THE CLINICAL PHENOTYPE OF MAJOR DEPRESSION WITH SUICIDAL IDEATION (MDD-SI)

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Our overall goal of this investigation was to broaden our understanding of MDD-SI. Specifically, we sought to document the associated features of MDD-SI, understand the phenomenology of MDD-SI, develop a clinical phenotype of MDD-SI, and discern whether the MDD-SI phenotype is associated with an unfavorable or differential initial response to treatment. We conceptualized this work as a preliminary investigation of the specific treatment needs of individuals with MDD-SI and potential identification of one subset of individuals who fail to experience an initial response to first-line monotherapies for major depression.

To this end, we completed a secondary analysis of data from a two-site, cross-national clinical trial in which individuals presenting in an episode of major depression were randomly allocated to an initial treatment protocol consisting of SSRI antidepressant pharmacotherapy (SSRI) or interpersonal psychotherapy (IPT).

In comparisons between individuals with MDD-SI and individuals without current, baseline suicidal ideation (MDD), we found that (1) few pre-treatment socio-demographic or baseline clinical characteristics significantly distinguished MDD-SI and MDD, (2) lifetime experiences of suicidal ideation and suicidal behavior were significantly different between MDD-SI and MDD, and (3) lifetime history and past month experiences of some mood and

panic-agoraphobic spectrum symptoms were significantly different between MDD-SI and MDD. In addition, we demonstrated that MDD-SI is negatively associated with initial treatment response, such that individuals with MDD-SI were significantly more depressed after six weeks of treatment than were individuals with MDD. Nonetheless, after six weeks of treatment, interviewer-rated suicidal ideation resolved for over 90% of individuals with MDD-SI and self-reported suicidal ideation resolved for all but about 11%.

Our findings provide preliminary support for the usefulness of assessing both syndromal and subsyndromal manifestations of major depression, establishing a lifetime assessment of suicidality as routine clinical practice, and conceptualizing MDD-SI as a subtype and clinical phenotype of major depression. Further research, including replication of our findings, is needed.

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PREFACE

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1.0 INTRODUCTION

Despite an arsenal of empirically-supported psychotherapies and pharmacotherapies for the treatment of unipolar major depression, the extant literature offers the practicing clinician little guidance for selecting an initial psychotherapy or pharmacotherapy treatment strategy (Frank et al., 2010; Gelenberg, 2010). Consequently, the proportion of individuals who access treatment and experience an initial response to first-line treatment is disappointingly small, rarely exceeding 50% (Cassano et al., 2009; Kessler et al., 2003a; Trivedi, Fava, Marangell, Osser, & Shelton, 2006). Indeed, according to the World Health Organization (WHO), less than 25% of individuals with major depression receive adequate treatment (WHO, 2005). Moreover, for a minority of individuals suffering from major depression, psychosocial and pharmacological treatments fail not only to reduce depressive symptomatology but also to halt the "suicidal process," or an individual's progression from mild to more severe forms of suicidality (Baldessarini et al., 2007; Joiner, 2005; Neeleman, de Graaf, & Vollebergh, 2004).

One way to increase response rates and the overall effectiveness of first-line treatment for major depression might be to identify clinical phenotypes within the disorder, and then determine if the defining symptoms and features moderate treatment response. Isolating clinical phenotypes to determine treatment needs and guide treatment selection is a potentially fruitful method, and may be more consistent with data from both treatment trials and biological

investigations (Cassano et al., 2009; Perlis et al., 2009). For example, there is substantial evidence that not all treatments work equally well for all individuals and that individual differences account for some of the variance in treatment response (Frank et al., 2000; Gelenberg, 2010; Stiles, Shapiro, Elliott, 1986). Some of these individual differences may be associated with a distinct clinical phenotype of major depression and, accordingly, specific treatment needs.

One potential clinical phenotype that has received relatively little attention is major depression with current suicidal ideation (MDD-SI) (Joiner, 2005; Oquendo, Baca-Garcia, Mann, & Giner, 2007). Suicidal ideation refers to thoughts of engaging in suicide-related behavior, with varying degrees of severity and elaboration (Brenner et al., 2010). It fluctuates within and among individuals in terms of presence, duration, frequency, persistence, depth, and intensity (Joiner, 2005; Joiner et al., 2003; Valtonen et al., 2009). Suicidal ideation falls on a broad continuum of suicidality. This continuum comprises a constellation of cognitions and suicidal behaviors, including fleeting and passive death wishes or escape fantasies, verbalization of suicidal ideation, risky and reckless behaviors, attempt planning and preparatory behaviors, repeated suicide attempts, and completed suicide (Brenner et al., 2010; Casey et al., 2008; Witte, Fitzpatrick, Joiner, & Schmidt, 2005). The suicidal trajectory may be either peripatetic with sudden jumps in intensity or follow a continuous progression of increasing severity (De Leo, Cerin, Spathonis, & Burgis, 2005; Joiner, 2005; Kessler, Borges, & Walters, 1999; Kessler, Ormel, Demler, & Stang, 2005; Nock et al., 2008b).

The phenomenology and clinical implications of suicidal ideation are complex. On one hand, among a minority of individuals, suicidal ideation is a marker for future risk (Gunnell,

Harbord, Singleton, Jenkins, & Lewis, 2004; Joiner, 2005; Valtonen et al., 2009). It is a precursor to more serious suicidal behavior, including death (Kessler et al., 1999, 2005; Konick & Gutierrez, 2005). On the other hand, suicidal ideation is a prevalent psychological, or cognitive, symptom of depression (Cox, Enns, & Clara, 2004; Michal et al., 2010). It is an extreme form of suffering and negative self-referent thinking (Williams, Crane, Barnofer, Van der Does, & Segal, 2006). Then again, suicidal ideation also is an indicator of current distress, disease presence, and illness severity (Minnix, Romero, Joiner, & Weinberg, 2007; Scocco, Girolamo, Vilagut, & Alonso, 2008). It is this very intricacy, this diversity in meanings, which highlights the potential clinical and empirical utility of defining the MDD-SI clinical phenotype. In fact, some researchers have suggested that suicidality should be a separate diagnostic category in the next edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (Leboyer, Slama, Siever, & Bellivier, 2005; Oquendo et al., 2008). In addition, there is some evidence that suicidal ideation is highly consistent across depressive episodes; only the severity seems to fluctuate (Antypa, Van der Does, & Pennix, 2010; Borges, Angst, Nock, Ruscio, & Kessler, 2008). That is, once suicidal ideation emerges, it often resurfaces during future episodes (Williams et al., 2006; Witte et al., 2005). Thus, the MDD-SI clinical phenotype might be able to distinguish individuals not only acutely but also longitudinally.

Yet, our understanding of suicidal ideation, especially in the absence of suicidal behaviors, is quite limited. The present literature tells us little about exactly who experiences MDD-SI, what distinguishes these patients from others, or whether this phenotype is associated with an unfavorable response to treatment. It tells us nothing about whether psychotherapy or pharmacotherapy is a preferable initial treatment strategy for MDD-SI (Baldessarini et al., 2007;

Heisel, Duberstein, Talbot, King, & Tu, 2009; Pompili et al., 2010; Szanto, Mulsant, Houck, Dew, & Reynolds, 2003).

A first step to increasing our understanding of these issues is developing a rich clinical phenotype of MDD-SI. To this end, the Spectrum Assessment Method (Cassano et al., 1997, 2004) seems particularly well suited. This method produces phenotypes characterized by an array of prodromal, subsyndromal, syndromal, and temperamental manifestations of the target disorder. Consequently, it provides a range of symptoms for specific treatments to address (Cassano et al., 1997; Frank et al., 2000). Furthermore, the Spectrum Assessment Method holds promise for the identification of symptoms or associated features that account for potential variance in initial treatment response. Indeed, if it becomes evident that individuals with MDD-SI are distinct from individuals without suicidal ideation and/or that individuals with MDD-SI respond poorly to first-line treatments, we can use the phenotype generated from the Spectrum Assessment Method to great benefit. Specifically, with this phenotype we can adapt treatments, or develop new treatments, to target both the suicidal ideation and the associated prodromal, subsyndromal, and syndromal symptomatology.

In sum, one way to increase response rates and the overall effectiveness of first-line treatment for major depression might be to identify clinical phenotypes that account for some of the variance in initial treatment response. Considering the generally low initial treatment response rate, coupled with the sometimes rapid or persistent nature of suicidal ideation, there are clear benefits of delineating the clinical phenotype and initial treatment needs of MDD-SI. Conceivably, if the proportion of individuals with MDD-SI who respond to an initial treatment is increased, then both the depression- and suicide-related disease burden will decrease (Dew et al.,

2001). There would be an optimization of treatment that, in turn, would reduce individuals' time to recovery, extend well-intervals between episodes, obviate the need for unnecessary exposure to somatic treatments, and decrease healthcare cost (Trivedi et al., 2006).

Against this background, we sought to (1) document the associated features of MDD-SI, (2) develop a clinical phenotype of MDD-SI by adopting the Spectrum Assessment Method, and (3) discern whether the MDD-SI phenotype is associated with an unfavorable or differential initial response to empirically-supported SSRI antidepressant pharmacotherapy (SSRI) or interpersonal psychotherapy (IPT) for major depression. For this investigation, we defined MDD-SI as a non-psychotic unipolar major depressive episode with current suicidal ideation.

