individual's propensity to experience daily hassles, and the magnitude to which they experience them, is thus a product of their cognitive appraisals of day-to-day interactions with their environment. Furthermore, the belief that chronic minor stressors are related to MDD is mirrored in the chronic mild stress (CMS) model of depression, the main animal research model of MDD in which rats or mice are chronically stimulated with micro-stressors, leading to the development of behaviors consistent with human depressive symptomatology (e.g., decreased reward response and anhedonia) (Willner, 2017). Previous research has demonstrated that both psychotherapeutic and pharmacologic treatments can target these mechanisms. Healthy adults administered cognitive therapy focusing on appraisal of stressors exhibited decreased general stress when compared to controls in a work-place environment (Gardner et al., 2005). Antidepressant medications may be conceptualized as working in ways similar to those of cognitive therapy in that rather than directly enhancing mood, they shift the axis of emotional processing toward the positive, allowing depressed individuals to appraise stressors, or other negative occurrences, in a more positive manner (Harmer et al., 2009).

To assess chronic minor stressors, the Hassles Scale, a 117-item questionnaire comprised of 117 potential day-to-day stressors in seven broad categories (i.e., work, family, social

activities, environment, practical considerations, finances, and health) was created (Kanner at al., 1981). Conversely, a 135-item questionnaire similarly constructed to the Hassles Scale was designed to assess the inverse of daily hassles, referred to as daily uplifts (i.e., minor positive day-to-day occurrences) (Kanner et al., 1981). Over time, the Hassles Scale and the Uplifts Scale were abbreviated and merged into a single, 53-item questionnaire, the Daily Hassles and Uplifts Scale, that simultaneously allows for appraisal of given events as either hassles or uplifts (DeLongis et al., 1988).

Studies utilizing the HUPS have demonstrated correlations between the number of reported hassles (hassle frequency) and somatic health status (DeLongis et al., 1982) and negative affect (Kanner et al., 1981). Additionally, further research suggests that hassle frequency may be a more effective predictor of current psychological symptomatology than life event metrics (Kanner et al., 1981; Wagner et al., 1988). Furthermore, a significant positive relationship between daily hassle frequency and symptomatology in patients with schizophrenia has been reported (Norman and Malla, 1994), as well as symptoms of depression and daily hassles in mothers (Pascoe, 1990), and depressive symptoms and hassle frequency in married, recent female Arabic immigrants (Aroian et al., 2016). A study of a general sample of Swedish military veterans suggests that a higher uplift frequency and lower hassle frequency and use of functional coping strategies as opposed to dysfunctional coping strategies were associated with lower levels of stress-related symptoms (Larsson et al., 2020). Furthermore, among male veterans, daily hassles were shown to moderate the relationship between emotional stability and stress-related symptoms; however, this moderative effect was not observed in female veterans (Larsson et al., 2020).

An elevated hassle frequency has been reported in patients diagnosed with MDD when compared to healthy controls (McIntosh et al., 2009). Elevated chronic minor stressors, as measured by the Everyday Problem Checklist (EPCL) (Vingerhoets et al., 1989), have also been shown to be a risk factor for MDD relapse, whereas adult major life events were demonstrated to have negligible predictive capabilities for relapse (Bockting et al., 2006). Taken together, these findings suggest that the HUPS used as a measure of chronic minor stressors may have utility as a predictor of MDD treatment outcomes and has potential to moderate the relationship between treatment type and treatment outcome.

Critical to successful treatment for MDD is patient adherence to treatment. Meta-analyses have demonstrated that patients who do not receive their preferred treatment method (i.e., their preferred option between psychotherapy and pharmacotherapy) exhibit an increased likelihood of ending their treatment prior to completion (Lindheim et al., 2014). Additionally, two meta-analyses that were not limited to randomly controlled trials found small effects for better outcomes for patients who received their preferred treatment (Swift and Callahan, 2009; Lindheim et al., 2014). Meta-analyses have suggested that younger patients and female patients are more likely to prefer psychotherapy over pharmacotherapy (McHugh et al., 2013); conversely, greater severity of depression has been associated with a preference for medication (Bedi et al., 2000). However, there has been little research done on identifying other predictive factors of patient preference (McHugh et al., 2013). As stress has been shown to be associated with MDD in various ways, it is reasonable to investigate the possibility of chronic minor stress levels to predict patient MDD treatment preferences. Patient preferences have also previously been investigated as a potential moderator between the relationship between treatment type and treatment outcome, with mixed findings (Dunlop et al., 2017). Given the suggested positive

association between chronic minor stress and mental illness symptomatology (Kanner et al., 1981; Norman and Malla, 1994; Pascoe, 1990; Aroian et al., 2016) and the association between greater depression severity and preference for medication, it is reasonable to believe that patients with elevated levels of chronic minor stress as measured by the HUPS may exhibit differential preferences for treatment when compared with patients with lower levels of chronic minor stress.

It is also pertinent to examine the potential association between patient-reported measures of stress (e.g., the HUPS) and biological measures of stress. Originally developed as a diagnostic test for Cushing syndrome, the dexamethasone suppression test (DST) involves the administration of dexamethasone, a synthetic glucocorticoid (Smith et al., 2013). By inhibiting adrenocorticotropic hormone (ACTH) release from the pituitary gland, dexamethasone administration should lower ACTH and cortisol concentrations in healthy patients (Smith et al., 2013). The DST has also been highly studied as a diagnostic test for MDD, as DST results are often abnormal (i.e., adrenocorticotropin and cortisol concentrations remain elevated) in patients with MDD (The APA Task Force on Laboratory Tests in Psychiatry, 1987). However, subsequent evaluation of the DST indicated its limited utility as a tool to either diagnose MDD or guide treatment (The APA Task Force on Laboratory Tests in Psychiatry, 1987). Stress has also been shown to influence DST results with elevated pre-DST plasma cortisol concentrations and acute anxiety levels being associated with non-suppression on the DST (Ceulemans et al., 1985). Given the established relationship with stress and the DST, it is reasonable to believe that a relationship between HUPS scores as a measure of chronic minor stress and DST results may exist.

Studies evaluating potential predictors and moderators of treatment outcome can fall victim to confounding arising from past treatments participants have received. Exposure to and

outcomes of previous treatment can impact the willingness of patients with MDD 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 that may impact an individual's response to study treatments. Thus, when investigating the capabilities of clinical measures to serve as predictors of treatment outcome and moderators for initial treatment selection, treatment-naïve patient samples are highly valuable.

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 can 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 a combination of the two demonstrate predictive or moderating effects on treatment outcomes in patients with MDD.

Chapter III: Methods

Study Overview

A design paper describing 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 was housed at two clinics: 1) the primary Mood and Anxiety Disorders Program Clinic at Emory University in Atlanta, Georgia, with a satellite location in Stockbridge, Georgia, and 2) an entirely Spanish-speaking clinic, Clínica Latina para el Tratamiento de la Depresión, at Grady Memorial Hospital in Atlanta, Georgia. The Dexamethasone-Corticopropin Releasing Hormone tests (DST) were conducted at the Clinical Interaction Network (CIN) of the Atlanta Clinical and Translational Science Institute housed at both Emory University Hospital and Grady Memorial Hospital. The PReDICT study enrolled 344 treatment-naïve patients diagnosed with MDD who were randomly assigned to one of three possible treatments: 1) a selective serotonin reuptake inhibitor (SSRI), escitalopram, 2) a serotonin norepinephrine reuptake inhibitor (SNRI), duloxetine), or 3) cognitive behavior therapy (CBT). During the first phase of the study, patients underwent a 12-week course of their assigned treatment. Patients that remitted after the acute treatment phase are eligible to enroll in a 21-month follow-up phase during which quarterly visits to monitor for recurrence are conducted. Patients who did not remit (defined below) following the initial 12-week treatment were offered the combination of psychotherapy and medication for another 12-week treatment course. Following the 12-week combination therapy stage, remitters and responders to combination therapy were entered into an 18-month follow-up phase with quarterly monitoring visits. Non-responders of the combination treatment phase were removed from the study. Patients who experienced an MDD recurrence were removed from the study following their recurrence.

Patient Population

The study patient population consisted of men and women between the ages of 18 and 65 with an MDD diagnosis from the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995), subsequently confirmed via interview by a study psychiatrist. To be enrolled in the study, patients must have had at least moderately severe depression, defined as having a Hamilton Depression Rating Scale (HAM-D) score ≥ 18 at the initial screening visit and ≥15 at the baseline visit. Additionally, patients were required to be treatment-naïve for MDD. Patients were deemed to not be treatment-naïve if they had reported prior treatment for either MDD, dysthymia, or depressive disorder not otherwise specified with an antidepressant at minimum effective dose for ≥ 4 weeks or ≥4 sessions of an evidence-based psychotherapy (e.g., CBT, interpersonal therapy, or behavioral marital therapy) for depression. Patients were excluded from the study if they had a history of bipolar disorder, a primary psychotic disorder, or dementia, or a diagnosis within the past year of obsessive-compulsive disorder, an eating disorder, or a dissociative disorder. Additionally, patients meeting the DSM-IV criteria for substance abuse within the last 3 months, or substance dependence within the last 12 months prior to initial screening visit, or those whose urine tested positive for drugs of abuse, were also excluded. Any prior treatment with citalopram, escitalopram, or duloxetine was also an exclusion criterion. Additionally, pregnant women, women who were breast-feeding, or women who were planning on becoming pregnant were excluded. Finally, patients with significant uncontrolled medical conditions, or any potentially interfering medical conditions, were also excluded.

Randomization

Study participants were randomly assigned in a 1:1:1 ratio to one of three possible treatment arms: 1) escitalopram 10-20 mg/day, 2) duloxetine 30-60 mg/day, or 3) CBT, 16

individual sessions. Before opening the study to enrollment, randomized permuted blocks were used to create treatment assignments ensuring equal allocation across treatment groups. Patients at the English-speaking and Spanish-speaking clinics were randomized separately. Before the study was opened to enrollment, a researcher at Emory University who was unaffiliated with the study placed the individual treatment assignments into sealed, opaque envelopes. At a study participant's baseline visit, a study coordinator opened the envelope to identify the participant's randomly assigned treatment of either medication or CBT, after the study psychiatrist's confirmation that all eligibility requirements for randomization had been met. For participants randomized into one of the two medication groups, the specific identity of the medication was blinded to both the treatment team and to the patient, with the unblinded medication list maintained by the Emory Investigational Drug Service.

Study Visits and Treatments

Following randomization, patients in all treatment groups returned to their respective study sites weekly during weeks 1-6 and biweekly during weeks 7-12 for symptom assessment and safety monitoring, further described below. To promote treatment and assessment consistency across clinical sites, Spanish-speaking raters and physicians conducted assessments at the English-speaking site as well as the Spanish-speaking site. To account for travel related expenses, participants were given gift cards with a value of $5.00 per visit.

Pharmacotherapy

All study medications were compounded by the Emory Investigation Drug Service pharmacy into uniform grey capsules containing either 10 mg of escitalopram or 30 mg of duloxetine. Patients randomized to pharmacotherapy were started on one capsule per day; if patients had not improved by week four, their dosage was increased to two capsules per day. If

deemed necessary for a patient by a study psychiatrist, the dosage could be increased one week early, at week three. Patients failing to achieve remission by week six were required to increase their dosage to two capsules per day; however, the dosage could be lowered if the patient experience significant adverse effects. Patients that were eligible to enter the follow-up phase were strongly encouraged to remain on their assigned medication through month 12. At month 12, a study psychiatrist discussed with the participant the risks and benefits of discontinuing the medication given the participant's number of previous untreated depressive episodes. Participants were eligible to continue into the second year of the follow-up phase regardless of their decision to continue or discontinue their medication at month 12.

CBT

Study CBT therapists were trained in Beck's standardized CBT protocol, an approach widely used in clinical trials of CBT for MDD (Beck et al., 1979). Patients randomized to CBT had sessions with their therapists twice a week during weeks one through four and then once a week for weeks five through twelve, though flexibility in this treatment schedule was accommodated as necessary. Therapist supervision occurred weekly, and the videotaped 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 study therapist's competency score fell below 40, the therapist received auxiliary training.

Concomitant Medications

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

Assessments

Sample Demographics, Childhood Trauma, and Patient Preferences for Treatment

Study participants' demographic data was collected via a self-report form at the initial screening visit as was a history of childhood abuse and neglect, collected using the Childhood Trauma Questionnaire (CTQ), a 28-item questionnaire containing five subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein et al., 1997). Responses to all 28 CTQ items are measured on a five-point Likert scale (1 = "never true"; 5 = "always true"), and scores on the CTQ can be classified into four categories: 1) none-to-low trauma exposure, 2) low-to-moderate trauma exposure, 3) moderate-to-severe trauma exposure, and 4) severe-to-extreme trauma exposure (Bernstein et al., 1997). Additionally, patient preference for treatment was assessed at the point of obtaining informed consent via the Patient Attitudes and Beliefs Scale (Elkin et al., 1989). The study psychiatrist informed participants that, across populations, individuals with MDD are equally likely to benefit from CBT or medication and informed patients that the overall goal of the study was identifying characteristics that could be used to guide clinical prescription of treatment in the future. Participants were informed that their treatment preference would not be reflected in their assigned treatment, as assigned treatments were entirely random. Participants could indicate their treatment preference as one of three options: 1) "no preference", 2), "cognitive behavior therapy", or 3) "medication".

Chronic Minor Stressors and their Inverse

To assess chronic minor stressors and their inverse, the abbreviated version of the HUPS was administered at baseline and week 12 during the acute treatment phase. Study participants who proceeded into the combined treatment or follow-up phases following the acute treatment phase were administered the abbreviated HUPS monthly from months four to six and then

quarterly from months six through 24. The abbreviated HUPS consists of 53 items across seven categories (i.e., work, family, social activities, environment, practical considerations, finances, and health) and is scored identically to its original version (DeLongis et al., 1988). The HUPS is a self-report questionnaire on which a participant indicates the degree to which each of the 53 items had been an issue over a specific time frame; in PReDICT, this specific time frame was the previous week. Specifically, the HUPS asks, "How much of a HASSLE was this item for you over the past 7 days?". Participants choose from one of four possible responses for each item: 1) "Not at all of not applicable" (=0), "Somewhat" (=1), "Quite a bit" (=2), or "A great deal" (=3). The same list of items is then repeated with participants instead responding to the question, "How much of an UPLIFT was this item for you over the past 7 days?" with the same rating options as for questions pertaining to hassles.

Four metrics have been derived from the HUPS questionnaire and used in previous analyses. The first class of metric, frequency, is a raw count of the number of hassles endorsed as >0 or uplifts as endorsed as >0. These scores were defined as Hassle Frequency (HF) and Uplift Frequency (UF), respectively. Another class of metric, intensity, is a summed total for all 53 hassle-item scores (Hassle Intensity, HI) and uplift-item scores (Uplift Intensity, UI) (DeLongis et al., 1982).

A total of eight metrics derived from the HUPS questionnaire were used in this analysis. The frequency of hassles and uplifts (HF and UF) were defined above. Raw intensity scores (HI and UI), defined above, are dependent on the number of items the patient endorsed as a hassle or uplift in the past week, which could vary substantially across individuals based on static and dynamic life factors, and thus are highly dependent upon the HF and UF scores and subject to interparticipant variability. Therefore, a Mean Hassle Intensity (MHI) and Mean Uplift Intensity

(MUI) were calculated to better measure the degree of perceived feeling around the negative and positive events experienced. MHI was calculated as HI/HF and MUI was calculated as UI/UF. Finally, because there were significant correlations at baseline (see **Table 23**) between HF and UF ($r= 0.56$, $p<0.001$) and MHI and MUI ($r=0.26$, $p<0.001$), ratios of HF:UF and MHI:MUI were calculated with the aim of controlling for the interparticipant 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").

Depressive Symptomatology

Symptom assessments were conducted at weeks one through six, eight, ten, and twelve after the baseline visit. The primary clinical outcome measure was the 17-item HAM-D, administered by trained raters blinded to the participant's treatment. The HAM-D's 17 items measure the severity of depressive symptoms and are scored between 0-4 points (Hamilton, 1967). Scores from 0-7 are considered normal, 8-16 indicate mild depression, 17-23 moderate depression, and above 24 severe depression (Hamilton, 1967). The maximum 17-item HAM-D score is 52 (Hamilton, 1967). The blinded raters also assessed anxiety by administering the 14-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 to 56 (Hamilton, 1959). A score below 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 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). 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 zero to three, such that zero signifies the symptom is not present and three the symptom is most severe, for a maximum score of sixty-three (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 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 three-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 zero to ten with zero representing no impairment and ten representing extreme impairment (Rush et al., 2000). A combined score above ≥15, or any individual score ≥5 are associated with significant functional impairment (Rush et al., 2000). The SDS was administered at the baseline visit and then every subsequent four 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 one through with one representing "very poor" satisfaction and five 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 six months and 2) the last seven months to one year (Sarason et al., 1978). Each life event can be endorsed as either positive or negative, ranging

from a scale from negative three (most negative) to positive three (most positive) (Sarason et al., 1978). The LES was administered at baseline and again at week 12.

Neuroendocrine function

To assess HPA axis function, the Dexamethasone Suppression Test (DST) was conducted. Orally dosed 1.5mg of dexamethasone was taken at 2100 h on the evening before the blood draw. The following day, blood for cortisol wase drawn at 1500 h and centrifuged at 4ºC within 10 minutes of collection, with the plasma frozen at -80ºC until thawed for analysis of cortisol concentrations using a radioimmunoassay kit (INC Biomedicals, Carlson, California, USA).

