DEFINING AND DIFFERENTIATING TREATMENT-RESISTANT DEPRESSION

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Dedicated in loving memory to

Rachel Elizabeth Wells

DEFINING AND DIFFERENTIATING TREATMENT-RESISTANT DEPRESSION

by

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DISSERTATION

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ABSTRACT

Individuals diagnosed with major depressive disorder (MDD), who are unable to achieve an adequate therapeutic response despite completing multiple antidepressant therapies, are commonly referred to as experiencing treatment-resistant depression (TRD). Despite the common occurrence and debilitating nature of TRD, currently there is no standardized and universally accepted definition for TRD. The Maudsley Staging Method (MSM) is a novel,

multidimensional staging method for TRD that incorporates clinical and treatment factors. Although the multidimensional nature of the MSM makes it an ideal method for staging and identifying TRD, additional research is needed to better understand this newly developed staging method. The objective of this study was to evaluate the psychometric characteristics and clinical utility of the MSM. This involved (1) determining a reliable MSM cutoff score to differentiate TRD from non-TRD, (2) examining the extent of agreement between the MSM and another commonly used method of defining TRD, and (3) examining the construct validity of the MSM. This study also used the MSM to identify patients with TRD in order to perform a preliminary examination of the frequency of individual depressive symptoms associated with TRD. The data for this study was derived from four clinical investigations and included socio-demographic, clinical, and antidepressant treatment information for 88 patients diagnosed with MDD. This study identified an optimal cutoff score (7.5) for the MSM for differentiating TRD from non-TRD, and demonstrated moderate agreement between the MSM and another commonly used method for defining TRD. Depression symptom severity and current MDE duration had a significant, positive relationship with the MSM, which provided support for its construct validity. However, the MSM was not associated with certain demographic characteristics (e.g., female sex, older age) assumed to be related to TRD. This study provided an initial description of the frequency of individual depressive symptoms experienced by patients with

TRD. Future research should further evaluate the individual subscales that comprise the MSM and the impact different prescription guideline may have on a patient's MSM score and TRD classification. The MSM should also be evaluated outside of a research setting to determine its practical use in a clinical setting.

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LIST OF ABBREVIATIONS

ATHF	Antidepressant Treatment History Form
AUC	Area Under the Curve
CGI	Clinician Global Impression
CRD	Chronic Resistant Depression
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECT	Electroconvulsive Therapy
GAF	Global Assessment of Functioning Scale
HRSD	Hamilton Rating Scale for Depression
$HRSD_{24}$	24- Item Hamilton Rating Scale for Depression
IDS	Inventory of Depressive Symptomatology
$IDS\text{-}SR_{30}$	30-Item Inventory of Depressive Symptomatology-Self Report
IRB	Institutional Review Board
LIFE	Longitudinal Interval Follow-up Evaluation
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MGH-S	Massachusetts General Hospital Staging Method
MMSE	Mini Mental State Examination
MSM	Maudsley Staging Method
MST	Magnetic Seizure Therapy
Non-TRD	Non-Treatment Resistant Depression

NDRI	Norepinephrine-Dopamine Reuptake Inhibitor
NRI	Norepinephrine Reuptake Inhibitor
PASW	Predictive Analytics SoftWare
ROC	Receiver Operating Characteristic
SARI	Serotonin Antagonist and Reuptake Inhibitors
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard Deviation
SD-TRD	Standard Definition for Treatment Resistant Depression
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SPSS	Statistical Package for Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TD	Transdermal
TeCA	Tetracyclic Antidepressant
TRD	Treatment Resistant Depression
US	United States
UTSW	University of Texas Southwestern Medical Center

SECTION I – STUDY SUMMARY

Chapter 1: Introduction

Treatment Resistant Depression

A significant number of patients suffering from major depressive disorder (MDD) are unlikely to respond or remit with multiple courses of antidepressant treatments (M. Fava, 2003; M. Fava & Davidson, 1996; Nierenberg & Amsterdam, 1990). Patients who are unable to achieve an adequate therapeutic effect from multiple treatments are commonly referred to as having treatment-resistant depression (TRD) (Berman, Narasimhan, & Charney, 1997; Fagiolini & Kupfer, 2003; M. Fava, 2003; Sackeim, 2001). The term treatment-refractory depression has also been used to describe and/or refer to patients experiencing TRD (Souery, et al., 1999). Although the term refractory suggests a greater degree of resistance, the terms *resistance* and *refractory* appear to represent overlapping constructs and as such are used interchangeably within the literature (Berlim & Turecki, 2007a). The impact of TRD includes sustained patient burden from continued illness, psychological distress, and societal burden due to decreased productivity and continuous demands on psychiatric services. Currently there is no standardized and universally accepted definition or criteria for TRD (Berlim & Turecki, 2007a; Berman, et al., 1997). In order to develop effective antidepressant strategies for depressed patients who do not benefit from

treatment, it is first necessary to develop an effective method of defining, identifying, and measuring TRD.

Although specific guidelines have not been adopted, the number of previously failed medication treatments is commonly used to classify a patient with TRD (Souery 1999). This method involves determining the quantity and type of medication treatments a patient has previously received, and how the patient responded following an adequate course of treatment. This approach of characterizing TRD based on the number of previously failed antidepressant treatments is almost exclusively restricted to psychopharmacological treatments. Defining TRD exclusively in terms of the number and type of previously failed medication treatments represents a limited and problematic approach. First, there is no consensus regarding the number and type of antidepressant medication treatments that need to be failed (Berlim & Turecki, 2007a; M. Fava, 2003; Souery, Papakostas, & Trivedi, 2006). Second, despite the development and utility of various forms of psychotherapy and neurostimulation modalities, non-psychopharmacological antidepressant treatments serve only a minimal role in determining treatment resistance (Berlim & Turecki, 2007a; M. Fava, 2003). In fact, among many of the proposed guidelines for defining TRD, electroconvulsive therapy (ECT) is the only non-pharmacological antidepressant treatment routinely evaluated as a measure of TRD (Fekadu, Wooderson, Donaldson, et al., 2009; Petersen, et al., 2005; Souery, et al., 1999; Souery & Van der Auwera, 2004;

Thase & Rush, 1997). Third, there is no consensus regarding the definition of a "failed" treatment (Keller, 2005). Although measures of depressive symptoms provide global scores that are useful in determining changes in depression symptom severity, the extent of change needed to determine if a treatment is a failure or success is not codified. Fourth, a significant and often impractical amount of information (with regards to medication dose and duration) must be obtained to sufficiently determine if a patient completed an adequate antidepressant trial. Fifth, there is also a continued debate regard what constitutes an adequate antidepressant trial in terms of dose and duration. For example, among two commonly used antidepressant prescription guidelines the minimum effective dose for the antidepressant sertraline differed from 50 mg (D. Taylor, Paton, & Kapur, 2010) to 100 mg (Sackeim, 2001). The definition of an adequate treatment duration has also varied, ranging from 4 to 12 weeks (Bird, Haddad, & Dursun, 2002; M. Fava, 2003; Sackeim, 2001). These limitations have contributed to the wide variation in how TRD is defined both in clinical and research settings (Berlim & Turecki, 2007b; Carvalho, Cavalcante, Castelo, & Lima, 2007; Souery, et al., 2006).

The Need for a Universal Definition of TRD

The current absence of an accurate and universal definition of TRD contributes to the misclassification of patients as having TRD (Sackeim, 2001). This misclassification is partly due to the wide variation in the definition of TRD.

Reducing variation in the definition of TRD could help to accurately differentiate between patients with and without TRD. Given the increased risk of relapse associated with TRD, better identification of TRD could help determine appropriate treatment strategies for these patients. Establishing a universal definition of TRD would benefit both clinical and research settings by allowing clinical and research data for TRD patients to be easily compared across different mental health settings. This is essential for insuring homogeneity among research samples and the application of clinical research findings to clinical practice.

A Symptom Based Approach

The number of patients who have demonstrated a significant degree of resistance to antidepressant treatments suggests a unique form of MDD. Establishing criteria that can be used to distinguish treatment resistance from non-resistance can help to characterize this subtype of MDD. Given the current difficulty in establishing a universally excepted definition of TRD based on previous medication failures, an alternative method of describing and defining TRD is needed. Previous research has attempted to define TRD in terms of demographic and clinical features; however, little attention has focused on the constitutional depressive symptoms of TRD. An attempt to identify specific symptoms unique to patients who have demonstrated resistance to antidepressant treatments represents a novel approach toward establishing an operational definition of TRD. A symptom based approach in defining TRD would allow

clinicians and researchers to avoid the laborious, and often misinformed, process of reviewing a patient's prior treatment history. Also a symptom based approach to defining TRD would be consistent with the diagnostic criteria used in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR). In order to determine the presence of a symptom based classification of TRD, it is first necessary to establish a method of accurately differentiating between treatment resistant and non-treatment resistant depression, and second to establish a reliable method for accurately rating TRD severity.

Defining and Differentiating TRD

The two methods currently used to define and measure TRD involve an examination of the number and type of previously failed medication treatments (Souery 1999) and the use of staging models (Souery, et al., 2006). Although using the number and type of failed medication trials to define TRD is the most commonly used method (Souery 1999), various limitations in this approach have led to the development of various staging models as an alternative method to defining and measuring TRD. Staging models are systematic methods of defining, measuring, and identifying TRD. Staging methods typically have specific scoring guidelines, the ability to stage treatment resistant severity, and can be examined with empirical methods.

The Maudsley Staging Method (MSM) represents one of the newest staging models for TRD (Fekadu, Wooderson, Donaldson, et al., 2009). The MSM was developed as a multidimensional staging method for TRD that incorporates various clinical and treatment factors. The clinical factors incorporated in the MSM include the duration of depressive episode and symptom severity. Regarding treatment factors, the MSM includes number of treatment failures, use of augmentation treatment strategies, and use of ECT. Augmentation treatment strategies involve the concomitant use of a drug (e.g. lithium, anticonvulsants, antipsychotics, secondary antidepressant, etc.), which is intended to enhance the efficacy of an antidepressant medication (Carvalho, et al., 2007; M. Fava, 2001). The multidimensional and comprehensive nature of the MSM makes it an ideal method for staging treatment resistant severity and differentiating TRD from non-TRD. Although initial studies have produced favorable results regarding the predictive validity of the MSM (Fekadu, Wooderson, Donaldson, et al., 2009; Fekadu, Wooderson, Markopoulo, et al., 2009), additional research is needed to better understand the psychometric properties and utility of the MSM as a method of differentiating between TRD and non-TRD.

Purpose of the Study

The purpose of this study was to address some of the unevaluated aspects of the MSM in order to better understand the psychometric properties and utility

of the MSM as a potential method of differentiating TRD from non-TRD. Aspects of the MSM that have not yet been established include: 1) the exact cutoff scores for discriminating TRD from non-TRD; 2) the relationship between the MSM total score and socio-demographic characteristics, and 3) the frequency rates of individual depressive symptoms of TRD as identified using the MSM. An examination of the frequency rates for individual depressive symptoms of TRD represents an initial step toward establishing a symptom based classification of TRD. Examining individual depressive symptoms of TRD, which is a relatively unexplored area with the TRD literature, would help to clarify if TRD is indeed a unique form of depression.

These study objectives are an initial step toward addressing the current limitations of the MSM, which will inform its psychometric properties and utility as a potential method of identifying TRD.

SECTION II – COMPREHENSIVE LITERATURE REVIEW OF MAJOR DEPRESSIVE DISORDER

Chapter 2: The Prevalence and Impact of Major Depressive Disorder

Prevalence Rates of Major Depressive Disorder

United States and Internationally

Major depressive disorder (MDD) is a common and debilitating psychiatric disorder that negatively impacts a significant portion of the population (Kessler, et al., 2003; World Health Organization, 2001). Epidemiological studies have indicated that annually an estimated 5.23% to 10% of adults in the United States (US) will experience a Major Depressive Episode (MDE) (Andrade, et al., 2003; Grant, et al., 2004; Hasin, Goodwin, Stinson, & Grant, 2005; Kessler, et al., 2003; Kessler, et al., 2010). Lifetime prevalence rates of MDD within the US have been reported to range from 13.23% to 16.9% (Andrade, et al., 2003; Hasin, et al., 2005; Kessler, et al., 2005). According to the lifetime prevalence rates of MDD reported by Kessler et al. (2003), which was 16.2%, a estimated 32.6 to 35.1 million adults in the US will be diagnosed with MDD. The prevalence rates of depression are variable in other countries. A study comparing developed versus developing countries reported 12-month prevalence rates of MDE ranging from 2.2% to 10.4% (Kessler, et al., 2010). The lifetime prevalence rates of MDD reported in other countries tended to be higher and ranged from 10.6% to 15.7% (Andrade, et al., 2003; Gabilondo, et al., 2010; Patten, et al., 2006).

Sex, Age, and Ethnicity

The prevalence rates of MDD do differ between men and women, with women more frequently diagnosed than men at a ratio of 2:1 (Kessler, 2003). The higher rate in which women are diagnosed with MDD and seek treatment has been reflected in both 12-month and lifetime prevalence rates (Hasin, et al., 2005; Kessler, et al., 2003; Marcus, et al., 2005). The difference in prevalence rates of MDD between men and women is independent of nationality and ethnicity (Andrade, et al., 2003; Ayuso-Mateos, et al., 2001; Dowrick, et al., 2002; Gabilondo, et al., 2010; Gavin, et al., 2010; Patten, 2009; Wilhelm, Mitchell, Slade, Brownhill, & Andrews, 2003).

Higher rates of depression in the US are also reported in younger cohorts (age ≤ 65) compared to older cohorts (age ≥ 65) (Hasin, et al., 2005; Kessler, et al., 2005), which is a finding that has been demonstrated in other developed countries (Kessler, et al., 2010; Wilhelm, et al., 2003). Regarding the prevalence rates of depression in ethnic groups within the US, significant rates of MDD ranging from 4.12% to 11.81% have been reported in ethnic minority groups (e.g. Asian/Pacific Islanders, African-Americans, Mexican Americans, Native Americans, etc.) (Gonzalez, et al., 2010; Hasin, et al., 2005; Riolo, Nguyen, Greden, & King, 2005; Sclar, Robison, & Skaer, 2008; D. R. Williams, et al., 2007).

Impact of Major Depressive Disorder

Major Depressive Disorder (MDD) is a severe debilitating condition that negatively impacts various aspects of an individual's life including family, social network, occupational function, and overall level of functioning. The extent of impact resulting from the debilitating nature of MDD is related to the degree of depressive symptoms and severity. Epidemiologic studies conducted internationally have reported that for individuals suffering from depression, 33.9% to 44.5% are considered severely depressed and 33.8% to 38.2% are considered moderately depressed (Caballero, et al., 2008; Gabilondo, et al., 2010; Kessler, et al., 2010). These rates are similar for the U.S. with severe and moderate depression accounting for approximately 76% of those diagnosed with MDD (Kessler, et al., 2003).

Impairment and Disability

Studies examining the extent of impairment resulting from MDD within specific domains have reported that between 43.4% and 79.3% of individuals with MDD experience severe to very severe social impairment (Kessler, et al., 2003; Slade & Sunderland, 2010). High rates of impairment were also reported in domains related to work, with 28.1% to 82.8% reporting severe to very severe occupational impairment. The debilitating nature of MDD is considered greater than any other psychiatric or general health condition (World Health Organization, 2001). Major depressive disorder is the fourth leading cause of disability and is predicted to be the second most disabling disease across all

counties by the year 2020 (Amital, Fostick, Silberman, Beckman, & Spivak, 2008). The impact of MDD in the US is highlighted by the estimated annual loss of $30 to $40 billion in depression-related medical and productivity costs (Elinson, Houck, Marcus, & Pincus, 2004).

Health Related Impact

The impact of MDD on an individual's physical health includes higher rates of mortality (Cuijpers & Smit, 2002) and heart disease (Ferketich, Schwartzbaum, Frid, & Moeschberger, 2000). Results from a 10-year National Health and Nutrition Survey reported that men (71%) and women (73%) had a greater chance of developing heart disease (Ferketich, et al., 2000). Depressive symptoms have also been associated with poor self-rated health (Thielke, Diehr, & Unutzer, 2010), and rates of obesity for certain populations (Heo, Pietrobelli, Fontaine, Sirey, & Faith, 2006). In fact, depressive symptoms have been reported in 16% of individuals with peripheral arterial disease (Smolderen, et al., 2008) and in over 20% of individuals seeking treatment for medical illnesses, which further demonstrates the association between MDD and negative physical health (Tylee & Gandhi, 2005).

Comorbid Psychiatric Disorders

The diagnosis of MDD increases the risk of having a comorbid psychiatric illness, such as anxiety, substance use, and personality disorders. Based on 12-month prevalence rates of MDD, comorbidity rates ranging from 55.8% to 64% have been reported in the US and other developed countries (Gabilondo, et al.,

2010; Kessler, et al., 2003; Kessler, et al., 2010). Comorbidity rates for individuals with MDD include 27.7% with one additional psychiatric diagnosis, 15.9% with two, and 18.7% with three of more comorbid psychiatric disorders (Kessler, et al., 2010). Anxiety related disorders are the most common comorbid psychiatric disorder, within the spectrum of Axis I disorders (Gabilondo, et al., 2010; Hasin, et al., 2005; Kessler, et al., 2003). Regarding Axis II, 37.9% of individuals with MDD also met criteria for a comorbid personality disorder (Hasin, et al., 2005).

Risk of Suicide

The most significant consequence associated with severe or chronic depression includes attempted and completed suicide. According to the American Association of Suicidology (2006) MDD has one of the highest mortality rates relative to other mental illnesses with 7 out of 100 men and 1 out of every 100 women completing suicide. The WHO reported that suicide attempts are 20 times more frequent than completed suicides, with mental health disorders, especially depression and substance abuse, accounting for more than 90% of all suicides (Kiyohara & Yoshimasu, 2009). Risk factors for suicide attempts among MDD include previous attempts, poor social support, and duration of depressive episode (Holma, et al., 2010). Studies have indicated that over 36% of individuals with MDD experience thoughts of suicide and over 17% of individuals with MDD in the US have attempted suicide (Hasin, et al., 2005; Lesser, et al., 2007; Marcus, et al., 2005).

Multiple studies have consistently demonstrated both the high prevalence and debilitating nature of MDD (Kessler, et al., 2003; Kessler, et al., 2010; Slade & Sunderland, 2010). The negative impact of MDD represents both a societal and individual burden resulting from depression-related medical cost, lost productivity, increased mortality rates, and significant impairment across multiple domains of functioning. Although the societal burden of MDD can be partly understood in terms of its high prevalence, an understanding of the debilitating nature of MDD requires a comprehensive review of the symptoms and features that have come to define MDD. An in depth understanding of the symptoms and features that characterize MDD is also essential to differentiate MDD from other debilitating psychiatric conditions, determine appropriate treatment planning, and develop better treatment strategies for patients that have failed to improve despite multiple antidepressant treatments.

Chapter 3: Symptoms and Features of Major Depressive Disorder

Diagnostic Criteria of Major Depressive Disorder

Unipolar versus Bipolar Depression

Major depressive disorder can be classified as either unipolar or bipolar depression, which is a distinction based on the type of mood episodes that are experienced. Unipolar depression is defined by the presence of only depressive episodes, while a diagnosis of bipolar depression is based on the presence of both depressive and manic episodes. Given the exclusion of bipolar depression from this present study, the following review will focus exclusively on unipolar depression.

Symptoms of a Major Depressive Episode

The diagnostic criteria for a MDE outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) includes a symptomatic period of at least two weeks in which there is either depressed mood or anhedonia, plus a minimum of four additional symptoms (American Psychiatric Association, 2000). The four additional symptoms can include any of the following: significant changes in weight or appetite, significant changes in sleep, psychomotor agitation or retardation, loss of energy, excessive feelings of worthlessness or guilt, difficulty concentrating, and suicidal ideation (American Psychiatric Association, 2000). A more detailed and comprehensive review of these symptoms will be provided later in this chapter; however, the

severity of these symptoms must be sufficient to cause clinically significant distress or impairment in domains of social, occupational, or other areas of functioning (American Psychiatric Association, 2000). In addition, the presence and severity of these symptoms cannot be due to a general medical condition or the result of a substance induced physiological response (American Psychiatric Association, 2000).

Clinical Characteristics of Major Depressive Disorder

Recurrent Depression and Relapse

Major depressive disorder is a chronic psychiatric disorder that typically involves multiple MDEs during an individual's lifetime. Approximately 60% of individuals who experience a MDE are likely to develop a second MDE (American Psychiatric Association, 2000), and over 75% of individuals seeking treatment for depression have reported having at least one prior MDE (Lesser, et al., 2007). Studies conducted in the U.S. have indicated that the average number of lifetime MDEs has ranged from 4.7 to 6.1 (Hasin, et al., 2005; Husain, et al., 2005; Lesser, et al., 2007). A much higher number of MDEs has recently been reported in a large scale epidemiological study (Kessler, et al., 2010). This study, which was conducted internationally, reported an average number of lifetime MDEs of 10.9 and 14.8 for developed and developing countries, respectively. The number of previous MDEs has been shown to be a risk factor for a lengthier clinical course of MDD. As individuals experience more MDEs, the period of

time decreases in which they are asymptomatic (Uebelacker, Keitner, Ryan, & Miller, 2004).

The high rates in which individuals experience multiple MDEs reflects the chronic nature of MDD, with the majority of patients relapsing. Rates of relapse and recurrence are significant even for individuals who receive adequate treatment during an immediate MDE. The rates of recurrence for MDD after being released from a hospital are approximately 25% within the first 6 months, 30% to 50% in the following 2 years, and 50% to 75% in 5 years (Sadock, Sadock, Ruiz, & Kaplan, 2009). Due to these high rates of relapse and recurrence, studies have attempted to identify predictive factors of relapse. Factors that have demonstrated a predictive value for relapse or recurrence of MDD include: obtaining only partial remission, high depression severity, number of previous MDEs, age, and the presence of a comorbid psychiatric diagnosis (Melartin, et al., 2004; Pintor, Torres, Navarro, Matrai, & Gasto, 2004). Although multiple factors have been found to increase the risk of relapse and recurrence for MDD, the concept of partial remission is considered the most consistent and important (Rush, et al., 2006). Compared to individuals who achieve full remission, individuals who continue to experience some degree of residual depressive symptoms are at a greater risk of relapse and recurrence of a MDE (American Psychiatric Association, 2000; G. A. Fava, Fabbri, & Sonino, 2002; Kanai, et al., 2003; Nierenberg & DeCecco, 2001).

Course and Prognosis of Illness

The clinical course of MDD, which can vary greatly among individuals, is typically described in terms of the age of onset, duration of illness, and number of prior MDEs. The exact age of onset can be difficult to determine given that approximately 50% of the individuals experiencing their first MDE also reported having significant depressive symptoms prior to receiving an official diagnosis of depression (Sadock, et al., 2009). Although MDD has been diagnosed in children and adolescents, the prevalence rates for these age cohorts is typically lower compared to adult populations (Coyle, et al., 2003; Lewinsohn, 1994; Shaffer, et al., 1996). According to the DSM-IV-TR, onset of MDD typically occurs in young adulthood, with an average age of onset reported to range from 25.1 to 28.9 (Husain, et al., 2005; Kessler, et al., 2010; Lesser, et al., 2007; Zisook, et al., 2007).

The duration of illness or length of a MDE is greatly influenced by the utilization of effective antidepressant treatment(s) and the severity of the initial episode. The duration of an untreated MDE is typically 6 to 13 months, which is significantly longer relative to a treated episode which usually resolves within 3 months (Sadock, et al., 2009). This disparity between the duration of a treated versus untreated MDE highlights the need to administer effective antidepressant treatments near the onset of a depressive episode. Research has suggested that a longer duration of an untreated MDE has been associated with a longer duration

of illness and increased rate of recurrence (Altamura, Dell'Osso, Mundo, & Dell'Osso, 2007). The severity of an individual's initial MDE has also been found to predict persistence of illness (American Psychiatric Association, 2000) and reduced rates of remission (Blom, et al., 2007).

Review of Depressive Symptoms

DSM-IV-TR Core Depressive Symptoms

As mentioned above, the diagnostic criteria for a MDE, outlined in the DSM-IV-TR, requires the presence of five or more specific depressive symptoms for a period of at least two weeks (American Psychiatric Association, 2000). These symptoms include: (1) depressed mood, (2) anhedonia, (3), significant changes in weight or appetite, (4) development of insomnia or hypersomina, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) excessive feelings of worthlessness or guilt, (8) difficulty concentrating, and (9) suicidal ideation. These nine symptoms can create over 100 different symptom profiles that meet diagnostic criteria for MDD (Minor, Champion, & Gotlib, 2005). Although the current DSM-IV-TR diagnostic criteria for a MDE includes a total of nine depressive symptoms, the symptoms of depressed mood and anhedonia are considered of greater importance then the remaining seven symptoms. This is reflected in the DSM-IV-TR diagnostic criteria that one of the five depressive symptoms must be either depressed mood or anhedonia (Zimmerman, McGlinchey, Young, & Chelminski, 2006b). Of the nine depressive symptoms,

many of them can be expanded to represent more specific depressive symptoms. A recent study examining accuracy of specific depressive symptoms in diagnosing MDD divided the nine DSM-IV-TR depressive symptoms into 17 separate items (Mitchell, McGlinchey, Young, Chelminski, & Zimmerman, 2009). The nine depressive symptoms included in the DSM-IV-TR diagnostic criteria for MDD and the subsequent division of these symptoms into 17 specific symptoms are outlined in Table 1.