1.1 SPECIFIC AIMS

To this end, we completed a secondary analysis of data from a two-site, cross-national clinical trial in which individuals presenting for treatment of a non-psychotic unipolar major depressive episode were randomly allocated to a treatment protocol involving SSRI, IPT, and, in the absence of a response or sustained remission, their combination. We examined:

- The pre-treatment socio-demographic and baseline clinical characteristics associated with baseline suicidal ideation, to document the associated features of MDD-SI;
- The lifetime and past month mood and panic-agoraphobic spectrum conditions associated with baseline suicidal ideation, to understand the phenomenology of MDD-SI and develop a clinical phenotype of MDD-SI; and

- The initial response to six weeks of monotherapy with either SSRI or IPT of individuals with baseline suicidal ideation, to discern whether MDD-SI is associated with an unfavorable or differential initial response to treatment.

In the next section, we concentrate on providing an overview of past research that is particularly relevant to these aims. This includes the (1) methods for assessing suicidal ideation, (2) prevalence of suicidal ideation, (3) major correlates of suicidal ideation, (4) relationship between suicidal ideation and treatment response, (5) association between subsyndromal mood and anxiety symptoms and treatment response, and (6) Spectrum Assessment Method. Then, we conclude with a presentation our hypotheses.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 ASSESSING SUICIDAL IDEATION

The study of suicidal ideation is challenging (Bongiovi-Garcia et al., 2009; De Leo et al., 2005; Valtonen et al., 2009). One reason is that suicidal ideation is a broad term without precise endpoints (Mission et al., 2010), and there is limited consensus about what exactly constitutes suicidal ideation (Brenner et al., 2010; Fawcett, Baldessarini, Coryell, Silverman, & Stein, 2009). Recently, to promote a common lexicon among mental health researchers and clinicians, Brenner and colleagues (2010), in collaboration with the Centers for Disease Control and Prevention (CDC), developed the Classification System of Self-Directed Violence (CSSV). Accordingly, suicidal ideation is defined as "self-reported thoughts of engaging in suicide-related behavior." Importantly, it does not include self-reported thoughts regarding an individual's desire to engage in self-inflicted, potentially injurious behavior without suicidal intent. Furthermore, anything beyond verbalizations or thoughts, such as acts or preparations (e.g., giving belongings away or hoarding medication for a potential over-dose), is classified as suicidal behavior. Notably, to date, most research is inconsistent with the CSSV. Mainly, many investigators group together individuals with suicidal ideation and individuals with mild suicidal behaviors (Brown, 2000; Mission et al., 2010).

Another reason the study of suicidal ideation is difficult is that suicidal ideation is hard to evaluate, and there is little consensus regarding the "best" method for assessing it (Nock et al., 2010; Valtonen et al., 2009). Namely, factors at both the individual- and methodological-level influence the validity and reliability of suicidality assessments, problems that the personal and variable nature of suicidal ideation exponentiate (Brown, 2000).

Individual-level factors include the subjectivity of suicidal ideation and the fear and stigma associated with suicidality. Depending on the elaboration, intensity, and effect of these thoughts, an individual may not report current or recall past suicidal ideation (Joiner et al., 2009; Szanto et al., 2001; Vannoy et al., 2007). He or she may not see it as relevant, noteworthy, or memorable (Goldney et al., 2009; Nock et al., 2010; Scocco et al., 2008; Valtonen et al., 2009). Conversely, he or she may see his or her experience with suicidal thoughts as important and significant but conceal such experiences because of concerns about hospitalization, fear of stigma and judgment, or feelings of shame, guilt, and embarrassment (Apter, Horesh, Gothelf, Graffi, & Lepkifker, 2001; Deane & Todd, 1996; Levinson, 2008; Scocco et al., 2008).

Methodological-level problems include the documented discrepancies between self-report and interviewer-rating scales, between semi-structured (e.g., SCID) and unstructured (e.g., clinical interview) assessments, and the failure of many assessments to differentiate among dimensions of suicidality (Nock et al., 2008b, 2010). Consequently, there is variability in the sensitivity (true positives) and specificity (true negatives). For example, Valtonen and colleagues (2009) explored how different assessment methods influenced which individuals in their sample were classified as current "suicidal ideators." Their assessments included asking individuals whether they had ever seriously considered suicide during the current affective

episode (an unstructured, interviewer-rating), requesting individuals to complete the structured self-report *Beck Depression Inventory* (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and administering both the structured, interviewer-rating *Scale for Suicidal Ideation* (SSI) (Beck, Kovacs, & Weissman, 1979) and *Hamilton Rating Scale for Depression* (HRSD) (Hamilton, 1960). Valtonen and colleagues report that, among their sample of 191 individuals with bipolar disorder, whereas 74% were classified as suicidal ideators by at least one method, only 29% were classified as suicidal ideators by all methods. Moreover, the SSI was only moderately correlated with the BDI (r = .58) and HRSD (r = .67) suicide items, and agreement of who was an ideator ranged from low to moderate (kappa coefficient 0.15 to 0.70). Likewise, Bongiovi-Garcia and colleagues (2009) investigated the agreement between structured (SSI) and unstructured (general clinical interview) interviewer-rated suicidality among 201 inpatients with unipolar or bipolar depression. They found only fair agreement for the presence of suicidal ideation; while structured assessments captured all inpatients identified as having suicidal ideation by unstructured assessments, unstructured assessments failed to identify 29.7% of inpatients identified by structured assessments. In another study, Bridge, Barbe, Birmaher, Kolko, and Brent (2005) demonstrated that, among 88 medication-free adolescent outpatients with major depression, self-reported suicidality was of significantly greater predictive value than was interviewer-rated suicidality. Similarly, in a sample of 328 young adults, Joiner, Rudd, and Rajab (1999) found discrepancies between self-reported and interviewer-rated suicidality, such that half of the sample who self-rated as low in suicidality were interviewer-rated as high in suicidality. Notably, their analyses of follow-up data of incidence of post-interview suicidal

behaviors suggested that, overall, interviewers over-estimated suicidality, particularly when the individual reported a previous suicide attempt or exhibited histrionic personality features.

Taken together, these findings suggest that each method for assessing suicidal ideation is somewhat flawed, and therefore, the "best" method might be an all-inclusive, comprehensive and structured approach (Brown, 2000; Joiner, Walker, Pettit, Perez, & Cukrowicz, 2005b; Valtonen et al., 2009). Yet, the current literature suggests that most investigators rely on a single method. For example, in a meta-analysis of treatment-emergent suicidality, Beasley et al. (2007) found that 16 of 18 clinical trials of fluoxetine for major depression assessed suicidality with one item on a depressive symptom rating scale, Question 3 on the HRSD. This question directly assesses suicidality using the anchors: 0 = "absent," 1 = "feels life is not worth living," 2 = "wishes he/she were dead or any thoughts of possible death to self," 3 = "suicide ideas or gestures," and 4 = "attempts at suicide." Notably, researchers have demonstrated that this single interviewer-rating of suicidality has high inter-rater reliability (r = .92; Reynolds, 1991), adequate test-retest reliability (r = .64; Williams, 1988), and strong concurrent and predictive validity (Brown, 2000). Nonetheless, the widespread use of this single question more likely reflects the extensive use of the HRSD as a "gold standard" in clinical trials rather than its validity as an assessment of suicidality.

The frequent use of the HRSD highlights another assessment issue, and a potential limitation of the retrospective use of depressive symptom scales: severity but little else is detailed. The HRSD question provides a score that essentially indicates only the current absence or presence of ideation and action. Ideation is less severe than is action, and higher scores reflect increased suicide risk – unmistakably, a distinction of important clinical concern. Yet, Joiner

and his group (Joiner et al., 2003, 2009; Witte et al., 2005) present data that suggests certain presumed and potential dimensions of suicidal ideation are more predictive of risk than are other dimensions of suicidal ideation; the HRSD item – and similar symptom measures – fails to differentiate among these elements (Brown, 2000).

Joiner and colleagues submit that the structure of suicidal ideation is multidimensional (Beck & Lester, 1976; Joiner et al., 2009; Witte et al., 2005; Steer, Rissmiller, Ranieri, & Beck, 1993). Specifically, they argue that suicidal ideation is adequately explained by two factors, namely "resolved plans and preparations" and "suicidal desire and ideation." The resolved plans and preparations factor comprises a sense of courage and competence to make an attempt, availability of means and opportunity to make an attempt, specificity of plan, and preparations for attempt. The suicidal desire and ideation factor involves reasons for living (negatively loaded), wish to die, wish not to live, passive attempt, desire for attempt, lack of deterrents to attempt, and talk of death or suicide. Joiner and his team theorize that the resolved plans and preparations factor is facilitated by previous suicidality. Specifically, past experiences with suicidal ideation allow the individual to habituate to the fear, pain, and taboo associated with self-harm. Accordingly, previous experiences with suicidality provide the individual with practice, and in turn, increase an individual's confidence and competence – he or she acquires the ability to engage in suicidal behaviors. Similarly, these previous experiences wear on the individual such that he or she experiences increased resolve and commitment to suicidal behaviors. Thus, for predictive purposes, previous and "worst-point" suicidal ideation might be more important than is current suicidal ideation (Beck, Brown, Steer, Dahlsgaard, & Grisham, 1999; Joiner et al., 2003; Witte et al., 2005). For the purpose of defining a clinical phenotype

and investigating initial treatment response, the value of current suicidal ideation compared to previous and worst-point is unclear.

To summarize, potential limitations of research on suicidal ideation include the lack of a widely-used nomenclature of suicidality, the heterogeneity of suicidal ideation, the over-reliance on a single interviewer-rating of suicidality and, to a lesser extent, a single self-report rating of suicidality, and the inability of many assessments to differentiate among potential dimensions of suicidality. Individual and methodological heterogeneity, coupled with the ensuing variance in sensitivity and specificity, influences the epidemiological estimates, correlates, and predictive value of suicidal ideation.