Depression Outcome Definitions

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. The analysis of acute treatment outcomes focuses only on remission. An additional outcome, *recurrence*, was defined as the occurrence of any one of the following four criteria during the follow-up phases: 1) meeting full criteria for a major depressive episode determined through a Longitudinal Internal Follow-up Evaluation (LIFE) (Keller et al., 1987) interview administered by a blind rater, 2) a HAM-D score ≥14 in consecutive weeks (i.e., a participant scoring ≥14 at a scheduled follow-up visit will be asked to return the subsequent week for a second rating, and if that rating is also ≥14, the participant is deemed to have had a recurrence), 3) a HAM-D score ≥14 at any follow visit and the participant requests an immediate change in

treatment for their depressive symptoms, and 4) high current risk for suicidality as assessed by the study psychiatrist that necessitates urgent intervention.

Statistical Analysis

All data were analyzed with IBM SPSS statistics software version 28

Missing Data

Due to a clerical error, on 55 of the 196 (28.1%) 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. In total, including the missing data points as a result of the clerical error, there were missing values for only 1.5% of the items on the HUPS. Given the small proportion of missing data from the overall HUPS data and the fact that if a participant neglected to score a particular HUPS item it was unlikely to be a particularly salient event, missing datapoints were assigned a score of zero. To assess for potential differences in mean HUPS scores among the participant cohort that received the erroneous HUPS form and the cohort that received the correct HUPS form, independent t-tests were performed (**Table 1**). For all HUPS measures, there were no statistically significant differences in mean scores between the patients who completed the correct (n=141) and incorrect (n=55) versions of the HUPS, and the effect sizes of the differences were very small (all eta-squared ≤ 0.01). Due to no significant differences in any of the HUPS metrics at baseline occurring between the group that received the correct HUPS form and the group that received the erroneous HUPS form, these groups were combined into one larger group that is used for all following analyses.

All patients that completed the 12-week acute treatment phase had valid week 12 HAM-D scores, so there were valid remission data points for all acute treatment phase completers. Additionally, all patients that continued into the long-term follow-up phase were either noted as

having experienced a recurrence or had valid HAM-D scores at study completion, so there were valid recurrence data points for all long-term follow-up phase completers. There were no missing datapoints for patient preferences for treatment. Fourteen of 196 (7.1%) participants with baseline HUPS scores had missing cortisol and dexamethasone concentration levels, so these cases were excluded in analyses pertaining to the DST. Among demographic variables, only race (7.7%) and number of children (8.2%) had more than 5% of datapoints missing. Descriptive analyses utilizing demographic variables were all bivariate analyses, so participants with missing datapoints were excluded on an analysis-by-analysis basis.

Escitalopram vs. Duloxetine

Independent-samples t-tests were conducted to compare the baseline HUPS scores between the escitalopram and duloxetine groups **(Table 2**). For all HUPS measures, there were no statistically significant differences in mean scores between patients in the escitalopram (n=64) and duloxetine (n=66) groups, and the effect sizes of the differences were very small (all eta-squared ≤ 0.01). Due to no significant differences in any baseline HUPS score across treatment groups being observed, for the remainder of the analyses the escitalopram and duloxetine groups were combined into one larger "medication" group. Thus, the two treatment groups for the purposes of this analysis were "CBT" and "medication."

Research Questions Analyses

Demographic characteristics across treatment groups were evaluated using chi-square tests of independence. The relationship between baseline and week-12 HUPS scores and other clinical factors at baseline and week 12 were evaluated using bivariate correlations. Statistical testing for group differences for each HUPS score was done using independent samples t-tests. T-tests were two-tailed with a significance level of $p<0.05$. Paired t-tests were used to assess the

change in HUPS scores from baseline to week-12 as well as HAM-D changes from baseline to week 12. To assess if week 12 HUPS scores differed by treatment group when controlling for baseline HUPS scores, a one-way analysis of covariance (ANCOVA) was performed with the week-12 HUPS score as the dependent variable, treatment group as the independent variable, and the baseline HUPS score was the covariate. ANCOVAs to assess if week 12 HUPS scores differed by treatment group when controlling for baseline HUPS scores were done for the whole sample, and then repeated among the portion of the sample that remitted, did not remit, recurred, and did not recur. An ANCOVA to assess if week 12 HAM-D scores differed by treatment group when controlling for baseline HAM-D scores was performed. To be included in ANCOVA analyses, SPSS requires participants have valid datapoints for all variables in the model (i.e., baseline scores, week 12 scores, and treatment group), so only participants that completed the 12-week acute treatment phase were assessed. Chi-square tests of independence were performed to assess for potential difference in remission and recurrence rates across treatment groups.

To test for predictors of remission and recurrence, logistic regressions were used. In each of the regression models, one baseline HUPS ratio measure (i.e., HF:UF or MHI:MUI) was used as the predictor variable. The ratio HUPS scores were used as the primary potential predictive variables, as they exhibited the most robust correlations with measures of depression severity at baseline (**Table 3**). If the ratio HUPS scored displayed significant predictive ability, the predictive power of their individual components was then assessed. HUPS scores were stratified via a median split, making them binary predictors. In the regression models, treatment outcome (i.e., remission or recurrence) was the dependent variable. Covariates in the regression model included baseline HAM-D score and any clinical or demographic characteristics shown to be associated at baseline with the HUPS score being used as the predictor. Moderation effects were

assessed by utilizing logistic regressions in the same manner outlined above with the addition of treatment group and an interaction term between treatment group and HUPS score. To be included in logistic regression models, SPSS required participants to have valid datapoints for all variables included in the model.

To investigate associations between baseline HUPS scores and treatment preferences, chi-square tests for independence were conducted to assess potential proportional differences in treatment preference across the median-split baseline HUPS score. To assess the potential association between baseline HUPS scores and cortisol levels from the DST, bivariate correlations were conducted.

Finally, as sensitivity analyses, all research question analyses were repeated among only the per-protocol completer population (i.e., individuals who had a week-12 HAM-D score) to when applicable.

To our knowledge, no research has been done analyzing the HUPS relationship with treatment for depression. To assess this, a broad, exploratory analysis was conducted. Bivariate correlations between both baseline and week 12 HUPS and other clinical measures were conducted, as were bivariate correlations between the baseline HUPS scores and their respective week 12 scores. Paired t-tests to assess change in HUPS scores over the 12-week acute treatment phase were conducted. These analyses were repeated for each treatment group as well as for the remitting, non-remitting, recurring, and non-recurring samples. ANCOVAs were conducted to assess potential differences in week-12 HUPS scores across treatment groups when controlling for baseline HUPS scores. As before, ANCOVAs were repeated for the remitting, non-remitting, recurring, and non-recurring samples. To assess if the change in HUPS scores from three months prior to recurrence to the point of recurrence differed between the change in HUPS scores from

three months prior to study conclusion to study conclusion for patients that did not experience a recurrence, independent samples t-tests were performed. Finally, to assess if change in HUPS scores could be potentially predictive of a recurrence, independent samples t-tests comparing change in HUPS scores from six months prior to recurrence to three months prior to recurrence in patients that experienced a recurrence to change in HUPS scores from six months prior to study conclusion to three months prior to study conclusion for patients that did not experience a recurrence were conducted.

Chapter IV: Results

Five hundred fifteen individuals consented to participate in the PReDICT trial, and 344 were randomly assigned. However, 28 patients did not return for post-randomization assessment, leaving 316 participants. The HUPS questionnaire was not part of the original PReDICT protocol; it was added part-way through the study. Consequently, of the 316 patients that returned for post-randomization assessment, 196 were administered the HUPS at baseline and 153 at week 12. Of the 153 participants with week 12 HUPS measures, 11 did not complete a baseline HUPS questionnaire; thus, 207 participants' baseline demographic and clinical data are analyzed and there were 146 per-protocol completers with both baseline and week 12 HAM-D data. Of the 114 participants who completed the long-term follow-up stage, 93 had HUPS data available for analysis.

Demographic and Clinical Characteristics

Baseline clinical and demographic characteristics of the randomized sample are outlined in **Tables 4 and 5**, respectively. There were no significant differences between the CBT group and the medication group in any of the clinical or demographic variables at baseline. For the whole sample, the average baseline HAM-D score was 19.9 indicating moderate depression severity.

The potential difference in mean baseline between HUPS scores across demographic groups are presented in **Tables 6-11**. At baseline, the only demographic group that displayed a significant difference in HF scores was employment status ($mean_{employed}$=21.92, $mean_{unemployed}$=25.65, t(192)=-2.81, p=0.006). Baseline UF significant differed between Hispanic (mean= 21.34) and non-Hispanic (mean=17.57) patients (t(194)=-2.65, p=0.009). Baseline MHI significantly differed between those that were not married or cohabitating (mean=1.76) versus

those that were (mean-1.65, t(192)=2.03, p=0.04). Among Hispanic (mean=1.28) and non-Hispanic (mean=1.74) patients, baseline HF:UF significant differed (t(192)=2.39, p=0.02); baseline HF:UF also significantly differed across participants with no children (mean=1.29) versus participants with children (mean=1.67, t(170.9)=-2.49, p=0.01). No statistically significant MUI or MHI:MUI differences were observed across any demographic groups.

Baseline HUPS Scores as Predictors of Remission

Remission rates are presented in **Table 12**. For the whole sample, 77 participants (49%) achieved remission. The difference in remission rates across the CBT (39.1%) and medication (53.2%) groups was not statistically significant (χ^2=2.03, p=0.15). Over the 12-week acute treatment phase, the mean HAM-D score for the whole sample significantly decreased from 19.25 to 7.53 (t(156)=23.18, p<0.001); the eta squared statistic (0.77) indicated a large effect size (**Table 13**). Significant decreases in HAM-D with large effect sizes were observed in each treatment group independently (**Table 13**). However, after adjusting for baseline HAM-D scores, there was a significant difference between the CBT and medication groups in week 12 HAM-D scores (F(1,154)=4.82, p<0.03, η_p^2=0.03) with participants treated with CBT displaying a higher mean week 12 HAM-D score (9.24) than patients treated with medication (6.82) (Table 13).

Two logistic regression models were performed (**Table 15**) to assess the impact of HF:UF and MHI:MUI scores on the likelihood that participants would achieve remission. A median split was applied to HF:UF (median= 1.24) and MHI:MUI (median= 1.19) to transform them into binary predictors. The HF:UF model contained four predictors, the median-split HF:UF, two demographic factors (ethnicity and number of children) that were associated with baseline HF:UF, and baseline HAM-D scores. The full model did not reach statistical significance, χ^2 (N=140, df=4) = 8.60 (p=0.06), indicating that the model was unable to

distinguish between participants who achieved remission and those that did not. Overall, the model only explained between six (Cox and Snell R square) and eight (Nagelkerke R square) percent of the variance in remission status.

The MHI:MUI model contained two predictors, the median-split MHI:MUI and baseline HAM-D scores. The full model was also statistically insignificant χ^2(N=146, df=2) = 5.611 (p=0.06). The overall model explained between only 4 (Cox and Snell R Square) and 5 (Nagelkerke R Square) percent of variance in remission status. Logistic regressions were repeated among each individual treatment group to assess HUPS scores potential within-group predictive power. Among patients treated with CBT, neither the HF:UF (χ^2(N= 41, df=4) = 4.71 (p=0.32) model nor MHI:MUI (χ^2 (N=43, df=2) = 3.99 (p=0.14) were significant predictors of remission (**Table 16**). Additionally, in the medication group, neither the HF:UF (χ^2 (N= 99, df=4) = 5.6*8* (p=0.23) model nor the MHI:MUI model (χ^2(N= 103, df= 2) = 2.85 (p=0.24) were significant predictors of remission (**Table 17**).

To be included in the logistic regression models, participants were required to have baseline and week 12 HAM-D scores and thus, all participants included in the analysis were per-protocol completers, so no sensitivity analysis was performed.

Baseline HUPS Scores as Moderators of the Relationship between Treatment Type and Remission

Two logistic regression models were performed (**Table 18**) to assess whether baseline HF:UF and MHI:MUI moderated the relationship between treatment type (i.e., psychotherapy or pharmacology) and remission. As before, baseline HUPS scores were stratified with a median split. The HF:UF model included six predictors: the median-split HF:UF, ethnicity, number of children, baseline HAM-D, treatment group, and an interaction term between median-split

HF:UF and treatment group. The full model was statistically insignificant χ^2 (N=140, df=6) = 9.28 (p=0.16), indicating that the model was unable to distinguish between participants who achieved remission and those that did not and that no moderative effects occurred. Overall, the model only explained between six (Cox and Snell R square) and nine (Nagelkerke R square) percent of the variance in remission status. The MHI:MUI included four predictors: the median-split MHI:MUI, baseline HAM-D, treatment group, and an interaction term between median-split MHI:MUI and treatment group. Again, the full model was statistically insignificant χ^2 (N=146, df=4) = 8.20 (p=0.09), indicating that the model was unable to distinguish between participants who achieved remission and those that did not and that no moderative effects occurred.

To be included in the logistic regression models, participants were required to have baseline and week 12 HAM-D scores and thus, all participants included in the analysis were per-protocol completers, so no sensitivity analysis was performed.

HUPS as Predictors of Recurrence

One hundred fourteen participants completed the long-term follow-up phase (i.e., completed the 24-month study or had a recurrence). Recurrence rates are presented in **Table 12**. For the whole sample, 18 participants (15.8%) experienced a recurrence. There were no significant differences in recurrence rates across the CBT (14.3%) and medication (16.5%) groups (χ^2=0.00, p=0.99). Neither baseline nor week 12 HUPS scores significantly differed between participants that experienced a recurrence and those that did not (**Table 19**).

Recurrence was assessed throughout the long-term follow-up phase. To enter the long-term follow-up phase, participants had to complete the acute treatment phase per-protocol, so no sensitivity analysis was performed.

Association between Baseline HUPS Scores and DST Response

In the whole sample, baseline HF was significantly correlated (ρ=0.15, $p<0.05$) with serum cortisol concentrations following dexamethasone administration (**Table 20**). No other HUPS scores were correlated with serum cortisol concentrations. In the per-protocol completer sample, baseline HF was also significantly correlated (ρ=0.24, $p<0.05$) with serum cortisol concentrations. As in the whole sample analysis, no other HUPS scores were correlated with cortisol concentrations. Due to the weak correlation strength between HF and post-DST serum cortisol concentration and the lack of correlation for all other baseline HUPS scores, the capacity of baseline HUPS scores to predict serum cortisol concentrations after the DST was not analyzed.

Association between Baseline HUPS Scores and Patient Preference for Treatment

Chi-square tests of independence were conducted to assess whether patient preferences for treatment at baseline differed across median-split (median baseline HF= 24, median baseline MHI= 1.67, median baseline UF=17, median baseline MUI= 1.33, median baseline HF:UF= 1.24, median baseline MHI:MUI=1.19) baseline HUPS scores. No significant differences in patient treatment preference across median split HUPS scores were observed (**Table 21**). Chi-square tests of independence were repeated among the per-protocol completer sample using the same median split method (median baseline HF= 24, median baseline MHI= 1.64, median baseline UF=17, median baseline MUI= 1.35, median baseline HF:UF= 1.25, median baseline MHI:MUI= 1.17), and no significant differences in patient treatment preference across median split HUPS scores were observed (**Table 22**).

Exploratory Analysis of the HUPS

<u>Distribution of Baseline and Week 12 HUPS Scores</u>

As shown in **Figure 1**, at baseline, HF was approximately normally distributed, while UF had a mildly positive skew suggesting that, sample participants at baseline were more likely to indicate more items as hassles than uplifts. Both baseline MHI and MUI were right skewed; however, the right skew in MUI was much more prominent than in MHI suggesting patients were more likely to indicate their uplifts were less salient than their hassles. At week 12, hassle distributions (i.e., HF and MHI) were more relatively right skewed than at baseline, indicating lower reported number of hassles and mean intensity of hassles after acute treatment for depression. Uplift distributions (i.e., UF and MUI) were more relatively left skewed than at baseline, indicating greater number of uplifts and mean intensity of uplifts after acute treatment for depression.

The HF:UF ratio distribution was moderately right skewed, suggesting that, at baseline, patients were more likely to report greater numbers of hassles than uplifts, and the baseline MHI:MUI ratio was slightly right skewed (**Figure 2**). Ratio measures (i.e., HF:UF and MHI:MUI) also were more relatively right shifted at week 12, reflecting the trends observed in the hassle and uplift measures

Similar patterns in distribution shifts over the 12-week acute treatment phase to those seen in the whole sample were observed independently in both treatment arms (**Figures 3-6**).

Associations between Baseline HUPS Scores and Other Characteristics

Table 23 displays the direction and relative strength of the correlations between HUPS scores at baseline. Notably, at baseline, HF was not significantly correlated with MHI, and UF was not significantly correlated with MUI demonstrating the utility of demining mean intensity scores rather than simply using the summed raw intensity scores. HF was also strongly correlated with UF (ρ=0.48, $p<0.01$) at baseline suggesting that individuals that endorse greater numbers of

hassles are likely to endorse greater numbers of uplifts. Additionally, at baseline, HF is only moderately correlated with HF:UF (ρ=0.28, $p<0.01$), while UF is strongly correlated with HF:UF (ρ=-0.64, $p<0.01$), suggesting that, at baseline, UF is the driving force behind HF:UF. In contrast, at baseline, both MHI (ρ=0.62, $p<0.01$) and MUI (ρ=-0.58, $p<0.01$) were strongly correlated with MHI:MUI suggesting a more equal contribution from MHI and MUI to MHI:MUI. Additionally, at baseline, HF:UF and MHI:MUI exhibited a strong (ρ=0.53, $p<0.01$) indicating that participants endorsing more hassles than uplifts tended to also indicate greater intensity to their hassles than to their uplifts.