Insert Table 1 here

Although these depressive symptoms are widely accepted in the literature, there are additional depressive symptoms that are unique to specific subtypes of depression and/or commonly included in various depression symptom severity measures.

DSM-IV-TR Other Depressive Symptoms

The additional depressive symptoms included in the DSM-IV-TR are unique to specific subtypes of depression. Many of these depressive symptoms are related to the quality, variation, and reactivity of an individual mood or affect during a MDE. Mood reactivity refers to the ability to experience a positive emotional reaction or an improvement in mood when exposed to pleasurable events or stimuli (American Psychiatric Association, 2000). Mood reactivity, specifically the presence or loss of this ability, is a symptom that differs for

certain forms of depression (Khan, et al., 2006; Thase, 2007). Although some individuals diagnosed with depression have reported a complete or near complete loss of mood reactivity (Rush & Weissenburger, 1994), other individuals have reported retention of this ability despite experiencing a current MDE (Singh & Williams, 2006). The quality of the sadness or depressed mood experienced is an additional depressive symptom that can be assessed. Although quality of mood can be a difficult symptom to quantify or measure, certain patients describe the quality of their depressed mood as being distinct from the type of sadness experienced during bereavement or times of grief (Leventhal & Rehm, 2005). Mood variation is a symptom that refers to the relationship between an individual's mood and the time of day (American Psychiatric Association, 2000). Certain subtypes of depression are characterized by a worsening of depression at certain times of the day such as increased depression in the morning compared to the afternoon or evening (American Psychiatric Association, 2000; Rush & Weissenburger, 1994)

In addition to mood related symptoms there are two other depressive symptoms that are unique to one subtype of MDD. Depressed patients have also reported experiencing heaviness in their limbs or a sensation of being weighted down (Benazzi, 2003a; Thase, 2007), which is a symptom commonly referred to as leaden paralysis (American Psychiatric Association, 2000). The duration of this symptom can vary, lasting from one hour to several hours at a time.

Interpersonal rejection sensitivity represents a more longstanding symptom, generally with an early onset and more persistent course (American Psychiatric Association, 2000). Individuals experiencing this symptom typically have considerable difficulty experiencing real or perceived interpersonal rejection and/or criticism. Their difficulty to process rejection from others can result in a history of unstable relationships or an avoidance of relationships. Compared to many other depressive symptoms, interpersonal rejection sensitivity occurs during and between periods of depression; however, an exacerbation of this symptom may occur during episodes of depression (Davidson, 2007; Davidson, Zisook, Giller, & Helms, 1989).

Depressive Symptoms Not Codified in the DSM-IV-TR

Additional depressive symptoms not codified in the DSM-IV-TR are frequently included in multiple inventories or measures of depression. Of the commonly used depression measures, the Inventory of Depressive Symptomatology (IDS) (Rush, et al., 1986) and the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960, 1967; J. B. W. Williams, 1988) are the most comprehensive. This section will only focus on describing the additional symptoms frequently included in measures of depression, while a more detailed description of the construction and use of the IDS and HRSD will be provided in the methods section. To help organize and better describe the additional depressive symptoms included in these two depression inventories, they are

divided into the following categories: *anxious/irritable, somatic anxiety, sleep disturbance, hedonic capacity, self-blame/hopelessness,* and *psychotic*. These categories are a modification of the symptom categories identified during an early study that attempted to establish a generalized model of observed depressive symptoms (Gullion & Rush, 1998). Although there is some overlap among many of these symptoms, categorizing these symptoms provides a framework to help understand the individual and collective relationship between these symptoms in the evaluation of depression. A more detailed categorization of the symptoms commonly assessed for depression is provided in Table 2.

Insert Table 2 here

Anxious/irritable symptoms are included in both the IDS (Rush, et al., 1986) and HRSD (Hamilton, 1960, 1967; J. B. W. Williams, 1988). The inclusion of items to capture anxiety symptoms is the result of the comorbidity between anxiety and depressive disorders. Epidemiology studies have repeatedly demonstrated that a significant number of patients diagnosed with depression also experience anxiety related symptoms (Husain, et al., 2005), and thus are classified as anxious depressed (M. Fava, et al., 2006) or meet diagnostic criteria for a comorbid anxiety-related disorder (Kessler, et al., 2003; Kessler, et al., 2010). Psychological symptoms of anxiety are assessed by items that measure subjective feelings or observed signs of anxiety, apprehension, and irritability.

Obsessive/compulsive thoughts and behaviors are also included in the HRSD (M. Fava, et al., 2004; M. Fava, et al., 2000).

S*omatic anxiety symptoms* measured by the HRSD and IDS involve items that capture changes in bowel movements (e.g. periods of constipation and/or diarrhea) as well as concerns or preoccupations involving physical health. Many of the symptoms included in the HRSD and IDS designed to assess somatic aspects of anxiety are derived from the diagnostic criteria for Panic Attack outlined in the DSM-IV-TR (American Psychiatric Association, 2000). These symptoms include heart palpitations, chest pain, excessive sweating, hot and cold flashes, and periods of derealization or depersonalization.

Although *sleep disturbance symptoms* are included in the DSM-IV-TR diagnostic criteria for MDD (American Psychiatric Association, 2000), the HRSD and IDS further divide insomnia into sleep onset insomnia, mid-nocturnal insomnia, and early morning insomnia, and also include hypersomnia. These terms, which are defined similarly on the HRSD and IDS, refer to the time or phase of sleep difficulty. Sleep onset insomnia occurs when individuals have difficulty falling asleep or it takes them a considerable amount of time to fall asleep. Mid-nocturnal insomnia refers to difficulty staying asleep or repeatedly waking up for extended periods of time during the night. Early morning insomnia is defined as a repeated pattern or frequently awakening before one has to awake, and being unable to go back to sleep. Hypersomnia refers to prolonged or

frequent periods of sleeping, which are considered uncharacteristic of a typical sleep pattern. Regardless of the type of somnia experienced, the insomnia and hypersomnia items are considered unintentional and undesired.

Hedonic capacity symptoms, which are included both in the HRSD and IDS, include items that capture the capacity to experience pleasure and any experienced pain or physical discomfort (e.g. occurrence of headaches, abdominal, back, or joint pain). An additional symptom included in many inventories of depression that is not included in the DSM-IV-TR diagnostic criteria for MDD, is the degree of interest or loss of interest in sexual activity (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Hamilton, 1967; Rush, et al., 1986).

The *self-blame/hopelessness symptoms* measured in the HRSD and IDS refer to feelings of hopelessness or pessimism toward the future, and feelings of helplessness. Although these two depressive symptoms are not included in the DSM-IV-TR diagnostic criteria for depression, they are commonly reported by depressed patients. The symptoms of hopelessness and helplessness are derived from Beck's Cognitive Triad theory of depression (Beck, Rush, Shaw, & Emery, 1979), which hypothesized that depression was the result of a distorted negative perception of the self, world, and future (Beckham, Leber, Watkins, Boyer, & Cook, 1986).

An assessment of *psychotic symptoms* is only included in the HRSD and is comprised of two items. These two items assess an individual's feeling or sense of depersonalization or derealization and symptoms of paranoia. These symptoms are more likely to occur in the presence of MDD with psychotic features (American Psychiatric Association, 2000). Although the combination of MDD and psychotic symptoms is commonly referred to as Psychotic Depression and has been proposed as a distinct subtype of depression (Rush, 2007), at this time the presence of psychotic symptoms is only used as a measure of depression severity by the DSM-IV-TR. A summary and comparison of all the symptoms included in the IDS, HRSD, and DSM-IV-TR diagnostic criteria for MDD is provided in Table 2.

Prevalence of Depressive Symptoms

Various studies have examined the prevalence rates for the depressive symptoms included in the DSM-IV-TR, as well as the additional depressive symptoms included in the HRSD and IDS. Due to variations in study design and the different measurements of depression symptoms, there is some variation in the prevalence rate for individual depressive symptoms. Prevalence studies that have focused predominately on symptoms included in the DSM-IV-TR diagnostic criteria for MDD have indicated that *depressed mood*, *anhedonia*, *fatigue*, *sleep disturbances*, and *decreased concentration* are five of the most commonly reported depressive symptoms (McGirr, et al., 2007; Mitchell, et al., 2009;

Zimmerman, McGlinchey, Young, & Chelminski, 2006a). The prevalence rates for depressed mood and anhedonia ranged from 83.9% to 93.0% and 84.7% to 64.0%, respectively. Given that one of these two symptoms must be present to meet the diagnostic criteria for MDD, these two symptoms are expected to be among the most commonly reported symptoms for depressed patients.

Although similar results have been reported with the use of more comprehensive symptom inventories, the prevalence rates for certain symptoms have varied. Among studies that have examined a greater number of symptoms, *depressed mood* is the most frequently reported symptom with prevalence rates ranging from 96.5% to 98.5% (Gaynes, et al., 2007; Husain, et al., 2005; Novick, et al., 2005). The next two commonly reported depressive symptoms include *fatigue* (88.4% to 96.6%) and *decreased concentration* (88.5% to 95.1%). Compared to prevalence studies that focused exclusively on the DSM-IV-TR diagnostic criteria for MDD, symptoms related to *anhedonia* were ranked as the fourth most frequently occurring symptom (Husain, et al., 2005; Novick, et al., 2005). Additional symptoms not listed in the DSM-IV-TR diagnostic criteria for MDD that were frequently reported by patients with a diagnosis of MDD included *irritable mood*, *feelings of hopelessness*, and *anxiety* (Husain, et al., 2005; Novick, et al., 2005).

Chapter 4: Subtypes of Major Depressive Disorder

Major Depressive Disorder Subtypes

The DSM-IV-TR includes a formulation to codify unique subtypes of MDD. These subtypes of MDD are defined by the presence of a specific set of symptoms. The four MDD subtypes included in the DSM-IV-TR include melancholic, atypical, catatonic, and postpartum (American Psychiatric Association, 2000). Although not identified as specific subtypes in the DSM-IV-TR, depression with psychotic or anxiety features has been proposed as two specific subtypes of depression (M. Fava, et al., 2004; Jeste, et al., 1996; Rush, 2007). A brief description of these MDD subtypes will be provided.

Melancholic Depression

The symptom profile necessary to diagnosis melancholic depression must occur during the course of a major depressive episode, but can be applied to either unipolar or bipolar depression. Melancholic depression includes the presence of severe anhedonia or a lack of reactivity to pleasurable activities, plus a minimum of three additional symptoms. The three additional symptoms can include any of the following: initial morning insomnia, significant decrease in weight or appetite, diurnal variation, psychomotor agitation or retardation, and excessive feelings of guilt (American Psychiatric Association, 2000). Melancholic depression is also referred to as "endogenous depression," due to the frequent development of these symptoms despite the lack of a precipitating event or external situational stressor

(Leventhal & Rehm, 2005). Approximately 25% to 30% of individuals with MDD also meet the diagnostic criteria for melancholic depression (M. Hill & Gorzalka, 2005).

Studies have provided support for melancholic depression as a unique subtype of depression (Ambrosini, Bennett, Cleland, & Haslam, 2002; Haslam & Beck, 1994). The identification of unique symptom based indicators has included loss of satisfaction, appetite, weight, and libido (Haslam & Beck, 1994), as well as preoccupation with health and social anhedonia (Beach & Amir, 2003). The identification of these symptom based indicators via taxometric analysis provides support for the categorically discrete nature of melancholic depression (Leventhal & Rehm, 2005).

Atypical Depression

Atypical depression was first identified by West and Dally in 1959 as a distinct subtype of depression that responded better to a class of antidepressant medications called monoamine oxidase inhibitors (MAOIs) (West & Dally, 1959). They observed that depressed patients with atypical symptoms experienced a rapid response to the MAOI medication iproniazid. These individuals experienced a significant increase in energy and decrease in anxiety, despite failing previous antidepressant treatments, including tricyclic antidepressants (TCAs) and electroconvulsive therapy (ECT). In the following decades, research continued to support the concept of atypical depression while

also helping to identify additional symptoms or characteristics unique to atypical depression (Hordern, 1965; Klein, 1967; Sargant, 1960).

Atypical depression was formally defined in the DSM-IV (American Psychiatric Association, 1994), and the current diagnostic criteria includes the occurrence of mood reactivity, which is defined by an individual's ability to respond emotionally to positive environmental events, plus two or more additional symptoms (American Psychiatric Association, 2000). The two additional symptoms can include increased appetite, weight gain, hypersomnia, leaden paralysis, or a pervasive pattern of interpersonal rejection sensitivity. Atypical depression is one of the most common forms of depression in outpatient psychiatric clinics (Singh & Williams, 2006). Studies have reported prevalence rates for atypical depression from 16.7% to 27.7% (Benazzi, 2003b; Novick, et al., 2005; Sullivan, Kessler, & Kendler, 1998; Thase, 2007). Atypical depression is also more likely to occur in females and to have an earlier age of onset relative to other forms of depression (Angst, Gamma, Sellaro, Zhang, & Merikangas, 2002; Horwath, Johnson, Weissman, & Hornig, 1992; Pae, Tharwani, Marks, Masand, & Patkar, 2009; Stewart, McGrath, & Quitkin, 2002).

Catatonic Depression

The symptom profile necessary to diagnosis catatonic features can be applied to either unipolar or bipolar depression, and can occur during a major depressive, manic, or mixed episode (American Psychiatric Association, 2000).

The specifier With Catatonic Features is characterized by motoric immobility, excessive motor activity, extreme negativism, peculiarities of voluntary movement, echolalia, or echopraxia. Two or more of these symptoms must be present to diagnose major depression with catatonic features. Although catatonia is usually associated with schizophrenia, most catatonic episodes occur in the context of mood disorders (M. A. Taylor & Fink, 2003). A prevalence rate of 20% has been reported for individuals with depression and catatonic features (Hung & Huang, 2006; Starkstein, Petracca, Teson, Chemerinski, & et al., 1996).

Postpartum Depression

The specifier of Postpartum Onset can be applied to a depressive, manic, or mixed episode that develops within four weeks after childbirth (American Psychiatric Association, 2000). The diagnostic criteria for MDE with postpartum onset are identical to MDE with a non-postpartum onset. Thus, within four weeks after childbirth the patient would need to experience a symptomatic period of at least two weeks in which there is either depressed mood or anhedonia plus a minimum of four additional depressive symptoms (American Psychiatric Association, 2000). Non-diagnostic symptoms/features that frequently occur during mood episodes with a postpartum onset include fluctuations in mood, mood lability, and preoccupation with infant well-being (O'Hara, 2009).

Hypothesized Subtypes of MDD

Anxious depression and psychotic depression represent two hypothesized subtypes of MDD (Rush, 2007). Because there is debate as to whether these represent subtypes of MDD or different diagnostic conditions, a more in-depth review of these depressive disorders will be provided. In this review, anxious depression and psychotic depression will be described as distinct subtypes of depression due to research suggesting each to have a different symptom presentation, onset, profile, and course of illness (Rush, 2007). Treatment-resistant depression represents a potentially third subtype of MDD. Given that TRD is the primary focus of this study, a more detailed description of TRD will be provided in the following chapter.

Anxious Depression

Anxious depression has been proposed as an additional subtype of MDD. Although specific diagnostic criteria for anxious depression has yet to be established, a collection of studies and clinical observations have demonstrated it to have a unique set of clinical features, course of illness, and treatment outcome (M. Fava, et al., 2006; Rao & Zisook, 2009; Rush, 2007; Seo, et al., 2011). Within the literature anxious depression has been conceptualized or defined in one of two ways: 1) MDD with a comorbid anxiety disorder, or 2) MDD with significant anxiety related symptoms (Rao & Zisook, 2009; Rush, 2007). The second definition is more commonly used (Rao & Zisook, 2009) and involves the

use of a dimensional rating scales with set threshold score to determine the presence of anxiety.

Independent of how anxious depression is defined, studies comparing individuals with anxious depression to those with non-anxious depression have found it to be associated with increased risk of functional impairment, suicide attempts and lengthier course of illness (Joffe, Bagby, & Levitt, 1993; Kessler, et al., 1994). Studies have also demonstrated that anxious depression is associated with a higher degree of treatment resistance (Kennedy, 2008), lower response rates (M. Fava, et al., 1997), and less satisfactory response to treatment (M. Fava, et al., 2008).

Psychotic Depression

Psychotic depression is characterized by the presence of either delusions or hallucinations that occur during a MDE (American Psychiatric Association, 2000). While the DSM-IV-TR includes psychotic features as an indication of disease severity, research suggest that it is a unique subtype (Schatzberg & Rothschild, 1992). Psychotic symptoms are classified as either mood-congruent or mood-incongruent based on the theme or content of these symptoms. In most cases, the experienced delusions or hallucinations are mood-congruent and involve themes of self-depreciation and self-punishment (Sadock, et al., 2009). Additional mood-congruent psychotic features involve delusions characterized with nihilistic, somatic, and impoverished themes. Although less common,

individuals can experience mood-incongruent psychotic features during a MDE. Non-congruent psychotic symptoms are absent of any depressive themes but can include delusions of persecution, thought insertion, thought broadcasting, and delusions of control.

An accumulation of data and clinical observations suggests that psychotic depression may in fact represent a distinct diagnostic condition versus just a specifier of depression severity (Sadock, et al., 2009). The presence of psychotic features during a MDE has been associated with higher treatment resistance and a worse overall prognosis or rates of remission (Gournellis & Lykouras, 2006; Schatzberg & Rothschild, 1992). Individuals experiencing psychotic depression have also demonstrated reduced neurocognitive functioning compared to individuals diagnosed with non-psychotic depression (S. K. Hill, Keshavan, Thase, & Sweeney, 2004; Jeste, et al., 1996).

The presence of psychotic symptoms during a MDE has important and distinct implications for determining treatment recommendations. Although the use of a single antidepressant is recommended for psychotic depression with less severity, medication trials that combine antidepressants and antipsychotics are considered a superior treatment option (Wheeler Vega, Mortimer, & Tyson, 2000). Electroconvulsive therapy (ECT) is considered one of the most effective treatments for psychotic depression (Gill & Lambourn, 1979; Swartz, 2009; Weiner, 2001). Response rates of 95% have been reported for patients diagnosed

with MDD and psychotic features (Husain, et al., 2004; Petrides, et al., 2001). Comparison studies have found ECT to be more effective in the treatment of psychotic depression compared to combined antidepressant and antipsychotic medication trials (Kroessler, 1985; Parker, Roy, Hadzi-Pavlovic, & Pedic, 1992).

SECTION III – COMPREHENSIVE LITERATURE REVIEW OF TREATMENT RESISTANT DEPRESSION

TRD Introduction

Given the significant prevalence rates and debilitating nature of major depressive disorder (Kessler, et al., 2003; World Health Organization, 2001), a considerable amount of effort has been spent in the development, study, and implementation of effective psychiatric treatments for depression. As the current fourth leading cause of disability, and the likelihood of becoming the second most disabling condition by the year 2020 (Amital, et al., 2008) the development of effective antidepressant treatments represents a beneficial goal for those suffering from depression and society as a whole. Effective treatments for depression that have been empirically studied include psychotherapy, psychopharmacological medication, and neurostimulation modalities.

The development of a broad range of antidepressant treatments also reflects a significant increase in the overall understanding of depression. However, despite these previous strides, a significant number of individuals diagnosed with MDD remain unable to achieve or maintain a satisfactory response to multiple antidepressant treatment (M. Fava, 2003; M. Fava & Davidson, 1996; Nierenberg & Amsterdam, 1990; Souery & Van der Auwera, 2004). Individuals suffering from depression, who are unable to achieve an adequate therapeutic response despite completing multiple antidepressant trials,

are commonly referred to as experiencing treatment-resistant depression (TRD) (Berman, et al., 1997; Fagiolini & Kupfer, 2003; M. Fava, 2003; Sackeim, 2001; Sharan & Saxena, 1998). Given the minimal role non-psychopharmacological antidepressant treatments serve in determining or describing treatment resistance (Berlim & Turecki, 2007a; M. Fava, 2003) the terms *antidepressant treatment*, *antidepressant trial*, and *antidepressant strategies* predominately refer to antidepressant pharmacological agents or electroconvulsive therapy (ECT).

Chapter 5: Prevalence and Impact of Treatment Resistant Depression

Prevalence of Treatment Resistant Depression

Determining the number of patients suffering from TRD is an arduous task because no consensus regarding its definition currently exists (M. Fava, 2003; Keller, 2005). An in-depth review of the various factors that have contributed to the ongoing debate regarding how to define and measure TRD will be discussed later in this chapter. Within the literature, prevalence rates for TRD are typically described in terms of the number of patients who fail to respond to antidepressant medication and the number of patient who continue to experience residual depression related symptoms following an antidepressant treatment.

Failure to Respond to Medication Prevalence Rates

The concept of a medication failure is commonly used to determine and describe the prevalence rate of TRD. The concept of a medication failure as it applies to TRD is described as the occurrence of an inadequate or insufficient clinical response following the completion of an antidepressant treatment, which was administered at an adequate dose and for an adequate length of time (Berman, et al., 1997; M. Fava, 2003; Kornstein & Schneider, 2001). Describing TRD in terms of medication failures is widely accepted in the literature and clearly emphasizes the underlying principle of treatment resistance. This description of TRD does not clearly outline what constitutes an inadequate or insufficient clinical response; however, a reduction in baseline symptom severity greater than

or equal to 50% is commonly accepted in efficacy trials for antidepressant treatments (Rush, et al., 2006; Souery, et al., 1999). Although similar guidelines are currently used to measure treatment response for TRD patients, it has been suggested that a greater reduction in symptom severity should be used to determine treatment response for TRD patients (Rush, Thase, & Dube, 2003).

Studies have reported that 30% to 50% of patients diagnosed with MDD fail to respond to an initial antidepressant trial of adequate dose and duration. Although most patients will respond to additional antidepressant trials or other adjustments in medication, a significant number of patients fail to achieve any significant decrease in the severity of their depressive symptoms. Multiple studies have found that approximately 20% of depressed patients continued to suffer from depression for up to two years following their initial onset (Keller, Shapiro, Lavori, & Wolfe, 1982; Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005; Paykel, 1994). Despite the completion of multiple antidepressant medication treatments and more aggressive treatment regimens, 15% of patients diagnosed with MDD will continue to suffer from depression (Berlim & Turecki, 2007a).

Presence of Residual Symptoms and Prevalence Rates

Although some patients will report a significant reduction in their depressive symptoms following an adequate antidepressant trial, many of these patients will continue to experience a considerable degree of residual depressive

symptoms. Residual depressive symptoms refer to the continued presence of depressive symptoms, despite responding to an adequate short-term treatment such as antidepressant medication or psychotherapy (G. A. Fava, Ruini, & Belaise, 2007; McClintock, et al., 2011; Paykel, 2009; Paykel, et al., 1995). Although a short-term treatment can include any antidepressant intervention, studies of residual depressive symptoms typically involve the use antidepressant medication (G. A. Fava, et al., 2002; Nierenberg, et al., 2010; Nierenberg, et al., 1999). The focus on residual depressive symptoms is due to the relationship between residual depressive symptoms and the risk of relapse. A study conducted by Paykel et al. (1995) found that the presence of residual depressive symptoms was associated with an increased risk of relapse for 76% of their study patients (Paykel, et al., 1995).

Among patients diagnosed with MDD, 12% to 15% will experience a partial response and, therefore, will continue to experience a significant degree of depressive symptoms following the completion of an adequate antidepressant trial (M. Fava & Davidson, 1996). The prevalence rate for patients who fail to obtain a complete remission of their depressive symptoms has been reported at 60% to 70% (Nierenberg, et al., 2010; O'Reardon & Amsterdam, 1998; Souery & Van der Auwera, 2004). Although the goal of a complete remission of all depressive symptoms would be ideal, it is unclear whether such a high standard should be

adopted to determine the prevalence rate of TRD or to classify depressed patients as treatment resistant.

Impact of Treatment Resistant Depression

The debilitating nature of MDD has been found to negatively impact both individual patients suffering from depression and society as a whole. Evidence suggests that TRD may represent the most disabling type of MDD, and that the cost of treating TRD patients represents half of the annual cost associated with the treatment of depression (Greden, 2001; Rost, Zhang, Fortney, Smith, & Smith, 1998). The impact of TRD includes sustained patient burden from continued disease illness, psychological distress, societal burden due to decreased productivity, and the cost and continuous demands placed on psychiatric services.

Individual Burden

Although few studies have systematically examined the extent to which TRD impacts individual patients diagnosed with MDD, the debilitating nature of MDD and the chronic nature of treatment-resistance suggests that TRD may be the most debilitating or distressing form of MDD. This has been supported based on the limited studies conducted and other indirect evidence regarding the personal impact or burden frequently reported in TRD patients (Greden, 2001). Of the few studies examining the impact of TRD, a study conducted by Petersen et al. (2004) used the Longitudinal Interval Follow-up Evaluation (LIFE) to assess psychosocial functioning in TRD patients (Petersen, et al., 2004). The LIFE

provides a means of recording the retrospective and prospective course of an illness and related treatments (Keller, et al., 1987). The LIFE also includes a measure of psychosocial functioning that is designed to measure domains of work, interpersonal relations, sexual functioning, and overall satisfaction and recreation. Peterson et al. (2004) found that TRD patients experienced mild impairment in their ability to enjoy sexual activity, mild to moderate impairment in work-related activities, poor level of involvement in recreational activities, and poor global social functioning. An interesting finding was the tendency for both patients and clinicians to rate global ratings as more impaired relative to specific functional areas. Additional research is needed to fully understand the negative impact of TRD on specific and global aspects of psychosocial functioning.