2.2 THE PREVALENCE OF SUICIDAL IDEATION

Thinking about suicide is much more common than is dying by suicide (Jamison, 1999). In general, as the severity of suicidality increases, the prevalence decreases (Kessler et al., 1999, 2005). For example, estimates of the lifetime prevalence of suicidal ideation range between 4.8% and 18.5% (Bernal et al., 2007; Paykel, Myers, Lindenthal, & Tanner 1974), whereas estimates of the lifetime prevalence of suicide attempts range between 1.1% and 4.3% (Kessler et al., 1999). Prevalence estimates, however, are influenced by methodological and assessment heterogeneity, including sampling techniques (De Leo et al., 2005). Prevalence estimates of lifetime suicidal ideation vary considerably across age-cohorts, general and clinical-populations, and countries and geographical areas (Bernal et al., 2007; Casey et al., 2008; De Leo et al., 2005; Kessler et al., 1999, 2005; Scocco et al., 2008). In general, these estimates are highest for

women, young and very old age-cohorts, clinical populations with psychiatric disorders, and Western, high-income Anglo-culture countries. Three major cross-sectional surveys, the National Comorbidity Study, Part Two (NCS-II) (Kessler et al., 1999), the European Study of the Epidemiology of Mental Disorders (ESEMED) (Bernal et al., 2007; Scocco et al., 2008), and the World Mental Health Survey (WMH) (Nock et al., 2008a), highlight the cross-national variance in estimates of suicidal ideation and consistency in risk factors for suicidal ideation.

The NCS-II, a cross-sectional survey of the general population in the United States during 1990 to 1992, estimates the national lifetime prevalence of ideation to be 13.5% and ideation with plan to be 3.9%. In the survey, interviewers asked individuals, "Have you ever seriously thought about committing suicide?" and "Have you ever made a plan for committing suicide?" NCS-II findings indicated that the highest risk for initial suicidal ideation is around the late teens and early twenties. Higher rates of suicidal ideation were associated with being female, previously married, less educated, and diagnosed with at least one mental disorder. Additionally, although risk for ideation was significantly higher in the presence versus absence of a mood, anxiety, or substance use disorder, risk was significantly elevated and highest for mood disorders.

The ESEMED, a cross-sectional survey of the general population in six European countries during 2001 and 2003, estimated the cross-national lifetime prevalence of suicidal ideation to be 7.8%, a rate substantially lower than the NCS rate. The ESEMED assessed suicidality in individuals' homes with the computer-adaptive WHO Composite International Diagnostic Interview (CIDI). The CIDI includes, "Have any of these experiences happened to you: You seriously thought about committing suicide? You committed suicide?" Similar to the

NCS results, higher rates of suicidal ideation were associated with being female, younger, and previously married. Among mental disorders, major depressive disorder followed by generalized anxiety disorder, post-traumatic stress disorder, and then alcohol dependence, conferred the greatest risk. Italy and Spain had the lowest frequency of suicidal ideation (3.0% and 4.4%, respectively) while France and Germany had the highest (12.4% and 9.8%, respectively). The authors postulate that Italy and Spain's traditional and conservative societies, in part, explain the cross-national differences. Yet, additional analyzes of the ESEMED Italian data only, demonstrated no differences in suicidality by Italian geographic areas (e.g., northern Italy, central Italy, etc.), even though these areas differ substantially in socio-cultural variables, health services, and climate.

Finally, the WMH, a cross-sectional survey of the general population of 17 countries, estimated the cross-national lifetime prevalence of suicidal ideation to be 9.2%. To assess suicidality, when financially and logistically possible, individuals completed the computer-adaptive CIDI; otherwise, interviewers read the CIDI questions aloud. Cross-national risk factors for suicidal ideation included being female, younger, and less educated. Among high-income countries (e.g., United States, Italy, Japan), mood disorders conferred the greatest risk for suicidal ideation while impulse control disorders did among low- or middle-income countries (e.g., Mexico, Nigeria, Ukraine).

Both the WMH and NCS-II assessed the time to transition from ideation to more severe forms of suicidality. Results are strikingly similar. In the WMH, across all 17 countries examined, more than 60% of the progressions from ideation to first attempts occurred within the first year of initial onset of ideation. In the NCS-II, among individuals reporting suicidal

ideation, cumulative probabilities were 34% for the transition from ideation to a plan and 26% from ideation to an unplanned attempt. Approximately 90% of unplanned and 60% of planned first attempts occurred within the first year after initial onset of suicidal ideation. Thus, the suicidal process can evolve swiftly. It is important to note, however, that most individuals who experience suicidal ideation will not plan or attempt suicide during their lifetime.

To summarize, multiple variables explain the variance in rates of the lifetime prevalence of suicidal ideation, including assessment and sampling techniques. Based on the NCS-II brief, structured interviewer-ratings, 13.5% of adults in the United States experience suicidal ideation during their lifetime. Estimates derived from the ESEMED and WMH structured, computer-adaptive self-report ratings suggest that Europeans, particularly Italians, have a lower likelihood of experiencing suicidal ideation during their lifetime, 7.8% and 3.0%, respectively, compared to US Americans. The NCS-II, ESEMED, and WHM show that risk for suicidal ideation is highly elevated among individuals who are female, young, and diagnosed with a mood disorder. Furthermore, the WMH and NCS-II results suggest that risk of planning an attempt and making an attempt is highest within the first year of onset of suicidal ideation but remains years afterwards. Moreover, for some individuals, the suicidal process may be abrupt or fail to follow a continuous progression of increasing severity. Collectively, these findings suggest that early intervention is key and support the importance of understanding whether the MDD-SI phenotype is associated with an unfavorable or differential initial response to treatment.

2.3 CORRELATES OF SUICIDAL IDEATION

Despite certain similarities, those who think about suicide, those who develop a plan, those who attempt, and those who die from suicide are distinct on a number of characteristics (Brent, 2010; Fawcett et al., 2009; Kessler et al., 2005). Most investigations have focused on the latter groups. Nonetheless, researchers have identified a number of variables that are associated with lifetime and/or current suicidal ideation in adults. These include psychiatric disorders and illness characteristics, physical health, socio-demographic variables, stressors, and personality and psychological dimensions. To clarify, these correlates of suicidal ideation might be distal or proximal, and might be risk factors or warning signs (Brenner et al., 2010). Risk factors are associated with a greater potential for experiencing suicidality, e.g., being female or younger (American Association of Suicidology [AAS], 2010). In contrast, warning signs are person-specific and are associated with imminent risk of engaging in suicidality or experiencing a suicidal crisis, e.g., loss of employment or worsening of severe depression (AAS, 2010).

First, researchers have found strong associations among suicidal ideation, psychiatric disorders, and illness characteristics. Specifically, mood, substance use, anxiety, and psychotic disorders increase vulnerability to suicidal ideation (Conner, Li, Meldrum, Duberstein, & Cornwell, 2003; Cottler, Campbell, & Krishna, 2005; Goodwin et al., 2001; Joiner, 2005; Kessler et al., 1999, 2005; Lloyd et al., 2007; Michal et al., 2010), and having more than one of these disorders confers added risk (Joiner, 2005; Kessler et al., 2005; Nock et al., 2008a; Nock, Hwang, Sampson, & Kessler, 2009). For instance, in the NCS-II sample, approximately 80% of individuals endorsing suicidal ideation met criteria for at least one DSM disorder during the previous 12-months. Furthermore, there was a dose-response relationship between the number

of disorders and risk for planning or making an attempt, such that each additional disorder increased risk. Major depression was the most common single disorder, and anxiety and mood disorders were the most common class of disorders. Likewise, in another report, using 2004 to 2005 National Survey on Drug Use and Health data, the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA) (Office of Applied Studies, 2006) found that, among individuals experiencing a past year major depressive episode, 56.3% thought during their worst or most recent episode that it would be better if they were dead (death ideation), 40.3% experienced suicidal ideation without a plan, and 14.5% experienced suicidal ideation with a plan.

A number of researchers have found major depression to be the most robust independent risk factor for suicidal ideation (Joiner, 2005; Kessler et al., 1999; 2005). Indeed, the estimates of point prevalence of suicidal ideation skyrockets to between 47% and 69% in clinical populations experiencing a major depressive episode (Sokero, 2006; Sokero et al., 2003). In addition, researchers have documented that specific features of major depression are additive to risk, including early age of first depression onset (Lynch et al., 1999), depression severity (Goldney et al., 2000), episode chronicity or treatment resistance (Buddeberg, Buddeberg-Fischer, Gnam, & Schmid, 1996; Papakostas et al., 2003; Pompili et al., 2010), and, in particular, the presence and intensity of hopelessness (Beck, Brown, Berchick, Stewart, & Steer, 1990; Beck, Steer, & Brown, 1993; Blankstein, 2007; Sokero et al., 2006; Whisman, Miller, Norman, & Keitner, 1995), anxiety (Frank et al., 2002; Cassano et al., 2004; Michal et al., 2010; Sareen et al., 2005; Sokero, 2006), and perceived burdensomeness (Joiner, 2005; Russell, Turner, & Joiner, 2009; Van Orden, Lynam, Hollar, & Joiner, 2006). Interestingly, Lynch et al. (1999)

documented that the risk conferred by early age of depression onset persisted into late-life. Conceivably, it might be that early-life depression opens a pathway through which other risk factors emerge, accumulate, and increase susceptibility to suicidal ideation.