In **Table 24**, correlations between HUPS scores at week 12 are tabulated. Like at baseline, HF was not correlated with MHI. However, UF became moderately correlated with MUI (ρ=0.28, $p<0.01$), suggesting that after treatment, individuals that experienced more uplifts also experienced them more intensely. This change is reflected in the correlations of HF and UF with MHI:MUI. While HF was weakly correlated with MHI:MUI (ρ=0.24, $p<0.01$), UF was moderately correlated with MHI:MUI (ρ=-0.38, $p<0.01$). Additionally, at week 12, HF was strongly correlated with HF:UF (ρ=0.64, $p<0.01$), and UF was moderately correlated with HF:UF (ρ=-0.35, $p<0.01$). At week 12 the strength of correlation of HF and UF reversed from that at baseline, indicating that after treatment HF is a greater contributor to HF:UF than is UF. Similar to the relationships at baseline, at week 12 both MHI (ρ=0.66, $p<0.01$) and MUI (ρ=-0.63, $p<0.01$) were strongly correlated with MHI:MUI. Finally, the two ratio measures were strongly correlated with each other at week 12 (ρ=0.54, $p<0.01$), a correlation magnitude nearly identical to that at baseline.

Table 25 indicates that the baseline individual HUPS scores (i.e., HF, UF, MHI, and MUI) were strongly correlated with their respective week 12 score, but the ratio HUPS scores

(i.e., HF:UF and MHI:MUI) were only moderately correlated. Similar effects were seen in both the CBT and medication groups. However, in the CBT group, the baseline and week 12 HF:UF ratios were strongly correlated (ρ=0.50, $p<0.01$), whereas in the medication group the correlation was weaker (ρ=0.31, $p<0.01$). Generally, among both remitting and non-remitting patients, individual baseline HUPS scores were tightly correlated with their week 12 counterparts. However, among non-remitting participants, baseline HF:UF was weakly (ρ=0.26, $p<0.05$) correlated with week 12 HF:UF, whereas the correlation between baseline and week 12 HF:UF was stronger (ρ=0.40, $p<0.01$) in participants who remitted. In both non-remitting and remitting CBT-treated participants, baseline HUPS ratios were not significantly correlated with their week 12 counterparts. However, among remitting medication-treated participants, baseline HF:UF (ρ=0.38, $p<0.01$) and MHI:MUI (ρ=0.40, $p<0.01$) were moderately correlated with their respective week 12 measures, while among non-remitting medication-treated participants, these two metrics were not significantly correlated. It is worth noting that in remitting CBT participants, the insignificant correlation coefficients between baseline HF:UF (ρ=0.47) and MHI:MUI (ρ=-0.26) were relatively strong, and the lack of significance is explained by a relatively small sample size (n=17).

At baseline, HUPS scores displayed stronger correlations with two measures of depression severity, the HAM-D and the BDI, than they did with a measure of anxiety severity, the HAM-A (**Table 3**). Additionally, HF was positively, but weakly correlated with measures of depression severity, and MHI exhibited a weak positive correlation with HAM-D but not BDI, while UF and MUI were negatively, but weakly correlated with measures of depression severity. These results support the construct validity of the HUPS and that it is not simply reflecting the same concept as a depression symptomatology questionnaire. Importantly, HUPS scores were

only minimally associated with scores on the Life Events Survey (LES). Only baseline MHI:MUI was correlated with LES (ρ=0.17, $p<0.05$), but the correlation was weak. This minimal correlation indicated that the HUPS measures a distinct phenomenon from the LES. Generally, the ratio measures (i.e., HF:UF and MHI:MUI) showed stronger correlations to the clinical measures of depression and anxiety as well as self-reported quality of life and functioning than did the individual HUPS scores. Correlations between HUPS scores and measures of depression and anxiety severity followed similar patterns at week 12 (**Table 26**), with HUPS scores being more strongly associated with measures of depression than anxiety and HUPS ratios exhibiting stronger correlations than individual measures. Additionally, stronger correlations between HUPS scores and measures for depression and anxiety severity occurred at week 12 than did at baseline.

Changes in HUPS Scores over 12 Week Acute Treatment Phase

Across the entire sample, hassle scores (i.e., HF and MHI) significantly decreased from baseline to week 12, and uplift scores (i.e., UF and MUI) significantly increased; ratio scores (i.e., HF:UF and MHI:MUI) also exhibited significant decreases, as the numerator (hassle scores) decreased, and the denominator (uplift scores) increased (**Table 27**). This pattern was repeated across both the CBT and medication treatment groups, except for UF. In the CBT treatment arm, baseline UF (mean=19.64) did not significantly differ from week 12 UF (mean=21.67, p=0.10), while in the medication treatment arm, baseline UF (mean=19.41) was significantly greater than week 12 UF (mean=25.36, $p<0.001$), a difference with a large effect size (eta squared= 0.25).

Generally, among patients that did not achieve remission, HUPS scores changed similarly to those of the whole sample across the 12-week acute treatment phase (**Table 28**). However, baseline MUI (mean=1.39) did not significantly differ from week 12 MUI (mean=1.45, p=0.11).

Notably, however, within treatment groups, HUPS scores exhibited different change patterns. Non-remitting CBT-treated participants' and non-remitting medication-treated participants' change in HUPS scores across the 12-week acute treatment phase mirrored that of the overall non-remitting population (i.e., hassle scores decreased and uplift scores increased with the exception of MUI in spite of non-remission). However, among the CBT group that did not achieve remission, no significant changes in HUPS scores from baseline to week 12 occurred, with the exception of HF, whose baseline score (mean=24.64) was significantly greater than its week-12 score (mean=20.76, p=0.01) and exhibited a large effect size (eta squared=0.23). In all remitting patients, all hassle scores significantly decreased, all uplift scores significantly increased, and all ratio scores significantly decreased from baseline to week 12 (**Table 29**). This pattern was reflected in both the CBT-treated participants that achieved remission and the medication-treated patients that achieved remission, with the exception of UF in the CBT sample (baseline mean=22.36, week-12 mean=22.82, p=0.07). Overall, these results indicate that, regardless of treatment outcome, participants treated with medication reported a reduction in hassles and an increase in uplifts following 12-week treatment, while participants treated with CBT only experienced fewer hassles and greater uplifts if treatment was successful.

Among non-recurring participants, HUPS scores changed from baseline to week 12 in the same manner those of the whole sample (i.e., all scores exhibited significant differences in the same direction as the differences observed in the whole sample) (**Table 30**). Medication-treated non-recurring patients change in HUPS scores reflected that of the whole sample. However, in CBT-treated non-recurring patients, UF (baseline mean= 19.00, mean 12-weeks=21.56, p=0.16), MUI (baseline mean =1.35, week-12 mean= 1.48, p=0.18), and HF:UF (baseline mean=1.67, weak 12 mean=1.07, p=0.10) did not significantly differ from baseline to week 12.

In patients who experienced a recurrence, the only score that did not exhibit a significant difference from baseline to week 12 was UF (baseline mean=21.41, week-12 mean-22.65, p=0.03), indicating that, for the majority of HUPS scores, HUPS scores changed over the 12-week acute treatment phase similarly between patients who experienced a recurrence and those that did not (**Table 31**). HUPS changes in patients who experienced a recurrence stratified by treatment group are presented in **Table 31**.

To further investigate HUPS scores' change over the 12-week acute treatment phase and its relationship with treatment type, analyses of covariance were conducted. In all analyses, preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. Unless otherwise stated, all assumptions were met. In the whole sample, after adjusting for baseline HUPS scores only week 12 HF:UF significantly differed between the CBT (mean=1.06) and medication (mean=0.81) groups ($F(1,139)=4.66$, $p=0.03$, partial eta squared=0.03), however the effect size was small (**Table 32**). Among non-remitters (**Table 33**), no significant differences in week-12 HUPS scores after adjusting for baseline HUPS scores were observed. This finding was replicated in the remitting patients (**Table 34**). Of note, in the MUI ANCOVA model, the assumption of homogeneity of regression slopes was violated. In the non-recurring sample (**Table 35**), after adjusting for baseline HUPS scores, week 12 UF significantly differed between the CBT (mean=21.56) and medication (mean=27.71) groups ($F(1,70)=6.54$, $p=0.01$) with a moderate effect size (partial eta squared=0.09), and week 12 HF:UF significantly differed between the CBT (mean=1.07) and medication (mean=0.72) groups ($F(1,70)=4.47$, $p=0.04$) with a moderate effect size (partial eta squared= 0.06). As in the remitting participants ANCOVA model, in the non-recurring participants MUI model did not

meet the assumption for homogeneity of regression slopes. Among recurring patients (**Table 36**), no significant differences in week-12 HUPS scores after adjusting for baseline HUPS scores occurred across treatment groups.

Change in HUPS Scores Prior to Recurrence Versus Prior to Study Completion

To assess whether HUPS scores changed differently prior to recurrence or study completion, for non-recurring patients, six new metrics were computed from the existing HUPS scores gathered during the long-term follow-up phase. The new HUPS metrics represented the change in HUPS scores from the three months prior to last visit (i.e., prior to recurrence or study completion). ΔHF = Month 24 HF – Month 21 HF (for non-recurring patients) or Month of Recurrence HF - 3 Months Prior to Recurrence HF. This formula is followed for all other HUPS scores (i.e., MHI, UF, MUI, HF:UF, and MHI:MUI). Differences in these computed ΔHUPS scores were assessed via independent-samples t-tests.

Generally, hassle scores and ratios increased at the time of recurrence but not prior to study completion, while uplift scores decreased at the time of recurrence but not prior to study completion (**Table 37**). Among participants who experienced a recurrence ΔMHI (mean=+0.27) was significantly different than for participants who did not experience a recurrence (mean= -0.03, t=2.19, p=0.048); ΔUF was significantly different between recurring participants (mean= -6.83) and non-recurring (mean=+0.41) participants (t=-3.34, p<0.01). ΔHF:UF among recurring participants (mean=+0.65) was significantly different from participants who did not experience a recurrence (mean=-0.02, t=2.23, p=0.046), and ΔMHI:MUI among recurring participants (mean=+0.38) was significantly different from participants that did not experience a recurrence (mean=+0.01, t=2.28, p=0.04). ΔHF and ΔMUI did not display significant differences between patients who experienced a recurrence and those that did not. HUPS ratio changes from six

months prior to recurrence to three months prior to recurrence in patients who experienced a recurrence were compared to HUPS ratio changes from six months prior to study completion to three months prior to study completion in non-recurring patients to assess whether change in HUPS ratios could be predictive of recurrence, however no such effects were observed (**Table 38**). A significant difference in ΔHF:UF among patients who experienced a recurrence (mean= -0.13) and patients who did not experience a recurrence (mean=+0.07) was observed (t=2.25, p=0.04), but the mean difference (0.20) and effect sizes (eta squared=0.05) were small. Additionally, the observed change in HF:UF from six-to-three months pre-recurrence was opposite to, and much lesser in magnitude than, the HF:UF change from three months to recurrence. Again, the small number of patients who experienced recurrence makes it difficult to draw definitive conclusions about the impact of HUPS scores on recurrence risk.

Chapter V: 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 157 patients who completed the 12-week acute treatment phase, the average benefits from 12 weeks of acute treatment with either CBT or medication did not significantly differ in terms of proportion of participants who achieved depression remission, although week 12 symptom severity, as assessed by the HAM-D, was higher in CBT-treated participants than in medication-treated participants. Importantly, within both treatment groups, HAM-D scores significantly decreased over the course of the 12-week treatment, and in both groups the mean week 12 HAM-D score was indicative of only mild depression severity. Additionally, no significant difference in recurrence rate between the CBT group and the medication group were detected. Overall, these results align with other studies of MDD which have suggested roughly equivalent efficacy of psychotherapeutic and pharmacologic treatments (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 (HUPS) as either predictors of treatment outcome or moderators of treatment efficacy in individuals diagnosed with MDD. Baseline HUPS scores, specifically HF:UF and MHI:MUI, failed, however, to significantly predict treatment outcome (i.e., remission) in spite of their association with somatic and mental health as demonstrated by both the findings of this study and other 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). Interestingly, baseline HUPS scores exhibited no relationship with depressive recurrence despite previous research indicating another measure of chronic stress having potential as predictors of MDD relapse; however, this study did not utilize a median split when assessing predictive effects

(Bockting et al., 2006). Consistent with the lack of predictive effects in terms of treatment outcome exhibited by the HUPS, HUPS scores failed to moderate the relationship between response to psychotherapeutic versus pharmacologic treatments. This finding was consistent with other analyses from the original PReDICT study which found that no clinical or sociodemographic variables moderated differential remission rates (Dunlop et al., 2017). Altogether, findings from this study indicate limited potential for pre-treatment scores on the HUPS to serve as a predictor for treatment response or as a moderator for the relationship between type of treatment and treatment outcome for patients with MDD, suggesting limited clinical applications for the HUPS as a tool to guide treatment assignment.

Baseline HUPS scores' non-association with treatment preference failed to generate a new characteristic associated with treatment preference in an area where research is relatively limited (McHugh et al., 2013) despite previous research suggesting an association between depression severity and preference for medication (Bedi et al., 2000) and the positive association of hassle scores with HAM-D scores demonstrated in this study. It is possible that while hassle scores were associated with depression severity, another factor influencing severity, not assessed in this study, could be the driving force behind the preference for medication in more severely depressed individuals. Given the importance of treatment adherence for treatment success and matching patients' preferences to maximize treatment adherence (Lindheim et al., 2014), further research should be conducted to assess variables associated with or predictive of treatment preference. Interestingly, HF was significantly associated with cortisol levels as part of the DST, whereas all other baseline HUPS scores, notably MHI, were not associated with cortisol levels as part of the DST. HF's association with cortisol levels is consistent with previous research suggesting that stress, as measured by pre-DST plasma cortisol concentrations, was associated

with non-suppression on the DST (Ceulemans et al., 1985). Furthermore, HF's association and MHI's non-association with cortisol levels as part of the DST suggest that a greater occurrence of stressors, and not their intensity, contributes to DST non-suppression.

In addition to this being the first study, to our knowledge, assessing the HUPS's predictive and moderative power in individuals diagnosed with MDD, this is also the first study to examine the relationship between HUPS scores and treatment for depression. Across the whole sample, mean hassle scores (i.e., HF and MHI) significantly decreased from baseline to the conclusion of the acute treatment phase, while uplift scores (i.e., UF and MUI) significantly increased over the same time frame. These changes were reflected in the ratio metrics (i.e., HF:UF and MHI:MUI) over the acute treatment phase, as the numerator (hassles) grew smaller and the denominator (uplifts) grew larger. 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, individuals with higher ratio scores (i.e., more hassles than uplifts) tended to have higher HAM-D scores, as exemplified by the positive correlation at baseline.

When stratified by treatment group, mean hassle scores and ratio scores decreased over the 12-week acute treatment phase in both the medication group and the CBT group, with the exception of UF, which did not significantly improve in CBT-treated participants from baseline to week 12. Across both groups, the direction and magnitude of the change in HUPS scores, except for UF, over the 12-week acute treatment phase were similar. Among all patients that achieved remission, HUPS scores again changed in a similar manner, with hassles decreasing and uplifts increasing, and an identical discrepancy (i.e., no significant change in CBT UF)

observed between treatment groups. When examining change in HUPS scores in patients that did not achieve remission, however, greater differences occurred. Among all non-remitting participants, hassle scores and ratios decreased from baseline to week 12, with the exception of MUI. This exact pattern was mirrored in non-remitting participants treated with medication. However, among non-remitting participants treated with CBT, only one HUPS score, HF, significantly declined from baseline to week 12. The small number of patients who experienced recurrence makes it difficult to draw definitive conclusions about the impact of HUPS scores on recurrence risk.

The findings of this research are consistent with findings of the effects of antidepressant medications on negative affective biases. Generally, depressed individuals tend to focus on and remember negative social information, while disregarding positive information (Harmer et al., 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 et al., 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). Findings from this study, specifically that uplift measures generally increased, and hassle measure generally decreased from baseline to week 12, provide supportive evidence for these measures. Importantly, the finding that hassle measures decreased and uplift measures increased from baseline to week-12 among the medication treatment, regardless of whether participants achieved remission supports previous research that suggests antidepressant medications inhibit negative affective biases and that this effect is a characteristic of treatment with antidepressant

medication regardless of treatment outcome. The finding that hassles decreased, and uplifts increased among medication-treated participants was not found in the CBT-arm. General hassle decreases and uplift increases over the 12-week acute treatment phase only occurred in CBT-treated patients that achieved remission. Taken together, these findings suggest that reductions in negative affective biases are characteristic of antidepressant treatment, regardless of whether the medication has an overall benefit for depression, whereas for treatment with CBT, lowered negativity biases only occur if the depression itself improves.

It is worth noting that the CBT treatment method employed in the PReDICT was based highly on the cognitive components of CBT (Beck et al., 1979), and most research with respect to CBT's effect as a treatment intervention has been done using cognitive therapy, a specific type of CBT (Hollon et al., 2021). In a sample of adults with elevated depressive symptoms, as assessed by the BDI, patients treated with a 4-week online course of behavioral activation exhibited diminished negative affective biases post-treatment compared to controls (Ruzickova et al., 2021). Additionally, in an analysis of patients with MDD, negativity bias decreased over a 16-week behavioral activation treatment; however, analyses were not stratified by treatment responders and non-responders (Gollan et al., 2016) To gain a deeper perspective on the apparent lack of diminished negative affective bias among CBT-treated non-remitters, in contrast to what is observed in medication-treated non-remitters, studies comparing the behavioral and cognitive components of CBT should be conducted.