Societal Burden

The impact of TRD also represents a societal burden in the form of decreased productivity, increased cost of treatment, and continuous demands placed on psychiatric services. The cost to receive and provide adequate treatment for TRD patients represents a much greater financial burden compared to the cost of treatment for non-TRD patients. In fact, 50% of the annual cost associated with the treatment of depression is due to TRD (Rost, et al., 1998). This figure is especially striking given that TRD patients only account for 15 to 30% of patients undergoing psychiatric treatment for depression (Burrows, Norman, & Judd, 1994; Ros, Aguera, de la Gandara, & de Pedro, 2005). A study

that examined the health care expenditures and changes in antidepressant medication regimens of TRD patients found that overall health care expenditures (depression and medical related) increased in concordance with the degree of treatment resistance (Russell, et al., 2004).

Further evidence of the considerable cost associated with TRD compared to non-TRD has been shown in retrospective studies of medical claims for depression related treatments or services. Studies that compared health care expenditures and medical claims for employees of large Fortune 100 companies in the US found that depression-related and general medical costs were significantly higher for depressed individuals classified as treatment-resistant (Corey-Lisle, Birnbaum, Greenberg, Marynchenko, & Claxton, 2002; Crown, et al., 2002; Greenberg, Corey-Lisle, Birnbaum, Marynchenko, & Claxton, 2004). The average cost of health care services for individuals classified as *TRD-likely* was reported to range from $10,954 to $14,490 per year, which was significantly higher compared to the $5,025 to $6,665 reported for those classified as depressed but *TRD-unlikely* (Corey-Lisle, et al., 2002; Greenberg, et al., 2004).

Regarding the utilization of services, patients classified as TRD were twice as likely to be hospitalized and had 12% more outpatient visits compared to non-TRD patients (Crown, et al., 2002). TRD patients also used between 1.4 to 3 times more psychotropic medications, which was significantly greater compared to non-TRD patients. Individuals classified as *TRD-likely* used approximately

twice as many medical services then individuals classified as depressed but *TRD-unlikely* (Corey-Lisle, et al., 2002; Greenberg, et al., 2004).

The above results provide clear evidence of the considerable economic cost, societal burden, and personal distress caused by TRD (Greden, 2001; Hirschfeld, et al., 1997; Keller, 2005). The disproportionate cost of TRD compared to other forms of depression supports the need for additional research regarding the etiology, course, and impact of TRD. This research is needed to assist in the development of effective psychiatric therapeutic interventions (Petersen, et al., 2004). However, the primary factor that has continued to limit the understanding of TRD is the lack of consensus regarding its definition and measurement. This lack of expert consensus will be highlighted by the various models and definitions of TRD that are reviewed in the next chapter.

Chapter 6: Defining and Measuring Treatment Resistant Depression

Defining Treatment Resistant Depression

The psychiatric literature involves a considerable amount of variability in the definition and measurement of TRD. The general concept of TRD is described as the lack of a response to an adequate trial of medication or other treatment intended to provide an adequate level of relief from depressive symptoms (Bird, et al., 2002; M. Fava, 2003). Although this definition provides a general guideline for how to potentially define and measure TRD, no universal specific guideline or standard regarding how to operationally define and measure TRD currently exists (Berlim & Turecki, 2007a; Berman, et al., 1997). This lack of consensus has been perpetuated by the ongoing debate regarding how to define key aspects of TRD including terminology, number and type of failed treatments, adequacy of treatments (dose and duration), and how to measure or determine treatment failures (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Souery, et al., 1999). Although specific guidelines have not been adopted, two methods have been proposed as a means of defining and measuring TRD severity. These two methods include 1) examining medication failure (Souery 1999), and 2) the use of staging models (Souery, et al., 2006).

Medication Failure Method of Treatment Resistant Depression

The number of previously failed medication treatments is commonly used to classify a patient as having TRD (Souery 1999). This method involves

determining the number and type of medication treatments a patient has previously received, and how the patient responded following an adequate course of treatment. This approach of characterizing TRD is almost exclusively reserved for clinical research involving psychopharmacological treatments. Although using the number and type of failed medication trials to define TRD clearly captures the treatment resistant aspect of TRD, no set guidelines regarding the number and type of treatment failures needed to define TRD exists (Souery, et al., 2006; Souery & Van der Auwera, 2004).

As reported by Berlim and Turecki (2007a), multiple guidelines have been proposed by various psychiatric researchers as a means of identifying and defining the categorical presence of TRD. These proposed guidelines included a failure to respond to an adequate dose of the following: a single tricyclic antidepressant (TCA); MAOI; a single adequate antidepressant treatment; 3 or more adequate trials of treatment including at least one TCA; 5 or more adequate treatments; at least one trial of ECT; and a single trial of the newer heterocyclic antidepressant. As these examples highlight, the general guidelines used in the various proposed definitions of TRD are based on (1) the number of antidepressant treatments completed, (2) the type of antidepressant medication completed (class of drug), or (3) some consideration for both the number and type of medication treatment completed (Souery, et al., 2006; Souery & Van der

Auwera, 2004). The primary limitation of using the medication failure method is the approaches and proposed guidelines lack evidentiary support.

Despite the lack of any well studied and validated definition of TRD, it is generally accepted that a patient who fails to respond to at least two adequate trials of antidepressant medications from different classes is considered to have some degree of treatment resistance (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003). Although the wide acceptance of this description for TRD provides some sense of direction in the identification of TRD, two methodological limitations have emerged from this description (M. Fava, 2003; Janicak & Dowd, 2009). First, this approach is based on the assumption that patients who fail to respond to two antidepressant medications from different classes of drugs are more treatment resistant or difficult to treat than patients who fail to respond to two antidepressant medications from the same class of drug. Second it assumes that changing antidepressant medications within the same class of drug is less effective than switching to an antidepressant medication from a different class. The various limitations that have emerged from defining TRD based on a simple review of the number and type of failed treatments has led to the development of different methods of rating and measuring TRD.

Staging Model Methods of Treatment Resistant Depression

The development of staging model methods have also been proposed as a means of describing and measuring treatment resistance for patient diagnosed with MDD. The staging methods of TRD are based on similar guidelines included in the previous definitions of TRD described above. However, a main difference involves the application of these staging methods as not only measures of TRD, but also of TRD severity.

These staging methods are designed to measure and rate the level of treatment resistant severity rather than simply identifying the categorical presence of TRD. This is based on the idea that greater treatment resistance is associated with a higher number of failed antidepressant treatments (Bird, et al., 2002; Fagiolini & Kupfer, 2003; M. Fava, 2003; Souery, et al., 1999). Therefore, a patient's level of treatment resistant severity, which is based on their response to previous antidepressant treatments, can be used to predict their likelihood of responding to additional antidepressant treatments (Rush, Thase, et al., 2003).

Some of the proposed staging methods also consider the use of augmentation and combined antidepressant treatment strategies (Fekadu, Wooderson, Donaldson, et al., 2009; Petersen, et al., 2005). Augmentation strategies refer to the concomitant use of a medication that is not considered a standard antidepressant treatment, but is used to enhance the efficacy of a known antidepressant drug (Carvalho, et al., 2007). Commonly used augmentation

strategies include adding an anticonvulsant, antipsychotic, or lithium to a current antidepressant medication (Barowsky & Schwartz, 2006). A combined treatment strategy involves the combined use of two or more antidepressant drugs (e.g. fluoxetine plus mirtazapine) (M. Fava, 2001). Given that augmentation and combination treatment strategies are consistently recommended and used as a treatment option for TRD, their inclusion in a measure of treatment resistant severity may result in a more comprehensive measure (Barowsky & Schwartz, 2006; Carvalho, Machado, & Cavalcante, 2008; Howland, 2006; Pridmore & Turnier-Shea, 2004).

The two primary limitations of the various proposed models for staging TRD involve the lack of empirical testing needed to validate these methods and the continued debate regarding how to operationally define key aspects of TRD (Berlim & Turecki, 2007a; O'Reardon & Amsterdam, 1998; Souery, et al., 2006). A lack of consensus continues to exist regarding how to define adequacy of treatments (dose and duration), and how to define a treatment response or failure (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Souery, et al., 1999). Despite these limitations, multiple TRD staging models have been developed.

Thase and Rush Staging Method

The Thase and Rush Staging Method (Thase & Rush, 1997) consists of five levels of treatment resistance, with higher levels representing greater levels of resistance (see Table 3). The application of this staging method involves

stratifying patients diagnosed with MDD based on the number and type of antidepressant medications and ECT that have been identified as treatment failures. Based on the guidelines outlined for the Thase and Rush Staging Method, only failed antidepressant medication trials of adequate dose and duration can be used to determine a patient's level of treatment resistance severity. The progression to higher levels of treatment resistance involves a progression from the more commonly used antidepressant treatments, such as selective serotonin reuptake inhibitors (SSRIs), to less frequently used antidepressant treatments (e.g. MAOIs).

Insert Table 3 here

Although the Thase and Rush Staging method does provide a systematic approach to the classification of TRD severity, certain limitations are present in this staging method. The Thase and Rush Staging Method involves the indirect implication of a hierarchy toward antidepressant medication efficacy, which suggests that SSRIs are less effective then TCAs, and that SSRIs and TCAs are less effective than MAOIs (Berlim & Turecki, 2007a). Additional limitations of the Thase and Rush Staging Method involve the exclusion of certain treatment and clinical factors related to treatment resistance. Treatment and clinical factors not considered in this staging method include: intensity and optimization of dosage and duration; use of augmentation and combined treatment strategies;

symptom severity, and illness duration (M. Fava, 2003). Also, the predictive value of the Thase and Rush Staging Method has not been comprehensively evaluated in clinical trials (Bird, et al., 2002).

Massachusetts General Hospital Staging Method

The Massachusetts General Hospital Staging Method (MGH-S) (Petersen, et al., 2005) was designed with the intent of addressing some of the limitations of the Thase and Rush Staging Method. As with the Thase and Rush Staging Method, the MGH-S also stages treatment resistance severity based on the number of previously failed antidepressant trials, with a higher number of failed medications representing greater treatment resistance. However, the MGH-S staging method considers the intensity and optimization of each previous treatment by including an evaluation of dose and duration. The MGH-S assigns points for each antidepressant trial based on certain criteria or details regarding each treatment (see Table 4). The MGH-S also assigns points based on combined treatment and augmentation strategies, and does not imply a hierarchy of efficacy regarding the various classes of antidepressant medications. This approach provides a continuous variable that represents the level of treatment resistance.

Insert Table 4 here

The validity of the MGH-S was demonstrated in a small scale study that compared the MGH-S to the Thase and Rush Staging Method (Petersen, et al.,

2005). That study found a significant positive correlation between the MGH-S and the Thase and Rush Staging Method. Further analysis also found that the MGH-S scores had a significantly greater ability to predict non-remission compared to the Thase and Rush Staging Method. The authors concluded that a continuous scoring system may be superior to the 5 level staging method used in the Thase and Rush Staging Method (Petersen, et al., 2005). Although these results are encouraging, the generalizability of these findings are limited due to certain methodological factors (e.g. small sample size, reliance on data derived from a chart review). Additionally, it is unclear how the MGH-S guidelines were determined for assigning points (Berlim & Turecki, 2007a).

European Staging Method

The European Staging Method (Souery, et al., 1999) includes both a classification and staging approach to TRD. Patients can be classified as Non-responders, experiencing TRD, or as experiencing Chronic Resistant Depression (CRD). As with the previously described TRD staging methods, the European Staging Method also requires an evaluation of previous antidepressant treatments and treatment response. Depressed patients who have failed to respond to one antidepressant medication of adequate dose and duration are classified as Non-responders to that class of medication (SSRI, TCA, MAOI, etc.). Based on the European Staging Method, patients are considered treatment resistant after failing to respond to two trials of different antidepressants of adequate dose and duration.

An adequate duration is defined by taking an antidepressant medication at an adequate dose for a period of six to eight weeks. After a classification of TRD has been established, the staging of TRD severity is based on the number of additional failed antidepressant medications. The European Staging Method provides consideration for the prolonged duration or chronic nature associated with TRD. Patients who have experienced a MDE for over a year, despite completing several antidepressant trials of adequate dose and duration, are classified as having CRD (see Table 5).

Insert Table 5 here

The two main features of the European Staging Method that are absent from other staging methods are (1) the establishment of a required minimum number (two) of failed antidepressant medications to classify a patient as having TRD, and (2) the consideration given to the chronic nature of TRD (Berlim & Turecki, 2007a; Souery, et al., 1999). Although a single failed treatment may represent some degree of treatment resistance (Souery, et al., 1999), requiring two failed antidepressant medications from different classes is generally accepted in the psychiatric literature as more representative of TRD (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003). Despite these added benefits, the European Staging Method does not address symptom severity or medication augmentation strategies.

Maudsley Staging Method

The Maudsley Staging Method (MSM) was developed as an attempt to address the various limitations in the previously described TRD staging methods (Fekadu, Wooderson, Donaldson, et al., 2009). The guiding principle in the development of the MSM was that treatment resistances occurs as a continuum, and is greatly influenced by various dimensional factors. Based on this description, the MSM was developed as multidimensional staging method for TRD that incorporates various treatment and clinical factors. The treatment factors incorporated in the MSM include number of treatment failures, use of augmentation treatment strategies, and use of ECT. Regarding clinical factors, the MSM includes illness duration and symptom severity in the staging process for TRD (see Table 6).

Insert Table 6 here

As with other staging methods, the MSM only considers antidepressant medication trials, including augmenting strategies, of adequate dose and duration to determine the total number of treatment failures (Fekadu, Wooderson, Donaldson, et al., 2009). A higher number of failed treatments of adequate dose and duration is generally viewed as representing a greater degree of treatment resistance (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; M. Fava, 2003; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003; Souery, et

al., 1999). The MSM does not differentiate between treatment failures of different medication classes, nor does it hierarchically arrange medication classes. Thus, the MSM does not make assumptions regarding the efficacy of antidepressant medication based on class. This is in contrast to the Thase and Rush Staging Method (Thase & Rush, 1997), which tacitly implies that SSRIs are less effective than TCAs, and that SSRIs and TCA are less effective than MAOIs (Berlim & Turecki, 2007a). The inclusion of depression severity and duration accounts for the nature and course of the patient's depression. Symptom severity and illness duration have both been associated with non-response to treatment and the persistence of depressive symptoms (Blom, et al., 2007; Katon, et al., 1994; McGrath, et al., 2006; Mynors-Wallis & Gath, 1997; Rubenstein, et al., 2007).

Although research using the MSM is limited, two small-scale studies have produced promising results regarding the predictive validity of this TRD staging method. The initial study that developed and tested the MSM involved a case review of a small set of TRD patients (N = 88), who were recently discharged from an inpatient unit that specialized in treatment resistant mood disorders (Fekadu, Wooderson, Donaldson, et al., 2009). Treatment resistance was independently predicted by all three factors (number of treatment failures, severity, and duration) that comprise the MSM. Overall, the MSM predicted treatment resistance in 85.5% of the study sample. Similar results were also demonstrated in a study that examined the long-term outcome of TRD patients

based on length of depressive episode and level of functional impairment (Fekadu, Wooderson, Markopoulou, & Cleare, 2009). The study found the MSM to have had reasonable predictive validity for TRD patients, and that higher MSM scores were associated with the persistence of MDE. Despite limited large-scale research trials and validation studies of the MSM, initial results have been promising. The MSM may represent a more comprehensive approach to the staging of TRD.

The development of TRD staging models has been an important step toward developing a more systematic method of defining TRD and measuring treatment resistant severity. Of the various TRD staging models that have been developed many have attempted to address the various limitations of simply looking at the number of previous antidepressant treatment failures. Newly developed staging models have continued to address various limitations of previous staging models, which has been encouraging given the comprehensive and complex nature of TRD. Although TRD staging models represent a potentially more comprehensive measure of TRD, few large scale studies have been conducted to validate any one staging model (Berlim & Turecki, 2007a; O'Reardon & Amsterdam, 1998; Souery, et al., 2006). Many of the factors that have contributed to the limited number of large-scale TRD studies involve the lack of consensus regarding how to define key aspects of TRD (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Souery, et al., 1999). An understanding

of the difficulty conducting TRD research is a necessary process before any attempt can be made to define, measure, or differentiate TRD.

Chapter 7: Studying Treatment Resistant Depression

The Difficulty Defining Treatment Resistant Depression

The general concept of TRD is described as the lack of a response to an adequate trial of medication or other treatments intended to provide an adequate level of relief from depressive symptoms (Bird, et al., 2002; M. Fava, 2003). However, beyond this general description, there is no standardized and universally accepted definition or criteria for TRD (Berlim & Turecki, 2007a; Berman, et al., 1997). The difficulty establishing a universally accepted definition for TRD is due to the considerable amount of variability in the psychiatric literature regarding specific aspects of TRD. For example, few guidelines have been widely adopted regarding the number and type of failed treatments, adequacy of treatments (dose and duration), and how to measure or determine treatment failures (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Souery, et al., 1999).

Number and Type of Failed Medication Trials

The number of failed antidepressant medication trials is generally considered a measure of TRD, with a higher number of medications failed representing a greater degree of treatment resistance (Souery, et al., 1999). The concept of treatment resistance also suggests a need for patients to demonstrate resistance to antidepressant medications across different classes (e.g. SSRIs, TCAs, and MAOIs). Despite a consensus in the literature, in which the number

and type of failed treatments is considered a measure of TRD, at this time, specific guidelines are not widely accepted regarding the number and class of failed treatments required to distinguish between treatment and non-treatment resistance (Berlim & Turecki, 2007b; O'Reardon, Brunswick, & Amsterdam, 2000; Souery, et al., 1999; Souery & Van der Auwera, 2004).

Of the multiple guidelines that have been proposed, the failure of two adequate trials of antidepressant medications from different classes is generally considered to reflect some degree of treatment resistance (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003). Although the idea of two treatment failures from different classes of medications provides a logical direction in the conceptualization of TRD, this approach has three methodological limitations (M. Fava, 2003; Janicak & Dowd, 2009). First, it is based on the assumption that patients who fail to respond to two antidepressant medications from different classes are more treatment resistant than patients who fail to respond to two antidepressant medications from the same class. Second, it assumes that changing antidepressant medications within the same class is less effective than switching to an antidepressant medication from a different class. Third, it does not consider the role of augmenting agents, which are commonly recommended and used treatment strategies for TRD.

Determining a Failed Medication Trial

Impedance toward the development of an operational definition of TRD involves the concept of a failed treatment. Although the number of failed antidepressant treatments is widely considered a result and measure of TRD, within the literature there is currently a lack of consensus regarding the definition of a "failed" treatment (Keller, 2005). The current method within a clinical research setting to determine if a treatment has failed is based on the presence and severity of various depressive symptoms following an adequate treatment course. Depressive symptoms are generally measured with the use of a standardized and validated depression rating instrument (e.g. HRSD, IDS).

Although depression symptom severity measures are useful in determining how a particular treatment affected a patient's level of depression severity, there is currently a debate regarding what degree of change in depression scores should be used to differentiate a failed treatment from a successful treatment (Berlim & Turecki, 2007a; Keller, 2005). This debate has introduced the concept of "response" and "remission," terms commonly used in clinical research. The concept of response is generally defined as a 50% reduction in depressive symptom severity; however, the concept of remission lacks an empirically validated definition (Keller, 2005; Nierenberg & DeCecco, 2001; Rush, et al., 2006). Some researchers have described remission as complete absence of depressive symptoms (Nierenberg & DeCecco, 2001), while others have proposed specific cutoff scores for the various depression rating instruments (Rush, et al.,

2006). Consequently, the idea of using a specific cutoff score versus an overall percent based reduction also introduces the issue in deciding which depression rating measure should be used to define remission.

Based on a review of the TRD literature, there is a debate regarding whether to use the definition of response or the criteria of remission when determining a failed treatment. The primary argument against a response based criteria for determining a treatment failure involves the issue of residual depressive symptoms (Bird, et al., 2002; Kornstein & Schneider, 2001; Nierenberg & DeCecco, 2001). Although a 50% reduction in depressive symptoms demonstrates a substantial improvement, it is unclear if this accurately represents a successful treatment. A 50% reduction in depressive symptoms may be less relevant or clinically significant for patients with extremely high depression scores at baseline (Bird, et al., 2002). However, it is also difficult to classify any treatment responsible for such a sizable reduction in depressive symptoms as a failure. In fact, for TRD some researchers have postulated that a lower overall reduction in depressive symptoms (25% to 40%) is sufficient to represent a meaningful clinical response (Ananth, 1998; Rush, et al., 2006).

The Difficulty Identifying Treatment Resistant Depression

Psychiatric Treatment History

Regardless of the definition used to define or measure TRD, a comprehensive review of a patient's psychiatric history must be performed to aid in the classification of TRD. Both researchers and clinicians are encouraged to

review previous antidepressant medication history (Kornstein & Schneider, 2001). As one might assume, a thorough review of a patient's antidepressant treatment history can be quite cumbersome for a variety of reasons. This is especially true for patients who have completed multiple medication trials and have a more extensive treatment history.

The task of determining whether a patient's previous antidepressant treatments were of adequate dose and duration requires obtaining and reviewing a considerable and often impractical amount of information. A patient's records must contain sufficient details regarding start and stop dates for each psychiatric medication trial, as well as the date of any dose modifications (Bird, et al., 2002). The task of reviewing a patient's previous psychiatric treatment history in order to determine the total number of failed treatments of adequate dose and duration is further complicated by variations in record keeping, insufficient data regarding duration and dosage, and a limited description regarding treatment response. For patients with a chronic form of depression and those suspected of having TRD, a complete review of their treatment history may involve requesting multiple psychiatric and medical records from a variety of medical settings such as family practitioners, community and specialty clinics, psychiatrists in private practice, psychiatric facilities, pharmacies, and general medical centers.

Pseudoresistance

Due to the difficulty in obtaining and verifying medication history, and the variation in clinical practice regarding prescription guidelines, multiple

antidepressant trials maybe inaccurately classified as failed despite completion of an inadequate trial (Berlim & Turecki, 2007a; Souery, et al., 2006). Studies have indicated that a considerable number of patients with a diagnosis of MDD are routinely under treated and prescribed antidepressant medications of inadequate dose (Hirschfeld, et al., 1997). Findings from community-based survey research suggested that approximately 50% of patients diagnosed with depression have been treated with antidepressants of inadequate dose or duration (Bird, et al., 2002; O'Reardon & Amsterdam, 1998). The sub-therapeutic dosing of antidepressant medications has been referred to as the primary reason for a non-response or treatment failure (Berlim & Turecki, 2007a; Bird, et al., 2002).

Factors that contribute to the frequent sub-therapeutic dosing of antidepressant medications can be categorized as physician-related, patient-related or medication related. Physician related factors include: prescribing an antidepressant medication at an inadequate dose or duration, misdiagnosing of the primary psychiatric disorder, and the limited training non-psychiatric physicians receive regarding depression (Hirschfeld, et al., 1997; Souery, et al., 2006). Patient related factors include: treatment noncompliance, underreporting symptom severity, and limited access to mental health services due to financial restraints (Berlim & Turecki, 2007a; Kornstein & Schneider, 2001). Medication related factors include: intolerable side effects and the concomitant use of medications that increase the metabolism and elimination of antidepressant medications (i.e. reduction in antidepressant blood levels) (M. Fava, 2003).

Due to the frequent misclassification of depressed patients as experiencing TRD, a focus has been brought to the phenomenon of *pseudoresistance* (Kornstein & Schneider, 2001). The term pseudoresistance refers to the non-response of an antidepressant treatment administered at an inadequate dose and/or duration (Nierenberg & Amsterdam, 1990). Regarding the number of patients initially classified as experiencing TRD, evidence has suggested that approximately 60% of these patients were misclassified and actually experienced pseudoresistance (Berman, et al., 1997; M. Fava, 2003). Although many of the factors that contribute to pseudoresistance involve inadequate dosing and/or duration due to premature discontinuation of an antidepressant trial, patient noncompliance has emerged as an additional factor to the misclassification of TRD. As with other psychiatric and medical conditions that require medication management, treatment adherence or noncompliance is also a concern for TRD patients. Treatment non-adherence has been estimated to account for approximately 20% of the treatment resistance in patients with MDD (Kornstein & Schneider, 2001; Souery, et al., 1999). Given that poor treatment adherence can result in inadequate dosing and duration, as well as a diminished clinical response, these patients may be more accurately described as experiencing pseudoresistance.

SECTION IV – RATIONALE, PURPOSE, AIMS AND HYPOTHESES

Chapter 8: Rationale for Current Proposal

The Rationale for Defining and Differentiating TRD

As with most diseases, effective treatment can only be developed and/or further refined through a comprehensive understanding of the etiology and progression of the condition. However, in order to conduct the type of empirical research needed to achieve this degree of understanding, it is first necessary to develop an accurate method of defining and measuring TRD, as well as a reliable means of differentiating between TRD and non-TRD.