Similarly, researchers have observed that specific psychiatric symptoms and illness characteristics amplify liability for suicidal ideation, particularly against the backdrop of major depression. These include sleep disturbances, such as difficulty falling or staying asleep and nightmares (Chellappa & Araujo, 2007; Cukrowicz et al., 2006; McCall et al., 2010; Wojnar et al., 2009), states of negative arousal, such as anxiety, agitation, irritability, impulsivity, and mixed states (Akiskal & Benazzi, 2005; Balazs, Benazzi, Rhimer, Rhimer, & Akiskal, 2006; Benazzi, 2004, 2006; Cassano et al., 2004; Dalrymple & Zimmerman, 2007; Fava et al., 2008; Goodwin et al., 2001; Olgiati, Serretti, & Colombom, 2006), depersonalization (Michal et al., 2010; Yoshimasu et al., 2006), psychosis (Cassano et al., 2004; Kessler et al., 1999), and syndromal or subsyndromal bipolarity (Angst, Gamma et al., 2003; Balestrieri et al., 2006; Benazzi, 2004, 2006; Maremmani et al., 2007). Additionally, alcohol or substance use (De Leo et al., 2005; Kessler et al., 1999, 2005; Pompili et al., 2010) and any anxiety (Michal et al., 2010; Sareen et al., 2005), independent or concurrent with these symptoms, increase risk. For instance, SAMHSA (Office of Applied Studies, 2006) reported that individuals experiencing past year major depression who also reported past month binge alcohol or illicit drug use were more likely to report suicidal ideation (61.8% and 67.0%, respectively) than were individuals with past year major depression but no alcohol or substance use (57.1% and 56.9%, respectively). They also noted that individuals experiencing a past year substance use disorder were more than three times

as likely to have seriously considered suicide compared to those without a substance use disorder.

Second, apart from mental health, researchers have found strong associations between poor or unstable physical health and suicidal ideation, particularly among males (Alexopoulos et al., 2009; Kessler, Ormel, Demler, & Stang, 2003b; Legleye, Beck, Peretti-Watel, Chau, & Firdion, 2010). These factors include presence of physical disability and functional impairment (Duberstein, Conwell, Conner, Eberly, & Caine, 2004; Russell, Turner, & Joiner, 2009), chronic pain (Edwards, Smith, Kudel, & Haythornthwaite, 2006; Fishbain, Bruns, Disorbio, & Lewis, 2009; Scott et al., 2010), and any medical comorbidity (De Leo et al., 2005; Goldney, Fisher, Wilson, & Cheok, 2001; Rollman & Shear, 2003). Remarkably, simply reporting poor physical health, irrespective of actual health status, and low quality of life seems to increase liability (Dennis, 2007; Goodwin et al., 2001; Goodwin & Olfson, 2002). Russell, Turner, and Joiner (2009) postulate that the contribution of these variables to increased risk of suicidal ideation might be that poor health or physical disability increases perceptions of burdensomeness and/or feelings of isolation. Of note, some researchers have demonstrated that elevated body mass index (BMI) and obesity increase risk for suicidal ideation (Carpenter, Hasin, Allison, & Faith, 2000; Fagiolini et al., 2004; Mather, Cox, Enns, & Sareen, 2009), whereas others have reported it protects against risk (Goldney et al., 2009).

Third, researchers have consistently reported elevated rates of suicidal ideation in the young and very old, women, individuals with low education, individuals lacking stable relationships, social support, or employment, and individuals in low socio-economic brackets (De Leo et al., 2005; Dennis, 2007; Gunnell et al., 2004; Hintikka et al., 2001a, 2001b; Kessler et

al., 2005; Legleye et al., 2010; McMillan, Enns, Asmundson, & Sareen, 2010; Michal et al., 2010; Nock et al., 2008a, 2009; Scocco et al., 2008; Sokero et al., 2003). Notably, these risk factors seem to be consistent cross-nationally (Nock et al., 2008a). Some evidence supports gender differences for a few of these factors. For example, males seem to be at greater risk than are females for developing suicidal ideation following the dissolution of a relationship (Kõlves, Ide, & De Leo, 2010) or employment (Legleye et al., 2010).

Fourth, researchers have consistently reported elevated rates of suicidal ideation among individuals with recent or lifetime histories of stressful or negative life events (Fanous, Prescott, & Kendler, 2004; Goldney et al., 2000; Hirsch, 2007; Marshall et al., 2001; Nock et al., 2008a, 2009; Weissman et al., 1999). These independent and robust predictors of suicidal ideation include family and romantic conflict (De Leo et al., 2005; Goldney et al., 2000; Konick & Gutierrez, 2005; Meneese & Yutrzenka, 1990), death of a loved one or child (Qin & Mortensen, 2007), loss of employment or income (Hintikka et al., 2001a, 2001b; McMillan et al., 2010; Michal et al., 2010; Turvey, Stromquist, Kelly, Zwerling, & Merchant, 2002), and legal or disciplinary problems (De Leo et al., 2005). Especially deleterious stressors include poor perinatal conditions, child maltreatment or abuse (Afifi, Boman, Fleisher, & Sareen, 2009; De Leo et al., 2005; Joiner et al., 2007; Silverman, Reinherz, & Giaconia, 1996), sexual abuse (Talbot, Duberstein, Cox, Denning, & Conwell, 2004), domestic violence (Afifi et al., 2009), and chronic stress, including frequent exposure to painful and provocative stimuli (Smith & Cukrowicz, 2010; Joiner, 2005). Nock and colleagues (2008a) suggest that, consistent with diathesis-stress models of suicidality, stress and negative life events might interact with other risk

factors, such that these events increase risk among individuals already predisposed to suicidality. Yet, it is unclear through which mechanisms these factors might increase susceptibility.

Another stressor that appears to predispose an individual to suicidal ideation is exposure to suicidality, including parental suicidal ideation (Goodwin, Beautrais, & Fergusson, 2004) or attempt (Lieb, Bronisch, Hofler, Schreier, & Wittchen, 2005), personal history of suicide attempt (Jamison, 1999; Joiner, 2005), and knowing anyone who attempted or completed suicide (De Leo et al., 2005). Importantly, although family studies provide evidence for a heritable risk of suicidal behavior, thus far, familial transmission of liability for suicidal ideation appears best explained by the risk associated with psychiatric disorders (Brent, 2010).

Finally, a number of researchers have suggested that certain personality and psychological dimensions contribute to an individual's vulnerability for developing suicidal ideation. These include Axis II pathology (McGirr et al., 2009; Starcevic, Bogojevic, Marinkovic, & Kelin, 1999), low self-esteem (Bhar, Ghahramanlou-Holloway, Brown, & Beck, 2008), low self-directedness and high self-transcendence (Conrad et al., 2009), high levels of neuroticism/negative emotionality and self-criticism (Beck, Steer, & Brown, 1993; Cox, Enns, & Clara, 2004), perfectionism (Blankstein, 2007; O'Connor & Forgan, 2007), cyclothymic temperament (Kochman et al., 2005), and depressogenic thinking (Smith et al., 2006). To clarify, self-esteem includes beliefs about oneself and beliefs about how other people regard oneself. Self-directedness refers to self-efficacy and a conviction of being able to positively influence a situation or solve a problem. Self-transcendence incorporates spirituality and creativity, and depressogenic thinking comprises dysfunctional attitudes, pessimism, and negative inferential styles. Notably, Bhar, Ghahramanlou-Holloway, Brown, and Beck (2008)

documented that low self-esteem added to the risk for suicidal ideation even after controlling for depression and hopelessness. Also of note, Cox, Ennis, and Clara (2004) found a significant association between neuroticism and ideation but not between neuroticism and attempts. They submit that some psychological dimensions, including neuroticism, might establish vulnerability to suicidal ideation and, in turn, suicidal ideation opens susceptibility to suicidal behaviors.

To summarize, a number of psychiatric disorders and symptoms, physical health factors, socio-demographic variables, stressful or negative life events, and personality and psychological dimensions distinguish individuals who experience suicidal ideation from those who do not experience suicidal ideation and from those who engage in suicidal behaviors. Major depression appears to be at least one of the major gateways through which suicidal ideation functions. Major depression can be both a distal and proximal risk factor, and a warning sign. On one hand, suicidal ideation might be the sequelae of major depression. On the other hand, major depression might open a pathway through which other risk factors surface, increasing an individual's susceptibility to suicidal ideation. Considering the nature of suicidal ideation, efficient and effective treatment for MDD-SI is key – and might be one way to prevent the transition from suicidal ideation to suicidal behaviors.

2.4 SUICIDAL IDEATION AND TREATMENT

Previous or chronic experiences with suicidal ideation might wear on an individual such that he or she slowly or quickly transitions from experiencing suicidal ideation to engaging in suicidal behaviors (Joiner, 2005; Kessler et al., 2005). Hence, there is an urgency to optimize the first-

line treatment of MDD-SI and, in turn, reduce time to recovery. Yet, to date, the literature is relatively uninformative about whether first-line treatments for MDD-SI and MDD should be the same, and whether psychotherapy or antidepressant pharmacotherapy is a preferable initial treatment strategy for MDD-SI (Baldessarini et al., 2007; Pompili et al., 2010; Szanto et al., 2003). There is some evidence, however, to indicate that MDD-SI is responsive to targeted treatment (Alexopoulos et al., 2009; Zisook et al., 2009), but that the effect is less than that which is observed in the absence of suicidal ideation. Conceivably, this finding may be explained by the fact that many of the variables correlated with an unfavorable response to treatment also are associated with suicidal ideation.