In contrast to the CBT-treatment arm, the lack of difference in HUPS score change patterns among remitting patients and non-remitting patients has potential implications on measurement. The primary outcome measures of this study were various treatment response outcomes (i.e., remission and recurrence) based on HAM-D scores. It is interesting then, that

patients whose depression was deemed not to improve by the HAM-D still exhibited improvements in terms of diminished negative affective bias, as an increased positive affective bias, has been shown to be associated with numerous positive mental characteristics such as trait resilience (Jopling et al., 2020). If patients treated with medication are viewing the world through even slightly rosier-tinted glasses after treatment, an improvement has occurred. Perhaps this improvement is not fully captured in the HAM-D, or any rating scale for depression. Depression is a highly nuanced disorder with varying symptomatology and presentation across patients, some of whom may display qualities not reflected in the HAM-D, or any depression rating scale. However, given that quantitative data is necessary for clinical research, inclusion of a scale in spite of its potential limitations in terms of capturing certain qualities is necessary. To address this potential limitation, incorporating qualitative research methods as an auxiliary measurement to the quantitative scales could allow future research to capture a wider range of qualities regarding treatment response for depression.

Finally, associations between HUPS scores and other clinical measures support the construct validity of the HUPS. Critically, non-correlations between HUPS scores and the Childhood Trauma Questionnaire and Life Experiences Survey validate the assumption that the HUPS measures a concept that is distinct from major life events. Hassle scores exhibited weak, positive correlations with depression and anxiety indices at baseline, while uplift scores exhibited weak, negative correlations with depression and anxiety indices at baseline. Importantly, the weak correlations suggest that HUPS scores, while related to depression severity, are their own discrete measure. Generally, HUPS ratios exhibited stronger correlations with depression severity, which may indicate their ability to resist inter-individual variability in terms of what a particular individual counts as a hassle or uplift and how intense they experience

it. The positive HF:UF correlation with depression severity may reflect the biased attention and memory for negative events previously demonstrated in MDD patients (Beck, 2008). The positive MHI:MUI correlation with HAM-D scores may reflect anhedonia, which would be expected to diminish the MUI score. Additionally, at week 12, correlations between HUPS scores and depression scales were all stronger than at baseline, a finding consistent with studies suggesting change in emotional outlook is associated with reduction in depression severity (Godlewska et al., 2016).

There are numerous strengths of this study. The primary strengths for this analysis can be found in its sample, which was well-characterized and the fact that all participants were randomized within a single institution, supporting treatment and rating consistency. The study sample was also highly diverse due to its partnership with an entirely Spanish-speaking clinic staffed by bilingual and bicultural physicians, which strengthens the study's generalizability. While previous research utilized on raw HUPS scores (i.e., HF, HI, UF, and UI), this study's computation of novel HUPS scores (i.e., MHI, MUI, HF:UF, and MHI:MUI) allowed for an analysis that minimized inter-participant variability.

This study is not without its limitations, however. The primary variable analyzed in this analysis, the HUPS, is a retrospective questionnaire, as it asks participants to assess whether certain issues were hassles or uplifts, and if they were, their intensity, over the course of the past week. Often, retrospective questionnaires, especially questionnaires that assess intensity suffer from potentially limiting biases. A frequent source of bias can be found from the "peak-end rule," a termed coined by Daniel Kahneman (Kahneman, 2011). Kahneman posits that when asked retrospective questions, individuals will focus on two key points, the peak intensity and the intensity at the end of the retrospective period, rather than on the entire retrospective period as a

whole leading to patients reporting a *retrospectively constructed* version of life events rather than *actually experienced* life events (Kahneman, 2011). Thus, any effects observed from HUPS scores may not be due to the actual occurrence of hassles or uplifts but by how participants mentally appraise them, which can be influenced by numerous cognitive properties both conscious and subconscious. Important to note, though, is Kahneman's caveats do not apply to only the HUPS, rather almost all rating scales frequently utilized in psychiatry and psychology, including the HAM-D, as they are retrospective measures as well. Other limitations in this study include a sub-clinical-maximum dose of duloxetine (60mg/day), which could introduce the possibility that the full efficacy of the medication was not achieved. Additionally, full treatment blinding for patients was not possible considering this study compared psychotherapeutic and pharmacologic treatments of depression. Another limitation can be found in the fact that individuals with only mild depressive symptoms were excluded from the study as were individuals with concomitant substance use disorders; these exclusions could hamper generalizability. Finally, many statistical comparisons were conducted in this study, and with increased number of comparisons comes increased likelihood of type-I error. As stated previously, this study was the first to assess the HUPS's predictive capability in terms of depression treatment outcomes. As such, a highly exploratory analysis approach was utilized, and no methods to control for multiple comparisons were utilized. Given that the HUPS's relationship with depression treatment has been extensively explored in the PReDICT dataset, any future analyses utilizing the HUPS should be more targeted (i.e., have fewer comparisons) and/or implement methods to control for multiple comparisons.

Tables and Figures:

Table 1: Baseline HUPS Scores for Patients Receiving the Correct HUPS Form Compared to Patients Receiving the Incorrect HUPS Form.

HUPS Score	HUPS Version	N	Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
HF	Incorrect	55	22.29	7.84	-1.33	123.3	0.19	-1.79	-4.58 – 0.87	0.01
	Correct	141	24.09	9.89						
UF	Incorrect	55	17.40	9.02	-1.34	194	0.18	-2.10	-5.18 – 0.99	0.01
	Correct	141	19.50	10.13						
HI	Incorrect	55	39.44	17.10	-0.46	194	0.65	-1.45	-7.73 – 4.83	<0.01
	Correct	141	40.89	21.07						
UI	Incorrect	55	26.11	16.48	-0.44	194	0.66	-1.13	-6.17 – 3.91	<0.01
	Correct	141	27.24	15.91						
MHI	Incorrect	55	1.76	0.38	1.23	192	0.22	0.08	-0.05 – 0.20	0.01
	Correct	139	1.68	0.40						
MUI	Incorrect	55	1.46	0.37	1.32	192	0.19	0.07	-0.03 – 0.17	0.01
	Correct	139	1.39	0.32						
HF: UF	Incorrect	55	1.60	1.13	0.16	192	0.88	0.03	-0.35 – 0.41	<0.01
	Correct	139	1.57	1.38						
MHI: MUI	Incorrect	55	1.28	0.43	0.62	83.3	0.54	0.04	-0.09 – 0.17	<0.01
	Correct	139	1.24	0.34						

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio, SD=Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval of Mean Difference. At baseline, two participants had an HI of 0, and two participants had a UI of 0, resulting in a divide by zero errors when computing MHI and MUI and the loss of two MHI and MUI data points. At baseline, two patients had an UF of 0, resulting in a divide by zero error when computing HF:UF and the loss of two data points. For 5 patients either baseline HI or UI was 0 resulting in undefined MHI and MUI, resulting in SPSS eliminating these responses when computing MHI:MUI. No significant (i.e., $p<0.05$) differences across the group that received the correct HUPS and the group that received the incorrect HUPS were observed.

Table 2: Baseline HUPS Scores Across Escitalopram and Duloxetine Treatment Groups

HUPS Score	Treatment Group	N	Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
HF	Escitalopram	64	23.50	8.95	-0.30	128	0.77	-0.48	-3.71 – 2.74	<0.01
	Duloxetine	66	23.98	9.61						
UF	Escitalopram	64	18.38	9.26	-1.33	128	0.19	-2.23	-5.56 – 1.09	0.01
	Duloxetine	66	20.61	9.89						
HI	Escitalopram	64	40.91	21.79	0.04	128	0.97	0.13	-6.97 – 7.24	<0.01
	Duloxetine	66	40.77	19.09						
UI	Escitalopram	64	27.25	17.55	-0.87	128	0.39	-2.54	-8.33 – 3.26	0.01
	Duloxetine	66	29.79	15.82						
MHI	Escitalopram	64	1.71	0.40	0.25	128	0.80	0.02	-0.12 – 0.16	<0.01
	Duloxetine	66	1.69	0.40						
MUI	Escitalopram	64	1.42	0.37	-0.35	128	0.73	-0.02	-0.14 – 0.10	<0.01
	Duloxetine	66	1.44	0.31						
HF: UF	Escitalopram	64	1.75	1.64	1.44	102.2	0.15	0.34	-0.13 – 0.81	0.02
	Duloxetine	66	1.41	0.98						
MHI: MUI	Escitalopram	64	1.26	0.40	0.92	128	0.36	0.06	-0.07 – 0.19	0.01
	Duloxetine	66	1.20	0.32						

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio, SD= standard deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval of Mean Difference. No significant (i.e., $p<0.05$) differences across the escitalopram group and duloxetine group, and, thus, the groups were combined into a single medication group going forward.

Table 3: Spearman's rho Correlations between Baseline HUPS Scores and Other Clinical Measures at Baseline

	HF	MHI	UF	MUI	HF:UF	MHI:MUI
Childhood Trauma Questionnaire	0.01	-0.01	-0.08	-0.13	0.12	0.11
Age of Onset	-0.03	0.01	-0.13	0.00	0.13	-0.01
HAM-D	0.17*	0.12	-0.16*	-0.24**	0.30**	0.26**
BDI	0.28**	0.21**	-0.07	-0.17*	0.28**	0.30**
HAM-A	0.18*	0.04	0.03	-0.22**	0.12	0.21**
Weight	0.06	0.18*	-0.15*	0.01	0.20**	0.09
LES	0.03	0.15	0.09	-0.01	-0.05	0.17*
Quality of Life	-0.02	-0.34**	0.38**	0.12	-0.37**	-0.36**
Functional Impairment	0.15*	0.26**	0.08	-0.18	0.25**	0.29**

*p<0.05
**p<0.01

HAM-D= Hamilton Depression Rating Scale. BDI= Beck Depression Inventory. HAM-A= Hamilton Anxiety Rating Scale, LES= Life Events Survey, 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

Table 4: Clinical Characteristics of the Sample at Baseline

Characteristic		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Age	Total	207	39.18	11.75						
	CBT	69	39.45	11.76	0.23	205	0.82	0.41	-3.02 – 3.83	<0.01
	Med	138	39.04	11.78						
HAM-D	Total	207	19.88	3.81						
	CBT	69	20.36	3.88	1.28	205	0.20	0.72	-0.39 – 1.82	0.01
	Med	138	19.64	3.76						
BDI	Total	207	23.14	7.02						
	CBT	69	23.20	7.11	0.09	205	0.93	0.09	-1.96 – 2.13	<0.01
	Med	138	23.11	7.00						
HAM-A	Total	207	16.12	5.23						
	CBT	69	16.70	5.00	1.12	205	0.26	0.86	-0.66 – 2.38	0.01
	Med	138	15.83	5.34						
HF	Total	196	23.58	9.37						
	CBT	66	23.26	9.65	-0.34	194	0.73	-0.49	-3.29 – 2.31	<0.01
	Med	130	23.75	9.26						
MHI	Total	194	1.71	0.39						
	CBT	64	1.71	0.38	0.16	192	0.87	0.01	-0.11 – 0.13	<0.01
	Med	130	1.70	0.40						
UF	Total	196	18.91	9.85						
	CBT	66	17.73	10.29	-1.20	194	0.23	-1.78	-4.71 – 1.15	0.01
	Med	130	19.51	9.61						
MUI	Total	194	1.41	0.33						
	CBT	64	1.36	0.32	-1.45	192	0.15	-0.07	-0.17 – 0.03	0.01
	Med	130	1.43	0.34						
HF:UF	Total	194	1.58	1.31						
	CBT	64	1.58	1.24	0.04	192	0.97	0.01	-0.39 – 0.40	<0.01
	Med	130	1.58	1.35						
MHI:MUI	Total	194	1.27	0.36						
	CBT	64	1.28	0.38	0.89	192	0.38	0.05	-0.06 – 0.16	0.01
	Med	130	1.23	0.36						

CBT=Cognitive Behavioral Therapy, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval of Mean Difference, HAM- D= 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.

Table 5: Demographic Characteristics of the Sample at Baseline

Characteristic		All Patients		CBT		Medication		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Sex	Female	124	59.9	39	56.5	85	61.6	0.30	1	0.58	-0.05
	Male	83	40.1	30	43.5	53	38.4				
Race	Non-white	123	59.4	36	52.2	87	63.0	2.25	1	0.13	-0.10
	White	84	40.6	33	47.8	51	37.0				
Ethnicity	Non-Hispanic	136	65.7	47	68.1	89	64.5	0.27	1	0.61	0.04
	Hispanic	71	34.3	22	31.9	49	35.5				
Marital/ cohabitation status	No	103	49.8	37	53.6	66	47.8	0.62	1	0.43	0.06
	Yes	104	50.2	32	46.4	72	52.2				
Full-time employment status	No	118	57.6	38	55.9	80	58.4	0.12	1	0.73	-0.02
	Yes	87	42.4	30	44.1	57	41.6				

CBT= Cognitive Behavior Therapy, df= Degrees of Freedom.

Table 6: Baseline Hassle Frequency Scores across Demographic Groups

Characteristic		N	HF		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	117	22.50	9.22	1.67	194	0.10	2.27	-0.41 – 4.95	0.01
	Male	79	22.23	9.48						
Ethnicity	Non-Hispanic	128	24.27	9.28	1.42	194	0.16	1.99	-0.77 – 4.76	0.01
	Hispanic	68	22.28	9.47						
Race	Non-white	115	23.46	9.75	-0.22	194	0.83	-0.29	-2.98 – 2.39	<0.01
	White	81	23.75	8.87						
Age	<38	93	22.85	9.04	-1.04	194	0.30	-1.39	-4.04 – 1.25	0.01
	≥ 38	103	24.24	9.65						
Marital/ cohabitation status	No	96	23.24	9.72	-0.50	194	0.62	-0.67	-3.32 – 1.97	<0.01
	Yes	100	23.91	9.06						
Employment status	No	110	21.92	9.09	-2.81	192	0.006 **	-3.74	-6.36 - - 1.11	0.04
	Yes	84	25.65	9.32						
Number of Children	0	60	22.58	9.35	-1.04	178	0.30	-1.58	-4.58 – 1.43	0.01
	1+	120	24.16	9.75						
Comorbid Anxiety Disorder	No	121	22.63	9.52	-1.82	194	0.07	-2.49	-5.19 – 0.21	0.02
	Yes	75	15.12	8.96						
Chronic Episode (2+ years)	No	142	23.41	9.20	-0.43	188	0.67	-0.67	-3.76 – 2.41	<0.01
	Yes	48	24.08	9.81						
Previous Suicide Attempt	No	178	23.52	9.55	-0.32	190	0.75	-0.84	-5.99 – 4.31	<0.01
	Yes	14	24.36	7.26						
Lifetime Substance Use	No	139	23.64	9.52	0.14	194	0.89	0.20	-2.71 – 0.31	<0.01
	Yes	57	23.44	9.06						

HF= Hassle Frequency, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 7: Baseline Mean Hassle Intensity Scores across Demographic Groups

Characteristic		N	MHI		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	116	1.73	0.41	1.01	192	0.32	0.06	-0.06 – 0.17	0.01
	Male	78	1.67	0.37						
Ethnicity	Non-Hispanic	127	1.74	0.38	1.53	192	0.13	0.09	-0.03 – 0.21	0.01
	Hispanic	67	1.65	0.41						
Race	Non-white	113	1.71	0.41	0.02	192	0.98	0.00	-0.11 – 0.11	<0.01
	White	81	1.71	0.37						
Age	<38	92	1.68	0.39	-0.90	192	0.37	-0.05	-0.16 – 0.06	<0.01
	≥ 38	102	1.73	0.39						
Marital/ cohabitation status	No	95	1.76	0.40	2.03	192	0.04*	0.11	0.00 – 0.22	0.02
	Yes	99	1.65	0.38						
Employment status	No	108	1.71	0.42	0.17	187.2	0.87	0.01	-0.10 – 0.12	<0.01
	Yes	84	1.70	0.37						
Number of Children	0	59	1.69	0.35	-0.27	176	0.79	-0.17	-0.14 – 0.11	<0.01
	1+	119	1.70	0.41						
Comorbid Anxiety Disorder	No	119	1.70	0.41	-0.15	192	0.88	-0.01	-0.12 – 0.11	<0.01
	Yes	75	1.71	0.38						
Chronic Episode (2+ years)	No	142	1.68	0.38	-1.54	186	0.13	-0.10	-0.21 – 0.03	0.01
	Yes	46	1.78	0.41						
Previous Suicide Attempt	No	176	1.70	0.40	-0.98	188	0.33	-0.11	-0.32 – 0.11	0.01
	Yes	14	1.81	0.36						
Lifetime Substance Use	No	138	1.68	0.40	-1.52	192	0.13	-0.09	-0.22 – 0.03	0.01
	Yes	56	1.77	0.37						

MHI= Mean Hassle Intensity, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 8: Baseline Uplift Frequency Scores across Demographic Groups

Characteristic		N	UF		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	117	19.50	9.22	1.03	194	0.30	1.48	-0.43 – 4.31	0.01
	Male	79	18.02	9.48						
Ethnicity	Non-Hispanic	128	17.57	9.08	-2.65	194	0.009**	-3.86	-6.73 – -0.98	0.03
	Hispanic	68	21.43	10.79						
Race	Non-white	115	19.64	10.29	1.25	194	0.21	1.78	-1.04 – 4.59	0.01
	White	81	17.86	9.17						
Age	<38	93	19.16	9.52	0.34	194	0.73	0.48	-2.30 – 3.27	<0.01
	≥ 38	103	18.68	10.19						
Marital/ cohabitation status	No	96	17.88	10.33	-1.44	194	0.15	-2.03	-4.79 – 0.74	0.01
	Yes	100	19.90	9.31						
Employment status	No	110	21.92	9.09	-1.76	192	0.08	-2.50	-5.30 – 0.31	0.02
	Yes	84	25.65	9.32						
Number of Children	0	60	18.90	8.78	-0.17	178	0.87	-0.27	-2.25 – 2.82	<0.01
	1+	120	19.17	10.38						
Comorbid Anxiety Disorder	No	121	18.85	9.49	-0.09	194	0.93	-0.13	-2.99 – 2.74	<0.01
	Yes	75	18.99	10.48						
Chronic Episode (2+ years)	No	142	19.41	9.68	0.61	188	0.54	0.99	-2.22 – 4.20	<0.01
	Yes	48	18.42	9.95						
Previous Suicide Attempt	No	178	18.80	9.96	-1.01	190	0.32	-2.77	-8.20 – 2.65	0.01
	Yes	14	21.47	9.08						
Lifetime Substance Use	No	139	19.10	10.06	0.43	194	0.67	0.66	-2.40 – 3.73	<0.01
	Yes	57	18.44	9.39						