The Negative Impact of TRD

Prevalence studies conducted in the US and internationally have repeatedly demonstrated the high prevalence, debilitating nature, and financial burden of MDD (Amital, et al., 2008; Elinson, et al., 2004; Kessler, et al., 2003; Slade & Sunderland, 2010; World Health Organization, 2001). Given the degree of impairment that results from MDD, a considerable amount of effort has been spent in the development, study, and implementation of effective psychiatric treatments for depression. However, despite the development of various forms of psychotherapy, psychopharmacological medication, and neurostimulation treatments a considerable number of patients diagnosed with MDD remain unable to achieve or maintain a satisfactory response to multiple antidepressant

treatments (M. Fava, 2003; M. Fava & Davidson, 1996; Nierenberg & Amsterdam, 1990; Souery & Van der Auwera, 2004). Research has suggested that TRD may represent the most disabling type of MDD and that the cost of treating TRD patients represents half of the annual cost associated with the treatment of depression (Greden, 2001; Rost, Zhang, Fortney, Smith, & Smith, 1998). The impact of TRD includes sustained patient burden from continued disease illness, psychological distress, and societal burden due to decreased productivity, and the cost and continuous demands placed on psychiatric services.

The Lack of a Universal Definition of TRD

A review of the literature clearly supports the occurrence of TRD. However, despite the various descriptions, definitions, and staging methods that have been proposed, there is no consensus regarding how best to define and measure TRD (Fagiolini & Kupfer, 2003; Guscott & Grof, 1991; Malhi, et al., 2005; Nelsen & Dunner, 1995; Sharan & Saxena, 1998; Souery, et al., 2006). In the absence of a universal definition, many different descriptions and guidelines have been proposed for defining or categorizing TRD. The high degree of variability in how TRD is defined was highlighted in a systematic literature review conducted by Berlim and Turecki (2007b). Their review examined how TRD was operationally or conceptually defined among randomized controlled trials that were published in peer-reviewed journals. A summary of their review

included 11 different terms used to refer to TRD and six different definitions used to define or categorically assess TRD (see Table 7).

Insert Table 7 here

A greater degree of variability in the definition of TRD was demonstrated in a more inclusive literature review that identified 15 different definitions for TRD (Souery, et al., 1999). The wide degree of variation in how TRD is defined and measured significantly contributes to the considerable number of depressed patients who are frequently misclassified as experiencing TRD (Bird, et al., 2002; Hirschfeld, et al., 1997).

Benefits of Establishing a Universal Definition of TRD

Adopting a universal definition for TRD and an accurate method of differentiating between TRD and non-TRD is necessary to reduce the degree of variability in how TRD is defined or measured and to reduce the misclassification of non-TRD. Given the increased risk of relapse for patients with TRD, better identification of TRD would aid in the development of sophisticated and targeted antidepressant strategies. Establishing a universal definition of TRD would benefit both clinical and research settings by allowing clinical and research data for TRD patients to be easily compared across different mental health settings. A consistent definition of TRD between clinical and research settings is essential for

insuring homogeneity among research samples and the application of clinical research to a clinical practice.

The Rationale for Using a Staging Method to Define and Differentiate TRD

The two methods currently used to define and measure TRD involve an examination of the number and type of previously failed medication treatments (Souery 1999) and the use of staging models (Souery, et al., 2006). Although using the number and type of failed medication trials to define TRD is the most commonly used method (Souery 1999), various limitations associated with its use have emerged that support the use of a staging model.

Benefits of the Maudsley Staging Method

The primary benefits of using a staging method to define, measure, and identify TRD involves the inclusion of specific scoring guidelines, the ability to stage treatment resistant severity, and the ability to empirically examine the utility and validity of proposed models for staging TRD. Although various staging models have been developed, only the Maudsley Staging Method (MSM) was designed to represent a comprehensive measure of TRD (Fekadu, Wooderson, Donaldson, et al., 2009). Developed as multidimensional staging method for TRD, the MSM incorporates various clinical and treatment factors. The clinical factors incorporated in the MSM include illness duration and symptom severity. Regarding treatment factors, the MSM includes number of treatment failures, use of augmentation treatment strategies, and the use of ECT in the staging process

for TRD. Symptom severity and illness duration have been included in the MSM, because both of these factors have been associated with non-response to treatment and the persistence of depressive symptoms (Blom, et al., 2007; Katon, et al., 1994; McGrath, et al., 2006; Mynors-Wallis & Gath, 1997; Rubenstein, et al., 2007). The scoring guidelines of the MSM were specifically designed to avoid arranging medication classes in a hierarchical manner. This decreases the confound of implicit and false assumptions regarding antidepressant medication potency. Although the multidimensional design of the MSM offers a more comprehensive measure of TRD and preliminary studies have shown promising results regarding its predictive validity (Fekadu, Wooderson, Donaldson, et al., 2009; Fekadu, Wooderson, Markopoulo, et al., 2009), additional research is needed to better understand its utility and psychometric properties as a method of differentiating between TRD and non-TRD.

Unresolved Issues with the Maudsley Staging Method

Determining the utility and understanding the properties of the MSM as means of measuring and identifying TRD involves addressing three points: 1) establishing a reliable cutoff score for the MSM that can be used to differentiate between TRD and non-TRD, 2) determining the extent of agreement between the MSM and another commonly used staging method (e.g. the Thase and Rush Staging Method), and 3) evaluating potential variables that contribute to the total score of the MSM. An attempt to address these three points could help to

establish the acceptance of the MSM, in both clinical and research practice as a reliable and practical method of differentiating between TRD and non-TRD, and staging treatment-resistant severity. Determining a reliable cutoff score for the MSM that can be used to identify TRD will allow the MSM to be compared to other staging models or operational definitions of TRD. Identifying variables that contribute to the total score of the MSM will help to understand the properties and identify potential limitations of the MSM. Overall, addressing these unresolved points to inform the MSM could help to establish TRD as a unique form of depression.

Does TRD Represent a Unique Form of Depression?

The existence or occurrence of TRD is clearly supported in the psychiatric literature (Fagiolini & Kupfer, 2003; Guscott & Grof, 1991; Malhi, et al., 2005; Nelsen & Dunner, 1995; Sharan & Saxena, 1998; Souery, et al., 2006). The number of patients who have demonstrated a significant degree of resistance to antidepressant treatments also suggests the presence of a unique form of MDD. Although previous studies have attempted to predict and categorize TRD in terms of clinical and demographic features (Berman, et al., 1997; Dyck, 1994; Kornstein & Schneider, 2001), little attention has focused on the constitutional symptoms of TRD. A symptom based approach in defining TRD offers many advantages over the current approach of evaluating the number of failed antidepressant medications of adequate dose and duration. Determining the presence or absence

of specific symptoms would not require a detailed review of a patient's previous psychiatric treatment history. It is generally easier for a patient to describe their current clinical symptoms, than for them to recall previous failed treatments including the dose and duration of each medication. The task of determining the total number of adequate (dose and duration) failed treatments is further complicated by the issue of patient compliance, which can lower the therapeutic efficacy of antidepressant medication (Kornstein & Schneider, 2001). An examination of the frequency rates for individual depressive symptoms of TRD represents an initial step toward establishing its symptom based classification. This would also fill a void in the existing literature and inform future research investigations.

Chapter 9: Purpose, Aims, and Research Hypotheses

Purpose of the Study

Primary Study Objective

The primary objective of this study was to examine the Maudsley Staging Method (MSM) in order to obtain a more comprehensive understanding of its properties and utility as a method of identifying TRD. In order to accomplish this objective, this study attempted to (1) determine a reliable cutoff score for the MSM to be used to differentiate TRD from non-TRD, (2) examine the extent of agreement between the MSM and another commonly used method of defining TRD, and (3) examine the construct validity of the MSM. This primary objective is intended to address the current unresolved issues of the MSM in differentiating patients with and without TRD.

Secondary Study Objective

The secondary objective of this study was to perform a preliminary examination of the frequency of individual depressive symptoms of TRD. This process involved using the MSM to classify patients with TRD, and then stage their level of treatment-resistant severity. This objective will provide information regarding the frequency of individual depressive symptoms for TRD, which is a relatively unexplored area.

Specific Study Aims and Research Hypotheses

Aim I and Research Hypotheses

This aim examined the Maudsley Staging Method (MSM) in order to better understand the utility and properties of the MSM for identifying TRD.

- *Hypothesis 1*: Will determine the ideal cutoff score for the MSM to accurately discriminate TRD from non-TRD patients. *Method*: The outcome score for the MSM was calculated for each patient, and a receiver operating characteristic (ROC) analysis of the MSM was used for analysis.
- *Hypothesis 2:* Symptom severity as measured with the $HRSD_{24}$ will be positively associated with the MSM. *Method*: A Pearson Product Moment correlation was performed between the MSM total score and the $HRSD_{24}$ total score, with the expectation that these two measures would be highly correlated.

Aim II and Research Hypotheses

This aim examined the construct validity of the Maudsley Staging Method by examining potential correlates of the total outcome score of the MSM that have been found to be positively associated with treatment resistance. Socio-demographic characteristics and clinical features were explored as potential moderators.

- *Hypothesis 3A:* Age will be positively associated with treatment resistant severity measured by the outcome score of the MSM. *Method*: The outcome scores on the MSM were correlated with age.
- *Hypothesis 3B:* Female sex will be associated with treatment resistance severity as measured by the outcome score of the MSM. *Method*: The outcome score on the MSM was calculated for male and female participants. A t-test comparing MSM outcome scores for males and females was expected to show that females have higher MSM scores (treatment resistant severity) compared to males.
- *Hypothesis 3C:* Longer lifetime duration of illness will be positively associated with treatment resistant severity as measured by the outcome scores on the MSM. *Method*: Lifetime duration of illness was calculated based on the age at which the patient was first diagnosed with MDD and the age at which they completed the SCID for inclusion in this study. The outcome scores on the MSM were expected to be positively correlated with lifetime duration of illness.
- *Hypothesis 3D:* Longer duration of current MDE will be positively associated with treatment resistant severity as measured by the outcome scores on the MSM. *Method*: A Pearson Product Moment correlation or Spearman Rank Order Correlation was performed between the MSM total score and the current duration of MDE. Current MDE duration was determined by the

SCID. The outcome scores on the MSM were expected to be positively correlated with current duration of MDE.

Aim III and Research Hypotheses (Exploratory)

This aim examined and calculated the frequency rates of individual depressive symptoms for TRD patients.

- *Hypothesis 4A:* The frequencies of individual depressive symptoms will be reported for patients with TRD. *Method*: Patients with TRD were identified based on the MSM cutoff score determined under hypothesis 1A of this study. The depressive symptoms that were reported included the individual depressive symptoms that comprise the $HRSD_{24}$ and the IDS-SR_{30}.
- *Hypothesis 4B:* The frequencies of individual depressive symptoms will be reported for the range of treatment resistance severity among patients with TRD. *Method*: Patients with TRD were identified based on the MSM cutoff score determined under hypothesis 1A. The range of treatment resistance severity was based on the range of MSM outcome scores among TRD patients. Patients with TRD were divided into tertiles based on their level of treatment resistant severity. The frequency of individual depressive symptoms were reported for the top third and bottom third of TRD patients.

SECTION V – RESEARCH METHODS AND DESIGN

Chapter 10: Participants and Material

Participants

Study Recruitment

The participants in this study were recruited from one of the following four clinical trials: (1) Consortium for Research in ECT Study – Continuation ECT versus Pharmacotherapy (IRB # 0695-21700); (2) Comparing Three Electrode Placements to Optimize ECT (IRB # 0402-216); (3) Magnetic Seizure Therapy for the Treatment of Major Depression (IRB # 0202-074); (4) Magnetic Seizure Therapy for the Treatment of Severe Mood Disorders (IRB # 042005-022). The first clinical trial was conducted from 1997 to 2004, and evaluated the efficacy of continuation ECT and the combination of lithium carbonate plus nortriptyline hydrochloride for the prevention of depressive relapse following an acute course of ECT (Kellner, et al., 2006). The second clinical trial was conducted from 2001 to 2006, and compared the efficacy and cognitive side effects of different electrode configurations during an acute ECT course (Kellner, et al., 2010). The third and fourth clinical trials that participants were recruited from were conducted from January to December 2003 and from 2008 to 2011, respectively. These two clinical trials were both conducted to examine the antidepressant properties and side effects associated with magnetic seizure

therapy (MST), which is a type of neurostimulation therapy that uses transcranial magnetic stimulation to intentionally induce a seizure for therapeutic purposes (Lisanby, 2002; Lisanby, Luber, Schlaepfer, & Sackeim, 2003; Lisanby, Morales, et al., 2003; White, et al., 2006). All four of these studies were approved by the University of Texas Southwestern Medical Center (UTSW) Institutional Review Board (IRB). Although all these studies had multiple recruitment centers, only participants recruited from the Neurostimulation Laboratory at UTSW were included in this current study.

Study Participation Criteria

Screening of Study Criteria: All potential study participants completed a screening process in order to confirm inclusion and exclusion criteria. This screening process included a review of available medical records, a physician assessment, and the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Gibbon, Spitzer, & Williams, 1996).

Preliminary Inclusion Criteria: Male and female participants were included in all four of the above mentioned clinical trials, if they met the following inclusion criteria:

1. Age 18-85
2. DSM-IV diagnosis of unipolar or bipolar MDD
3. Baseline $HRSD_{24}$ (Hamilton, 1960, 1967) score of 21 or greater
4. Electroconvulsive therapy (ECT) was clinically indicated

5. Able to provide informed consent

Preliminary Exclusion Criteria: Male and female participants were excluded from all four of the above mentioned clinical trials if they met any of the following criteria:

1. Life-time psychiatric history of schizophrenia, schizoaffective disorder, or mental retardation
2. Current primary psychiatric diagnosis of anxiety disorder, obsessive-compulsive disorder, or any eating disorder
3. Current psychiatric diagnosis of delirium, dementia, or amnestic disorder
4. Any active unstable or serious medical condition that increased the risk of ECT (i.e., heart disease), central nervous system disease, or substance abuse or dependence
5. Received ECT within the past six months

Additional Inclusion/Exclusion Criteria for This Study: Although all four of the above mentioned clinical trials included both unipolar and bipolar participants, the purpose of this dissertation focuses exclusively on unipolar TRD. Therefore, all participants with a diagnosis of bipolar depression were excluded from this present study.

Sample Characteristics and Diagnostic Measures

Demographic and Clinical Features

In addition to the clinical measures described below, information regarding patient demographics and clinical features were collected for all study participants. The following demographic information was collected: age, gender, race, education, employment status, and marital status. The following clinical features were also collected: depressive type (unipolar or bipolar), depressive subtype specifiers (psychotic features, melancholic features, atypical features), number of MDEs, number of psychiatric hospitalizations, and age of MDD onset.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The SCID-I (First, et al., 1996) is a semistructured diagnostic interview designed for diagnosing DSM-IV Axis I psychopathology. The SCID-I provides a standardized approach toward the diagnostic process, and was specifically developed as a means of increasing the diagnostic reliability and validity based on DSM-IV diagnostic criteria. The SCID-I is comprised of ten diagnostic modules including: Module A (Mood Episodes), Module B (Psychotic Symptoms), Module C (Psychotic Disorders), Module D (Mood Disorders), Module E (Substance Use Disorders), Module F (Anxiety Disorders), Module G (Somatoform Disorders), Module H (Eating Disorders), Module I (Adjustment Disorders), and Module J (Optional Module).

The SCID-I can be administered to individuals who are 18 years-of-age or older, with at least an eighth grade education, and is appropriate for both psychiatric and medical patients. The length of time required to administer the SCID-I can vary based on the complexity of the patient's psychiatric history; however, in most cases the SCID-I can be completed in one to two hours. The reliability of the SCID-I can vary based on how it is being used and the setting in which it is administered with kappa coefficients ranging from .70 to 1.00 (First, et al., 1996). Administration of the SCID-I was performed by trained certified clinicians or other trained mental health professionals.

Mini Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, & McHugh, 1975) is an assessment of global cognitive functioning commonly used as a brief screening measure of cognitive impairment (Crum, Anthony, Bassett, & Folstein, 1993). The MMSE can be administered in approximately 10 minutes and includes items that assess domains of orientation, attention, memory, graphomotor ability, and comprehension. Scoring involves calculating a total raw score from all items which can be converted into a demographically adjusted score based on age and education. The following cutoff scores for the MMSE have been recommended: >24 = no cognitive impairment, 18-23 = mild cognitive impairment, and <17 = severe cognitive impairment (Tombaugh & McIntyre, 1992). Regarding the psychometric characteristics of the MMSE within a large community sample, the

overall Chronbach's alpha was found to be .77 (Holzer, Tischler, Leaf, & Myers, 1984). Depending on the cutoff score used, the internal consistency of the MMSE has been found to range from r=.76 to r=.80 (Lopez, Charter, Mostafavi, Nibut, & Smith, 2005).

Depression Rating Instruments

Hamilton Rating Scale for Depression (HRSD)

The HRSD (Hamilton, 1960, 1967) is a commonly used clinician administered depression rating instrument that measures the presence of depressive symptoms, individual symptom severity, and overall depression severity. Due to its long history and frequent use, the HRSD is largely considered the "gold standard" for rating depressive symptoms and severity. When the HRSD was first introduced it consisted of only 17 items that measured affective and somatic symptoms. The items included depression, guilt, anxiety, sleep disturbances, suicidal ideation, anhedonia, weight loss, decreased libido, and somatic anxiety. Currently there are different versions of the HRSD that include 21 items, 24 items, 28 items, and 30 items (Bagby, Ryder, Schuller, & Marshall, 2004; Overall & Rhoades, 1982). Retaining the original 17 items and adding newer items has allowed the HRSD to provide a more comprehensive measure of depression symptoms and overall depression severity.

For this study, depressive symptoms were evaluated with the 24-item HRSD ($HRSD_{24}$). In addition to the original 17 items, the $HRSD_{24}$ includes seven

additional items intended to measure paranoia, depersonalization, hypochondriasis, obsession-compulsion, hopelessness, helplessness, and worthlessness. Of the items included in the $HRSD_{24}$, eleven are rated on a scale of 0 to 2 and thirteen are rated on a scale of 0 to 4 (Hamilton, 1969, 1980). The grading guidelines for how items are rated are described in Table 8. The $HRSD_{24}$ provides an overall score of depression severity, which can range from 0-74 or 0-76. The two point difference in the maximum possible score on the $HRSD_{24}$ is due to an inconsistency in the grading guidelines for how item nine (psychomotor agitation) is rated. Some versions of the $HRSD_{24}$ rate item nine on a 0 to 2 rating scale, while other versions of the $HRSD_{24}$ use a 0 to 4 rating scale. Regardless of the $HRSD_{24}$ version used the different ranges of scores and their respected severity levels are as follow: 0-9, normal; 10-18, mild; 19-26, moderate; 27-34, severe; 35-76, very severe. Regarding the psychometric characteristics of the HRSD, the internal reliability has been reported to vary between .46 and .97, Pearson's *r* for interrater reliability ranged from .82 to .98, and the intraclass *r* ranged from .46 to .99 (Bagby, et al., 2004).

Insert Table 8 here

Inventory of Depressive Symptomatology Self-Report (IDS-SR)

The IDS-SR (Rush, et al., 1986; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) is a patient rated depression symptom severity inventory used in both

clinical and research settings that provides a comprehensive measure of depressive symptom severity. The 30-item IDS-SR (IDS-SR_{30}) was specifically designed to incorporate all the DSM-IV (American Psychiatric Association, 1994) symptom-based criteria for MDE, as well as the diagnostic symptoms for both melancholic and atypical depression (Gullion & Rush, 1998). The IDS-SR_{30} was developed in combination with the clinician rated version (IDS-C_{30}), which provides a comparable subjective and objective measure of a patient's depressive symptoms severity. The main strengths of the IDS are a result of its design and include equivalent weighting (0-3) for each item, unambiguous anchors that estimate symptom frequency and severity, and to be sensitive to change over time (Biggs, et al., 2000; Rush, et al., 1986; Rush, et al., 1996; Rush, Trivedi, et al., 2005; Rush, Trivedi, et al., 2003).

Compared to the HRSD (Hamilton, 1969, 1980), all items included in the IDS-SR are rated on a four point scale that ranges from 0 to 3. The scoring guidelines for how items are rated are described in Table 8. The IDS-SR_{30} provides an overall score of depression severity, which can range from 0 to 84. The different ranges of the IDS-SR scores and their respective severity levels are as follow: < 15, normal; 16-24, mild; 25-32, moderate; 33-40, moderate to severe; and > 41, severe. The strong psychometric properties of the IDS-SR_{30} have been well documented with a Cronbach's alpha level of .93, and correlations of .91 and .88 with IDS-C_{30} and $HRSD_{17}$, respectively (Rush, Carmody, & Reimitz, 2000).

Antidepressant Treatment Resistant Measures

Antidepressant Treatment History Form (ATHF)

The ATHF is a commonly used instrument in clinical research to organize a patient's prior treatment history to determine the efficacy of previous antidepressant treatments (Sackeim, 2001). The ATHF provides criteria to rate the strength of prior antidepressant treatments, which ensures the completion of an adequate dose and duration of prior treatments. The ATHF documents the reason that prior trials were discontinued, and provides a rating scale that is used to score the global confidence for each antidepressant trial. The global confidence score reflects the source, reliability, and certainty of the information or records used to complete the ATHF and determine the strength of each prior antidepressant trial. Although using an instrument like the ATHF provides clear guidelines for documenting failed treatments of adequate dose and duration, this instrument does not provide guidelines for staging, measuring, or defining TRD.

Maudsley Staging Method

Treatment resistance was measured using the Maudsley Staging Method (MSM) (Fekadu, Wooderson, Donaldson, et al., 2009). This staging model has been developed to provide guidelines for how to stage treatment resistance. The MSM focuses on various illness and treatment related factors, which are reviewed in chapter 6 of the TRD literature review. The MSM only includes treatment failures of adequate dose and duration, which are based on the prescribing

guidelines outlined in the *Maudsley Prescribing Guidelines* (D. Taylor, et al., 2010). The *Maudsley Prescribing Guidelines* provides prescription and treatment guidelines for various psychopharmacologic treatments and psychiatric disorders.

Chapter 11: Study Procedure

Administration of Measures

A total of 88 participants' files were included in the analyses. See Figure 1 for a rundown of the original sample size. Trained, certified clinical raters and psychometrists administered all depression rating instruments, treatment resistant measures, diagnostic measures, and the MMSE.

The patients completed the IDS-SR_{30}.

Defining Treatment Resistant Depression

For this study, two different methods were used to identify TRD patients. These methods required a detailed review of each participant's file, including any available medical records. In addition, all TRD patients were required to have a confirmed diagnosis of MDD based on the SCID-I (First, et al., 1996). The first method of defining TRD was based on the failed response to at least two adequate trials of antidepressant treatments from at least two different classes of drug. For example, a patient who failed to respond to adequate trials of citalopram (SSRI) and amitriptyline (TCA) would be classified as TRD based on this method, because these two antidepressants are from different classes of drug. In comparison, a patient who failed to respond to adequate trials of citalopram (SSRI), sertraline (SSRI), and fluoxetine (SSRI) would not be classified as TRD with this method, because these three antidepressants are all from the same class of drug. This is the most commonly agreed upon definition of TRD within the

literature (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003), therefore for this study, this method was referred to as the Standard Definition for TRD (SD-TRD). The SD-TRD method was used in this study as a means of comparing the accuracy of the MSM at differentiating TRD from non-TRD patients. The second method used to identify TRD patients was based on the MSM total score (Fekadu, Wooderson, Donaldson, et al., 2009). The MSM was designed to stage TRD, with higher scores reflecting a greater degree of treatment resistance. The cutoff score for the MSM used to differentiate patients with and without TRD was calculated as part of this study.

Insert Table 9 here

Defining Adequate Dosing and Duration

Guidelines outlined in the ATHF (Sackeim, 2001) were used to determine adequate dosing and duration for the SD-TRD. Antidepressant treatments were only counted for the SD-TRD if they were taken at an adequate dose for at least four weeks. A list of the antidepressant medication and dosing guidelines included in the ATHF are provided in Table 9. Medications prescribed as augmenting agent (e.g. lithium, antipsychotics, anticonvulsants) are not included in the SD-TRD, therefore adequate dose and duration of augmenting agents were not calculated.

The dose and duration guidelines for the MSM were based on guidelines outlined by the authors of the MSM (Fekadu, Wooderson, Donaldson, et al., 2009; Wooderson, et al., 2011). Antidepressant treatments were only counted as failed treatments if they were taken at an adequate dose for at least six weeks. Adequate dosing was determined using the prescription guidelines outlined in the *Maudsley Prescribing Guidelines* (D. Taylor, et al., 2010) as a primary source, and the dosing guidelines in the ATHF as a secondary source. The *Maudsley Prescribing Guidelines* were also used to determine adequate dosing and duration for augmenting agents, which are included in the MSM total score. Augmenting agents were only counted if they were taken at an adequate dose for at least six weeks. A list of the antidepressant medication and dosing guidelines used for the MSM are provided in Table 9.

For antidepressant medication not listed in the ATHF or *Maudsley Prescribing Guidelines*, adequate dosage was defined by the minimum therapeutic dose recommended by the drug manufacture. This guideline was only used for a transdermal form of selegiline (EMSAM) and desvenlafaxine (Pristiq). These medications were approved after the publication of the ATHF and the *Maudsley Prescribing Guidelines*, and as such were not included in those manuals.