First, there is evidence that suicidal ideation remits with antidepressant pharmacotherapy (Mulder, Joyce, Frampton, & Luty, 2008; Tondo, Lepri, & Baldessarini, 2008; Zisook et al., 2009) and combined antidepressant pharmacotherapy and psychosocial treatment (Szanto et al., 2001, 2003). For example, in a secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, Zisook et al. (2009), report that among 1,738 individuals with baseline suicidal ideation (indicated by a score of one or greater on the QIDS item 12, where 1 = life empty or not worth living), 74% experienced improvement in suicidal ideation and depressive symptoms following 12 to 14 weeks of antidepressant pharmacotherapy (citalopram). Importantly, they found that reduction of suicidal ideation was strongly related to overall response and remission of depressive symptoms. Specifically, individuals with MDD-SI who did not experience a response or remission with treatment were significantly more likely to report suicidal ideation post-treatment than were individuals with MDD-SI who did experience a response or remission. In another study, Alexopoulos and

colleagues (2009) demonstrated that care management reduces suicidal ideation (defined as present or not presented with the SSI) and depressive symptoms more than does usual treatment among primary care patients, aged sixty or older, experiencing major or minor depression. Specifically, care managers helped detect depression, offered algorithm-based recommendations, monitored symptoms and medication side-effects, conducted interpersonal psychotherapy with individuals who refused medication, and provided follow-up. At four months, suicidal ideation had declined by 12.8% in the care management group compared with 3.0% in the usual care group; this was the sharpest decline during the study. At eight and twelve months, the rates of suicidal ideation were similar between groups. At twenty-four months, suicidal ideation had declined 18.4% in the care management group compared to 8.3% in the usual care group. Notably, at twenty-four months, 11.4% of the care management group (a decline of 18.3% from baseline) and 12.1% of the usual care group (a decline of 8.3% from baseline) continued to experience death or suicidal ideation.

Surprisingly, although there were reports documenting the effect of antidepressant pharmacotherapy, with or without an adjunctive psychosocial intervention, we were able to find only one investigation of the efficacy of psychotherapy as a monotherapy for suicidal ideation in the absence of self-injurious or suicidal behaviors (Heisel et al., 2009). In this pilot study, Heisel and colleagues (2009) assessed the feasibility, tolerability, and acceptability of a 16-week course of interpersonal psychotherapy adapted for 12 older adults experiencing MDD-SI. Heisel and colleagues assessed suicidal ideation with the self-report Geriatric Suicide Ideation Scale (Heisel & Flett, 2006) and clinician-administered SSI. Preliminary findings demonstrated that the intervention was efficacious for reducing suicidal ideation and depressive symptoms but

insufficient to bring about a complete remission of depressive symptoms; average post-treatment HRSD scores remained high (M = 12.8, SD = 7.6).

Second, there is some preliminary evidence to suggest that MDD-SI and MDD might be associated with different treatment needs (Szanto et al., 2001) and treatment response trajectories (Pompili et al., 2010; Szanto et al., 2003). For example, in one study, Szanto et al. (2001) compared treatment needs and remission rates among elderly individuals with MDD-SI to those with MDD. Szanto and colleagues classified individuals as experiencing MDD-SI if they scored a two or higher on the Question 3 of the HRSD. Both groups received acute and continuation treatment with combined interpersonal psychotherapy and antidepressant pharmacotherapy (nortriptyline). Remission rates between the MDD-SI and MDD groups were nearly identical, 77% versus 78%, respectively. The MDD-SI group, however, was more likely to need augmentation pharmacotherapy (e.g., lorazepam for anxiety or insomnia, lithium or paroxetine as augmentation, or perphenazine for severe agitation) than was the MDD group, 43% versus 23%, respectively. Essentially, the MDD-SI group needed "more" than did the MDD group to achieve remission. In a secondary analysis of this data, combined with data from two other late-life depression treatment trials, Szanto and colleagues (2003) investigated the course of suicidal ideation and treatment response during the first twelve weeks of treatment among three groups: a high-risk group (recent attempt or current suicidal ideation, HRSD Question 3 score $\geq$ 3; n = 45), a moderate-risk group (recurrent thoughts of death, HRSD Question 3 score = 2; n = 284), and a low-risk group (none of the above, HRSD Question 3 score $\leq$ 1; n = 65). By week twelve of treatment, suicidal ideation had resolved among all individuals, and only 4.6% continued to experience thoughts of death. Median time to response, however, was significantly longer in the

high-risk group (6 weeks) and moderate-risk group (5 weeks) compared to the low-risk group (3 weeks). Moreover, compared to individuals in the moderate- and low-risk groups, individuals in the high-risk group were significantly less likely to be full responders at week twelve. Thus, whereas suicidal ideation in late-life depression rapidly resolved with antidepressant pharmacotherapy or antidepressant pharmacotherapy and psychotherapy, depressive symptoms did not. Specifically, compared to individuals with MDD, individuals with MDD-SI or suicidal behavior needed "longer" to experience relief from depressive symptoms. Likewise, in another study, Pompili and colleagues (2010) specifically addressed the question of whether MDD-SI was associated with an unfavorable response to intravenous antidepressant treatment (citalopram) by comparing treatment response among 82 individuals with major depression and a unipolar or bipolar diagnosis, with or without suicidality (ideation or behaviors) at intake to treatment. An HRSD Question 3 score greater than or equal to three indicated presence of suicidality. Of note, all individuals were eligible for intravenous antidepressant treatment because they had failed to respond to at least one month of standard oral antidepressant treatment. Individuals with suicidality were more likely than were individuals without suicidality to have been ill longer, have lifetime substance abuse, have received a mood stabilizer, and be young and unmarried. At intake to treatment, depression severity between the two groups was nearly identical; however, after six weeks of treatment, compared to individuals without suicidality, individuals with suicidality improved only 46.6% as much and were less likely to experience at least a 20% improvement in symptoms, 57% versus 26%, respectively. Furthermore, despite experiencing reductions in overall depression severity and suicidality, individuals' suicidality ratings remained elevated at six weeks of treatment. Finally, in logistic

regression analyses, suicidality was the only factor among many (e.g., depression severity, substance use history) to be significantly associated with a less favorable treatment response. Pompili and colleagues argue that since the groups did not differ in depression severity at intake, greater depression severity cannot easily explain the inferior treatment response associated with suicidality. Rather, they assert that something associated with or part of the phenotype is accounting for the variance in treatment response.

Of note, a major limitation of the aforementioned investigations is the grouping of individuals with suicidal ideation and suicidal behaviors. Again, preliminary investigations indicate that those who experience suicidal ideation are distinct from those who engage in suicidal behaviors (Brent, 2010; Kessler et al., 2005).

Third, and complicating speculation about MDD-SI and initial treatment response even further, is the indirect evidence supporting both a differential response favoring psychotherapy and favoring pharmacotherapy. For example, on one hand, some of the factors identified as presumably predictive of poorer treatment response to psychotherapy for major depression also are associated with suicidal ideation. These include early age of illness onset (Klein et al., 1999), psychotic features (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Moller, 1994; Mueller et al., 1999; Volz, Muller, Sturm, Preussler, & Moller, 1995), and neuroticism (Berlanga et al., 1999; Joyce et al., 2007; Luty et al., 2007; Nelson & Cloninger, 1997).

On the other hand, some of the factors identified as presumably predictive of poorer treatment response to antidepressant pharmacotherapy for major depression also are associated with suicidal ideation. These include undiagnosed or subthreshold bipolarity (Akiskal & Benazzi, 2005; Akiskal, Benazzi, Perugi, & Rhimer, 2005; Baldessarini et al., 2007), “anxious”

depression (Fava et al., 2008), high social dysfunction (Sotsky et al., 1991), being unemployed (Fournier et al., 2009), and having a greater number of recent life events (Fournier et al., 2009). Then again, some of the factors associated with suicidal ideation are predictive of poorer response to both psychotherapy and pharmacotherapy. These include severe or chronic major depressions (Fournier et al., 2010; Frank, Novick, & Kupfer, 2005; Judd et al., 1998; Mueller et al., 1999), medical comorbidities (Iosifescu, 2007), alcohol use (Klein et al., 1999; Worthington et al., 1996), anxiety (Fawcett et al., 1990; Feske, Frank, Kupfer, Shear, & Weaver, 1998; Frank et al., 2000, 2010), and personality pathology (Cyranowski et al., 2004; Frank et al., 2005; Thase, 1996).

To summarize, the extant literature is inconclusive about the relationship between MDD-SI and treatment. One, although there is evidence indicating MDD-SI is responsive to antidepressant pharmacotherapy, there is a paucity of research on the efficacy of psychosocial monotherapies for MDD-SI. Hence, it is premature to speculate whether psychotherapy or antidepressant pharmacotherapy is a preferable initial treatment strategy for MDD-SI. Two, while there is evidence demonstrating that MDD-SI and MDD have different treatment needs and response curves, this work is preliminary. Moreover, it has questionable generalizability since researchers often grouped individuals with suicidal ideation and suicidal behaviors. Finally, while there is evidence indicating that some of the predictors of suicidal ideation also are robust predictors of an unfavorable response to antidepressant pharmacotherapy, these predictors also are associated with an unfavorable response to psychotherapy. Consequently, one could hypothesize that either (or neither) treatment might be the best first-line initial treatment strategy for MDD-SI. Taken together, findings from the current literature are promising, and suggestive

of future avenues for exploration. What remains unresolved, however, is what feature, or cluster of features, associated with MDD-SI explains between group variance. One explanation might be subsyndromal and syndromal mood and anxiety comorbidity.