UF= Uplift Frequency, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 9: Mean Uplift Intensity Scores across Demographic Groups

Characteristic		N	MUI		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	116	1.39	0.32	-0.82	192	0.41	-0.04	-0.14 – 0.06	<0.01
	Male	78	1.43	0.35						
Ethnicity	Non-Hispanic	126	1.39	0.32	-0.96	192	0.34	-0.05	-0.15 – 0.05	<0.01
	Hispanic	68	1.44	0.35						
Race	Non-white	113	1.44	0.35	1.67	192	0.10	0.08	-0.01 – 0.18	0.01
	White	81	1.36	0.30						
Age	<38	92	1.41	0.31	0.10	192	0.92	0.00	-0.09 – 0.10	<0.01
	≥ 38	102	1.41	0.35						
Marital/ cohabitation status	No	94	1.42	0.30	-0.52	188.3	0.60	-0.02	-0.12 – 0.07	<0.01
	Yes	100	1.70	0.36						
Employment status	No	109	1.45	0.37	1.77	189.8	0.62	0.08	-0.01 – 0.17	0.02
	Yes	83	1.36	0.27						
Number of Children	0	59	1.43	0.32	0.34	176	0.63	0.02	-0.09 – 0.12	<0.01
	1+	119	1.41	0.35						
Comorbid Anxiety Disorder	No	120	1.43	0.37	1.43	188.7	0.16	0.06	-0.02 – 0.15	0.01
	Yes	75	1.37	0.26						
Chronic Episode (2+ years)	No	142	1.41	0.33	-0.04	187	0.97	-0.00	-0.11 – 0.11	<0.01
	Yes	47	1.41	0.33						
Previous Suicide Attempt	No	176	1.41	0.34	-0.17	188	0.87	-0.02	-0.20 – 0.17	<0.01
	Yes	14	1.43	0.28						
Lifetime Substance Use	No	138	1.43	0.36	1.53	134.9	0.13	0.07	-0.02 – 0.16	0.02
	Yes	56	1.36	0.27						

MUI= Mean Uplift Intensity, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 10: Hassle Frequency to Uplift Frequency Scores across Demographic Groups

Characteristic		N	HF:UF		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	116	1.55	1.34	-0.32	192	0.75	-0.06	-0.33 – 0.32	<0.01
	Male	78	1.62	1.27						
Ethnicity	Non-Hispanic	126	1.74	1.44	2.39	192	0.02*	0.47	0.08 – 0.85	0.03
	Hispanic	68	1.28	0.97						
Race	Non-white	113	1.52	1.42	-0.79	192	0.43	-0.15	-0.53 – 0.23	<0.01
	White	81	1.67	1.14						
Age	<38	92	1.43	1.23	-1.56	192	0.12	-0.29	-0.66 – 0.08	0.01
	≥ 38	102	1.72	1.36						
Marital/ cohabitation status	No	94	1.70	1.50	1.27	192	0.20	0.24	-0.13 – 0.61	0.01
	Yes	100	1.46	1.10						
Employment status	No	109	1.63	1.49	0.50	190	0.62	0.10	-0.28 – 0.48	<0.01
	Yes	83	1.53	1.04						
Number of Children	0	59	1.29	0.59	-2.49	170.9	0.01*	-0.39	-0.69 - -0.08	0.04
	1+	119	1.67	1.47						
Comorbid Anxiety Disorder	No	120	1.50	1.13	-1.08	192	0.28	-0.21	-0.59 – 0.17	0.01
	Yes	74	1.71	1.56						
Chronic Episode (2+ years)	No	142	1.49	1.12	-1.19	187	0.23	-0.26	-0.69 – 0.17	0.01
	Yes	47	1.75	1.73						
Previous Suicide Attempt	No	176	1.59	1.35	0.91	188	0.36	0.33	-0.39 – 1.05	<0.01
	Yes	14	1.26	0.59						
Lifetime Substance Use	No	138	1.63	1.49	1.21	189.3	0.23	0.19	-0.12 – 0.50	0.01
	Yes	56	1.44	0.68						

HF:UF= Hassle Frequency to Uplift Frequency, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 11: Mean Hassle Intensity to Mean Uplift Intensity Scores across Demographic Groups

Characteristic		N	MHI:MUI		Analysis					
			Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
Sex	Female	116	1.28	0.41	1.46	189.8	0.15	0.07	-0.01 – 0.17	0.01
	Male	78	1.21	0.30						
Ethnicity	Non-Hispanic	126	1.29	0.35	1.95	192	0.05	0.11	-0.01 – 0.22	0.01
	Hispanic	68	1.18	0.39						
Race	Non-white	113	1.22	0.40	-1.14	192	0.26	-0.07	-0.17 – 0.04	<0.01
	White	81	1.29	0.32						
Age	<38	92	1.21	0.36	-1.26	192	0.21	-0.07	-0.17 – 0.04	0.01
	≥ 38	102	1.28	0.37						
Marital /cohabitation status	No	94	1.30	0.36	1.80	192	0.07	0.09	-0.01 – 0.20	0.01
	Yes	100	1.20	0.38						
Employment status	No	109	1.22	0.39	-1.07	190	0.29	-0.06	-0.16 – 0.05	<0.01
	Yes	83	1.28	0.35						
Number of Children	0	59	1.19	0.31	-1.04	176	0.30	-0.06	-0.17 – 0.05	<0.01
	1+	119	1.25	0.36						
Comorbid Anxiety Disorder	No	120	1.23	0.37	-1.06	192	0.29	-0.06	-0.75 – 0.05	<0.01
	Yes	74	1.29	0.37						
Chronic Episode (2+ years)	No	142	1.23	0.35	-0.87	187	0.39	-0.05	-0.18 – 0.07	0.01
	Yes	47	1.29	0.43						
Previous Suicide Attempt	No	176	1.25	0.38	-0.52	188	0.61	-0.05	-0.26 – 0.15	<0.01
	Yes	14	1.30	0.31						
Lifetime Substance Use	No	138	1.22	0.39	-1.96	192	0.05	-0.11	-0.23 – 0.01	0.02
	Yes	56	1.33	0.30						

MHI:MUI= Mean Hassle Intensity to Mean Uplift Frequency, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval for the Mean Difference.

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

Table 12: Remission and Recurrence Rates by Treatment Group

Treatment Outcome		All Patients		CBT		Medication		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Remission	No	80	51.0	28	60.9	52	46.8	2.03	1	0.15	0.11
	Yes	77	49.0	18	39.1	59	53.2				
Recurrence	No	96	84.2	30	85.7	66	83.5	0.00	1	0.99	0.03
	Yes	18	15.8	5	14.3	13	16.5				

CBT= Cognitive Behavior Therapy, df= Degrees of Freedom

Table 13: Change in HAM-D over the Twelve Week Acute Treatment Phase for the Whole Sample and by Treatment Group

Whole Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HAM-D	0M	157	19.25	3.49	11.72	6.34	10.72 – 12.72	23.18	156	<0.001**	0.77
	3M	157	7.53	6.20							

Medication		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HAM-D	0M	111	19.16	3.42	12.34	5.92	11.23 – 13.46	21.95	110	<0.001**	0.81
	3M	111	6.82	5.63							

CBT		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HAM-D	0M	46	19.46	3.70	10.22	7.08	8.11 – 12.32	9.79	45	<0.001**	0.68
	3M	46	9.24	7.18							

*p<0.05
**p<0.01

HAM- D= Hamilton Depression Rating Scale, 0M= Baseline, 3M= Month 3, SD= Standard Deviation, Mean Δ Mean= Average Mean Change, SD Δ Mean= Standard Deviation of the Average Mean Change, 95% CI= 95% Confidence Interval of the Mean Change, df= Degrees of Freedom

Table 14: One-Way ANCOVA Assessing Difference in Week-12 HAM-D Scores Across Treatment Groups Controlling for Baseline HAM-D

		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HAM-D	N	46	111	(1,154)	4.82	0.03*	0.03	9.39	0.003**	0.06
	Mean 0M	19.46	19.16							
	Mean 3M	9.24	6.82							

CBT= Cognitive Behavior Therapy, Med= Medication, HAM- D= Hamilton Depression Rating Scale, df= Degrees of Freedom, BL= Baseline HAM-D Score

Table 15: Logistic Regressions Predicting Likelihood of Depression Remission for the Whole Sample

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical HF:UF_0M	-0.60	0.36	2.74	1	0.10	0.55	0.27 – 1.12
Ethnicity	0.20	0.40	0.26	1	0.61	1.23	0.56 – 2.67
Number of Children	0.27	0.38	0.51	1	0.48	1.31	0.62 – 2.76
HAM-D_0M	-0.10	0.05	3.66	1	0.06	0.90	0.81 – 1.00
Constant	2.01	1.00	4.03	1	0.045	7.44	

df= Degrees of Freedom, HF:UF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical MHI:MUI_0M	-0.35	0.34	1.06	1	0.30	0.70	0.26 – 1.37
HAM-D_0M	-0.10	0.05	3.69	1	0.06	0.91	0.82 – 1.00
Constant	1.98	0.96	4.21	1	0.04	7.23	

df= Degrees of Freedom, MHI:MUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

Table 16: Logistic Regressions Predicting Likelihood of Depression Remission for the CBT Group

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical HF:UF_0M	-0.71	0.68	1.09	1	0.30	0.49	0.13 – 1.86
Ethnicity	-0.24	0.77	0.10	1	0.75	0.79	0.17 – 3.53
Number of Children	1.03	0.75	1.91	1	0.17	2.81	0.65 – 12.12
HAM-D_0M	-0.13	0.10	1.58	1	0.21	0.88	0.72 – 1.08
Constant	2.15	1.89	1.30	1	0.25	8.60	

df= Degrees of Freedom, HF:UF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical MHI:MUI_0M	-0.96	0.65	2.18	1	0.14	0.38	0.11 – 1.37
HAM-D_0M	-0.11	0.09	1.26	1	0.26	0.90	0.75 – 1.08
Constant	2.19	1.83	1.43	1	0.23	8.94	

df= Degrees of Freedom, MHI:MUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

Table 17: Logistic Regressions Predicting Likelihood of Depression Remission for the Medication Group

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical HF:UF_0M	-0.50	0.44	1.31	1	0.25	0.61	0.26 – 1.43
Ethnicity	0.34	0.48	0.51	1	0.48	1.41	0.55 – 3.61
Number of Children	-0.09	0.47	0.04	1	0.85	0.92	0.37 – 2.29
HAMD_0M	-0.10	0.06	2.32	1	0.13	0.91	0.80 – 1.03
Constant	2.13	1.20	3.14	1	0.08	8.39	

df= Degrees of Freedom, HF:UF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical MHI:MUI_0M	-0.07	0.41	0.03	1	0.87	0.93	0.42 – 2.08
HAMD_0M	-0.10	0.06	2.57	1	0.11	0.91	0.81 – 1.02
Constant	1.96	1.15	2.93	1	0.09	7.09	

df= Degrees of Freedom, MHI:MUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

Table 18: Logistic Regressions Assessing HUPS Scores as Moderators of the Relationship between Treatment Type and Remission

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical HF:UF_0M	-0.71	0.66	1.15	1	0.28	0.49	0.14 – 1.79
Ethnicity	0.23	0.40	0.32	1	0.57	1.25	0.57 – 2.74
Number of Children	0.22	0.39	0.33	1	0.57	1.25	0.58 – 2.68
HAMD_0M	-0.10	0.05	3.61	1	0.06	0.90	0.81 – 1.00
Treatment Group	0.14	0.56	0.06	1	0.80	1.15	0.38 – 3.46
HF:UF_0M*Treatment Group	0.17	0.78	0.05	1	0.83	1.18	0.26 – 5.44
Constant	1.92	1.08	3.17	1	0.08	6.82	

df= Degrees of Freedom, HF:UF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio
Categorical MHI:MUI_0M	-0.96	0.65	2.21	1	0.14	0.38	0.11 – 1.36
HAMD_0M	-0.10	0.05	3.82	1	0.05	0.91	0.82 – 1.00
Treatment Group	-0.04	0.53	0.01	1	0.94	0.96	0.24 – 2.72
MHI:MUI_0M*Treatment group	0.90	0.76	1.39	1	0.24	2.47	0.55 – 10.95
Constant	2.05	1.05	3.81	1	0.05	7.78	

df= Degrees of Freedom, MHI:MUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, HAM-D_0M= Baseline Hamilton Depression Rating Scale.

Table 19: Baseline and Week 12 HUPS Scores Across Recurring and Non-Recurring Participants

Baseline HUPS Score	Recurrence Status	N	Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
HF	No	74	24.73	9.08	0.57	90	0.57	1.34	-3.37 – 6.05	<0.01
	Yes	18	23.39	8.77						
MHI	No	74	1.71	0.39	1.14	90	0.26	0.12	-0.09 – 0.32	0.01
	Yes	18	1.60	0.38						
UF	No	74	20.14	9.96	-0.29	90	0.78	-0.75	-6.00 – 4.49	<0.01
	Yes	18	20.89	10.41						
MUI	No	74	1.42	0.34	0.21	90	0.83	0.02	-0.15 – 0.19	<0.01
	Yes	18	1.40	0.26						
HF: UF	No	74	1.58	1.18	1.20	90	0.23	0.34	-0.22 – 0.90	0.01
	Yes	18	1.24	0.41						
MHI: MUI	No	74	1.26	0.34	0.99	90	0.32	0.09	-0.09 – 0.26	0.01
	Yes	18	1.18	0.31						

Week 12 HUPS Score	Recurrence Status	N	Mean	SD	t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
HF	No	81	18.43	9.87	0.19	96	0.85	0.49	-4.71 – 5.69	<0.01
	Yes	17	17.94	9.60						
MHI	No	79	1.43	0.34	0.66	94	0.51	0.06	-0.12 – 0.24	<0.01
	Yes	17	1.37	0.30						
UF	No	81	22.52	10.24	1.01	96	0.31	2.87	-2.76 – 8.50	0.01
	Yes	17	22.65	12.40						
MUI	No	81	1.63	0.41	-0.40	96	0.69	-0.04	-0.25 – 0.17	<0.01
	Yes	17	1.67	0.35						
HF: UF	No	81	0.83	0.66	-0.60	96	0.55	-0.10	-0.45 – 0.24	<0.01
	Yes	17	0.94	0.62						
MHI: MUI	No	79	0.93	0.29	0.76	94	0.45	0.06	-0.10 – 0.22	<0.01
	Yes	17	0.87	0.33						

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

Table 20: Spearman's rho Correlations between Baseline HUPS Scores and Post-DST Cortisol Levels in the Whole Sample and Per-Protocol Completers

Whole Sample	HF	MHI	UF	MUI	HF:UF	MHI:MUI
Cortisol	0.15*	0.03	0.09	0.01	0.03	0.01

Per-Protocol Completers	HF	MHI	UF	MUI	HF:UF	MHI:MUI
Cortisol	0.24**	0.06	0.09	0.05	0.09	0.09

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

Table 21: Chi-Square Tests of Independence for Patient Preference for Treatment by Median-Split HUPS Scores for the Whole Sample

HF		All Patients		Low HF		High HF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	68	34.7	34	30.4	34	40.5	2.56	2	0.28	0.11
	CBT	71	36.2	45	40.2	26	31.0				
	Medication	57	29.1	33	29.5	24	28.6				

MHI		All Patients		Low MHI		High MHI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	68	35.1	32	31.7	36	38.7	2.31	2	0.32	0.11
	CBT	71	36.6	42	41.6	29	31.2				
	Medication	55	28.4	27	26.7	28	30.1				

UF		All Patients		Low UF		High UF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	68	34.7	31	30.7	37	38.9	1.90	2	0.39	0.10
	CBT	71	36.2	37	36.6	34	35.8				
	Medication	57	29.1	33	32.7	24	25.3				

MUI		All Patients		Low MUI		High MUI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	67	34.5	31	34.4	36	34.5	0.13	2	0.94	0.03
	CBT	71	36.6	34	37.8	37	36.6				
	Medication	56	28.9	25	27.8	31	28.9				

HF:UF		All Patients		Low HF:UF		High HF:UF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	67	34.5	34	25.1	33	34.0	0.65	2	0.72	0.06
	CBT	71	36.6	33	34.0	38	39.2				
	Medication	56	28.9	30	30.9	26	26.8				

MHI:MUI		All Patients		Low MHI:MUI		High MHI:MUI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	67	35.1	33	34.0	34	35.4	1.15	2	0.56	0.08
	CBT	71	36.6	39	40.2	32	33.3				
	Medication	55	28.4	25	25.8	30	31.3				

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio, CBT= Cognitive Behavior Therapy, df= Degrees of Freedom

Table 22: Chi-Square Tests of Independence for Patient Preference for Treatment by Median-Split HUPS Scores for Per-Protocol Completers