Measuring Depressive Severity and Symptoms

Depressive severity was measured using the $HRSD_{24}$ (Hamilton, 1960, 1967) total score, while both the $HRSD_{24}$ and IDS-SR_{30} (Rush, et al., 1986; Rush,

et al., 1996) were used to determine the presence of depressive symptoms. The $HRSD_{24}$ was utilized to examine clinician identified depressive symptoms and the IDS-SR_{30} was used to examine patient reported depressive symptoms. Because participants in this study were comprised of participants from four different clinical trials, two different versions of the $HRSD_{24}$ were used among these four clinical trials. These two versions used different grading guidelines for item nine (psychomotor agitation), with one version designed with a 0 to 2 rating scale and the other version designed with a 0 to 4 rating scale. This discrepancy in the rating scale for item nine resulted in a two point difference in the maximum possible $HRSD_{24}$ total score, ranging from 74 to 76.

Due to the discrepancy on item nine, which allowed some patients to obtain a higher $HRSD_{24}$ total score, patients that received a score greater than two on this item were excluded from any analysis involving $HRSD_{24}$ total scores. The scoring discrepancy for item nine on the $HRSD_{24}$ did not influence the examination of individual depressive symptoms. The individual items included in the $HRSD_{24}$ and the IDS-SR_{30} were searched in terms of endorsed items. Any endorsed item was examined as a dichotomous or binary item, meaning each item was rated as either absent (score of 0) or present (score ≥ 1).

Statistical Analyses

The proposed aims and hypotheses were explored using a variety of statistical analyses described in chapter nine under each respective hypothesis.

Socio-demographic characteristics and clinical features for the sample were calculated and reported as percentages or means and standard deviations, based on each variable's respected scale of measurement. Percentages were calculated for the following categorical data point: sex, race, relationship status, living situation, education, employment, depressive subtype, recurrent specifier, and chronic specifier. The mean and standard deviation were calculated, for the sample as a whole, for the following data points: age, scores on measures of depressive severity, number of psychiatric hospitalizations, and MMSE scores. The mean and standard deviation was calculated for number of previous MDEs and duration of current MDE; however, these clinical characteristics were also divided into categorical data points and reported as percentages. Data was analyzed using the Predictive Analytics SoftWare (PASW) version 18 Statistics package (SPSS Inc., Chicago, Illinois). This statistics package is commonly referred to as the Statistical Package for Social Sciences (SPSS), but was published under the title PASW for version 18.

SECTION VI – RESULTS

Chapter 12: Study Sample and Statistical Analyses

Overview of Study Sample

The sample for this current study was comprised of 88 participants who had a confirmed primary diagnosis of MDD, and a complete antidepressant treatment history. These participants were identified from an initial sample of 303 participants identified from the following four clinical trials: (1) Consortium for Research in ECT Study – Continuation ECT versus Pharmacotherapy; (2) Comparing Three Electrode Placements to Optimize ECT; (3) Magnetic Seizure Therapy for the Treatment of Major Depression; (4) Magnetic Seizure Therapy for the Treatment of Severe Mood Disorders. A total of 174 participants were excluded from analyses due to incomplete antidepressant treatment histories and 41 participants were excluded for having a diagnosis of bipolar disorder. See Figure 1 for an overview of the initial sample and a distribution of the excluded participants across all four clinical trials that comprised the initial sample.

Insert Figure 1 here

Overview of Statistical Analyses

Distributions of data were assessed prior to statistical analyses. All variables that were used in the statistical analyses were approximately normally

distributed, and therefore, no transformations were performed. Because all variables were independent observations, and met the assumptions of normality, equal variance, homoscedasticity, and linearity, parametric analyses including independent samples t-test and Pearson Product Moment correlation were chosen to assess the respective hypotheses of the present study. Power analyses were performed using G*Power 3 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007).

Sample Characteristics – Total Sample

Demographic Characteristics – Total Sample

The mean age of patients in this study was 52.1 years old (*SD*=15.5; median=51.0; range=21-84). The sample was mainly comprised of females (*n*=51, 58%) and most patients were employed (*n*=46, 52.5%). Ninety-three percent of the sample was Caucasian, 2.3% Asian, 3.4% Hispanic, and 1.1% Pacific Islander. The majority of patients received a degree from an institution of higher education (*n*=54, 61.4%). A comprehensive summary of demographic characteristics for the total sample is presented in Table 10.

Insert Table 10 here

Clinical Features – Total Sample

The majority of patients had recurrent depression (*n*=84, 95.5%) with melancholic features (*n*=78, 88.6%). The mean number of major depressive

episodes was 3.4 (*SD*=3.1; median=3.0; range=0-19), and the mean duration was 22.0 months (*SD*=39.1; median=6.2; range=0.69-239.7). The mean number of psychiatric hospitalizations was 2.4 (*SD*=2.8; median=2.0; range=0-20), and the mean Hamilton Rating Scale for Depression ($HRSD_{24}$) total score was 34.3 (*SD*=5.8; median=35.0; range=21-49). The mean Maudsley Staging Method (MSM) total score was 7.7 (*SD*=1.9; median=7.0; range=4-13), and the mean MMSE total score was 27.2 (*SD*=2.8; median=28.0; range=18-30). See Table 11 for additional clinical features for the overall sample.

Insert Table 11 here

A list of all reported antidepressant medications used by study patients is presented in Table 12. The total number of adequate and inadequate medication trials have also been included, based on the MSM dosing and duration guidelines (Fekadu, Wooderson, Donaldson, et al., 2009; Fekadu, Wooderson, Markopoulou, et al., 2009).

Insert Table 12 here

Sample Characteristics – TRD Patients

Demographic Characteristics – TRD Patients

The socio-demographic characteristics of patients who were classified as TRD (*n*=43) by the MSM are presented in Table 13. The mean age of the TRD patients in this study was 47.1 years old (*SD*=14.2; median=45.0; range=21-81). The sample was mainly comprised of females (*n*=23, 53.5%) and patients who were unemployed (*n*=23, 53.5%). Ninety percent of the sample was Caucasian, 2.3% Asian, 4.7% Hispanic, and 2.3% Pacific Islander. A majority of patients received a degree from an institution of higher education (*n*=29, 81.5%).

Insert Table 13 here

Clinical Features – TRD Patients

The majority of TRD patients had recurrent depression (*n*=41, 95.3%) with melancholic features (*n*=39, 90.7%). The mean number of major depressive episodes was 3.6 (*SD*=3.0; median=3.0; range=0-15), and the mean duration of the current major depressive episode was 35.2 months (*SD*=49.8; median=18.2; range=1.8-239.7). The mean number of psychiatric hospitalizations was 1.7 (*SD*=1.9; median=1.0; range=0-6), and the mean $HRSD_{24}$ was 35.3 (*SD*=5.4; median=35.5; range=25-49). The mean MSM total score was 9.2 (*SD*=1.4; median=9.0; range=8-13), and the mean MMSE total score was 27.6 (*SD*=2.3;

median=28.0; range=20-30). See Table 14 for a comprehensive list of clinical features for the TRD patients.

Insert Table 14 here

Chapter 13: Research Hypotheses

Hypothesis One

Hypothesis 1 stated that an ideal cut-off score for the MSM would be determined that distinguished between TRD and non-TRD patients. A receiver operating characteristic (ROC) analysis of the MSM was conducted to determine a cut-off score for the MSM based on the highest possible accuracy and furthest perpendicular distance from the ROC curve to the diagonal line (line of no-discrimination) (Riffenburgh, 2006; Zhang, 2009). This determined a cut-off score for the MSM that balanced specificity and sensitivity in differentiating TRD from non-TRD. Specificity refers to the proportion of positives (TRD) identified by the measure, and sensitivity refers to the proportion of negatives (non-TRD) that are identified by the MSM. The area under the curve (AUC) was 0.86, suggesting that the MSM was a good measure that differentiated TRD from non-TRD. The specificity, sensitivity, and accuracy of optimal cut-off scores are presented in Table 15.

Insert Table 15 here

A cut-off score of 7.5 was found to have the optimal ratio of sensitivity (0.79) and specificity (0.78), with an accuracy of 78.4%. Based on a cutoff score of 7.5, the percentages of true positives and negatives and false positives and false negatives are presented in Table 16.

Insert Table 16 here

A Kappa statistic was also used to examine the extent of agreement between the MSM and the Standard Definition for TRD (SD-TRD) at discriminating TRD from non-TRD patients. A Kappa statistic of 0.57 was found between the MSM and SD-TRD, indicating moderate agreement (Landis & Koch, 1977) between the two measures ($p<.0001$).

Hypothesis Two

Hypothesis 2 stated that depressive symptom severity as measured by the $HRSD_{24}$ would be positively associated with the MSM. A Pearson Product Moment correlation was computed to assess the relationship between depressive symptom severity as measured by the total scores of the $HRSD_{24}$ and the MSM. There was a significant positive correlation between the two variables ($r= 0.31$, $n=86$, $p=.002$). Increases in depressive symptom severity (as measured by the $HRSD_{24}$ total score) were correlated with increases in MSM scores.

An additional Pearson Product Moment correlation was computed to assess the relationship between depressive symptom severity as measured by the total scores of the $HRSD_{24}$ and the depressive symptoms severity subscale within the MSM. There was a significant positive correlation between the two variables ($r= 0.54$, $n=86$, $p<.0001$). Increases in depressive symptom severity (as measured

by the $HRSD_{24}$ total score) were correlated with increases in the MSM depressive symptoms severity subscale.

The $HRSD_{24}$ and the IDS-SR_{30} were also examined to determine the relationship between an objective (clinician-rated) and subjective (patient-completed) measure of depressive symptom severity. A Pearson Product Moment correlation was computed to determine if the total score on the $HRSD_{24}$ would be positively associated with the total score on the IDS-SR_{30}. There was a significant positive correlation between the $HRSD_{24}$ and the IDS-SR_{30} (r= 0.49, n=72, p<.0001).

Hypothesis Three Part A

Hypothesis 3A stated that age would be positively associated with treatment resistant severity as measured by the outcome score of the MSM. A Pearson Product Moment correlation was computed to assess the relationship between age and treatment resistant severity as measured by the MSM outcome score. There was a significant negative correlation between these two variables (r= -0.39, n=88, p<.0001). Increases in age were associated with decreases in MSM scores.

These findings are counter to what has been presented in the literature (Flint, 2002; Nemeroff, 2007; Souery, et al., 1999). In order to explain this discrepancy, independent samples t-tests were also conducted to determine if there was an age difference between TRD and non-TRD patients as defined with

the MSM. As classified with the MSM, patients with TRD were significantly younger (*M*=47.1, *SD*=14.2) than patients without TRD (*M*=56.8, *SD*=15.3), *t* (86) =3.09, *p*=0.003.

Hypothesis Three Part B

Hypothesis 3B stated that women would have higher treatment resistant severity relative to men, as measured by the MSM outcome score. An independent-samples t-test was conducted to compare MSM scores in males and females. There was no significant difference between MSM scores of females (*M*=7.6, *SD*=1.8) and males (*M*=7.8, *SD*=2.1), *t* (86) =0.70, Cohen's *d*=0.15, *p*=0.49. Therefore, treatment resistant severity was similar between women and men.

Hypothesis Three Part C

Hypothesis 3C stated that longer lifetime duration of depressive illness would be positively associated with treatment resistant severity as measured by the MSM outcome score. Lifetime duration of depressive illness was calculated as the difference between the age in years at which the patient was first diagnosed with MDD and the age in years at which they completed the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, et al., 1996). A Pearson Product Moment correlation was computed to assess the relationship between longer lifetime duration of depressive illness and treatment resistant severity.

There was no significant correlation between the lifetime duration of depressive illness and treatment resistant severity (r= 0.02, n=84, p=.44).

An additional Pearson Product Moment correlation was computed to assess the relationship between the age at which the patient was first diagnosed with MDD (i.e. age of first onset) and treatment resistant severity as measured by the MSM outcome score. There was a significant negative correlation between the two variables (r= -0.38, n=84, p<.0001). An earlier age of MDD onset was associated with increased treatment resistant severity.

Hypothesis Three Part D

Hypothesis 3D stated that longer duration of the current MDE would be positively associated with treatment resistant severity as measured by the MSM outcome score. A Pearson Product Moment correlation was used to determine the relationship between treatment resistant severity and current MDE duration in months (as determined by the SCID). There was a significant positive relationship between current MDE duration and treatment resistant severity (r= 0.48, n=80, p<.0001). A longer duration of the current MDE was associated with higher treatment resistance severity.

The relationship between current MDE duration and treatment resistant severity as measured by the MSM was further examined using a modified MSM outcome score. This modified score reflected a patient's total MSM score without including the MSM subscale for MDE duration. An additional Pearson Product

Moment correlation was computed to determine if current MDE duration in months would be positively associated with treatment resistant severity as measured by the modified MSM outcome score. There was a significant positive correlation between current MDE duration and treatment resistant severity based on the modified MSM outcome score (r= 0.41, n=80, p<.0001). Therefore, current MDEs of longer duration were still associated with higher treatment resistant severity based on a modified MSM score that did not include the MSM subscale for MDE duration.

Hypothesis Four Part A

Hypothesis 4A examined the frequency of individual depressive symptoms reported for patients with TRD as identified by the MSM cutoff score of 7.5. The frequencies of the individual depressive symptoms that comprise the $HRSD_{24}$ and the IDS-SR_{30} for TRD and non-TRD patients are presented in Tables 17 and 18, respectively.

Insert Table 17 and 18 here

On the $HRSD_{24}$, patients with TRD frequently reported *depressed mood* (100%), *decreased pleasure in work and activities* (100%), and *feelings of helplessness* (100%) and *hopelessness* (100%). Patients without TRD frequently reported *depressed mood* (100%), *middle insomnia* (100%), dec*reased pleasure in work and activities* (100%), *psychic anxiety* (100%), and *somatic complaints* (100%).

On the IDS-SR_{30}, patients with TRD frequently reported *quality of depressed mood* (100%), *fatigue or loss of energy* (100%), and *anhedonia* (100%). Patients without TRD frequently reported *decreased involvement* (100%) and *fatigue or loss of energy* (100%).

Hypothesis Four Part B

Hypothesis 4B examined the frequency of individual depressive symptoms for the range of treatment resistant severity among patients with TRD as identified by the MSM cutoff score of 7.5. Patients with TRD were divided into tertiles based on their level of treatment resistant severity. Those patients with a score of eight on the MSM were in the bottom tertile, and those who scored 10 or greater on the MSM were in the top tertile. The frequencies of the individual depressive symptoms that comprise the $HRSD_{24}$ and the IDS-SR_{30} for the bottom and top tertiles are presented in Tables 19 and 20, respectively.

Insert Tables 19 and 20 here

On the $HRSD_{24}$, patients who were in the bottom tertile of the TRD group frequently reported *depressed mood* (100%), *feelings of guilt* (100%), *middle insomnia* (100%), *decreased pleasure in work and activities* (100%), and *feelings of helplessness* (100%) and *hopelessness* (100%). Patients who were in the top tertile in the TRD group frequently reported *depressed mood* (100%), *suicidal ideation* (100%), *decreased pleasure in work and activities* (100%), *psychic*

anxiety (100%), *somatic complaints* (100%), and *feelings of helplessness* and *hopelessness* (100%).

On the IDS-SR_{30}, patients who were in the bottom tertile of the TRD group commonly reported *depressed mood* (100%), *quality of depressed mood* (100%), *decreased involvement* (100%), *fatigue or loss of energy* (100%), and *anhedonia* (100%). Patients who were in the top tertile in the TRD group commonly reported *loss of mood reactivity* (100%), *quality of depressed mood* (100%), *difficulty concentrating or indecisiveness* (100%), *fatigue or loss of energy* (100%), *anhedonia* (100%), and *psychomotor retardation* (100%).

SECTION VII – DISCUSSION

Summary of Study Objectives

The primary objective of this study was to examine the Maudsley Staging Method (MSM) in order to obtain a more comprehensive understanding of its utility as a method of differentiating TRD from non-TRD. In order to accomplish this objective, an attempt was made to (1) determine a reliable cutoff score for the MSM to be used to differentiate TRD from non-TRD, (2) examine the extent of agreement between the MSM and another commonly used method of defining TRD, and (3) examine the construct validity of the MSM. The secondary objective of this study was to perform a preliminary examination of the frequency of individual TRD depressive symptoms. This secondary objective was an attempt to provide initial information regarding the frequency of individual depressive symptoms for TRD, which is a relatively unexplored area.

Chapter 14: The Properties and Utility of the MSM in Identifying TRD

The Cutoff Score for the Maudsley Staging Method

A cut-off score of 7.5 on the MSM was identified as the optimal cutoff score for differentiating TRD from non-TRD. This cutoff score was found to represent a balanced ratio of sensitivity and specificity, which consequently provided the highest degree of accuracy for identifying TRD from a sample of patients diagnosed with MDD. To our knowledge, this is the first cutoff score for the MSM, which is a relatively new and comprehensive TRD staging model. Although the multidimensional design of the MSM was developed primarily as a TRD staging model in order to quantify treatment resistance, the identification of an accurate cutoff score suggests that the MSM could also be used as a method to operationally define TRD. As such, clinical and research practice could benefit from the ability to use a standard tool to consistently classify TRD. A measure that could be easily administered, scored, and interpreted in order to differentiate TRD from non-TRD, represents a measure that is currently missing and greatly needed within the TRD area.

Agreement between the MSM and the SD-TRD

A moderate degree of agreement (Landis & Koch, 1977) was demonstrated between the SD-TRD and MSM at discriminating TRD from non-TRD patients. The SD-TRD represents the most commonly agreed upon definition of TRD, which defines TRD based on the failed response to at least two

antidepressant treatments of adequate dose and duration, and from different pharmacologic classes (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003). The extent of agreement between the SD-TRD and MSM at discriminating TRD from non-TRD patients demonstrates the utility of the MSM at identifying TRD. The ability to accurately define TRD would benefit both research and clinical settings by ensuring the homogeneity of a TRD research sample, and informing clinical decision making and treatment planning.

Given the multidimensional design of the MSM, which includes treatment and clinical factors, the moderate agreement between the MSM and the SD-TRD supports the complexity of TRD. The guiding principle in the development of the MSM was that treatment resistance in MDD is influenced by various dimensional factors. Therefore, in addition to antidepressant treatment failures, depression severity and illness duration were included in the MSM in order to account for the nature and course of the depressive illness. Depression severity and illness duration have both been associated with non-response to treatment and the persistence of depressive symptoms (Blom, et al., 2007; Katon, et al., 1994; McGrath, et al., 2006; Mynors-Wallis & Gath, 1997; Rubenstein, et al., 2007). Studies have found that patients diagnosed with MDD who have greater depression severity, defined by either higher scores on depression measures (e.g. $HRSD_{17}$) or the presence of psychotic features, are less likely to respond to

antidepressant medication, psychotherapy, and ECT (Blom, et al., 2007; de Vreede, Burger, & van Vliet, 2005; Howland, et al., 2008; Rubenstein, et al., 2007). Greater depression severity has also been found to be a predictor of residual depressive symptoms and relapse following an antidepressant treatment (McGrath, et al., 2000; McGrath, et al., 2006). Regarding the relationship between illness duration and treatment response, patients rated as having greater chronicity or a longer duration of illness have consistently been found to have poorer response rates and a higher likelihood of relapse following treatment (Blom, et al., 2007; McGrath, et al., 2000; McGrath, et al., 2006; Mynors-Wallis & Gath, 1997). Although the term chronicity is not universally defined within the literature, patients who have MDE longer than 12 months have been found to have poorer response rates (Blom, et al., 2007). The extent of agreement between the MSM and the SD-TRD (which only includes treatment related factors) supports the inclusion of illness severity and duration in the MSM, and the relevance of considering additional clinical factors when studying or defining TRD.

Although the moderate agreement between the MSM and the SD-TRD at discriminating TRD from non-TRD represents a strength of the MSM, the interdependence of the SD-TRD and the MSM cutoff score can also be interpreted as a limitation. For instance, despite the general agreement of defining TRD based on the SD-TRD criteria, there still remains no universal definition of TRD.

Given that the cutoff score for the MSM was determined based on analysis that used the SD-TRD, any changes in the SD-TRD criteria may alter the optimal MSM cutoff score.

Relationship between the MSM and Depression Severity

Depressive symptom severity was found to be positively and significantly associated with treatment resistant severity. Patients who had higher depression severity (as measured by the $HRSD_{24}$ total score) were found to have higher treatment resistant severity (as measured by the MSM total score). The presence of a positive correlation between $HRSD_{24}$ and MSM total scores is consistent with the current TRD literature, which has described higher depression severity as a risk factor for treatment resistance (Berman, et al., 1997; Blom, et al., 2007; Kornstein & Schneider, 2001; Nelsen & Dunner, 1995). As a known risk factor for treatment resistance, the positive relationship between the $HRSD_{24}$ and the MSM support the value of considering depression severity when attempting to stage or evaluate treatment resistant severity.

The positive relationship between depression severity and the MSM total score was statistically significant and classified as a "*moderate*" correlation. Although a larger correlation may have been expected, the strength of the relationship between depression severity and the MSM total score was limited due to the multiple factors that contribute to the MSM total score. The MSM total score represented the sum of four subscales including depression severity, illness

duration, treatment failures, and the use of ECT or any augmentation agents. However, a large association was found when the $HRSD_{24}$ total scores were compared only with the depressive symptom severity subscale within the MSM. The detection of a larger association suggests that the depressive symptom severity subscale within the MSM may adequately account for variations in symptom severity. Given the negative impact of depression severity on antidepressant treatment response, the positive correlation between $HRSD_{24}$ total scores and both the MSM total scores and depressive symptom severity subscale within the MSM supports the need to incorporate known risk factors associated with TRD.

Construct Validity of the MSM

Age and Treatment Resistant Severity

The results of this study represent the first attempt to examine the construct validity of the MSM by examining a commonly reported risk factor for TRD. Age was found to be significantly negatively correlated with treatment resistant severity as measured by the MSM total score. Therefore, counter to the expectations of this present study and current TRD literature (Flint, 2002; Nemeroff, 2007; Souery, et al., 1999), increases in age were found to be associated with lower treatment resistant severity.

The discrepancy between these current findings and the TRD literature suggests three possible explanations. First, because the MSM was designed to

stage or rate the level of treatment resistant severity rather than simply identify the categorical presence of TRD, this study included both TRD and non-TRD patients. A positive association between age and the MSM total score was predicted regardless of TRD or non-TRD categorization. In order to ensure that the negative association between age and treatment resistant severity reported was not due to the inclusion of non-TRD patients, an additional analysis was performed to determine if there was an age difference between patients with TRD and without TRD. As classified by the MSM, patients with TRD were found to be significantly younger than those without TRD. This additional analysis supports the initial negative correlation between age and treatment resistant severity. Second, the sample in the current study may be too small to adequately represent the variability in age that can occur within a TRD patient population. Although the age range for the patients with TRD included in this study was 21 to 81, our sample was likely not large enough to comprehensively represent that range. For example the mean age of the TRD patients in this study was 47.1 with a standard deviation of 14.2, meaning that the majority of our sample fell between 32.8 and 61.3 years of age. In order to address this limitation future studies should be based on patient samples that take into account both high and low age ranges. Third, the sample in the current study may actually represent a better defined TRD sample in which age is negatively associated with treatment resistance; however, further research is needed to substantiate this possibility.

Sex and Treatment Resistant Severity

A comparison of MSM total scores for males and females did not reveal any significance difference between the degree of treatment resistant severity for men or women. The absence of a significant difference between the MSM total scores of males and females indicated that they had equivalent treatment resistant severity. This was an unexpected finding of the study. Based on existing TRD literature, women were expected to demonstrate a significantly higher MSM total score, which would represent higher treatment resistant severity relative to men (Fagiolini & Kupfer, 2003; Souery, et al., 1999). The failure to detect a significant difference between treatment resistant severity for men and women could be the result of certain methodological issues involving the sample of this current study. For example, the generalizability (i.e. validity) of these findings may have been limited by only including patients who were clinically indicated to receive ECT. However, it is possible that these findings could represent a legitimate challenge to the inclusion of female gender as a risk factor for TRD.

The literature has become more critical of the relationship between female sex and treatment resistance by highlighting the limitations of previous TRD research (Berlim & Turecki, 2007a; Berman, et al., 1997). Factors that may have contributed to the inclusion of female sex as a possible risk factor include: 1) differences in prevalence rates of depression for men and women, 2) gender differences in treatment response based on treatment type, 3) and any of the

methodological issues frequently described in and across early TRD studies (e.g. TRD samples comprised of both unipolar and bipolar patients, variation in how studies operationally defined TRD, results and conclusions based on limited sample sizes, and use of different outcome measures (Berlim & Turecki, 2007a; Berman, et al., 1997; Dyck, 1994; Kornstein & Schneider, 2001; MacEwan & Remick, 1988; Malhi, et al., 2005; Russell, et al., 2004).