2.5 SUBSYNDROMAL ANXIETY AND MOOD SYMPTOMS

Based on the literature, it is important to assess a broad array of lifetime and concurrent anxiety and mood symptomatologies potentially associated with MDD-SI. First, co-occurrence of major depression, both with other Axis I disorders and with Axis II disorders, appears to be the rule. It has long been acknowledged that these comorbidities at a syndromal level make depression difficult to treat because they complicate and prolong the treatment process (Cyranowski et al., 2004; Feske et al., 1998; Frank et al., 2000). Yet, investigators also have demonstrated negative effects of comorbidity at the *subsyndromal* level. For example, among individuals with recurrent major depression, Frank and colleagues (2000) reported that while only 18% met criteria for lifetime panic disorder, 37.7% experienced subsyndromal anxiety. Compared to individuals without, individuals with subsyndromal anxiety were significantly less likely to respond to monotherapy with interpersonal psychotherapy and more likely to experience a delay in time to full remission with combination interpersonal psychotherapy and antidepressant pharmacotherapy (18.1 weeks versus 10.3 weeks, respectively). Similarly, Feske, Frank, Kupfer, Shear, & Weaver (1998) found that women with recurrent major depression and a lifetime history of panic and somatic anxiety symptoms were less likely to respond to interpersonal psychotherapy than were women with major depression without these panic features. Overall,

the presence of subsyndromal or syndromal anxiety is associated with more severe symptom profiles, including greater depression severity and higher rates of suicidality, poorer psychosocial functioning and quality of life, and less favorable outcomes to pharmacotherapy and psychotherapy, (Benvenuti et al., 2010; Frank et al., 2000; Michal et al., 2010).

Second, it is important to explore a broad array of lifetime and concurrent mood symptoms potentially associated with MDD-SI because the unipolar-bipolar dichotomy, as represented in DSM-IV-TR, is a simplification of clinical reality. Indeed, some individuals with "unipolar" disorders experience "bipolar" symptoms. For these individuals, their mood disorders exist along a continuum of affective pathology that cannot be parsed into two discrete mood states (Akiskal & Benazzi, 2005; Akiskal et al., 2005; Angst et al., 2003; Balestrieri et al., 2006; Cassano et al., 2004, 2009). Importantly, these subtle features may contribute to suicidality. For instance, investigators have demonstrated strong associations among subsyndromal hypomanic symptoms and suicidal ideation (Cassano et al., 2004, 2009, 2010; Frank et al., 2000; Wildes, Marcus, Gaskill, & Ringham, 2007). In one study, Cassano et al. (2004) found that individuals with recurrent unipolar disorder reported a significant number of subsyndromal hypomanic and manic symptoms, and that the more of these items they endorsed, the greater the likelihood of reporting suicidal ideation. In another study, Balestrieri et al. (2006) found that the greater the number and type of depressive and manic-hypomanic symptoms endorsed, the greater the incidence of suicidality among individuals with a psychiatric illness (schizophrenia, borderline personality disorder, bipolar disorder, unipolar depression, or panic disorder) and in a comparison group of healthy controls.

To summarize, major depression often co-occurs with anixety and other mood features. Importantly, these conditions negatively impact response to psychological and pharmacological interventions. Yet, most – if not all – investigations of MDD-SI fail to assess both syndromal and subsyndromal anxiety and mood conditions. Consequentially, the delineated MDD-SI phenotype is artificially restricted. Thus, a first step to increasing our understanding of MDD-SI might be developing a rich clinical phenotype of MDD-SI that includes lifetime and concurrent mood and anxiety symptomatologies. To this end, the Spectrum Assessment Method (Cassano et al., 1997, 1999, 2004) seems particularly well suited.

2.6 THE SPECTRUM ASSESSMENT METHOD

The Spectrum Assessment Method is a reliable and valid way to document the phenomenology and clinical phenotype of MDD-SI (Cassano et al., 1997, 1999, 2004; Fagiolini et al., 1999). This method is a dimensional approach to describing psychopathology that produces clinical phenotypes characterized by a broad array of manifestations of the target disorder, including its core and most severe symptoms, as well as a range of more subtle features related to the core condition, including prodromal, early-onset, attenuated, trait-like, and residual symptoms. Indeed, Cassano and the Pittsburgh-Pisa Spectrum Collaborative Project Group developed the spectrum assessments, in part, as a way to investigate the continuum between the criterion symptoms of each disorder and the sub-threshold symptomatology which precede, follow, or are manifested in concurrence with the main disorder. They assert that these “spectrum conditions”

have important implications for illness course and treatment outcomes (Benvenuti et al., 2010; Cassano et al., 2009; Frank et al., 2000, 2010).

Of particular interest to this investigation are both the mood and panic-agoraphobic spectrum conditions, as assessed by the lifetime and past month versions of the *Mood Spectrum, Self-Report* (MOODS) and *Panic-Agoraphobic Spectrum, Self-Report* (PAS) instruments, respectively. Both questionnaires were developed simultaneously in English and Italian, and based on corresponding structured clinical interviews. Cassano and colleagues have demonstrated that the MOODS and PAS are reliable and have good-to-outstanding psychometric properties (Rucci & Maser, 2000).

The MOODS was designed to evaluate the lifetime and past month presence or absence of the full range of mood pathology an individual may experience including DSM-IV core symptoms of depression, hypomania and mania, atypical symptoms, subthreshold manifestations, and behavioral traits and lifestyles that arise as a means of coping with mood symptoms (Cassano et al., 2004; Dell'Osso et al., 2002; Fagiolini et al., 1999). In general, the MOODS attempts to characterize the "temperamental" affective dysregulation present throughout an individual's lifetime or recent affective episode.

Specifically, the MOODS is a self-report instrument that asks the individual to answer "Yes" or "No" to 161 items coded as present or absent for one or more periods of at least three to five days during an individual's lifetime (MOODS-Lifetime) or past month (MOODS-PM). For some questions, such as those exploring temperamental features or specific events, the duration is not specified because it would not be applicable. Items are organized into three manic-hypomanic and three depressive domains exploring mood, energy, and cognition, plus a domain

that explores disturbances in rhythmicity and vegetative functions. Fifteen factors have been identified with exploratory factor analysis (Cassano et al., 2009, 2010). These factors, and the feature or core domain(s) of assessment are: (1) depressive mood: core symptoms of depression, anhedonia, and temperamental features; (2) psychomotor retardation: contra-polar features of mania, retardation in different areas of daily activities, physical weakness, and tiredness; (3) suicidality: ideation, planning, and severity of attempts; (4) drug or illness related depression: mood dysregulation during common physical illness and/or following medication or substance use; (5) psychotic features: paranoid thoughts and psychotic features; (6) neurovegetative symptoms: rhythm disruption, problems with sleep, appetite, and sexual functioning; (7) psychomotor activation: core symptoms of mania; (8) creativity: bursts of artistic creativity and sensitivity; (9) mixed instability: instability in mood, work, friendships, and personal relationships; (10) sociability/extraversion: optimism, sociability, and extraversion; (11) spirituality/mysticism: ecstatic experiences and heightened sense of reality; (12) mixed irritability: mood dysregulation, hostility, and irritability during common physical illness and/or following medication or substance use; (13) inflated self-esteem: grandiose self-esteem; (14) euphoria: euphoric mood elevation of pure mania or "sunny" hypomania; and (15) recklessness: engagement in risky behaviors. Of particular interest, the suicidality factor provides information about the suicidal process, such that it provides information across the suicidality continuum, assessing experiences of death wishes and passive ideation, attempt planning, attempt, and need for medical attention following attempt (Cassano et al., 2009).

The PAS was designed to evaluate the lifetime and past month presence or absence of a broad array of manifestations of panic disorder including DSM-IV core symptoms of panic,

subthreshold manifestations, and behavioral traits that arise as a means of coping with anxiety symptoms. The PAS is a self-report instrument that asks the individual to answer "Yes" or "No" to 114 items as present or absent. Items fall into one of ten factors. These factors, and the feature or core domain(s) of assessment are: (1) panic symptoms: somatic symptoms of panic attacks; (2) separation anxiety: uneasiness when sleeping alone or away from home and fearful of harm coming to family members; (3) agoraphobia: avoidance behaviors related to fear of panic; (4) medical reassurance: excessive requests for test, calls to doctor, and use of emergency services; (5) rescue object: magical ideas about the "protective" power of specific objects; (6) depersonalization: sense of detachment from one's own being and a sense of unreality; (7) family reassurance: excessive help-seeking from family, friends, and neighbors; (8) drug phobia: reluctance to ingest substances (e.g., caffeinated beverage, psychotropic medication) and sensitivity to effects; (9) claustrophobia: uneasiness in situations that can be broadly characterized as evoking suffocation or entrapment fears; and (10) loss sensitivity: excessive difficulty with ending relationships.

To summarize, the Spectrum Assessment Method is a dimensional approach to psychopathology and produces clinical phenotypes characterized by a broad array of overt and subtle prodromal, subsyndromal, and syndromal manifestations of the target disorder. Assessing the mood and panic-agoraphobic spectrum conditions in MDD-SI may produce a more full clinical phenotype and, subsequently, lead to a more refined understanding of the illness and treatment needs.

2.7 HYPOTHESES

Based on the literature to date, we hypothesized that among a group of adults entering treatment for unipolar major depression, individuals with baseline suicidal ideation (MDD-SI) and individuals without baseline suicidal ideation (MDD) would differ in:

H_1 Pre-treatment socio-demographic and baseline clinical characteristics such that individuals with MDD-SI would be younger, would be more likely to be female, would be more likely to be single or separated, would be more likely to be unemployed, would have lower quality of life and satisfaction, would have greater depression severity, would have a greater number of previous depressive episodes, and would have higher rates of medical comorbidities and obesity, early onset major depressive disorder, comorbid anxiety disorders, alcohol abuse, and cigarette smoking.

H_2 Lifetime experience of suicidal ideation and suicidal behavior, such that individuals with MDD-SI would be more likely to report a history of suicidal ideation and previous suicide attempts.