HF		All Patients		Low HF		High HF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	25	30.9	25	38.5	2.13	2	0.34	0.12
	CBT	52	35.6	33	40.7	19	29.2				
	Medication	44	30.1	23	28.4	21	32.3				

MHI		All Patients		Low MHI		High MHI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	22	30.1	28	38.4	1.41	2	0.49	0.10
	CBT	52	35.6	29	39.7	23	31.5				
	Medication	44	30.1	22	30.1	22	30.1				

UF		All Patients		Low UF		High UF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	19	25.7	31	43.1	5.00	2	0.08	0.19
	CBT	52	35.6	29	39.2	23	31.9				
	Medication	44	30.1	26	35.1	18	24.0				

MUI		All Patients		Low MUI		High MUI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	22	30.1	28	38.4	1.41	2	0.49	0.10
	CBT	52	35.6	29	39.7	23	31.5				
	Medication	44	30.1	22	30.1	22	30.1				

HF:UF		All Patients		Low HF:UF		High HF:UF		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	27	37.0	23	31.5	1.91	2	0.38	0.12
	CBT	52	35.6	22	30.1	30	41.1				
	Medication	44	30.1	24	32.9	20	27.4				

MHI:MUI		All Patients		Low MHI:MUI		High MHI:MUI		Analysis			
		N	%	N	%	N	%	χ^2	df	p	phi
Preference	None	50	34.2	26	35.6	24	32.9	1.21	2	0.55	0.09
	CBT	52	35.6	28	38.4	24	32.9				
	Medication	44	30.1	19	26.0	25	34.2				

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio, CBT= Cognitive Behavior Therapy, df= Degrees of Freedom

Table 23: Spearman's rho Correlations between HUPS Scores at Baseline

HUPS Scores	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HF	-	0.08	0.48**	-0.28**	0.28**	0.30**
MHI	-	-	-0.22**	0.24**	0.27**	0.62**
UF	-	-	-	0.13	-0.64**	-0.25**
MUI	-	-	-	-	-0.37**	-0.58**
HF:UF	-	-	-	-	-	0.53**
MHI:MUI	-	-	-	-	-	-

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

Table 24: Spearman's rho Correlations between HUPS Scores at Week 12

HUPS Scores	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HF	-	0.13	0.40**	-0.29**	0.64**	0.24**
MHI	-	-	-0.19*	0.10	0.26**	0.66**
UF	-	-	-	0.28**	-0.35**	-0.38*
MUI	-	-	-	-	-0.52**	-0.63**
HF:UF	-	-	-	-	-	0.54**
MHI:MUI	-	-	-	-	-	-

*p<0.05
**p<0.01

HF= Hassle Frequency, UF= Uplift Frequency, HI= Hassle Intensity, UI= Uplift Intensity, MHI= Mean Hassle Intensity, MUI= Mean Uplift Intensity, HF:UF= Hassle Frequency to Uplift Frequency Ratio, MHI:MUI= Mean Hassle Intensity to Mean Uplift Intensity Ratio

Table 25: Spearman's rho Correlations between Baseline HUPS Scores and their Respective Week 12 Score

HUPS scores	Whole Sample	CBT	Medication
HF_0M and HF_3M	0.54**	0.63**	0.50**
MHI_0M and MHI_3M	0.51**	0.47**	0.52**
UF_0M and UF_3M	0.60**	0.72**	0.55*
MUI_0M and MUI_3M	0.44**	0.38*	0.48**
HF:UF_0M and HF:UF_3M	0.37**	0.50**	0.31**
MHI:MUI_0M and MHI:MUI_3M	0.27**	0.25	0.28**

HUPS scores	All Non-Remitters	CBT Non-Remitters	Medication Non-Remitters
HF_0M and HF_3M	0.57**	0.69**	0.48**
MHI_0M and MHI_3M	0.40**	0.36	0.41**
UF_0M and UF_3M	0.66**	0.76**	0.60**
MUI_0M and MUI_3M	0.55**	0.54**	0.54**
HF:UF_0M and HF:UF_3M	0.26*	0.31	0.20
MHI:MUI_0M and MHI:MUI_3M	0.23	0.34	0.16

HUPS scores	All Remitters	CBT Remitters	Medication Remitters
HF_0M and HF_3M	0.52**	0.57*	0.51**
MHI_0M and MHI_3M	0.59**	0.65**	0.59**
UF_0M and UF_3M	0.51**	0.59*	0.46**
MUI_0M and MUI_3M	0.41**	0.10	0.51**
HF:UF_0M and HF:UF_3M	0.40**	0.47	0.38**
MHI:MUI_0M and MHI:MUI_3M	0.28*	-0.26	0.40**

*p<0.05
**p<0.01
HF_0M= Baseline Hassle Frequency, UF_0M= Baseline Uplift Frequency, MHI_0M= Baseline Mean Hassle Intensity, MUI_0M= Baseline Mean Uplift Intensity, HFtoUF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, MHItoMUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, HF_3M= Baseline Hassle Frequency, UF_3M= Baseline Uplift Frequency, MHI_3M= Baseline Mean Hassle Intensity, MUI_3M= Baseline Mean Uplift

Intensity, HFtoUF_3M= Baseline Hassle Frequency to Uplift Frequency Ratio, MHItoMUI_3M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio.

Table 26: Spearman's rho Correlations between Week 12 HUPS Scores and Other Clinical Measures at Week 12

	HF	MHI	UF	MUI	HF:UF	MHI:MUI
HAM-D	0.35**	0.25**	-0.24**	-0.48**	0.54**	0.54**
BDI	0.37**	0.31**	-0.24**	-0.50**	0.59**	0.57**
HAM-A	0.29**	0.21**	-0.22**	-0.45**	0.48**	0.47**
Weight	-0.01	0.05	-0.05	0.03	0.01	0.02

*p<0.05
**p<0.01

HAM-D= 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

Table 27: Paired t-Tests Assessing HUPS Score Changes over Acute Treatment Phase for Whole Sample and Broken Down Across Treatment Group

Whole Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	142	24.43	9.20	5.83	8.99	4.34 – 7.23	7.73	141	<0.001 **	0.30
	3M	142	18.49	10.20							
MHI	0M	140	1.68	0.38	0.24	0.39	0.17 – 0.31	7.19	139	<0.001**	0.27
	3M	140	1.44	0.40							
UF	0M	142	19.83	9.73	-4.44	9.20	-5.96 - -2.91	-5.75	141	<0.001**	0.12
	3M	142	24.27	10.88							
MUI	0M	142	1.41	0.33	-0.20	0.39	-0.26 - -0.13	-5.96	141	<0.001**	0.20
	3M	142	1.61	0.41							
HF: UF	0M	142	1.49	0.98	0.61	1.12	0.43 – 0.80	6.54	141	<0.001**	0.23
	3M	142	0.88	0.63							
MHI: MUI	0M	140	1.23	0.33	0.28	0.40	0.22 – 0.35	8.37	139	<0.001**	0.34
	3M	140	0.95	0.32							

CBT		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	42	24.60	9.52	5.24	7.69	2.84 – 7.63	4.42	41	<0.001**	0.32
	3M	42	19.36	9.41							
MHI	0M	41	1.66	0.36	0.22	0.38	0.10 – 0.34	3.69	40	<0.001**	0.25
	3M	41	1.44	0.37							
UF	0M	42	19.64	10.61	-2.02	7.71	-4.43 – 0.38	-1.70	41	0.10	0.07
	3M	42	21.67	10.50							
MUI	0M	42	1.36	0.30	-0.15	0.44	-0.29 - -0.01	-2.18	41	0.04*	0.10
	3M	42	1.51	0.41							
HF: UF	0M	42	1.53	1.11	0.47	1.40	0.03 – 0.91	2.17	41	0.04*	0.10
	3M	42	1.06	0.82							
MHI: MUI	0M	41	1.25	0.30	0.23	0.37	0.11 – 0.35	3.96	40	<0.001**	0.28
	3M	41	1.02	0.32							

Medication		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	100	24.21	9.11	6.08	9.51	4.19 – 7.97	6.39	99	<0.001**	0.29
	3M	100	18.13	10.53							
MHI	0M	99	1.68	0.39	0.25	0.40	0.17 – 0.33	6.15	98	<0.001**	0.28
	3M	99	1.43	0.42							
UF	0M	100	19.41	9.38	-5.45	9.61	-7.36 - -3.54	-5.67	99	<0.001**	0.25
	3M	100	25.36	10.91							
MUI	0M	100	1.43	0.34	-0.21	0.37	-0.29 – 0.14	-5.86	99	<0.001**	0.26
	3M	100	1.65	0.41							
HF: UF	0M	100	1.48	0.93	0.67	0.97	0.48 – 0.87	6.91	99	<0.001**	0.33
	3M	100	0.81	0.52							
MHI: MUI	0M	99	1.22	0.35	0.30	0.41	0.22 – 0.39	7.39	98	<0.001**	0.36
	3M	99	0.92	0.31							

*p<0.05
**p<0.01

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. SD= Standard Deviation. Mean ΔMean= Average Mean Difference. SD ΔMean= Standard Deviation for the Average Mean Difference. 95% CI= 95% Confidence Internal for Average Mean Difference. df= Degrees of Freedom.

Table 28: Paired t-Tests Assessing HUPS Score Changes over Acute Treatment Phase for Non-Remitting Participants and Broken Down Across Treatment Group

Whole Non-Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	72	24.39	9.57	3.63	8.66	1.59 – 5.66	3.55	71	<0.001**	0.15
	3M	72	20.76	9.98							
MHI	0M	71	1.71	0.38	0.17	0.41	0.07 - 0.27	3.51	70	<0.001**	0.15
	3M	71	1.54	0.40							
UF	0M	72	18.47	9.99	-2.99	8.30	-4.94 - -1.04	-3.05	71	0.003**	0.12
	3M	72	21.45	10.79							
MUI	0M	72	1.39	0.32	-0.07	0.34	-0.14 – 0.01	-1.63	71	0.11	0.04
	3M	72	1.45	0.36							
HF: UF	0M	72	1.66	1.18	0.55	1.41	0.22 – 0.88	3.29	71	0.002**	0.13
	3M	72	1.11	0.73							
MHI: MUI	0M	71	1.27	0.34	0.17	0.40	0.08 – 0.26	3.60	70	<0.001**	0.16
	3M	71	1.10	0.30							

CBT Non-Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	25	24.64	9.59	3.89	7.16	0.92 – 6.84	2.71	24	0.01*	0.23
	3M	25	20.76	9.89							
MHI	0M	24	1.68	0.36	0.16	0.44	-0.03 – 0.34	1.78	23	0.09	0.12
	3M	24	1.52	0.41							
UF	0M	25	17.80	10.21	-1.04	6.61	-3.77 – 1.69	- 0.79	24	0.44	0.03
	3M	25	18.84	10.16							
MUI	0M	25	1.30	0.25	-0.04	0.33	-0.17 – 0.10	- 0.57	24	0.57	0.01
	3M	25	1.33	0.33							
HF: UF	0M	25	1.73	1.36	0.46	1.81	-0.29 – 1.20	1.26	24	0.22	0.06
	3M	25	1.28	0.97							
MHI: MUI	0M	24	1.32	0.32	0.13	0.38	-0.03 – 0.29	1.67	23	0.11	0.11
	3M	24	1.19	0.30							

Medication Non-Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	47	24.26	9.66	3.49	9.43	0.72 – 6.26	2.54	46	0.02*	0.12
	3M	47	20.77	10.14							
MHI	0M	47	1.72	0.39	0.18	0.40	0.06 – 0.30	3.02	46	0.004**	0.17
	3M	47	1.54	0.40							
UF	0M	47	18.83	9.95	-4.02	8.96	-6.65 - -1.39	-3.08	46	0.004**	0.17
	3M	47	22.85	10.96							
MUI	0M	47	1.43	0.34	-0.08	0.35	-0.18 – 0.02	-1.58	46	0.12	0.05
	3M	47	1.51	0.37							
HF: UF	0M	47	1.62	1.08	0.59	1.16	0.25 – 0.94	3.51	46	0.001**	0.21
	3M	47	1.03	0.56							
MHI: MUI	0M	47	1.25	0.35	0.19	0.41	0.07 – 0.31	3.19	46	0.003**	0.18
	3M	47	1.06	0.29							

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

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. SD= Standard Deviation. Mean ΔMean= Average Mean Difference. SD ΔMean= Standard Deviation for the Average Mean Difference. 95% CI= 95% Confidence Internal for Average Mean Difference. df= Degrees of Freedom.

Table 29: Paired t-Tests Assessing HUPS Score Changes over Acute Treatment Phase for Remitting Participants and Broken Down Across Treatment Group

Whole Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	70	24.26	8.88	8.10	8.81	6.00 – 10.20	7.69	69	<0.001**	0.46
	3M	70	16.16	9.94							
MHI	0M	69	1.64	0.38	0.31	0.37	0.22 – 0.40	7.04	68	<0.001**	0.42
	3M	69	1.33	0.38							
UF	0M	70	21.23	9.31	-5.93	9.88	-8.28 - -3.57	-5.02	69	<0.001**	0.27
	3M	70	27.16	10.27							
MUI	0M	70	1.44	0.34	-0.33	0.40	-0.42 - -0.23	-6.92	69	<0.001**	0.41
	3M	70	1.77	0.40							
HF: UF	0M	70	1.32	0.71	0.68	0.70	0.51 – 0.85	8.11	69	<0.001**	0.49
	3M	70	0.64	0.38							
MHI: MUI	0M	69	1.19	0.32	0.40	0.37	0.31 – 0.49	8.95	68	<0.001**	0.54
	3M	69	0.79	0.25							

CBT Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	17	25.53	9.71	7.24	8.20	3.02 – 11.45	3.64	16	0.001**	0.45
	3M	17	17.29	8.53							
MHI	0M	17	1.63	0.36	0.31	0.28	0.16 – 0.45	4.50	16	<0.001**	0.56
	3M	17	1.32	0.27							
UF	0M	17	22.36	10.90	-3.47	9.10	-8.15 – 1.21	-1.57	16	0.07	0.13
	3M	17	22.82	9.83							
MUI	0M	17	1.44	0.34	-0.31	0.54	-0.59 - -0.03	-2.38	16	0.02*	0.26
	3M	17	1.76	0.41							
HF: UF	0M	17	1.22	0.48	0.49	0.37	0.29 – 0.68	5.37	16	<0.001**	0.64
	3M	17	0.73	0.36							
MHI: MUI	0M	17	1.15	0.24	0.38	0.33	0.21 – 0.54	4.76	16	<0.001**	0.59
	3M	17	0.78	0.17							

Medication Remitting Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	53	24.17	8.69	8.38	9.06	5.99 – 10.87	6.74	52	<0.001**	0.47
	3M	53	15.79	10.40							
MHI	0M	52	1.64	0.39	0.31	0.39	0.20 – 0.42	5.72	51	<0.001**	0.39
	3M	52	1.33	0.31							
UF	0M	53	20.87	8.83	-6.72	10.07	-9.49 - -3.94	-4.86	52	<0.001**	0.31
	3M	53	27.58	10.46							
MUI	0M	53	1.43	0.34	-0.33	0.35	-0.43 – -0.24	-7.05	52	<0.001**	0.49
	3M	53	1.77	0.40							
HF: UF	0M	53	1.36	0.77	0.74	0.77	0.53 – 0.95	7.00	52	<0.001**	0.49
	3M	53	0.61	0.39							
MHI: MUI	0M	52	1.20	0.35	0.41	0.39	0.30 – 0.52	7.56	51	<0.001**	0.52
	3M	52	0.79	0.27							

*p<0.05
**p<0.01

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. SD= Standard Deviation. Mean ΔMean= Average Mean Difference. SD ΔMean= Standard Deviation for the Average Mean Difference. 95% CI= 95% Confidence Internal for Average Mean Difference. df= Degrees of Freedom

Table 30: Paired t-Tests Assessing HUPS Score Changes over Acute Treatment Phase for Non-Recurring Participants and Broken Down Across Treatment Group

Whole Non-Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	73	24.74	9.14	6.19	9.57	3.96 – 8.43	5.53	72	<0.001**	0.30
	3M	73	18.55	9.80							
MHI	0M	71	1.71	0.39	0.30	0.38	0.20 – 0.39	6.49	70	<0.001**	0.38
	3M	71	1.42	0.34							
UF	0M	73	20.10	10.03	-5.51	9.18	-7.65 - -3.36	-5.12	72	<0.001**	0.27
	3M	73	25.60	10.45							
MUI	0M	73	1.42	0.34	-0.20	0.40	-0.29 - -0.10	-4.20	72	<0.001**	0.20
	3M	73	1.61	0.42							
HF: UF	0M	73	1.58	1.18	0.74	1.35	0.43 – 1.06	4.68	72	<0.001**	0.23
	3M	73	0.84	0.67							
MHI: MUI	0M	71	1.26	0.34	0.32	0.39	0.23 – 0.41	6.82	70	<0.001**	0.40
	3M	71	0.94	0.30							

CBT Non-Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	25	24.32	9.91	5.68	8.51	2.17 – 9.19	3.34	24	0.003**	0.32
	3M	25	18.64	8.88							
MHI	0M	24	1.70	0.40	0.30	0.32	0.17 – 0.44	4.66	23	<0.001**	0.49
	3M	24	1.40	0.33							
UF	0M	25	19.00	11.08	-2.56	8.87	-6.22 – 1.10	-1.44	24	0.16	0.08
	3M	25	21.56	10.23							
MUI	0M	25	1.35	0.33	-0.14	0.50	-0.34 – 0.07	-1.37	24	0.18	0.07
	3M	25	1.48	0.40							
HF: UF	0M	25	1.67	1.40	0.61	1.79	-0.13 – 1.34	1.70	24	0.10	0.11
	3M	25	1.07	0.98							
MHI: MUI	0M	24	1.28	0.30	0.27	0.34	0.12 – 0.41	3.86	23	<0.001**	0.39
	3M	24	1.01	0.31							