Among the TRD literature, studies are frequently based on patient samples that include a higher percentage of females (Avery, et al., 2006; George, et al., 2005; Malone, et al., 2009; Miniussi, et al., 2005; Rossini, Lucca, Zanardi, Magri, & Smeraldi, 2005; Rush, Marangell, et al., 2005; Russell, et al., 2004; Sackeim, Rush, et al., 2001). This pattern of including more female then male study participants was also observed in this current study, with females accounting for 58% of the overall patient sample. Although the consistency of this occurrence suggests a higher rate of TRD among females, it is more likely a reflection of the gender difference within the overall prevalence rate of MDD (Kornstein & Schneider, 2001). The overall prevalence rate of MDD tends to include more females then males, with a ratio of 2:1, with women more frequently diagnosed with MDD than men (Kessler, 2003).

Studies that found lower response rates among women (compared to men) may not have considered the relationship between *treatment type* and *response rates* between men and women (Berlim & Turecki, 2007a; M. Fava, 2003;

Kornstein & Schneider, 2001). Although studies have found that women are less likely to respond to certain types of antidepressant treatments, a similar relationship has also been found for men. For example, women have been found to be less responsive to TCAs compared to men; however, women demonstrated a preferential response to SSRIs and MAOIs compared to men (Kornstein, et al., 2000; Young, et al., 2009). The various methodological issues that may have contributed to the inclusion of female sex as a potential risk factor for TRD mainly involve the considerable variability in how patients were classified as TRD (Berman, et al., 1997). As discussed in greater detail in Chapter 7 of this present study, the current lack of a standardized and universally accepted definition or criteria for TRD has introduced a considerable degree of variability within the TRD literature (Berlim & Turecki, 2007b). The presence of variability in how TRD is defined may lead to the unavoidable presence of significant heterogeneity among TRD studies and samples.

Lifetime Duration and Treatment Resistant Severity

An examination of lifetime duration of depressive illness and MSM outcome scores found no significant relationship between lifetime duration of illness and treatment resistant severity. The lack of a relationship between lifetime duration and treatment resistant severity was an unexpected finding. Lifetime duration of depressive illness has previously been found to have a positive relationship with unresponsiveness to psychopharmacological treatments

and higher ratings of TRD (Fagiolini & Kupfer, 2003; Malhi, et al., 2005). Therefore, it was expected that patients with a longer lifetime history of depression, based on the age at which they were first diagnosed with MDD, would have higher MSM outcome scores.

An attempt to explain the lack of relationship between lifetime duration of depressive illness and treatment resistant severity has centered around three possible explanations. First, methodological issues surrounding the recruitment and composition of the patient sample used in this present study requires consideration. Although the patient sample used in this study is comparable to similar TRD studies, in terms of size and TRD severity, the task of identifying predictors of response (TRD risk factors) likely requires a much larger and generalizable sample of TRD patients (i.e. minimal exclusion criteria).

Second, due to partial reliance on self-report measures, the lifetime duration of depressive illness may have been imprecisely calculated for some study patients. The lifetime duration of depressive illness was calculated based on the patients' age at which they were first diagnosed with MDD and the age in which they completed the SCID. For the vast majority of patients in our sample, the age at which they were first diagnosed with MDD was based on patient self-report with no additional supporting documentation. Although medical records were available for the majority of our patients, these records frequently only provided a general description of the patient's first MDE (e.g. patient has been

depressed for 20 plus years; patient first diagnosed as a teenager; patient has suffered from depression most of their adult life). The exclusive reliance of self-report data, when calculating lifetime duration of illness, limits the reliability of demonstrating a lack of relationship between lifetime duration of depressive illness and treatment resistant severity.

Third, any relationship between lifetime duration of depressive illness and treatment resistant severity may involve the presence of an additional variable or set of variables. For example, the presence of a comorbid personality disorder could potentially influence any relationship between lifetime duration of illness and treatment resistant severity. The presence of a comorbid personality disorder has frequently been associated with TRD or reduced responsiveness to antidepressant treatments (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Shea, et al., 1990; Souery, et al., 2006). Personality disorders have also been found to correlate with an earlier age of onset of depression (Fagiolini & Kupfer, 2003; Kornstein & Schneider, 2001; Thase, 1996). For this present study, a patient's reported age of onset (first diagnosed with MDD) was used to calculate their lifetime duration of depressive illness; however, patients were not evaluated for an Axis II diagnosis.

This study represents the first attempt to examine the relationship between lifetime duration of depressive illness and treatment resistant severity using the MSM. Although the results of the present study provided no support for a

relationship between lifetime duration of illness and treatment resistant severity, these results do highlight the need for additional research in order to better understand the contribution of assessing lifetime duration of illness for patients classified as TRD. At minimum, these results do support the need to determine the presence and consider the impact of personality disorders when examining or attempting to identify predictors of TRD.

Duration of Current MDE and Treatment Resistant Severity

The results from this study demonstrated a significant, positive relationship between duration of current MDE and treatment resistant severity as measured by the MSM outcome score. These findings demonstrated that MDEs of longer duration were associated with higher treatment resistance severity. These findings are consistent with the current TRD literature, which has found MDEs of longer duration to be predictive of increased unresponsiveness to antidepressant treatments (M. Fava, 2003; Joyce, et al., 2002; Keller, Lavori, Endicott, Coryell, & Klerman, 1983; Kornstein & Schneider, 2001; Mynors-Wallis & Gath, 1997; Nelson, Mazure, & Jatlow, 1994).

In addition to demonstrating the construct validity of the MSM, these findings also support the inclusion of a MDE duration rating subscale within the MSM. That subscale, which was designed to factor in the length of a patient's current MDE when assessing treatment resistant severity, represents one of the defining features of the MSM compared to other TRD staging models (Fekadu,

Wooderson, Donaldson, et al., 2009; Fekadu, Wooderson, Markopoulou, et al., 2009).

By supporting the inclusion of the MDE duration subscale within the MSM, the results from this current study have brought attention to the potential value of considering the length of a patient's current MDE when determining the categorical presence of TRD. A MDE of longer duration is highly suggestive of at least some degree of treatment resistance, especially if the patient is not naïve to antidepressant treatments of adequate dose and duration. This is supported by the positive relationship between duration of current MDE and treatment resistant severity demonstrated in this current study, and the predictive value of longer duration of MDE and poor treatment response/outcome within the TRD literature (M. Fava, 2003; Joyce, et al., 2002; Keller, et al., 1983; Kornstein & Schneider, 2001; Mynors-Wallis & Gath, 1997; Nelson, et al., 1994). Therefore, as concluded by the authors of the MSM, a measure of current MDE duration, which contains a multi-categorical scoring design, can provide a more comprehensive and possibly more accurate measure of TRD (Fekadu, Wooderson, Donaldson, et al., 2009; Fekadu, Wooderson, Markopoulou, et al., 2009).

The value of considering the length of a patient's current MDE when determining the categorical presence of TRD is further supported by the ease and relative accuracy of measuring MDE duration. Determining the duration of a patient's current MDE is primarily dependent on a patient's personal account of

when their current MDE started, which can typically be obtained during a thorough clinical interview or the completion of a SCID (First, et al., 1996). Although the use of patient-reported data can bring the accuracy of this data into question, the presence of additional factors can increase confidence in this data. Unlike determining lifetime duration of depressive illness, which requires identifying the age at which a patient was first diagnosed with MDD, establishing the start of a current MDE typically involves more recent information. Also, available medical records from a physician currently providing treatment can be reviewed as a secondary source to confirm the MDE length.

Despite the lucid connection between the duration of a current MDE and treatment resistance and the ease of its measurement, the idea of using the length of a MDE to help define TRD has received little attention. In fact, the length of a patient's current MDE has not been included in any proposed definition of TRD, and has only been included in one TRD staging model prior to the MSM (Berlim & Turecki, 2007b; Bird, et al., 2002; Janicak & Dowd, 2009; Petersen, et al., 2005; Souery, et al., 1999; Thase & Rush, 1997). The European Staging Method, which is reviewed in greater detail in Section III, Chapter 6 of this current study, includes as its third and highest level of TRD the classification of Chronic Resistant Depression (CRD) (Souery, et al., 1999). Patients diagnosed with MDD are classified as CRD after demonstrating both treatment resistance to several adequate antidepressant trials and a current MDE of at least 12 months. Although

the European Staging Method acknowledges the chronic nature of TRD, the extent of this acknowledgment is limited due to the design of this staging method. The European Staging Method only includes three levels of TRD and no additional consideration is given to current MDEs of longer duration (>12 months).

Chapter 15: The Individual Depressive Symptoms of TRD

Frequency of Depressive Symptoms Based on TRD Classification

The process of examining the individual depressive symptoms of TRD was dependent on the ability to accurately identify patients with TRD from a sample of patients diagnosed with MDD. Determining the categorical presence of TRD was achieved by using a cutoff score of 7.5 on the MSM, as based on the findings of this study. This method identified 43 patients with TRD from a total sample of 88, which provided a comparison group of 45 patients without TRD. The differentiation of TRD and non-TRD allowed for both an examination of TRD depressive symptoms and a comparison of these symptoms to a non-TRD set of patients.

The most frequently endorsed individual depressive symptoms on the $HRSD_{24}$ for patients with TRD included *depressed mood*, *decreased pleasure in work and activities*, and *feelings of helplessness*, and *hopelessness*. These individual depressive symptoms were endorsed by all patients with TRD (i.e. 100% of the TRD patient sample). Of these symptoms, *depressed mood* and *decreased pleasure in work and activities* were also endorsed by all patients without TRD (i.e. 100% of the non-TRD patient sample). Three additional depressive symptoms endorsed by all patients without TRD were *middle insomnia*, *psychic anxiety*, and *somatic complaints*.

In order to gain a comprehensive description of the individual depressive symptoms of TRD, data was also examined from the IDS-SR_{30}. The IDS-SR_{30}, a self-report measure of depressive symptoms, provided a subjective description (patient-report) of the depressive symptoms experienced by patients with TRD. The utilization of the IDS-SR_{30} also allowed the examination of additional individual depressive symptoms that are not included in the $HRSD_{24}$. On the IDS-SR_{30}, all patients with TRD reported experiencing *quality of depressed mood, fatigue or loss of energy*, and *anhedonia*. The two most frequent endorsed depressive symptoms for patients without TRD (100% of the non-TRD sample) were *decreased involvement* and *fatigue or loss of energy*. A comparison of the frequency rates of individual depressive symptoms between the TRD and non-TRD samples was conducted to determine which symptoms were most endorsed for each group. The individual depressive symptoms on the $HRSD_{24}$ with the greatest difference in frequency rates between patients with and without TRD were *decreased weight* (TRD=34.9%, non-TRD=57.8%, Difference=22.9%), *hypochondriasis* (TRD=37.2%, non-TRD=55.6%, Difference=18.4%), and sex*ual interest* (TRD=88.4%, non-TRD=73.3%, Difference=15.1%). The individual depressive symptoms on the IDS-SR_{30} with the greatest difference in frequency rates between patients with and without TRD were *psychomotor agitation* (TRD=59%, non-TRD=77.8%, Difference=18.8%), *changes in appetite*

(TRD=90%, non-TRD=72.2%, Difference=17.8%), and *hypersomnia* (TRD=64.1%, non-TRD=47.1%, Difference=17%).

During the process of comparing the frequency rate for anxiety related symptoms, a consistent pattern was observed for the TRD patient sample. Specifically, patients with TRD had a lower frequency rate for every anxiety related item on the $HRSD_{24}$, and all but one on the IDS-SR_{30}. On the $HRSD_{24}$ these items included *psychic anxiety*, *sympathetic arousal*, *decreased appetite*, *somatic complaints*, *hypochondriasis*, and *loss of insight*. For the IDS-SR_{30}, the items included *anxious mood*, *sympathetic arousal*, *panic/phobic symptoms*, and *gastrointestinal symptoms*. Although the frequency rate of anxiety related symptoms was less than 5% for some items (e.g. *psychic anxiety*, *sympathetic arousal*, *somatic complaints*, and *anxious mood*), it is interesting that this pattern occurred across all but one of the anxiety related items. The consistency of this pattern could reflect an inverse relationship between TRD and anxiety related symptoms; however, this is a preliminary finding and can only be determined through additional research.

The utilization of both the $HRSD_{24}$ and IDS-SR_{30} in order to examine the frequency of individual TRD depressive symptoms has resulted in obtaining a objective and subjective account, respectively of the depressive symptoms experienced by patients with TRD. Although it was hoped that a distinct symptom profile would have been observed among patients with TRD, this

present study was unable to find such a pattern. The method used to identify endorsed items on the $HRSD_{24}$ and IDS-SR_{30} may have contributed to the inability to observe a distinct symptom profile among patients with TRD. An endorsed item on the $HRSD_{24}$ and IDS-SR_{30} was defined as any item with a score of 1 or greater. This liberal definition may have led to the inclusion of less relevant depressive symptoms. Future attempts to examine the individual depressive symptoms of TRD should consider using a more conservative scoring guideline to identify endorsed items (e.g. score of 2 or greater). Although a distinct symptom profile was not observed among patients with TRD, this study did provide an initial description of the frequency of individual TRD depressive symptoms. This description has increased our understanding of TRD symptomatology by contributing to a relatively unexplored area within the TRD literature.

Frequency of Depressive Symptoms Based on TRD Severity

The examination of individual TRD depressive symptoms based on treatment resistant severity required staging the level of treatment resistant severity for patients with TRD. In addition to identifying patients with TRD, the MSM also provided a metric for determining a patient's level of treatment resistant severity that allowed patients with TRD to be divided into tertiles based on their level of treatment resistant severity. Based on the MSM outcome scores for patients with TRD, 20 patients were placed in the bottom tertile and 16

patients were placed in the top tertile. Because lower scores on the MSM reflect a lower degree of treatment resistant severity, the bottom tertile was referred to as the Low Treatment Resistant Severity (Low-TRS) group, while the top tertile was labeled the High Treatment Resistant Severity (High-TRS) group.

Of the 24 items that comprise the $HRSD_{24}$, *depressed mood, decreased pleasure in work and activities,* and *feelings of helplessness,* and *hopelessness* were endorsed by all patients with TRD in both the Low-TRS and High-TRS groups. Three additional depressive symptoms endorsed by all the patients in the High-TRS group included *suicidal ideation, psychic anxiety,* and *somatic complaints*. All the patients in the Low-TRS group endorsed *feelings of guilt* and *middle insomnia*. On the $IDS\text{-}SR_{30}$, all patients in the High-TRS and Low-TRS groups reported experiencing *quality of depressed mood*, *fatigue or loss of energy*, and *anhedonia*. The entire High-TRS group also reported experiencing *loss of mood reactivity*, *difficulty concentrating or indecisiveness,* and *psychomotor retardation*. Additional depressive symptoms that were endorsed by all the patients with TRD in the Low-TRS group included *depressed mood* and *decreased involvement*.

A comparison of the frequency rates of individual depressive symptoms for the High-TRS and Low-TRS groups was conducted to determine which symptoms had the greatest difference between those with high and low treatment resistant severity. On the $HRSD_{24}$, the two depressive symptoms with the greatest

difference in frequency rates between the High-TRS and Low-TRS groups were *Psychomotor agitation* (High-TRS=31.3%, Low-TRS=60%, Difference=28.7%) and *late insomnia* (High-TRS=50%, Low-TRS=70%, Difference=20%). The two depressive symptoms on the IDS-SR_{30} with the greatest difference in frequency rates were *changes in weight* (High-TRS=81.3%, Low-TRS=55.6%, Difference=25.7%) and *decreased sexual interest* (High-TRS=81.3%, Low-TRS=94.1%, Difference=12.8%).

These results represent a preliminary description of the frequency rate of individual depressive symptoms for patients with TRD in terms of their level of treatment resistant severity. As with the examination of the frequency of individual depressive symptoms between patients with and without TRD, this additional examination also utilized the $HRSD_{24}$ and IDS-SR_{30}. The combined use of a clinician and patient completed measure allowed us to capture a more comprehensive description of the individual depressive symptoms experienced by those with low and high treatment resistant severity. A further comparison of the individual depressive symptoms of TRD allowed us to identify which depressive symptoms had the greatest difference in frequency rates between those with low and high treatment resistant severity. Although noticeable differences in the frequency rates for some individual depressive symptoms (*psychomotor agitation*, *late insomnia*, *changes in weight*, and *decreased sexual interest*) were observed, these differences did not constitute a distinct symptom profile. Due to the

exploratory nature in which the frequency rates of individual depressive symptoms were examined in this study, future studies are necessary in order to understand any symptom related differences between patients with low and high treatment resistant severity.

Chapter 16: Study Limitations, Future Directions, and Summary

Study Limitations

The limitations of this study have been organized under three general categories, including (1) limitations in data collection, (2) assessment related limitations, and (3) factors limiting generalizability.

Data Collection Limitations

The primary data collected for this study included a patient's antidepressant treatment history, clinical characteristics (e.g. length of MDE, depression severity), and socio-demographic variables (e.g. age, sex, race). Although the majority of this information was obtained during baseline visits as part of prospective studies, and based on the patient's current clinical status, the process of documenting a patient's antidepressant treatment history had to be completed and scored retrospectively. The process of documenting a patient's antidepressant treatment history retrospectively may introduce concerns regarding data accuracy.

For the patients included in this study, their antidepressant treatment history was based on information gathered during the completion of the ATHF and a review of any available medical records. Although the ATHF has been empirically validated in studies involving antidepressant treatment outcome (Sackeim, 2001), completion of this measure was heavily based on a patient's ability to recall specific aspect of his or her prior antidepressant treatment

regimens. For example, to adequately complete the ATHF, a patient must be able to list all his or her prior antidepressant treatments including the dose, duration, and therapeutic outcome (e.g. partial improvement, no change, worse). To highlight the difficulty in obtaining all this information, of the 262 patients who met study criteria, 174 were excluded due to incomplete antidepressant treatment histories. Although medical records were available for some patients, which helped to further document their treatment history, the utility of these records was inconsistent. For example, there was considerable variability in how physicians documented changes to a patient's antidepressant medication, which in some cases made it difficult to determine adequate dose and duration.

The duration of a patient's current MDE and their lifetime duration of depressive illness are two additional variables that were determined primarily by patient self-report. These two variables were assessed during the completion of the SCID-I (First, et al., 1996), which documents clinical characteristics. Although the SCID-I is a semistructured diagnostic interview, and for this study was administered by trained certified clinicians, it still requires patients to recall specific details including the start date of their current MDE and the age at which they were first diagnosed with MDD. Patients who have a current MDE of long duration or were first diagnosed with MDD at a very young age may have difficulty accurately recalling this information. Available medical records were

useful to document the length of the current MDE, but they did not always provide the age at which a patient was first diagnosed with MDD.

Although collecting data retrospectively brings the accuracy of the data into question, documenting a patient's prior and current antidepressant treatment history is an essential step in the process of establishing the presence of TRD. Treatment failures are considered a core component of TRD that have been incorporated in every proposed TRD definition and staging method. Given the importance of collecting this data, it may be necessary to develop a more convenient method for documenting a patient's antidepressant treatments.

Assessment Related Limitations

There are three assessment related limitations of this study. The first involves the combined use of the $HRSD_{24}$ and IDS-SR_{30} to determine the individual depressive symptoms of TRD. These two measures were selected because of their individual strengths and as a means of obtaining a comprehensive account of the depressive symptoms experienced by patients with TRD. The $HRSD_{24}$, which is largely considered the "gold standard" for rating depressive symptoms and severity, provided an objective (clinician administered) measure of individual depressive symptoms. To supplement the $HRSD_{24}$, the IDS-SR_{30} was used to obtain a subjective (patient-rated) measure of the individual depressive symptoms experienced by patients with TRD. Despite the individual strengths of

these two depression rating instruments, differences in their design make it difficult to compare or interpret certain items.

Differences between the $HRSD_{24}$ and IDS-SR_{30} include the inclusion/exclusion of different items and differences in the definition and measurement of certain depressive symptoms. For example, the $HRSD_{24}$ includes 7 items (e.g. *feelings of guilt*, *feelings of helplessness*, etc.) that are not included in the IDS-SR_{30}, while the IDS-SR_{30} included 13 items (e.g. *difficulty concentrating*, *hypersomnia*, etc.) not included on the $HRSD_{24}$. See Table 2 for a complete comparison of the different items included in these two measures. A more subtle difference between these measures involves how the $HRSD_{24}$ and IDS-SR_{30} measure identical symptoms. For example, both of these instruments measure *anxious mood*; however, the $HRSD_{24}$ measures this symptom with one item that includes two domains (i.e. anxiety and irritability), while the IDS-SR_{30} separates those two domains into separate, unique items. These differences, although slight, introduce variability that minimizes the ability to comprehensively compare certain items (i.e. depressive symptoms) between these two measures. Future attempts to describe the individual depressive symptoms of TRD should consider using the IDS-C_{30} in place of, or in addition to the $HRSD_{24}$. Because the IDS-C_{30} was developed in combination with the IDS-SR_{30}, these measures provide a more comparable objective and subjective account of a patient's depressive symptom profile.

The second assessment related limitation of this study involves the use of two different prescription guidelines to determine the adequacy (dose and duration) of an antidepressant medication. As described in Section V, Chapter 11, two different methods (SD-TRD and MSM) were used to identify patients with TRD. The SD-TRD defined TRD based on the failed response to at least two adequate trials of antidepressant treatments from different classes of drug. The MSM defined TRD as a cutoff score of 7.5, which was identified during this study as the optimal cutoff score for differentiating TRD from non-TRD. Both of these methods required determining the total number of treatment failures for each patient, only counted treatment failures of adequate dose and duration, and used different guidelines to determine adequate dosing and duration of a treatment.

The SD-TRD used the prescription guidelines outlined in the ATHF (Sackeim, 2001), which requires that a treatment be taken at an adequate dose for at least four weeks. For the MSM, adequate dosing was determined using the prescription guidelines outlined in the *Maudsley Prescribing Guidelines* (D. Taylor, et al., 2010), and required treatments to be taken for at least six weeks. The use of different prescription guidelines means that an antidepressant medication can be considered an adequate treatment failure for the MSM and inadequate for the SD-TRD, or vice versa. For example, the minimum effective (i.e. adequate) dose for the antidepressant drug sertraline is 50 mg under the *Maudsley Prescribing Guidelines* (D. Taylor, et al., 2010) and 100 mg under the

ATHF guidelines (Sackeim, 2001). This demonstrates how an antidepressant medication trial can be considered an adequate treatment failure when using the MSM, but inadequate with the SD-TRD. Refer to Table 9 for a list of antidepressant medication and the different dosage guidelines for the ATHF and MSM.

This study was unable to determine if the decision to use two different prescription guidelines had any significant effect on its findings. However, the use of different prescription guidelines does introduce a new variable that was not accounted for in this study. Although an obvious solution for future studies would be to apply the same prescription guidelines to both the SD-TRD and MSM, there is currently no consensus regarding which prescription guidelines to use when determining the adequacy of an antidepressant medication (Berlim & Turecki, 2007a; Janicak & Dowd, 2009; Souery, et al., 1999). There is also a similar degree of discord within the literature regarding how long an antidepressant medication needs to be taken in order to constitute an adequate duration. The length of time that has been used to establish an antidepressant treatment as being of adequate duration has ranged from 4 to 12 weeks (Bird, et al., 2002; M. Fava, 2003; Sackeim, 2001). The potential impact of using two different prescription guidelines should be considered when designing and conducting future studies that compare the MSM to other TRD definitions or staging models.

The third assessment related limitation of this study involves the decision to not screen or evaluate patients for DSM-IV-TR Axis II personality disorders. Although the main objectives of this study did not involve or require an examination of personality disorders, a strong relationship between comorbid personality disorders and TRD has recently been found in the literature (Berlim & Turecki, 2007a; Fagiolini & Kupfer, 2003; Janicak & Dowd, 2009; Kornstein & Schneider, 2001; Shea, et al., 1990; Souery, et al., 2006; Thase, 1996). Specifically, personality disorders have been found to be associated with reduced responsiveness to antidepressant treatments. Determining the extent and type of personality disorders within our sample could have helped to explain certain unexpected findings. For example, this study did not find a significant relationship between a patient's lifetime duration of depressive illness and their level of treatment resistant severity, which was unexpected based on prior studies (Fagiolini & Kupfer, 2003; Malhi, et al., 2005). The presence of a comorbid personality disorder could have potentially mediated the relationship between a patient's lifetime duration of illness and level of treatment resistant severity. Given the relationship between personality disorders and treatment resistance, screening study patients for a DSM-IV-TR Axis II diagnosis should be included in future TRD studies.

Factors Limiting Generalizability

The final limitation of this study involves the presence of certain factors that may have affected the generalizability of the study. These factors include a modest sample size, certain exclusion criteria, and the source and location of patient recruitment. The reduction of a study's generalizability can often be interpreted as a reduction in the study's clinical application, utility, and relevance. As such, these factors should be considered when interpreting or applying these study results.

The first factor limiting the generalizability of the results from this study involves the modest size of the patient sample. Due to the modest size of this study's sample, certain socio-demographic variables may have been underrepresented. For example, the study sample did not include any African-American patients and only 6.8% of the sample was comprised of participants who were of Asian, Hispanic, or Pacific Islander ethnicity. This potential decrease in the external validity of this study, in terms of representing patients of different ethnicities, should be considered when diagnosing underrepresented racial or ethnic groups with TRD. Although conducting future TRD studies with patient samples that have more racial variability and are more representative would be ideal, this may be difficult given the considerable effort conducting large scale TRD studies. An alternative may be to try and replicate this study in

different geographic regions or treatment facilities, which might provide a greater level of racial diversity.