H_3 Lifetime and past month spectrum assessment scores such that individuals with MDD-SI would have higher:

H_{3A} Lifetime and past month Mood Spectrum – Self-Report (MOODS) total scores and higher lifetime and past month depressive mood, neurovegetative symptoms, spirituality, and recklessness factor scores; and

H_{3B} Lifetime and past month Panic-Agoraphobic Spectrum – Self-Report (PAS) total scores and higher lifetime and past month panic symptoms and depersonalization factor scores.

H_4 Depression severity after six weeks of monotherapy, such that individuals with MDD-SI would have greater depression severity, as evidenced by higher adjusted *Hamilton Rating Scale for Depression, 25-item* (HRSD-25-A) total scores at week seven[1]. Furthermore, suicidal ideation would not be associated with a differential treatment response to SSRI or IPT. Accordingly, suicidal ideation would be a non-specific predictor of initial treatment response because it is a pre-treatment characteristic that has a main effect but no interactive effect on initial treatment response.

To test these hypotheses, we completed a secondary analysis of data from a two-site, cross-national clinical trial in which individuals presenting for treatment of a non-psychotic unipolar major depressive episode were randomly allocated to a treatment protocol involving SSRI, IPT, and, in the absence of a response or sustained remission, their combination.

[1] HRSD-25-A total scores are HRSD-25 total scores minus the score on the suicide item.

3.0 METHODS

This investigation was a secondary analysis of data from the pilot and full depression phenotypes studies (MH65376), directed by Drs. Ellen Frank and Giovanni B. Cassano, conducted between 2003 and 2008 at outpatient research clinics associated with the Departments of Psychiatry at the University of Pittsburgh, Pennsylvania, United States of America and University of Pisa, Italy. In the depression phenotypes studies, participants were treated with acute and continuation protocol pharmacotherapy with the SSRI antidepressant citalopram (pilot study at Pisa) or escitalopram (pilot study at Pittsburgh; full study at both sites), protocol psychotherapy with interpersonal psychotherapy (IPT), and, in absence of a response or remission, their combination (IPT/SSRI or SSRI/IPT). The ultimate goal of the depression phenotype studies was to define clinically useful and specific profiles of participants who would benefit from pharmacotherapy versus psychotherapy and of those who would require treatment augmentation. Notably, the pilot and full study were identical except with regard to psychotropic agent; escitalopram was not available in Europe during the pilot study period. To avoid confusion and redundancy, from this point forward, we reference the pilot and full depression phenotype studies as one study.

The University of Pittsburgh's Biomedical Institutional Review Board (IRB) and the Ethics Committee of the Azienda Ospedaliero-Universitaria of Pisa approved all recruitment,

assessment, and treatment procedures. All participants provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

3.1 PARTICIPANTS

The sample for this report comprised 368 male and female adult outpatients experiencing a non-psychotic unipolar major depressive episode (MDE). Participants were recruited from the outpatient mental health clinics of Western Psychiatric Institute and Clinic (Pittsburgh, PA) and the University of Pisa (Pisa, Italy).

To enter the study, participants were required to be between 18 and 64 years of age with a current, index episode of non-psychotic unipolar major depression, as defined by the *Diagnostic and Statistical Manual for Mental Disorder, Fourth Edition* (DSM-IV) (American Psychiatric Association [APA], 2000), and determined by the *Structured Clinical Interview for Axis I DSM-IV Disorders* (SCID-I) (First, Gibbon, Spitzer, & Williams, 2001). The index MDE was required to meet minimum severity criteria, defined as a score of 15 or greater on the *17-item Hamilton Rating Scale for Depression* (HRSD-17; Hamilton, 1960). Diagnostic exclusion criteria were (a) history of manic or hypomanic episode(s), (b) history of schizophrenia or schizoaffective disorder, (c) organic affective syndrome, (d) current psychosis, (e) current primary diagnosis of anorexia nervosa or bulimia nervosa, (f) drug or alcohol abuse/dependence within the past three months, and (g) satisfying full criteria for antisocial personality disorder, as determined by the *Structured Clinical Interview for Axis II DSM-IV Disorders* (SCID-II) (First, Gibbon, Spitzer, & Williams, 1996). No other Axis I or II disorder constituted exclusion. Treatment and medical

exclusion criteria were (a) well-established, well-documented history of intolerance or non-response to one or more of the study treatments, (b) pregnancy or breastfeeding, (c) unable or unwilling to provide informed consent, and (d) specific medical exclusions. Medical exclusions included (a) index episode was a secondary effect of medically prescribed drugs, (b) presence of uncontrolled medical illness, and (c) concomitant psychotropic medications (with the exception of low-dose benzodiazepines, permitted only in participants who could not be fully withdrawn) or over-the-counter and herbal therapies.

Participants with current suicidal ideation or behaviors were not excluded if, in the treatment team's judgment, the suicidality could be managed on an outpatient basis. Participants who required inpatient treatment because of suicide risk were excluded or discontinued from the study and referred to an inpatient mood disorder unit, voluntarily or, if required, involuntarily.

3.2 PROCEDURE

Of relevance to the aims and hypotheses of this secondary investigation is only the first six weeks of the protocol, including treatment and assessment. Therefore, the complete study design and treatment algorithm is only briefly described (for a full description, see Frank et al., 2010).

3.2.1 Overview of study design

Participants were randomly allocated (with simple randomization) to an initial treatment strategy of SSRI or IPT. Participants received augmentation with the other treatment if the initial

treatment strategy was unsuccessful in bringing about a response within six weeks of treatment or stabilization within twelve weeks of treatment. We defined response as a fifty percent reduction in baseline HRS-D-25 scores and stabilization as three consecutive weeks during which the HRS-D-17 score was equal to or averaged seven (Frank et al., 1991). If the treatment team deemed it clinically necessary, deviations from the algorithm were permitted such that participants could receive acute treatment augmentation earlier than week seven. Participants remained in weekly acute treatment for at least twelve weeks and, if applicable, ten sessions of IPT. Once participants achieved stabilization and minimum acute treatment criteria, they entered the continuation phase and maintained their acute treatment regimen for six months. If participants failed to meet criteria for stabilization with sixty-four weeks of acute treatment, they were terminated from the study and referred to other treatment.

3.2.2 Initial treatment strategies

Participants allocated to an initial treatment strategy of pharmacotherapy were seen by experienced psychopharmacologists for weekly 20 to 30 minute visits. Citalopram (pilot study at Pisa) was started at 20 mg/day and titrated up or down as needed, with the aim of achieving symptom stabilization and/or a dose of 40 mg/day. Escitalopram (pilot study at Pittsburgh; full study at both sites) was started at 10 mg/day and titrated up or down as needed, with the aim of achieving symptom stabilization and/or a dose of 20 mg/day. Maximum permissible dose was 60 mg/day for citalopram and 40 mg/day for escitalopram. After six weeks of treatment, those participants initially allocated to SSRI who had achieved the targeted dose and had not evidence a response began treatment augmentation with IPT. Of note, escitalopram is an enantiomer of

citalopram; therefore, escitalopram and citalopram are similar psychotropic agents. Escitalopram is marketed as an enhanced citalopram. Escitalopram was not available in Europe during the pilot study period. Therefore, pilot study participants treated at the Pisa site received citalopram. All full study participants received escitalopram.

Pittsburgh participants allocated to an initial treatment strategy of IPT were seen by masters- or doctoral-level psychologists or social workers for weekly 50-minute sessions. These therapists were trained by either G. Klerman, M. Weissman, B. Rounsaville and E. Chevron or one of two clinicians initially trained by that group. Pisa participants allocated to IPT were psychiatrists trained to research-level IPT competence by a co-investigator. At both sites, IPT sessions were digitally voice recorded and rated for IPT specificity. After six weeks of treatment, those participants initially allocated to IPT who had attended at least five sessions of IPT and had not evidence a response began treatment augmentation with SSRI.

Participants in either initial treatment condition who complained of sleep difficulties were permitted up to two mg/day of lorazepam until the sleep difficulties resolved. Similarly, any participant reporting agitation could receive up to four mg/day of lorazepam. In practice, the median dose of lorazepam was 1.0 mg (range 0.25-3 mg)[2].

3.2.3 Assessment

Non-blind, independent clinical evaluators completed in-person intake psychiatric evaluations (SCID-I, -II), symptom assessments, and socio-demographic interviews, including medical

[2] Lorazepam dose information is based on full study sample only (n = 303).

history, with potential participants. Then, clinical evaluators reviewed each evaluation with a team of experts (i.e. the principal investigator, the project coordinator, and a study physician) to come to a consensus diagnosis for each potential participant. Next, clinical evaluators and study investigators determined study eligibility based on inclusion and exclusion criteria. Finally, eligible participants were randomized to an initial treatment strategy and informed of both their study eligibility and treatment condition. The study coordinator contacted ineligible participants and provided an appropriate referral.

To determine severity of depression and monitor treatment response, at each clinic visit, evaluators administered the HRSD-25 and participants completed the *Quick Inventory of Depressive Symptoms, 16-Item* (QIDS-16). At entry to treatment (start of week one of treatment), evaluators administered the *Interview on Suicidal Feelings* (ISF) and participants completed various self-reports, including the *Mood Spectrum - Lifetime* (MOODS-Lifetime), the *Panic-Agoraphobic Spectrum - Lifetime* (PAS-Lifetime), and the *Quality of Life and Satisfaction Questionnaire* (Q-LES-Q). After one week of treatment (start of week two of treatment), participants completed the *Mood Spectrum – Past Month* (MOODS-PM) and *Panic-Agoraphobic Spectrum – Past Month* (PAS-PM). After six weeks of treatment (start of week seven of treatment), evaluators again administered the ISF and participants again completed the Q-LES-Q.