Medication Non-Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	48	24.96	8.82	6.46	10.16	3.51 – 9.41	4.41	47	<0.001**	0.29
	3M	48	18.50	10.34							
MHI	0M	47	1.72	0.39	0.29	0.42	0.17 – 4.14	4.81	46	<0.001**	0.33
	3M	47	1.43	0.36							
UF	0M	48	20.67	9.50	-7.04	9.05	-9.67 - -4.41	-5.39	47	<0.001**	0.38
	3M	48	27.71	10.04							
MUI	0M	48	1.45	0.35	-0.23	0.34	-0.33 - -0.13	-4.60	47	<0.001**	0.31
	3M	48	1.68	0.41							
HF: UF	0M	48	1.54	1.07	0.81	1.08	0.50 – 1.12	5.23	47	<0.001**	0.37
	3M	48	0.72	0.39							
MHI: MUI	0M	47	1.25	0.37	0.34	0.42	0.22 – 0.47	5.62	46	<0.001**	0.41
	3M	47	0.90	0.30							

*p<0.05
**p<0.01

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. SD= Standard Deviation. Mean ΔMean= Average Mean Difference. SD ΔMean= Standard Deviation for the Average Mean Difference. 95% CI= 95% Confidence Internal for Average Mean Difference. df= Degrees of Freedom

Table 31: Paired t-Tests Assessing HUPS Score Changes over Acute Treatment Phase for Recurring Participants and Broken Down Across Treatment Group

Whole Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	17	23.53	9.02	5.59	9.39	0.76 – 10.42	2.45	16	0.03*	0.27
	3M	17	17.94	9.60							
MHI	0M	17	1.57	0.37	0.20	0.36	0.02 – 0.39	2.32	16	0.03*	0.25
	3M	17	1.37	0.30							
UF	0M	17	21.41	10.45	-1.24	9.68	-6.16 – 0.37	-0.53	16	0.30	<0.01
	3M	17	22.65	12.40							
MUI	0M	17	1.40	0.27	-0.27	0.42	-0.49 - -0.05	-2.65	16	0.009**	0.31
	3M	17	1.67	0.35							
HF: UF	0M	17	1.21	0.41	0.27	0.57	-0.02 – 0.56	1.95	16	0.04*	0.19
	3M	17	0.94	0.62							
MHI: MUI	0M	17	1.15	0.30	0.28	0.41	0.07 – 0.49	2.82	16	0.006**	0.33
	3M	17	0.87	0.33							

CBT Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	4	21.75	4.79	7.00	6.83	-3.87 – 17.87	2.05	3	0.13	0.58
	3M	4	14.75	6.99							
MHI	0M	4	1.62	0.36	0.34	0.39	-0.27 – 0.96	1.79	3	0.17	0.52
	3M	4	1.28	0.29							
UF	0M	4	18.00	6.22	-0.25	7.72	-12.53 – 12.03	-0.07	3	0.95	<0.01
	3M	4	18.25	11.32							
MUI	0M	4	1.41	0.14	-0.26	0.48	-1.01 – 0.50	-1.08	3	0.36	0.28
	3M	4	1.67	0.51							
HF: UF	0M	4	1.25	0.25	0.21	0.69	-0.90 – 1.31	0.59	3	0.60	0.10
	3M	4	1.05	0.70							
MHI: MUI	0M	4	1.15	0.22	0.33	0.45	-0.39 – 1.04	1.46	3	0.24	0.42
	3M	4	0.82	0.32							

Medication Recurring Sample		N	Mean	SD	Analysis						
					Mean ΔMean	SD ΔMean	95% CI	t	df	P (two-tailed)	Eta^2
HF	0M	13	24.08	10.07	5.15	10.25	-1.04 – 11.35	1.81	12	0.10	0.21
	3M	13	18.92	10.31							
MHI	0M	13	1.56	0.38	0.16	0.36	-0.06 – 0.38	1.61	12	0.13	0.18
	3M	13	1.40	0.30							
UF	0M	13	22.46	11.49	-1.54	10.34	-7.79 – 4.71	-0.54	12	0.60	0.02
	3M	13	24.00	12.83							
MUI	0M	13	1.40	0.30	-0.28	0.43	-0.53 - -0.02	-2.34	12	0.04	0.31
	3M	13	1.68	0.31							
HF: UF	0M	13	1.19	0.45	0.29	0.55	-0.05 – 0.62	1.87	12	0.09	0.23
	3M	13	0.91	0.62							
MHI: MUI	0M	13	1.15	0.33	0.26	0.41	0.02 – 0.51	2.31	12	0.04	0.31
	3M	13	0.88	0.34							

*p<0.05
**p<0.01

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. SD= Standard Deviation. Mean ΔMean= Average Mean Difference. SD ΔMean= Standard Deviation for the Average Mean Difference. 95% CI= 95% Confidence Internal for Average Mean Difference. df= Degrees of Freedom

Table 32: One-Way ANCOVA Assessing Difference in Week-12 HUPS Scores Across Treatment Groups Controlling for Baseline HUPS Scores in the Whole Sample

HUPS Scores		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HF	N	42	100	(1,139)	0.41	0.53	0.003	68.40	<0.001 **	0.33
	Mean 0M	24.60	24.21							
	Mean 3M	19.36	18.13							
MHI	N	41	99	(1,137)	0.07	0.79	0.001	43.82	<0.001 **	0.24
	Mean 0M	1.66	1.68							
	Mean 3M	1.44	1.43							
UF	N	42	100	(1,139)	4.98	0.03*	0.04	83.25	<0.001 **	0.38
	Mean 0M	19.64	19.41							
	Mean 3M	21.67	25.36							
MUI	N	42	100	(1,139)	2.18	0.14	0.02	35.65	<0.001 **	0.30
	Mean 0M	1.36	1.43							
	Mean 3M	1.51	1.65							
HF: UF	N	42	100	(1,139)	4.66	0.03*	0.03	1.32	0.25	0.01
	Mean 0M	1.52	1.48							
	Mean 3M	1.06	0.81							
MHI: MUI	N	41	99	(1,137)	2.76	0.10	0.02	8.14	0.005 **	0.06
	Mean 0M	1.25	1.22							
	Mean 3M	1.02	0.92							

*p<0.05

**p<0.01

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. SD= Standard Deviation. CBT= Cognitive Behavior Therapy. Med= Medication., df= Degrees of Freedom, BL= HUPS Score

Table 33: One-Way ANCOVA Assessing Difference in Week-12 HUPS Scores Across Treatment Groups Controlling for Baseline HUPS Scores in the Non-Remitting Sample

HUPS Scores		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HF	N	25	47	(1,69)	0.02	0.90	0.00	40.53	<0.001**	0.37
	Mean 0M	24.64	24.26							
	Mean 3M	20.76	20.77							
MHI	N	24	47	(1,68)	0.00	0.99	0.00	16.50	<0.001**	0.20
	Mean 0M	1.68	1.72							
	Mean 3M	1.52	1.54							
UF	N	25	47	(1,69)	2.82	0.10	0.04	61.49	<0.001**	0.47
	Mean 0M	17.80	18.83							
	Mean 3M	18.84	22.85							
MUI	N	25	47	(1,69)	1.74	0.19	0.03	21.83	<0.001**	0.24
	Mean 0M	1.30	1.43							
	Mean 3M	1.33	1.51							
HF: UF	N	25	47	(1,69)	1.95	0.17	0.03	0.14	0.71	0.002
	Mean 0M	1.73	1.62							
	Mean 3M	1.28	1.03							
MHI: MUI	N	24	47	(1,68)	2.66	0.11	0.04	3.21	0.09	0.05
	Mean 0M	1.32	1.25							
	Mean 3M	1.19	1.06							

*p<0.05
**p<0.01
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. SD= Standard Deviation. CBT= Cognitive Behavior Therapy. Med= Medication., df= Degrees of Freedom, BL= HUPS Score

Table 34: One-Way ANCOVA Assessing Difference in Week-12 HUPS Scores Across Treatment Groups Controlling for Baseline HUPS Scores in the Remitting Sample

HUPS Scores		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HF	N	17	53	(1,67)	0.30	0.58	0.005	31.68	<0.001 **	0.32
	Mean 0M	25.53	24.17							
	Mean 3M	17.29	15.79							
MHI	N	17	52	(1,66)	0.00	0.97	0.00	26.57	<0.001 **	0.29
	Mean 0M	1.63	1.64							
	Mean 3M	1.32	1.33							
UF	N	17	53	(1,67)	1.06	0.31	0.02	22.60	<0.001 **	0.25
	Mean 0M	22.36	20.87							
	Mean 3M	22.82	27.58							
MUI	N	17	53	(1,67)	0.03	0.87	0.00	15.03	<0.001 **	0.18
	Mean 0M	1.44	1.43							
	Mean 3M	1.76	1.77							
HF: UF	N	17	53	(1,67)	1.93	0.17	0.03	6.60	0.01*	0.09
	Mean 0M	1.22	1.36							
	Mean 3M	0.73	0.61							
MHI: MUI	N	17	52	(1,66)	0.01	0.91	0.00	2.09	0.15	0.03
	Mean 0M	1.15	1.20							
	Mean 3M	0.78	0.79							

*p<0.05
**p<0.01
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. SD= Standard Deviation. CBT= Cognitive Behavior Therapy. Med= Medication., df= Degrees of Freedom, BL= HUPS Score

Table 35: One-Way ANCOVA Assessing Difference in Week-12 HUPS Scores Across Treatment Groups Controlling for Baseline HUPS Scores in the Non-Recurring Sample

HUPS Scores		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HF	N	25	48	(1,70)	0.05	0.82	0.001	22.29	<0.001 **	0.24
	Mean 0M	24.32	24.96							
	Mean 3M	18.64	18.50							
MHI	N	24	47	(1,68)	0.08	0.79	0.001	18.79	<0.001 **	0.22
	Mean 0M	1.70	1.72							
	Mean 3M	1.40	1.42							
UF	N	25	48	(1,70)	6.54	0.01*	0.09	39.84	<0.001 **	0.36
	Mean 0M	19.00	20.67							
	Mean 3M	21.56	27.71							
MUI	N	25	48	(1,70)	2.53	0.12	0.04	15.97	<0.001 **	0.19
	Mean 0M	1.35	1.45							
	Mean 3M	1.48	1.68							
HF:UF	N	25	48	(1,70)	4.47	0.04*	0.06	0.001	0.98	0.00
	Mean 0M	1.67	1.54							
	Mean 3M	1.07	0.72							
MHI: MUI	N	24	47	(1,68)	1.97	0.17	0.03	4.90	0.03*	0.07
	Mean 0M	1.28	1.25							
	Mean 3M	1.01	0.90							

*p<0.05
**p<0.01
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. SD= Standard Deviation. CBT= Cognitive Behavior Therapy. Med= Medication., df= Degrees of Freedom, BL= HUPS Score

Table 36: One-Way ANCOVA Assessing Difference in Week-12 HUPS Scores Across Treatment Groups Controlling for Baseline HUPS Scores in the Recurring Sample

HUPS Scores		CBT	Med	Analysis						
				df	F_{group}	P_{group}	$\eta_p^2{}_{group}$	F_{BL}	P_{BL}	$\eta_p^2{}_{BL}$
HF	N	4	13	(1,14)	0.35	0.57	0.02	4.27	0.06	0.23
	Mean 0M	21.75	24.08							
	Mean 3M	14.75	18.92							
MHI	N	4	13	(1,14)	0.82	0.38	0.06	3.41	0.09	0.20
	Mean 0M	1.62	1.56							
	Mean 3M	1.28	1.40							
UF	N	4	13	(1,14)	0.17	0.69	0.01	10.17	0.007 **	0.42
	Mean 0M	18.00	22.46							
	Mean 3M	18.25	24.00							
MUI	N	4	13	(1,14)	0.03	0.96	0.00	0.07	0.80	0.01
	Mean 0M	1.41	1.40							
	Mean 3M	1.67	1.68							
HF: UF	N	4	13	(1,14)	0.09	0.77	0.07	3.54	0.08	0.20
	Mean 0M	1.25	1.19							
	Mean 3M	1.05	0.90							
MHI: MUI	N	4	13	(1,14)	0.10	0.75	0.01	0.40	0.54	0.03
	Mean 0M	1.15	1.15							
	Mean 3M	0.82	0.88							

*$p<0.05$

**$p<0.01$

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. SD= Standard Deviation. CBT= Cognitive Behavior Therapy. Med= Medication., df= Degrees of Freedom, BL= HUPS Score

Table 37: Differences in Change in HUPS Scores in the Three Months Prior to Recurrence or End of Treatment (for Non-Recurrers)

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔHF	Recurrers	15	1.53	6.40	-0.02	91	0.98	-0.05	-4.20 – 4.11	<0.001
	Non Recurrers	78	1.49	7.58						

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔMHI	Recurrers	12	0.27	0.47	2.19	12.49	0.048*	-0.30	-0.61 - - 0.003	0.05
	Non Recurrers	74	-0.03	0.30						

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔUF	Recurrers	12	-6.83	8.98	3.34	88	0.001**	7.24	-2.93 – 11.56	0.11
	Non Recurrers	78	0.41	6.67						

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔMUI	Recurrers	12	-0.29	0.43	1.79	88	0.08	0.22	-0.03 – 0.46	0.04
	Non Recurrers	78	-0.07	0.39						

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔHF: UF	Recurrers	12	0.65	1.03	-2.23	11.83	0.046*	-0.68	-1.34 - - 0.01	0.05
	Non Recurrers	78	-0.02	0.51						

		N	Mean	SD	Analysis					
					t	df	P (two-tailed)	Mean Diff.	95% CI	Eta^2
ΔMHI: MUI	Recurrers	12	0.38	0.57	-2.28	11.49	0.04*	-0.38	-0.74 - -0.02	0.06
	Non Recurrers	74	0.01	0.21						

*p<0.05
**p<0.01
ΔHF= 3-Month Change in Hassle Frequency, ΔMHI= 3-Month Change in Mean Hassle Intensity, ΔUF= 3-Month Change in Uplift Frequency, ΔMUI= 3-Month Change in Mean Uplift Intensity, ΔHF:UF= 3-Month Change in Hassle Frequency to Uplift Frequency Ratio, ΔMHI:MUI= 3-Month Change in Mean Hassle Intensity to Mean Uplift Intensity Ratio, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval of Mean Difference

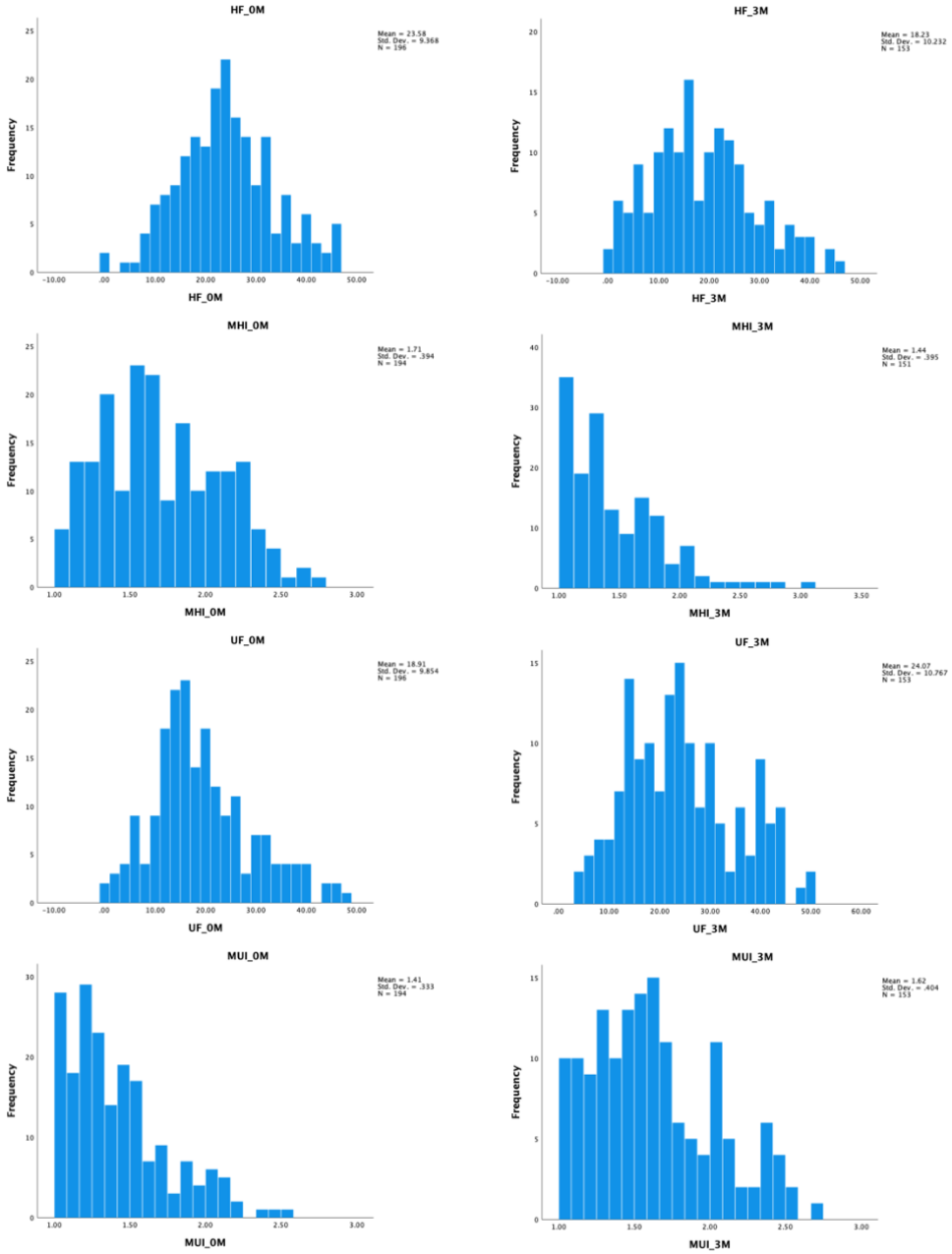
Table 38: Differences in Change in HUPS Ratios From Six to Three Months Prior to Recurrence or End of Treatment (for Non-Recurrers)