Certain age cohorts were also underrepresented in this study. Although the age for the overall patient sample ranged from 21 to 84, due to the size of the sample, the upper and lower reaches of this range were represented only partially. This partial representation is evident when considering that the mean age of the sample was 52.1 with a standard deviation of 15.5. Therefore the age of the majority of patients (65.9%) fell between 36.6 and 67.6 (M ± SD), with the remaining patients only representing 15.9% and 18.2% or the lower and upper ends, respectively. Because of the limited number of patients whose age was below 36.6 or above 67.6, it is unclear to what extent the results from this study are reflective of patients below or above these ranges.

The second factor limiting the generalizability of these results was the decision to use specific exclusion criteria during the screening and enrollment process. Although establishing exclusion criteria helps to limit the introduction of potential confounding variables, it also reduces the overall heterogeneity of the study cohort. The exclusion criteria used for this study specifically excluded patients who had an active, unstable, or serious medical condition that increased the risk of ECT, as well as patients with an active substance abuse or dependence disorder. The exclusion of patients with significant or unstable medical conditions or a substance related disorder is commonly practiced when

conducting both ECT and TRD related research (Kellner, et al., 2010; Kellner, et al., 2006; Lisanby, Maddox, Prudic, Devanand, & Sackeim, 2000; Malone, et al., 2009; Navarro, et al., 2008; Papakostas, Petersen, Denninger, et al., 2003; Papakostas, Petersen, Pava, et al., 2003; Petersen, et al., 2001; Petersen, et al., 2004; Sackeim, Haskett, et al., 2001; Sackeim, et al., 2000). However, due to the relationship between medical and psychiatric comorbidity and TRD, the decision to exclude these patients warrants consideration when interpreting the results from any TRD study.

Medical comorbidity has been described as a potential risk or contributing factor for the occurrence of TRD. General medical conditions that may contribute to TRD, due to not being diagnosed or adequately managed, include diabetes, coronary artery disease, cancer, and chronic pain (Kornstein & Schneider, 2001; Sonawalla, et al., 2002). A comorbid medical condition can interfere with both antidepressant treatment efficacy and patient compliance (Berlim & Turecki, 2007a; Bird, et al., 2002; M. Fava, 2003; Sharan & Saxena, 1998). A similar relationship involving substance related comorbidity and TRD has also been consistently reported in the literature. The lifetime prevalence rate of a comorbid alcohol or drug related disorder among MDD has been reported at 40.3% and 17.2%, respectively (Hasin, et al., 2005). The effects of substance use can cause both an increase in depressive symptom severity and a decrease in a patient's treatment compliance (Kornstein & Schneider, 2001). Even just modest alcohol

use has been associated with greater antidepressant treatment resistance (Castaneda, Sussman, Westreich, Levy, & O'Malley, 1996; Worthington, et al., 1996). Given the relationship between medical and substance related comorbidity and TRD, the decision to exclude patients with these conditions likely decreases the external validity of this study's findings. Therefore, the extent to which these results can be considered a representation of the variability that can occur between TRD patients with and without a comorbid medical or substance related disorder is currently unclear and should be considered when designing future TRD studies.

The third factor limiting the generalizability of these results involved the source and location of patient recruitment. All the patients included in this study were recruited from one clinical site, the Neurostimulation Laboratory at UTSW (Dallas, TX). Due to the absence of multicenter patient recruitment, the results of this study are based on a region specific sample, which may have constrained the population sociodemographic characteristics. The four clinical trials that patients were recruited from all involved some form of neurostimulation treatment (e.g. ECT, MST). Thus, all study patients had to meet similar physical health and safety guideline, which represents an additional restriction to sample heterogeneity. Future studies should attempt to include a more heterogeneous patient sample in order to further evaluate the generalizability of these current findings, as well as the overall clinical application and relevance of the MSM.

The extent to which these limitations have influenced the results of this study is not entirely clear; however, they should be considered when interpreting these results and designing future TRD studies. Many of these limitations can be addressed by the use of a larger sample size, performing additional clinical assessments, and having less restrictive exclusion criteria.

Future Research Directions

Future MSM Research

The results from this study have provided support for the MSM in terms of its construct validity and potential application as a means of differentiating TRD from non-TRD and measuring treatment resistant severity. The ability to identify patients with TRD and then further differentiate their level of treatment resistant severity has allowed this study to describe individual depressive symptoms experienced by patients with TRD. Though these results have demonstrated the potential application of the MSM and provided a greater understanding of TRD symptomatology, future research is warranted to determine which prescription guidelines should be used to determine the adequacy of failed antidepressant treatments. The prescription guidelines used for the MSM are based on the prescription guidelines outlined in the *Maudsley Prescribing Guidelines* (D. Taylor, et al., 2010), which for certain antidepressants, differ significantly from the more commonly used ATHF guidelines (Sackeim, 2001). Future studies are

needed to determine what impact using different prescription guidelines will have on a patient's MSM score and their TRD classification.

Additional research is also needed to further evaluate the individual subscales that comprise the MSM. This will help to identify potential modifications that may improve the psychometrics of the MSM. For example, restructuring the MDE duration rating subscale within the MSM is a modification that could potentially enhance the accuracy of the MSM. The results from this study demonstrated a significant, positive relationship between duration of current MDE and treatment resistant severity as measured by the MSM outcome score, and provided support for the inclusion of a MDE duration rating subscale within the MSM. The MDE duration rating subscale has three categorical parameters based on the length of a patient's current MDE (*Acute* ≤ 12 months, *Sub-acute* 13-24 months, and *Chronic* > 24 months). Scoring is based on a three point scale 1 point assigned to *Acute*, 2 points assigned to *Sub-acute*, and 3 points assigned to *Chronic*. Given the positive relationship between the duration of a patient's current MDE and their level of treatment resistant severity, which has consistently been supported in the TRD literature, expanding the MDE duration rating subscale or increasing its scoring may provide a better measure of treatment resistance (M. Fava, 2003; Joyce, et al., 2002; Keller, et al., 1983; Kornstein & Schneider, 2001; Mynors-Wallis & Gath, 1997; Nelson, et al., 1994). An effort to increase the weight or scoring of this subscale is also supported by the connection

between MDE duration and treatment resistance, as well as the relative ease of measuring the duration of a MDE compared to determining a patient's entire antidepressant treatment history.

Guidelines for Future TRD Research

The process of reviewing the TRD literature and designing this study have also helped to identify additional recommendation that should be considered when designing and conducting future TRD studies. The most essential recommendation for all future TRD research is the adoption of a universal definition of TRD. The absence of a universal definition of TRD has contributed to the frequent misclassification of patients as having TRD, which has been further exacerbated due to the wide variation in different definitions of TRD that have been proposed and used in the literature (M. Fava, 2003; Sackeim, 2001). The frequent use of different TRD definitions has also limited the extent to which the results from different TRD studies can be interpreted collectively. This in part may account for inconsistency regarding potential risk factors for TRD and ideal treatment recommendations.

Given the current lack of consensus regarding the definition of TRD, an intermediate recommendation would be for studies to include a more comprehensive description of how they defined the presence of TRD. This definition should include outlined criteria for defining TRD, the source of patients' antidepressant treatment history, and prescription guidelines for

establishing the adequacy (dose and duration) of failed antidepressant treatments. Due to the continued debate regarding what constitutes an adequate dose and duration, the specific prescription guidelines that were used should be indicated and described for each TRD study (Bird, et al., 2002; M. Fava, 2003; Sackeim, 2001). Establishing a universal definition of TRD will be the inevitable solution, but in the interim, providing greater detail of how studies define TRD may help to increase the interpretability of result from different TRD studies.

Study Summary

The primary objective of this study was to evaluate the Maudsley Staging Method (MSM) in order to obtain a more comprehensive understanding of its psychometric properties and utility as a method of differentiating TRD from non-TRD. Accomplishing this objective involved determining a reliable cutoff score for the MSM to differentiate TRD from non-TRD, and examining the agreement between the MSM and another commonly used method of defining TRD. This required establishing the Standard Definition for TRD (SD-TRD), which was used to compare the accuracy of the MSM at differentiating TRD from non-TRD. The SD-TRD defined TRD based on the failed response to at least two adequate trials of antidepressant treatments from different classes of drug, which is the most commonly agreed upon definition of TRD within the literature (Ananth, 1998; Berlim & Turecki, 2007a; Bird, et al., 2002; Janicak & Dowd, 2009; Keller, 2005; Rush, Thase, et al., 2003). This evaluation of the MSM also involved

examining the construct validity of the MSM by exploring various clinical characteristics and socio-demographic variables that have been found to be positively associated with treatment resistance. As a secondary objective, this study also used the MSM to identify patients with TRD in order to perform a preliminary examination of the frequency of individual TRD depressive symptoms.

This study was successful in identifying an optimal cutoff score for the MSM for differentiating TRD from non-TRD, and demonstrating a moderate degree of agreement (Landis & Koch, 1977) between the MSM and the SD-TRD. The identification of an accurate cutoff score and extent of agreement between the MSM and SD-TRD indicated that the MSM can be used to operationally define and accurately identify patients with TRD. The extent of agreement between the MSM and SD-TRD also supports the multidimensional design of the MSM and the proposed complexity of TRD. A comprehensive understanding and definition of TRD is believed to include an evaluation of illness severity and duration versus relying exclusively on treatment failures. This study supported the need for future research to consider the relevance and value of including measures of illness severity and duration when attempting to measure or define TRD.

Evaluating the construct validity of the MSM involved exploring both clinical characteristics and socio-demographic variables. Among the three clinical characteristics that were explored, symptom severity and current MDE

duration were both found to have a significant, positive relationship with the MSM outcome score. These findings provided support for the construct validity of the MSM as a measure of treatment resistant severity. The clinical characteristic that was unrelated to the MSM was lifetime duration of depressive illness. This was an unexpected finding based on the TRD literature, which has previously demonstrated a positive relationship between lifetime duration of depressive illness and treatment resistance (Fagiolini & Kupfer, 2003; Malhi, et al., 2005). Although it is currently unclear why no relationship was found, possible explanations include reliance on imprecise, self-report measures for lifetime duration of depressive illness and a lack of consideration for potential baseline variables (e.g. personality disorders) needed for this relationship to be present. These factors should be considered in future studies.

The socio-demographic variables that were explored to demonstrate the construct validity of the MSM included age and female sex. Based on existing TRD literature, increases in age were expected to be positively associated with the MSM outcome score, and women were expected to demonstrate significantly higher MSM outcome scores. However, neither of these socio-demographic variables were found to be related to higher MSM outcomes scores (i.e. higher treatment resistant severity). Age was actually found to be significantly negatively correlated with the MSM, meaning that increases in age were found to be associated with lower treatment resistant severity. A possible explanation for

the negative relationship between age and the MSM involves the restricted age range of the study sample. Although the age range for the patients in this sample was 21 to 84, the vast majority of patients were between the ages of 36.6 and 67.6. Therefore, ages above and below these ranges were not adequately represented.

Although the failure to detect a significant difference between treatment resistant severity for men and women may have been the result of methodological limitations, these findings can also be interpreted as support against classifying female sex as a risk factor for TRD. The literature has become more critical of the relationship between female sex and treatment resistance, and various factors have been proposed that may have contributed to its inclusion as a possible risk factor for TRD. Two of these factors involve the differences in prevalence rates of depression for men and women and gender differences in treatment response based on treatment type. An inadequate consideration of these factors may have contributed to higher prevalence rates of TRD among female patients. Although these findings were unexpected, it is not yet clear if these results should be viewed as evidence against the validity of the MSM as a measure to define treatment resistant severity.

This study was successful at obtaining an initial description of the frequency of individual depressive symptoms experienced by patients who were identified as having TRD. In addition, this study was able to use the MSM to

further divide patients with TRD in terms of their level of treatment resistant severity, which allowed a further examination of the individual depressive symptoms of TRD. This description of the individual depressive symptoms of TRD is based on data from both a clinician ($HRSD_{24}$) and patient ($IDS\text{-}SR_{30}$) completed measure, and as a result, represents an objective and subjective account of the depressive symptoms experienced by patients with TRD. Although this examination was exploratory in nature and unable to detect a distinct symptom profile for TRD, it has provided an initial description of the frequency of individual depressive symptoms of TRD, which is currently a relatively unexplored area.

Despite the accomplishments of this study, additional research is warranted with regard to TRD. The MSM should be further evaluated outside of a research setting in order to determine its practical use in a clinical setting. Although some of the limitations of this study are specific to the MSM, many are relevant to TRD research in general and should be considered when designing and conducting future TRD studies.

SECTION VIII – TABLES, FIGURES, AND REFERENCES

TABLE 1

DSM-IV-TR DIAGNOSTIC CRITERIA FOR MDE

Symptom	Description	Duration
1. Depressed Mood	Subjectively reported or observed by others	Most of the day Nearly everyday
2. Anhedonia	Significant reduction or loss of interest or pleasure in most activities	Most of the day Nearly everyday
3. Changes in Weight or Appetite ▪ Weight – Gain/Loss ▪ Appetite – Increase/Decrease	Changes must occur in the absence of dieting	Nearly everyday
4. Sleep Disturbances ▪ Insomnia ▪ Hypersomnia ▪ Mixed Insomnia/Hypersomnia	Insomnia or hypersomnia	Nearly everyday
5. Psychomotor Changes ▪ Psychomotor Agitation ▪ Psychomotor Retardation	Must be severe enough to be observed by others	Nearly everyday
6. Fatigue or Loss of Energy	Decreased energy or tiredness that reduces efficiency or makes it hard to complete simple tasks	Nearly everyday
7. Worthlessness or Guilt ▪ Feelings of Worthlessness ▪ Feelings of Excessive Guilt	An unrealistically negative evaluation of one's worth or excessive or inappropriate guilt	Nearly everyday
8. Difficulty Concentrating or indecisiveness	Subjectively reported or observed by others	Nearly everyday
9. Suicidal Ideation	Recurring thoughts of death, suicidal ideation, or suicide attempts	Frequency and duration can vary

❖ Five or more of these symptoms must be present for a minimum of two weeks, and one of these symptoms must be (1) depressed mood or (2) anhedonia

Abbreviations: DSM-IV-TR, Diagnostic Statistical Manual of Mental Disorders 4th Edition Text Revision; MDE, Major Depressive Episode

TABLE 2

COMPARISON OF DSM-IV-TR MDE, DEPRESSIVE SUBTYPES, IDS-SR$_{30}$, AND HRSD$_{24}$ SYMPTOMS

	DSM-IV-TR			Depression Rating Instrument	
	MDD	**Melancholic**	**Atypical**	**HRSD**	**IDS**
Mood Related Disturbances					
1. Depressed Mood	X			X	X
2. Irritable Mood					X
3. Anxious Mood				X	X
Cognitive Disturbances					
4. Feelings of Hopelessness				X	X
5. Feelings of Helplessness				X	
6. Feelings of Worthlessness	X			X	X
7. Feelings of Guilt	X	X		X	
8. Difficulty Concentrating/Indecisiveness	X				X
9. Interpersonal Sensitivity			X		X
10. Suicidal Ideation	X			X	X
Somatic Related Symptoms					
11. Somatic Complaints (Pain)				X	X
12. Fatigue or Loss of Energy	X				X
13. Leaden Paralysis/Physical Energy			X		X
14. Psychomotor Agitation	X	X		X	X
15. Psychomotor Retardation	X	X		X	X
16. Increase in Weight	X		X		X
17. Decrease in Weight	X	X		X	X
18. Increase in Appetite	X		X		X
19. Decrease in Appetite	X			X	X

Table Continues

TABLE 2 continued

COMPARISON OF DSM-IV-TR MDE, DEPRESSIVE SUBTYPES, IDS-SR$_{30}$, AND HRSD$_{24}$ SYMPTOMS

	DSM-IV-TR			Depression Rating Instrument	
	MDD	**Melancholic**	**Atypical**	**HRSD**	**IDS**
Anxiety Related Symptoms					
20. Sympathetic Arousal				X	X
21. Panic/Phobic Symptoms					X
22. Gastrointestinal					X
23. Hypochondriasis				X	
24. Obsessional/Compulsive				X	
25. Paranoid Symptoms				X	
26. Depersonalization or Derealization				X	
Endogenous Related Symptoms					
27. Quality of Depressed Mood		X			X
28. Loss of Mood Reactivity		X			X
29. Diurnal Variation of Mood		X		X	X
30. Anhedonia	X				X
31. Involvement	X			X	X
32. Pleasure or Enjoyment	X	X		X	
33. Sexual Interest				X	X
Sleep Related Disturbances					
34. Insomnia	X				
35. Hypersomnia	X		X		X
36. Insomnia Initial				X	X
37. Insomnia Middle				X	X
38. Insomnia Late		X		X	X

Abbreviations: MDE, Major Depressive Episode; DSM, Diagnostic Statistical Manual of Mental Disorders 4th Edition Text Revision; HRSD$_{24}$, Hamilton Rating Scale for Depression 24-Item; IDS-SR$_{30}$, Inventory of Depressive Symptomatology Self-Report 30-Item.

TABLE 3

THASE AND RUSH STAGING METHOD – ANTIDEPRESSANT TREATMENT RESISTANCE

Stage	Description
▪ Stage 0	Any medication trials, to date, determined to be inadequate
▪ Stage I	Failure of at least 1 adequate trial of 1 major class of antidepressants
▪ Stage II	Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants
▪ Stage III	Stage II resistance plus failure of an adequate trial of a tricyclic antidepressant
▪ Stage IV	Stage III resistance plus failure of an adequate trial of an monoamine oxidase inhibitor
▪ Stage V	Stage IV resistance plus a course of bilateral electroconvulsive therapy

(Thase & Rush, 1997)

TABLE 4

MASSACHUSETTS GENERAL HOSPITAL STAGING METHOD FOR TREATMENT RESISTANT-DEPRESSION

Stage	Description	Points Toward Resistance Score
1	No response to each adequate (at least 6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant	1 point per trial (overall score of resistance)
2	Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire)	0.5 point per trial per optimization/strategy
3	Electroconvulsive therapy	3 points

(Petersen, et al., 2005)

TABLE 5

THE EUROPEAN STAGING METHOD FOR TREATMENT-RESISTANT DEPRESSION

Stage	Definition	Duration of Trial
A. Nonresponder	Nonresponse to 1 adequate antidepressant trial of: TCA, SSRI, MAOI, SNRI, ECT, or Other antidepressant(s)	6-8 weeks
B. Treatment Resistant Depression (TRD)	Resistance to 2 or more adequate antidepressant trials	TRD 1:12-16 weeks TRD 2: 18-24 weeks TRD 3: 24-32 weeks TRD 4: 30-40 weeks TRD 5: 36 weeks-1 year
C. Chronic Resistant Depression (CRD)	Resistance to several antidepressant trials, including augmentation strategy	At least 12 months

Abbreviations: TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitors; MAOI, monoamine oxidase inhibitors; SNRI serotonin-norepinephrine reuptake inhibitors; ECT, electroconvulsive therapy.

(Souery, et al., 1999)

TABLE 6

MAUDSLEY STAGING METHOD FOR TREATMENT RESISTANT DEPRESSION – RECOMMENDED SCORING CONVENTIONS

Parameter/Dimension	Parameter Specification	Score
Duration	Acute (≤ 12 months)	1
	Sub-acute (13-24 months)	2
	Chronic (> 24 months)	3
Symptom Severity (at baseline)	Subsyndromal	1
	Syndromal	
	▪ Mild	2
	▪ Moderate	3
	▪ Severe without psychosis	4
	▪ Severe with psychosis	5
Treatment Failures		
▪ Antidepressants	Level 1: 1 – 2 Medications	1
	Level 2: 3 – 4 Medications	2
	Level 3: 5 – 6 Medications	3
	Level 4: 7 – 10 Medications	4
	Level 5: > 10 Medications	5
▪ Augmentation[1]	Not Used	0
	Used	1
▪ Electroconvulsive Therapy	Not Used	0
	Used	1
Total		(15)

[1] Augmentation refers exclusively to the use of medication. Non-pharmacological treatments e.g. psychotherapy are not rated.

(Fekadu, Wooderson, Donaldson, et al., 2009)

TABLE 7

TREATMENT RESISTANT DEPRESSION DEFINITIONS USED IN RANDOMIZED CONTROLLED TRIALS

Required Number and Type of Antidepressant Failures		
Number of Failures	**Type of Failures**	**Number of Studies**
= 1 Antidepressant Treatment	Any Class of Drug	5
≥ 1 Antidepressant Treatment	Any Class of Drug	8
= 2 Antidepressant Treatment	Any Class of Drug	6
= 2 Antidepressant Treatment	Different Classes of Drug	3
≥ 2 Antidepressant Treatment	Different Classes of Drug	9
≥ 2 Antidepressant Treatment	Different Classes of Drug	8

(Berlim & Turecki, 2007b)

TABLE 8

HRSD AND IDS – INDIVIDUAL ITEM GRADING/SCORING GUIDELINES

	HRSD (24-items)		IDS (30-items)
Item Score	**Items Scored 0-4**	**Items Scored 0-2**	**Items Scored 0-3**
0	– Symptom Absent	– Symptom Absent	– Symptom Absent
1	– Mild, Trivial	– Doubtful, Trivial, Mild	– Mild
2	– Moderate	– Clearly Present	– Moderate
3	– Severe		– Severe
4	– Incapacitating		

Abbreviations: HRSD, Hamilton Rating Scale for Depression; IDS, Inventory of Depressive Symptomatology

TABLE 9

ANTIDEPRESSANT MEDICATION – MINIMUM EFFECTIVE DOSING

Drug Class	Antidepressant Medication		Minimum Effective Dosage	
	Generic Name	**Trade Name**	**ATHF**	**MSM**
SSRIs	▪ citalopram	▪ Celexa	20	20
	▪ escitalopram	▪ Lexapro	10	10
	▪ fluoxetine	▪ Prozac	20	20
	▪ fluvoxamine	▪ Luvox	200	50
	▪ paroxetine	▪ Paxil	20	20
	▪ sertraline	▪ Zoloft	100	50
TCAs	▪ amitriptyline	▪ Elavil	200	75
	▪ clomipramine	▪ Anafranil	200	75
	▪ doxepin	▪ Sinequan	200	75
	▪ imipramine	▪ Tofranil	200	75
	▪ nortriptyline	▪ Pamelor	76	75
	▪ trimipramine	▪ Surmontil	200	75
	▪ Desipramine	▪ Norpramin	200	200
	▪ maprotiline	▪ Ludiomil	200	200
	▪ protriptyline	▪ Vivactil	41	41
MAOIs	▪ isocarboxazid	▪ Marplan	41	30
	▪ phenelzine	▪ Nardil	61	60
	▪ tranylcypromine	▪ Parnate	41	20
	▪ selegiline	▪ Eldepryl	41	41
	▪ Selegiline (TD)	▪ EMSAM	9	6
SNRIs	▪ duloxetine	▪ Cymbalta	40	60
	▪ venlafaxine	▪ Effexor	225	75
TeCAs	▪ mirtazapine	▪ Remeron	30	30
	▪ amoxapine	▪ Asendin	400	400
SARIs	▪ nefazodone	▪ Serzone	300	300
	▪ trazodone	▪ Desyrel	400	150
NRI	▪ Reboxetine	▪ Vestra	8	8
NDRI	▪ bupropion	▪ Wellbutrin	300	N/A

Abbreviations: ATHF, Antidepressant Treatment History Form; MSM, Maudsley Staging Method; TD, Transdermal; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitors; SNRI serotonin-norepinephrine reuptake inhibitor; TeCA, tetracyclic antidepressant; SARI, serotonin antagonist and reuptake inhibitors; NRI, norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor.

(Fekadu, Wooderson, Donaldson, et al., 2009; Sackeim, 2001)

TABLE 10

SOCIO-DEMOGRAPHIC CHARACTERISTICS – TOTAL SAMPLE

		Total Sample (N = 88)	
Socio-demographic Variables		**% or Mean**	**N or (SD)**
Age (M ± SD)	▪ Years	52.1	(15.5)
Gender (%)	▪ Male	42.0%	37
	▪ Female	58.0%	51
Race (%)	▪ White	93.2%	82
	▪ Asian	2.3%	2
	▪ Hispanic	3.4%	3
	▪ Pacific Islander	1.1%	1
Relationship Status (%)	▪ Single	22.7%	20
	▪ Married	54.5%	48
	▪ Separated	3.4%	3
	▪ Divorced	13.6%	12
	▪ Widowed	5.7%	5
Living Situation (%)	▪ Alone	22.7%	20
	▪ Family	20.5%	18
	▪ Spouse or Significant Other	52.3%	46
	▪ Other	2.3%	2
	▪ Unknown	2.3%	2
Education (%)	▪ Graduate Degree or Some Graduate Work	18.2%	16
	▪ 4 Year College Degree	30.7%	27
	▪ 2 Year College Degree	12.5%	11
	▪ Some College (No Degree)	15.9%	14
	▪ High School Degree or GED	14.8%	13
	▪ Some High School or Less	4.5%	4
Employment (%)	▪ Employed	25.0%	22
	▪ Unemployed	52.5%	46
	▪ Retired	22.7%	20

Abbreviations: SD, Standard Deviation.

TABLE 11

CLINICAL FEATURES – TOTAL SAMPLE

		Total Sample (N = 88)[1]	
Clinical Variables		**% or Mean**	**N or (SD)**
Course Features	▪ Recurrent Depression	95.5%	84
	▪ Chronic Depression	26.1%	23
	▪ Postpartum Onset	2.3%	2
Number of MDEs	▪ Mean No. of MDE (N=65)	3.4	(3.1)
	□ 0 - 1 MDE	14.7%	13
	□ 2 - 3 MDE	33.0%	29
	□ 4 - 5 MDE	17.0%	15
	□ > 5 MDE	8.9%	8
Duration of MDE	▪ Mean No. of Months (N=80)	22.0	(39.1)
	□ Acute (≤ 12 months)	69.3%	61
	□ Sub-acute (13-24 months)	8.0%	7
	□ Chronic (> 24 months)	22.7%	20
Symptom Features	▪ Melancholic	88.6%	78
	▪ Psychotic	13.6%	12
	▪ Atypical	5.7%	5
	▪ Catatonic	0.0%	0
Depression Severity	▪ Mean $HRSD_{24}$ (N=86)	34.3	(5.8)
	▪ Mean CGI	5.1	(0.9)
	▪ Mean $IDS\text{-}SR_{30}$ (N=72)	45.2	(10.7)
	▪ Mean GAF (N=46)	43.2	(13.7)
Additional Features	▪ Mean No. of Psychiatric Hospitalizations [2]	2.4	(2.8)
	▪ Mean MSM Score	7.7	(1.9)
	▪ Mean MMSE Score (N=87)	27.2	(2.8)

[1] The total number of patients included was 88. However, due to incomplete patient histories, not all variables were calculated base on this number. Variables calculated based on a different number of patients are noted above.

[2] One patient was considered an outlier (reporting 150 psychiatric hospitalizations) and was excluded from the mean number of psychiatric hospitalizations for the sample.

Abbreviations: SD, Standard Deviation; MDE, Major Depressive Episode; $HRSD_{24}$, Hamilton Rating Scale for Depression-24 Item; CGI, Clinician Global Impression; $IDS\text{-}SR_{30}$, Inventory of Depressive Symptomatology-Self Report; GAF, Global Assessment of Functioning Scale; MSM, Maudsley Staging Method; MMSE, Mini-Mental State Examination.

TABLE 12

FREQUENCY OF ADEQUATE ANTIDEPRESSANT TRIALS BASED ON THE MSM DOSE AND DURATION GUIDELINES – TOTAL SAMPLE

		Total		Adequate		Inadequate	
Class	**Medication**	**%**	**N**	**%**	**N**	**%**	**N**
SSRI's	▪ Escitalopram	42.0%	37	35.2%	31	6.8%	6
	▪ Citalopram	25.0%	22	19.3%	17	5.7%	5
	▪ Paroxetine	27.3%	24	18.2%	16	9.1%	8
	▪ Sertraline	31.8%	28	27.3%	24	4.5%	4
	▪ Fluvoxamine	1.1%	1	1.1%	1	0.0%	0
	▪ Fluoxetine	29.5%	26	27.3%	24	2.3%	2
SNRI's	▪ Duloxetine	27.3%	24	19.3%	17	8.0%	7
	▪ Venlafaxine	45.5%	40	34.1%	30	11.4%	10
	▪ Desvenlafaxine	9.1%	8	5.7%	5	3.4%	3
MAOI's	▪ Phenelzine	5.7%	5	2.3%	2	3.4%	3
	▪ Selegiline	0.0%	0	0.0%	0	0.0%	0
	▪ Tranylcypromine	4.5%	4	4.5%	4	0.0%	0
	▪ Isocarboxazid	0.0%	0	0.0%	0	0.0%	0
	▪ Selegiline (TD)	5.7%	5	3.4%	3	2.3%	2
TCA's	▪ Amitriptyline	5.7%	5	3.4%	3	2.3%	2
	▪ Imipramine	4.5%	4	3.4%	3	1.1%	1
	▪ Desipramine	5.7%	5	2.3%	2	3.4%	3
	▪ Trimipramine	0.0%	0	0.0%	0	0.0%	0
	▪ clomipramine	3.4%	3	1.1%	1	2.3%	2
	▪ maprotiline	0.0%	0	0.0%	0	0.0%	0
	▪ doxepin	1.1%	1	1.1%	1	0.0%	0
	▪ nortriptyline	17.0%	15	8.0%	7	9.1%	8
	▪ protriptyline	1.1%	1	0.0%	0	1.1%	1
TeCA's	▪ mirtazapine	27.3%	24	15.9%	14	11.4%	10
	▪ amoxapine	0.0%	0	0.0%	0	0.0%	0
SARI's	▪ nefazodone	10.2%	9	5.7%	5	4.5%	4
	▪ trazodone	2.3%	20	9.1%	8	13.6%	12
NRI	▪ Reboxetine	1.1%	1	0.0%	0	1.1%	1

Abbreviations: MSM, Maudsley Staging Method; TD, Transdermal; SSRI, Selective Serotonin Reuptake Inhibitors; TCA, Tricyclic Antidepressant; MAOI, Monoamine Oxidase Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; TeCA, Tetracyclic Antidepressant; SARI, Serotonin Antagonist and Reuptake Inhibitors; NRI, Norepinephrine Reuptake Inhibitor.

TABLE 13

SOCIO-DEMOGRAPHIC CHARACTERISTICS – TRD PATIENTS

		TRD Sample (N = 43)	
Socio-demographic Variables		**% or Mean**	**N or (SD)**
Age (M ± SD)	▪ Years	47.1	(14.2)
Gender (%)	▪ Male	46.5%	20
	▪ Female	53.5%	23
Race (%)	▪ White	90.7%	39
	▪ Asian	2.3%	1
	▪ Hispanic	4.7%	2
	▪ Pacific Islander	2.3%	1
Relationship Status (%)	▪ Single	32.6%	14
	▪ Married	53.5%	23
	▪ Separated	4.7%	2
	▪ Divorced	7.0%	3
	▪ Widowed	2.3%	1
Living Situation (%)	▪ Alone	23.3%	10
	▪ Family	27.9%	12
	▪ Spouse or Significant Other	48.8%	21
Education (%)	▪ Graduate Degree or Some Graduate Work	14.0%	6
	▪ 4 Year College Degree	39.5%	17
	▪ 2 Year College Degree	14.0%	6
	▪ Some College (No Degree)	14.0%	6
	▪ High School Degree or GED	16.3%	7
	▪ Some High School or Less	2.3%	1
Employment (%)	▪ Employed	32.6%	14
	▪ Unemployed	53.5%	23
	▪ Retired	14.0%	6

Abbreviations: SD, Standard Deviation; TRD, Treatment Resistant Depression.

TABLE 14

CLINICAL FEATURES – TRD PATIENTS

		TRD Sample (N = 43)[1]	
Clinical Variables		**% or Mean**	**N or (SD)**
Course Features	▪ Recurrent Depression	95.3%	41
	▪ Chronic Depression	48.8%	21
	▪ Postpartum Onset	2.3%	1
Number of MDEs	▪ Mean No. of MDE (N = 33)	3.6	(2.9)
	□ 0 - 1 MDE	14.0%	6
	□ 2 - 3 MDE	30.3%	13
	□ 4 - 5 MDE	21.0%	9
	□ > 5 MDE	11.6%	5
Duration of MDE	▪ Mean No. of Months (N = 38)	35.2	(49.8)
	□ Acute (≤ 12 months)	41.9%	18
	□ Sub-acute (13-24 months)	16.3%	7
	□ Chronic (> 24 months)	41.9%	18
Symptom Features	▪ Melancholic	90.7%	39
	▪ Psychotic	14.0%	6
	▪ Atypical	9.3%	4
	▪ Catatonic	0.0%	0
Depression Severity	▪ Mean $HRSD_{24}$ (N = 42)	35.3	(5.4)
	▪ Mean CGI	5.4	(0.8)
	▪ Mean $IDS\text{-}SR_{30}$ (N = 37)	47.0	(9.5)
	▪ Mean GAF (N = 31)	48.3	(10.1)
Additional Features	▪ Mean No. of Psychiatric Hospitalizations	1.7	(1.9)
	▪ Mean MSM Score	9.2	(1.4)
	▪ Mean MMSE Score	27.6	(2.3)

[1] The total number of TRD patients as identified by the MSM was 43. However, due to incomplete patient histories, not all variables were calculated base on this number. Variables calculated based on a different number of TRD patients are noted above.
Abbreviations: TRD, treatment resistant depression; SD, Standard Deviation; MDE, Major Depressive Episode; $HRSD_{24}$, Hamilton Rating Scale for Depression-24 Item; CGI, Clinician Global Impression; $IDS\text{-}SR_{30}$, Inventory of Depressive Symptomatology-Self Report; GAF, Global Assessment of Functioning Scale; MSM, Maudsley Staging Method; MMSE, Mini-Mental State Examination.

TABLE 15

MSM OPTIMAL CUT-OFF SCORES FOR TREATMENT RESISTANCE SEVERITY

Score	Sensitivity	Specificity	Accuracy (%)
5.5	0.98	0.28	61.4
6.5	0.98	0.39	67.0
* 7.5	0.79	0.78	78.4
8.5	0.50	0.96	73.9
9.5	0.36	0.98	68.2

*Cut-off scored used to differentiate TRD from non-TRD. This score was selected as te cut-off score because it was found to have the highest accuracy and optimal ratio of sensitivity and specificity for differentiating TRD from non-TRD.
Abbreviations: MSM, Maudsley Staging Method; TRD, treatment resistant depression; non-TRD, non-treatment resistant depression

TABLE 16

CONTINGENCY TABLE OBTAINED WHEN USING A CUT-OFF SCORE OF 7.5 ON THE MSM

	Total Sample (N=88)	
MSM score	**TRD**	**Non-TRD**
Score > 7.5	*n* = 33 (true positives)	*n* = 10 (false positives)
Score < 7.5	*n* = 9 (false negatives)	*n* = 36 (true negatives)

Abbreviations: MSM, Maudsley Staging Method; TRD, Treatment Resistant Depression; Non-TRD, Non-Treatment Resistant Depression.

TABLE 17

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE $HRSD_{24}$ FOR TRD AND NON-TRD PATIENTS

	TRD (N = 43)		Non-TRD (N = 45)	
$HRSD_{24}$ Item	**%[1]**	**N**	**%[1]**	**N**
1. Depressed Mood	**100.0%**	**43**	**100.0%**	**45**
2. Feelings of Guilt	**97.7%**	**42**	**88.9%**	**40**
3. Suicidal Ideation	**97.7%**	**42**	**91.1%**	**41**
4. Insomnia Initial	79.1%	34	68.9%	31
5. Insomnia Middle	**93.0%**	**40**	**100.0%**	**45**
6. Insomnia Late	62.8%	27	64.4%	29
7. Work and Activities	**100.0%**	**43**	**100.0%**	**45**
8. Psychomotor Retardation	51.2%	22	57.8%	26
9. Psychomotor Agitation	27.9%	12	40.0%	18
10. Psychic Anxiety	**97.7%**	**42**	**100.0%**	**45**
11. Sympathetic Arousal	83.7%	36	86.7%	39
12. Decrease in Appetite	74.4%	32	82.2%	37
13. Somatic Complaints	**97.7%**	**42**	**100.0%**	**45**
14. Sexual Interest	88.4%	38	73.3%	33
15. Hypochondriasis	37.2%	16	55.6%	25
16. Decrease in Weight	34.9%	15	57.8%	26
17. Loss of Insight	2.3%	1	11.1%	5
18. Diurnal Variation of Mood	60.5%	26	68.9%	31
19. Depersonalization or Derealization	34.9%	15	26.7%	12
20. Paranoid Symptoms	25.6%	11	35.6%	16
21. Obsessional Compulsive Symptoms	30.2%	13	37.8%	17
22. Feelings of Helplessness	**100.0%**	**43**	**97.8%**	**44**
23. Feelings of Hopelessness	**100.0%**	**43**	**93.3%**	**42**
24. Feelings of Worthlessness	**95.3%**	**41**	**93.3%**	**42**

[1] Percentages reflect the frequency in which an item on the $HRSD_{24}$ was endorsed (a score ≥ 1).

Bolded Items represents all items endorsed by 90% or more of TRD patients.

Abbreviations: $HRSD_{24}$, Hamilton Rating Scale for Depression-24 Item; TRD, Treatment Resistant Depression; Non-TRD, Non-Treatment Resistant Depression.

TABLE 18

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE IDS-SR$_{30}$ FOR TRD AND NON-TRD PATIENTS

	TRD (N = 43)		Non-TRD (N = 45)	
IDS-SR$_{30}$ Item	**%[1]**	**N**	**%[1]**	**N**
1. Insomnia Initial	87.5%	35	88.9%	32
2. Insomnia Middle	**92.5%**	**37**	**94.3%**	**33**
3. Insomnia Late	66.7%	26	72.2%	26
4. Hypersomnia	64.1%	25	47.1%	16
5. Depressed Mood	**97.5%**	**39**	**91.7%**	**33**
6. Irritable Mood	77.5%	31	77.8%	28
7. Anxious Mood	**92.5%**	**37**	**94.4%**	**34**
8. Loss of Mood Reactivity	**97.5%**	**39**	**83.3%**	**30**
9. Diurnal Variation of Mood	64.1%	25	51.4%	18
10. Quality of Depressed Mood	**100.0%**	**39**	**94.4%**	**34**
11. Changes in Appetite[2]	**90.0%**	**36**	**72.2%**	**26**
12. Changes in Weight[3]	70.0%	28	69.4%	25
13. Difficulty Concentrating/Indecisiveness	**97.5%**	**39**	**94.4%**	**34**
14. Feelings of Worthlessness	82.5%	33	80.6%	29
15. Feelings of Hopelessness	87.5%	35	86.1%	31
16. Suicidal Ideation	84.6%	33	77.8%	28
17. Involvement	**95.0%**	**38**	**100.0%**	**36**
18. Fatigue or Loss of Energy	**100.0%**	**40**	**100.0%**	**36**
19. Anhedonia	**100.0%**	**40**	**97.2%**	**35**
20. Sexual Interest	89.7%	35	97.2%	35
21. Psychomotor Retardation	**94.9%**	**37**	**86.1%**	**31**
22. Psychomotor Agitation	59.0%	23	77.8%	28
23. Somatic Complaints	81.6%	31	72.2%	26
24. Sympathetic Arousal	71.8%	28	77.8%	28
25. Panic/Phobic Symptoms	56.4%	22	72.2%	26
26. Gastrointestinal	60.5%	23	75.0%	27
27. Interpersonal Sensitivity	84.2%	32	91.4%	32
28. Leaden Paralysis or Physical Energy	87.2%	34	88.6%	31

Table Continues

TABLE 18 continued

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE IDS-SR_{30} FOR TRD AND NON-TRD PATIENTS

[1] Percentages reflect the frequency in which an item on the IDS-SR_{30} was endorsed (a score $\geq$ 1). Due to incomplete responding on the IDS-SR_{30} not all percentages were calculated base on the total sample of TRD (N=43) and non-TRD (N=45) patients. For example on item 16 *Suicidal Ideation* of the 43 patients included in the TRD sample a total of 33 patients endorsed this item; however, only 39 patients completed this item. Therefore the percentage of TRD patients that endorsed *Suicidal Ideation* (84.6%) was calculated based on a total sample of 39 versus 43 TRD patients.

[2] *Changes in Appetite* is comprised of two items from the IDS-SR_{30} (Decreased Appetite and Increased Appetite).

[3] *Changes in Weight* is comprised of two items from the IDS-SR_{30} (Decreased Weight and Increased Weight).

Bolded Items represents all items endorsed by 90% or more of TRD patients.

Abbreviations: IDS-SR_{30}, Inventory of Depressive Symptomatology-Self Report 30 Items; TRD, Treatment Resistant Depression; Non-TRD, Non-Treatment Resistant Depression

TABLE 19

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE $HRSD_{24}$ FOR TRD PATIENTS BASED ON TREATMENT RESISTANT SEVERITY

$HRSD_{24}$ Item	MSM Score = 8 (N = 20)		MSM Score = 9 (N = 7)		MSM Score ≥ 10 (N = 16)	
	%[1]	N	%[1]	N	%[1]	N
1. Depressed Mood	100.0%	20	100.0%	7	100.0%	16
2. Feelings of Guilt	100.0%	20	100.0%	7	93.8%	15
3. Suicidal Ideation	95.0%	19	100.0%	7	100.0%	16
4. Insomnia Initial	85.0%	17	42.9%	3	87.5%	14
5. Insomnia Middle	100.0%	20	100.0%	7	81.3%	13
6. Insomnia Late	70.0%	14	71.4%	5	50.0%	8
7. Work and Activities	100.0%	20	100.0%	7	100.0%	16
8. Psychomotor Retardation	60.0%	12	71.4%	5	31.3%	5
9. Psychomotor Agitation	25.0%	5	14.3%	1	37.5%	6
10. Psychic Anxiety	95.0%	19	100.0%	7	100.0%	16
11. Sympathetic Arousal	85.0%	17	100.0%	7	75.0%	12
12. Decrease in Appetite	80.0%	16	57.1%	4	75.0%	12
13. Somatic Complaints	95.0%	19	100.0%	7	100.0%	16
14. Sexual Interest	95.0%	19	85.7%	6	81.3%	13
15. Hypochondriasis	40.0%	8	28.6%	2	37.5%	6
16. Decrease in Weight	30.0%	6	42.9%	3	37.5%	6

Table Continues

TABLE 19 continued

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE $HRSD_{24}$ FOR TRD PATIENTS BASED ON TREATMENT RESISTANT SEVERITY

	MSM Score = 8 (N = 20)		MSM Score = 9 (N = 7)		MSM Score ≥ 10 (N = 16)	
$HRSD_{24}$ Item	**%[1]**	**N**	**%[1]**	**N**	**%[1]**	**N**
17. Loss of Insight	0.0%	0	0.0%	0	6.3%	1
18. Diurnal Variation of Mood	65.0%	13	57.1%	4	56.3%	9
19. Depersonalization or Derealization	35.0%	7	42.9%	3	31.3%	5
20. Paranoid Symptoms	20.0%	4	42.9%	3	25.0%	4
21. Obsessional Compulsive Symptoms	25.0%	5	14.3%	1	43.8%	7
22. Feelings of Helplessness	100.0%	20	100.0%	7	100.0%	16
23. Feelings of Hopelessness	100.0%	20	100.0%	7	100.0%	16
24. Feelings of Worthlessness	95.0%	19	100.0%	7	93.8%	15

[1] Percentages reflect the frequency in which an item on the $HRSD_{24}$ was endorsed (a score ≥ 1) relative to the total number of patients that completed the item.

Abbreviations: $HRSD_{24}$, Hamilton Rating Scale for Depression-24 Item; TRD, Treatment Resistant Depression; MSM, Maudsley Staging Method.

TABLE 20

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE IDS-SR$_{30}$ FOR TRD PATIENTS BASED ON TREATMENT RESISTANT SEVERITY

IDS-SR$_{30}$ Item	MSM = 8 (N = 20)		MSM = 9 (N = 7)		MSM ≥ 10 (N = 16)	
	%[1]	N	%[1]	N	%[1]	N
1. Insomnia Initial	88.9%	16	83.3%	5	87.5%	14
2. Insomnia Middle	94.4%	17	100.0%	6	87.5%	14
3. Insomnia Late	66.7%	12	60.0%	3	68.8%	11
4. Hypersomnia	64.7%	11	66.7%	4	62.5%	10
5. Depressed Mood	100.0%	18	100.0%	6	93.8%	15
6. Irritable Mood	83.3%	15	66.7%	4	75.0%	12
7. Anxious Mood	94.4%	17	100.0%	6	87.5%	14
8. Loss of Mood Reactivity	94.4%	17	100.0%	6	100.0%	16
9. Diurnal Variation of Mood	70.6%	12	50.0%	3	62.5%	10
10. Quality of Depressed Mood	100.0%	18	100.0%	5	100.0%	16
11. Changes in Appetite[2]	94.4%	17	83.3%	5	87.5%	14
12. Changes in Weight[3]	55.6%	10	83.3%	5	81.3%	13
13. Difficulty Concentrating or Indecisiveness	94.4%	17	100.0%	6	100.0%	16
14. Feelings of Worthlessness	77.8%	14	100.0%	6	81.3%	13
15. Feelings of Hopelessness	88.9%	16	83.3%	5	87.5%	14
16. Suicidal Ideation	88.2%	15	83.3%	5	81.3%	13

Table Continues

TABLE 20 continued

FREQUENCY OF DEPRESSIVE SYMPTOMS ON THE IDS-SR$_{30}$ FOR TRD PATIENTS BASED ON TREATMENT RESISTANT SEVERITY

IDS-SR$_{30}$ Item	MSM = 8 (N = 20)		MSM = 9 (N = 7)		MSM ≥ 10 (N = 16)	
	%[1]	N	%[1]	N	%[1]	N
17. Involvement	100.0%	18	100.0%	6	87.5%	14
18. Fatigue or Loss of Energy	100.0%	18	100.0%	6	100.0%	16
19. Anhedonia	100.0%	18	100.0%	6	100.0%	16
20. Sexual Interest	94.1%	16	100.0%	6	81.3%	13
21. Psychomotor Retardation	94.1%	16	83.3%	5	100.0%	16
22. Psychomotor Agitation	52.9%	9	66.7%	4	62.5%	10
23. Somatic Complaints	75.0%	12	100.0%	6	81.3%	13
24. Sympathetic Arousal	70.6%	12	83.3%	5	68.8%	11
25. Panic/Phobic Symptoms	52.9%	9	83.3%	5	50.0%	8
26. Gastrointestinal	56.3%	9	50.0%	3	68.8%	11
27. Interpersonal Sensitivity	81.3%	13	100.0%	6	81.3%	13
28. Leaden Paralysis/Physical Energy	88.2%	15	100.0%	6	81.3%	13

[1] Percentages reflect the frequency in which an item on the IDS-SR$_{30}$ was endorsed (a score ≥ 1). Due to incomplete responding on the IDS-SR$_{30}$ not all percentages were calculated base on the total number of TRD patients within each treatment resistant severity group. For example on item 16 *Suicidal Ideation* of the 20 TRD patients with a MSM score of 8 a total of 15 patients endorsed this item; however, only 17 patients completed this item. Therefore the percentage of TRD patients with a MSM score of 8 that endorsed *Suicidal Ideation* (88.2%) was calculated based on a total sample of 17 versus 20 TRD patients.

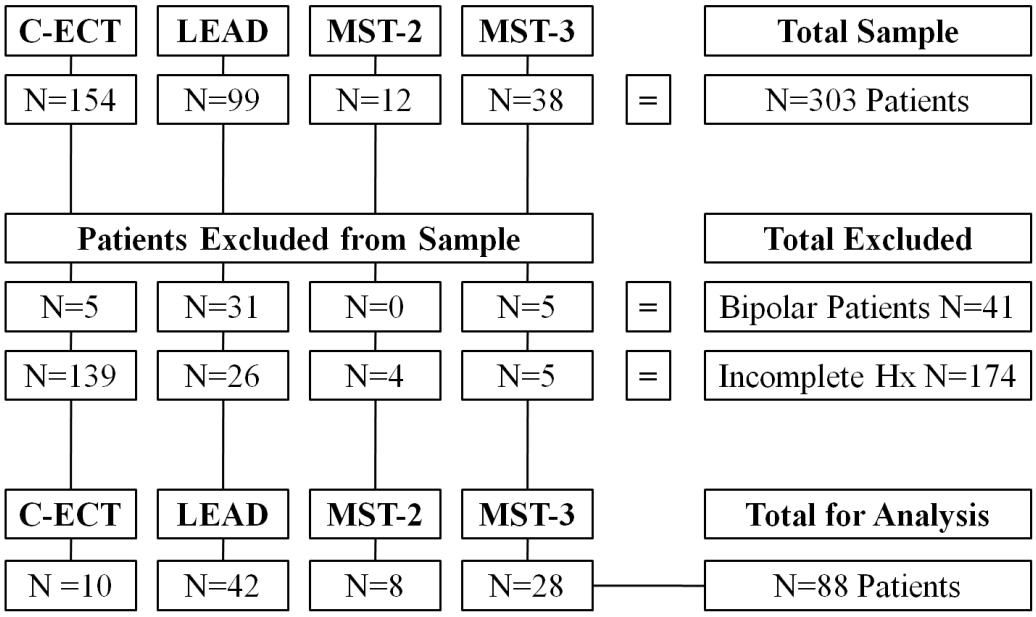
[2] *Changes in Appetite* is comprised of two items from the IDS-SR$_{30}$ (Decreased Appetite and Increased Appetite).

[3] *Changes in Weight* is comprised of two items from the IDS-SR$_{30}$ (Decreased Weight and Increased Weight).

Abbreviations: IDS-SR$_{30}$, Inventory of Depressive Symptomatology-Self Report 30 Items; TRD, Treatment Resistant Depression; MSM, Maudsley Staging Method.

FIGURE 1

SAMPLE SIZE OF CLINICAL STUDIES AND DISSERTATION STUDY



Abbreviations: C-ECT, Consortium for Research in ECT Study – Continuation ECT versus Pharmacotherapy (IRB # 0695-21700); LEAD, Comparing Three Electrode Placements to Optimize ECT (IRB # 0402-216); MST-2, Magnetic Seizure Therapy for the Treatment of Major Depression (IRB # 0202-074); MST-3, Magnetic Seizure Therapy for the Treatment of Severe Mood Disorders (IRB # 042005-022); Hx, History.

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