					Analysis					
		N	Mean	SD	t	df	P (two-tailed)	ΔMean	95% CI	Eta^2
ΔHF:UF	Recurrers	16	-0.13	0.36	2.05	89	0.04*	0.20	0.01 – 0.39	0.05
	Non Recurrers	75	0.07	0.29						

					Analysis					
		N	Mean	SD	t	df	P (two-tailed)	ΔMean	95% CI	Eta^2
ΔMHI:MUI	Recurrers	16	-0.03	0.30	0.11	84	0.91	0.01	-0.14 – 0.16	<0.01
	Non Recurrers	70	-0.02	0.27						

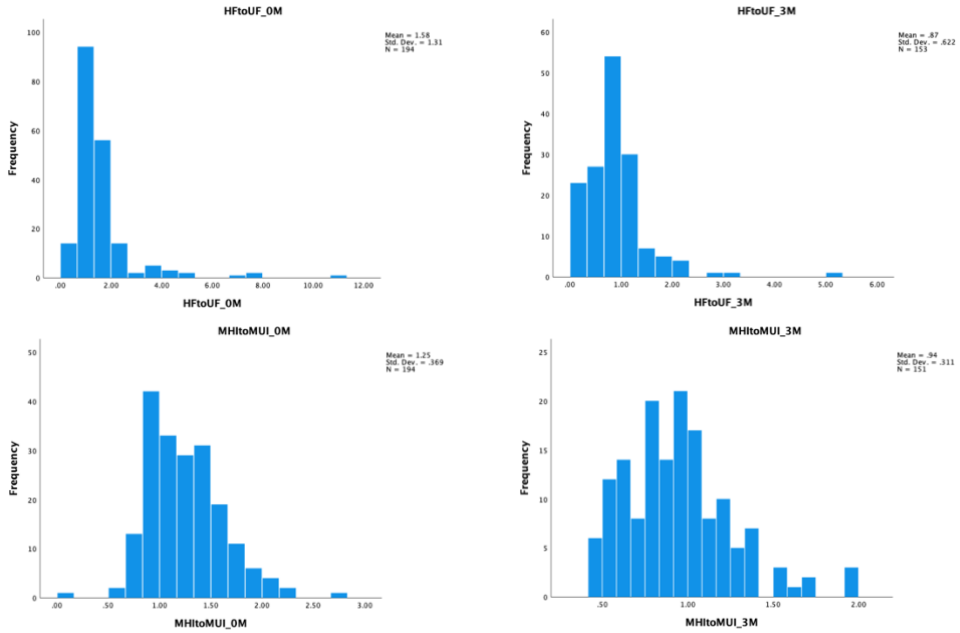
*p<0.05
**p<0.01
ΔHF= 6-to-3-Month Change in Hassle Frequency, ΔMHI= 6-to-3-Month Change in Mean Hassle Intensity, ΔUF= 6-to-3-Month Change in Uplift Frequency, ΔMUI= 6-to-3-Month Change in Mean Uplift Intensity, ΔHF:UF= 6-to-3-Month Change in Hassle Frequency to Uplift Frequency Ratio, ΔMHI:MUI= 6-to-3-Month Change in Mean Hassle Intensity to Mean Uplift Intensity Ratio, SD= Standard Deviation, df= Degrees of Freedom, Mean Diff.= Mean Difference, 95% CI= 95% Confidence Interval of Mean Difference

Figure 1: Distributions of Baseline and Week 12 HF, MHI, UF, and MUI Scores for the Whole Sample



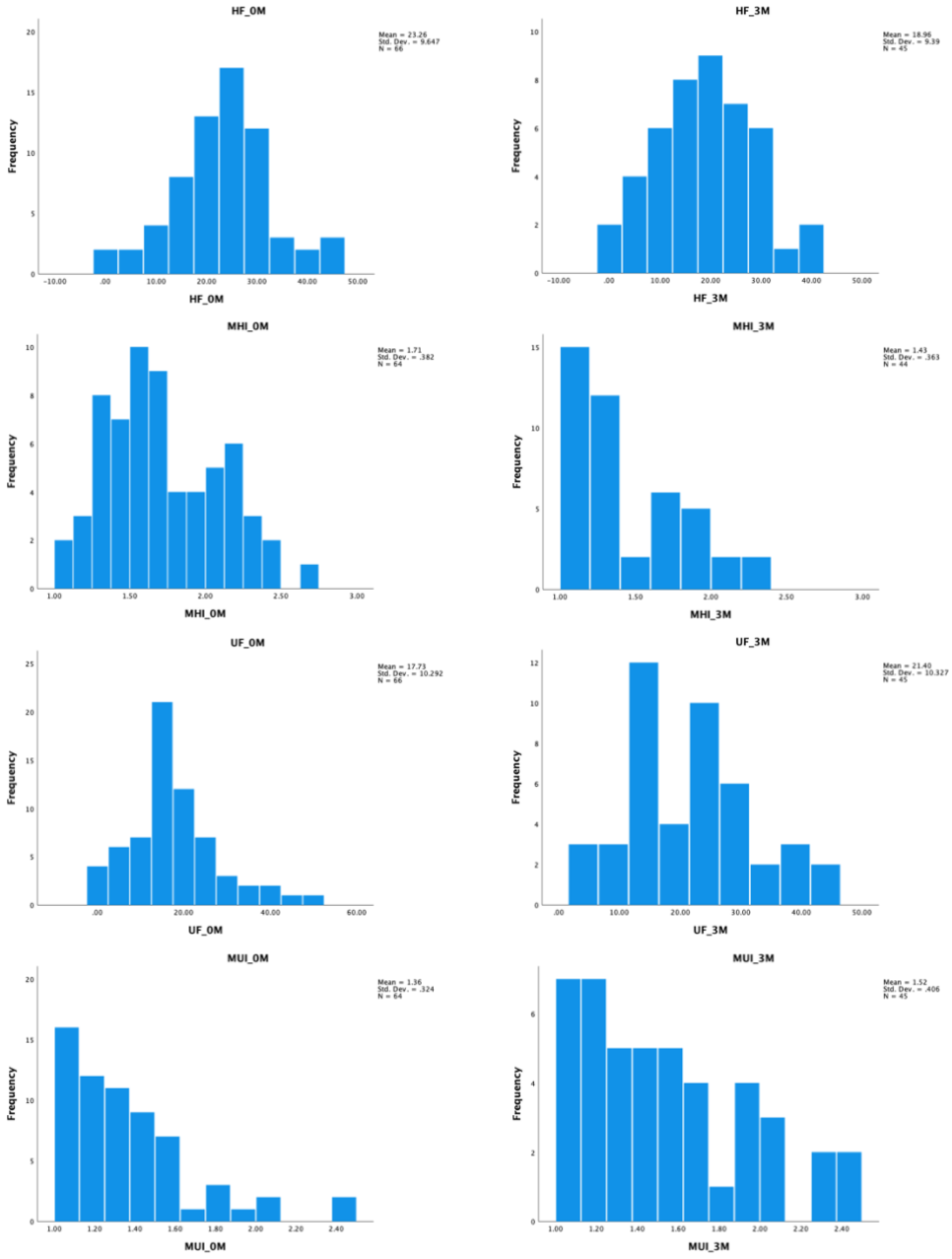
HF_0M= Baseline Hassle Frequency, MHI_0M= Baseline Mean Hassle Intensity, UF_0M= Baseline Uplift Frequency, MUI_0M= Baseline Mean Uplift Intensity, HF_3M= Baseline Hassle Frequency, MHI_3M= Baseline Mean Hassle Intensity, UF_3M= Baseline Uplift Frequency, MUI_3M= Baseline Mean Uplift Intensity

Figure 2: Distributions of Baseline and Week 12 HF:UF and MHI:MUI Scores for the Whole Sample



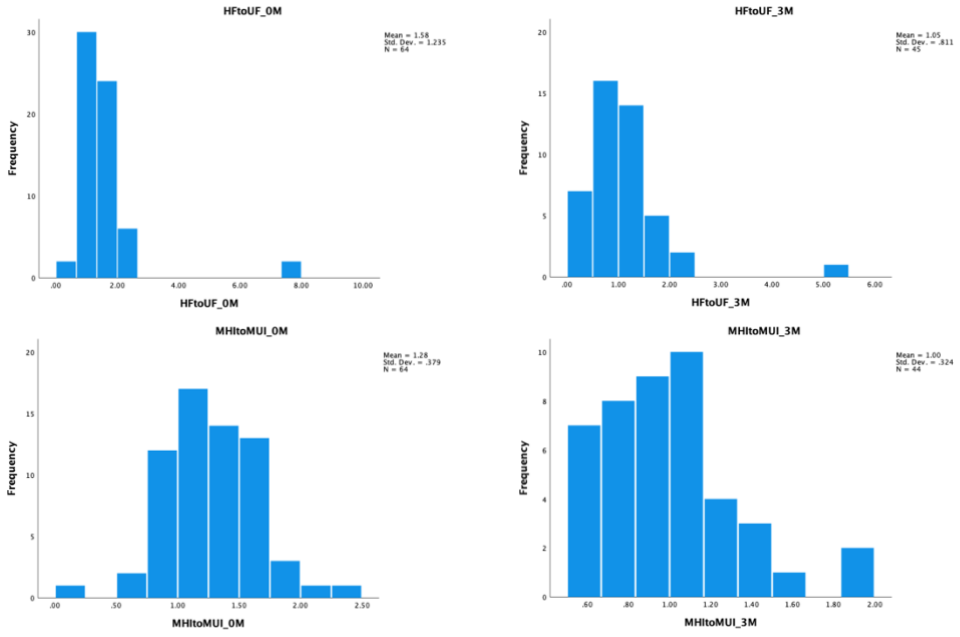
HFtoUF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, MHItoMUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, MHItoMUI_3M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio

Figure 3: Distributions of Baseline and Week 12 HF, MHI, UF, and MUI Scores for the CBT Group



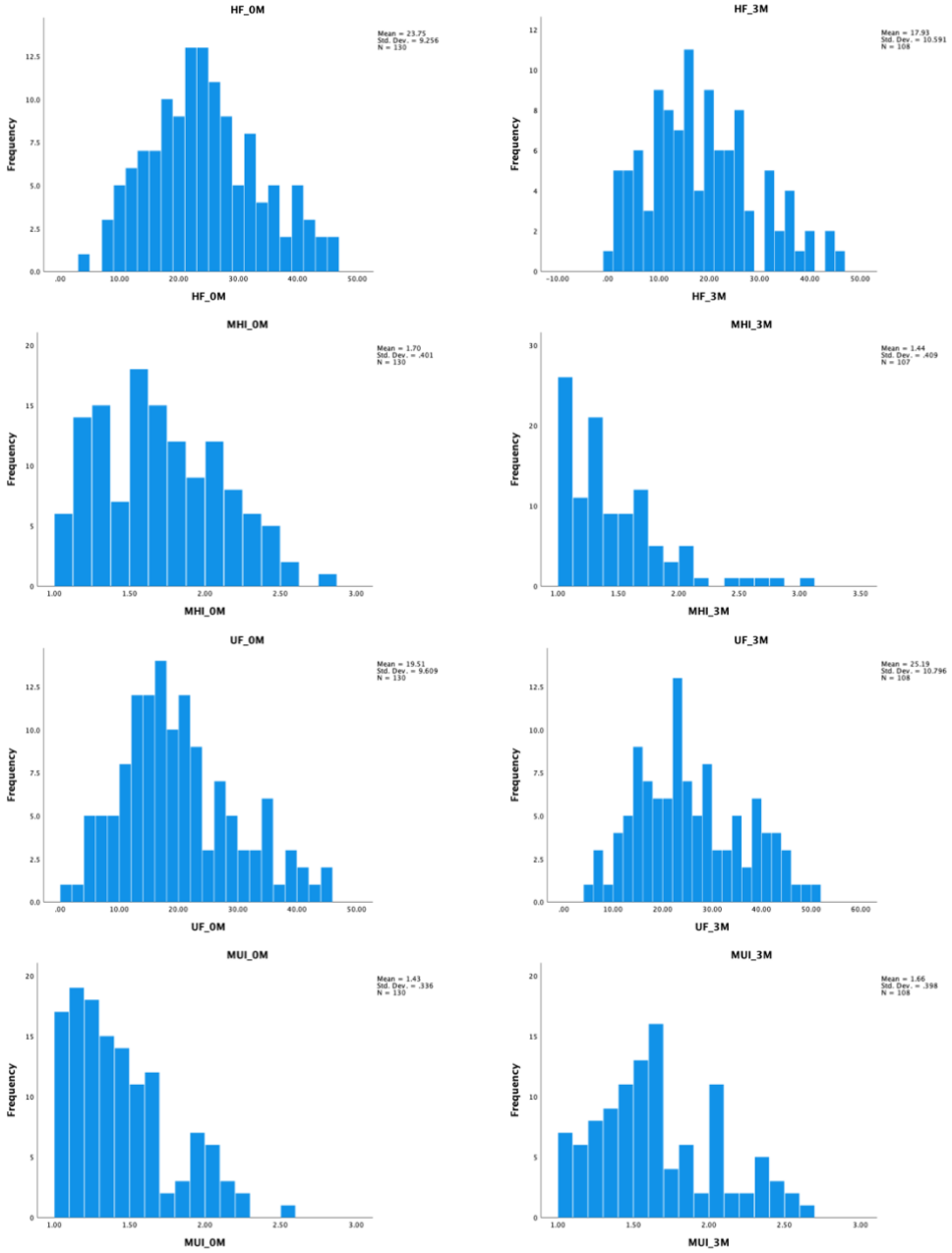
HF_0M= Baseline Hassle Frequency, MHI_0M= Baseline Mean Hassle Intensity, UF_0M= Baseline Uplift Frequency, MUI_0M= Baseline Mean Uplift Intensity, HF_3M= Baseline Hassle Frequency, MHI_3M= Baseline Mean Hassle Intensity, UF_3M= Baseline Uplift Frequency, MUI_3M= Baseline Mean Uplift Intensity

Figure 4: Distributions of Baseline and Week 12 HF:UF and MHI:MUI Scores for the CBT Group



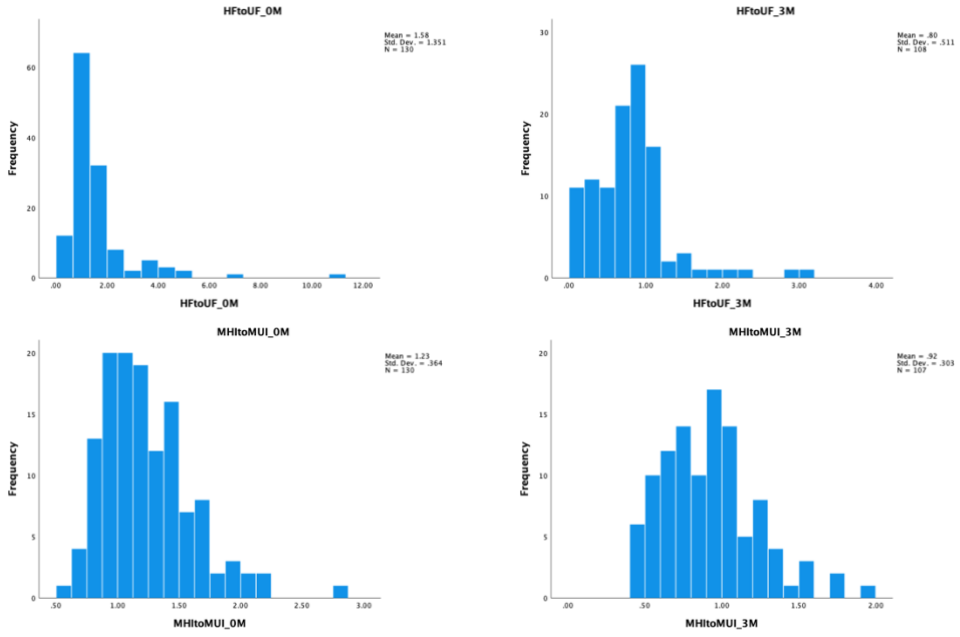
HFtoUF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, MHItoMUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, MHItoMUI_3M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio

Figure 5: Distributions of Baseline and Week 12 HF, MHI, UF, and MUI Scores for the Medication Group



HF_0M= Baseline Hassle Frequency, MHI_0M= Baseline Mean Hassle Intensity, UF_0M= Baseline Uplift Frequency, MUI_0M= Baseline Mean Uplift Intensity, HF_3M= Baseline Hassle Frequency, MHI_3M= Baseline Mean Hassle Intensity, UF_3M= Baseline Uplift Frequency, MUI_3M= Baseline Mean Uplift Intensity

Figure 6: Distributions of Baseline and Week 12 HF:UF and MHI:MUI Scores for the Medication Group



HFtoUF_0M= Baseline Hassle Frequency to Uplift Frequency Ratio, MHItoMUI_0M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio, MHItoMUI_3M= Baseline Mean Hassle Intensity to Mean Uplift Intensity Ratio

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