To ensure consistency between sites, a bilingual psychiatrist from Pisa was trained over the course of one year at Pittsburgh and certified as the "gold standard" rater for Pisa. Inter-rater agreement at each site and between sites was recalibrated approximately every six months and was maintained at an intra-class coefficient (ICC) greater than 0.85.

3.2.3.1 Identification of MDD-SI

We classified participants as experiencing an index episode that was either major depression without current, baseline suicidal ideation (MDD) or major depression with current, baseline suicidal ideation (MDD-SI). Participants were classified as MDD-SI if they met *at least one* of the following criteria:

(a) Endorsed a score of two (I think of suicide or death several times a week for several minutes) or three (I think of suicide or death several times a day in some detail, I have made specific plans for suicide, or I have actually tried to take my life) on QIDS Question 12: Thoughts of death or suicide, and/or

(b) Received a score of two (Wishes to be dead or any thoughts of possible death to self) or three (Suicide ideas or gestures) on HRSD Question 3: Suicide, and/or

(c) Answered, "Yes, within the past week," to ISF Item 3: Thought to attempt, and/or

(d) Answered, "Yes, within the past week," to ISF Item 4: Seriously thought to attempt or made plans.

First, this operational definition ensured that all participants with serious or continuous active suicidal ideation, with or without a plan, were classified as MDD-SI, regardless of whether they self-reported, expressed to the evaluator, or did both. We believed that this

minimized the influence of potential assessment biases. Second, these cut points categorized participants who experienced passive death ideation, (e.g. life is empty), as MDD. We believe that death ideation is distinct from suicidal ideation.

Notably, the HRSD Question 3 is incongruent with the definition of suicidal ideation in the Classification System of Self-directed Violence (CSSV) (Brenner et al., 2010); a score of two might indicate persistent death wishes without thoughts of engaging in suicidal behavior and a score of three might denote preparatory behaviors or gestures. For the QIDS Question 12, a score of two is consistent with the CSSV definition of suicidal ideation but a score of three is inconsistent since it might include suicidal behaviors. Similarly, ISF Item 3 is consistent, whereas ISF Item 4 is not because it might include preparatory behaviors.

3.2.3.2 Identification of lifetime suicidality

We identified participants as positive for a history of suicidal ideation, excluding index episode, if participants answered "Yes" to MOODS-Lifetime Questions 104 to 107. These questions ask the participant whether he or she has ever experienced (either in isolation or as part of a depressive episode) periods of three to five days or more when he or she (104) wanted to die or hurt self, (105) made plans to die, (106) made an attempt to die, and (107) required medical attention after an attempt. Questions 105, 106, and 107 are congruent with the CSSV.

We categorized participants as positive for a history of suicide attempt if they answered "Yes" to (a) MOODS-Lifetime Question 106 and/or (b) MOODS-Lifetime Question 107 and/or (b) ISF Item 5: Attempted suicide. Again, we believed that including both a self-report and interviewer rating of suicidality might minimize assessment bias.

3.2.3.3 Assessment measures

The *Hamilton Rating Scale for Depression* (HRSD) (Hamilton, 1960) is an interviewer rating scale designed to assess the severity of depressive symptoms with a scale of zero to four or zero to two, where higher numbers indicate higher severity. Researchers have used the HRSD as a principal outcome measure (Gibbons et al., 1993) and standard assessment of depression for more than 40 years (Bagby et al., 2004). The HRSD-25 (Thase, Carpenter, Kupfer, & Frank, 1991) is an adapted version of the original HRSD-17 and assesses reverse neurovegetative symptoms, including hypersomnia, oversleeping, napping, increased appetite, weight gain, psychic retardation, motor retardation, and diurnal variation. After administering the HRSD-25 interview, interviewers can parse the items, yielding an HRSD-17 score. Moderate depression is indicated by a score between 15 or and 25. Suicidal ideation is noted by a score of two (Wishes to be dead or any thoughts of possible death to self) or three (Suicide ideas or gestures) on Question 3. Since our MDD-SI criteria included Question 3, to avoid inflating any potential statistical associations, we calculated adjusted HRSD scores by subtracting the zero to four score from the total HRSD-25 scores. This adjusted score is specified as HRSD-25-A.

The *Quick Inventory of Depressive Symptomatology* (QIDS) (Rush, Carmody, & Reimitz, 2000; Trivedi et al., 2004) is a 16-item self-report questionnaire designed to measure the signs and symptoms of depression. It has excellent psychometric properties (Rush et al., 2003). Both somatic and cognitive features of depression, DSM-IV criteria, and subtypes of depression, such as atypical and melancholic features, are queried. Most items are scored on a zero to three scale, where three indicates greatest severity. All items are weighted equally in the composite score. Moderate depression is indicated by a score between 11 and 15. Suicidal ideation is indicated by

a score of two (I think of suicide or death several times a week for several minutes) or three (I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life) on Question 12. For the same reasons outlined for the HRSD-25-A scores, we calculated an adjusted score, the QIDS-A scores, by subtracting the zero to three score on the suicide item from the total QIDS scores.

The *Interview on Suicidal Feelings* (ISF) (Paykel, Meyers, Lindenthal, & Tanner, 1974) is a 5-item structured interview composed of separate questions regarding suicide: 1) Have you ever had the feeling that life is not worth living? 2) Have you ever wished to die, for example, to go to sleep and not wake up again? 3) Have you ever thought of taking your own life, even though you would never do so? 4) Have you ever seriously considered taking your own life, or made plans on how to go about doing so? 5) Have you ever attempted to take your own life? Individuals that answer yes are asked if they experienced the symptom in the past week, two weeks to twelve months ago, or more than a year ago. Psychometric properties are not established for this instrument.

The *Mood Spectrum Self-Report* (MOODS) (Fagiolini et al., 1999) is a self-report instrument that evaluates the lifetime (MOODS-Lifetime) and past month (MOODS-PM) presence or absence of the full range of mood pathology someone may experience, including DSM-IV core symptoms of depression, hypomania and mania, atypical symptoms, subthreshold manifestations, and behavioral traits that arise as a means of coping with mood symptoms (See Section 2.6.). The Spectrum Project Group has demonstrated that the MOODS has good internal consistency (0.79-0.92) and high test-retest reliability (r = 0.93-0.94) (Fagiolini et al., 1999; Rucci & Maser, 2000).

The *Panic-Agoraphobic Spectrum Self-Report* (PAS) (Cassano et al., 1999; Shear et al., 2001) was designed to evaluate the lifetime (PAS-Lifetime) and past month (PAS-PM) presence or absence of a broad array of manifestations of panic disorder including DSM-IV core symptoms of panic, subthreshold manifestations, and behavioral traits that arise as a means of coping with anxiety symptoms (See Section 2.6.). A total score that exceeds 35 is clinically significant. The Spectrum Project Group has demonstrated that the PAS has high inter-rater reliability and test-retest reliability (r = 0.65-0.89), and strong concurrent validity (>0.65 between PAS domains & instruments measuring similar constructs) (Rucci & Maser, 2000).

The *Quality of Life Enjoyment and Satisfaction Questionnaire* (Q-LES-Q) (Endicott, Nee, Harrison, & Blumenthal, 1993; Rossi et al., 2005) is a self-report questionnaire designed to measure the degree of enjoyment and satisfaction an individual experiences in eight areas of life. These include physical health or activities, feelings, work, household duties, school or course work, leisure time activities, social relations, and general activities. Items are scored on a one to five scale, where higher scores indicate higher levels of satisfaction. The total score is the sum of the first fourteen items (raw score) minus fourteen (minimum possible score), divided by 56. The Q-LES-Q has substantive test–retest reliability and internal consistency (>0.80).

3.3 DATA ANALYSIS

For our investigation, we adopted the McArthur approach (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Kraemer, Wilson, Fairburn, & Agras, 2002) to conceptually distinguish among a non-specific predictor, moderator, and mediator variable. Accordingly, there are four potential

relationships between suicidal ideation (SI) and initial treatment response (R). One possibility is that SI is unrelated to R. Another possibility is that SI moderates R. If SI is a moderator, then SI is a pre-treatment/baseline characteristic, SI is uncorrelated with treatment (SSRI or IPT), and SI has an interactive effect (with or without a main effect) on R. If our analyses demonstrate that SI is a moderator of R, then SI does not help explain the initial effect of treatment. However, the interactive effect means that the effect of treatment on individual participants' initial response depends on the presence of SI and thus, SI helps explain individual differences in the initial effect of treatment; presence of SI indicates on whom the treatment may have the most (or least) clinically significant initial effects. A third possibility is that SI is a nonspecific predictor of R. If our analyses demonstrate that SI is a non-specific predictor of R, then SI is a pre-treatment/baseline characteristic, SI is uncorrelated with treatment, and SI has a main effect but no interactive effect on R. A fourth scenario is that SI mediates R. However, a mediator is a variable or event that occurs *during* R, is correlated with R, and has a main or interactive effect with R. Baseline SI does not meet these criteria. Treatment-emergent SI or changes in baseline SI – neither of which we were examined in this investigation – may be mediators but cannot be moderators. A moderator precedes and is not associated with that which it moderates; a mediator follows and is associated with that which it mediates.

3.3.1 Assumption testing and preliminary analyses

We conducted data analysis with SPSS Statistical Software, Version 17.0 (SPSS Inc., USA). We examined the data for normality, multicollinearity and singularity, homoscedasticity, univariate and multivariate outliers, homogeneity of variance, and missing data. Since our hypothesis

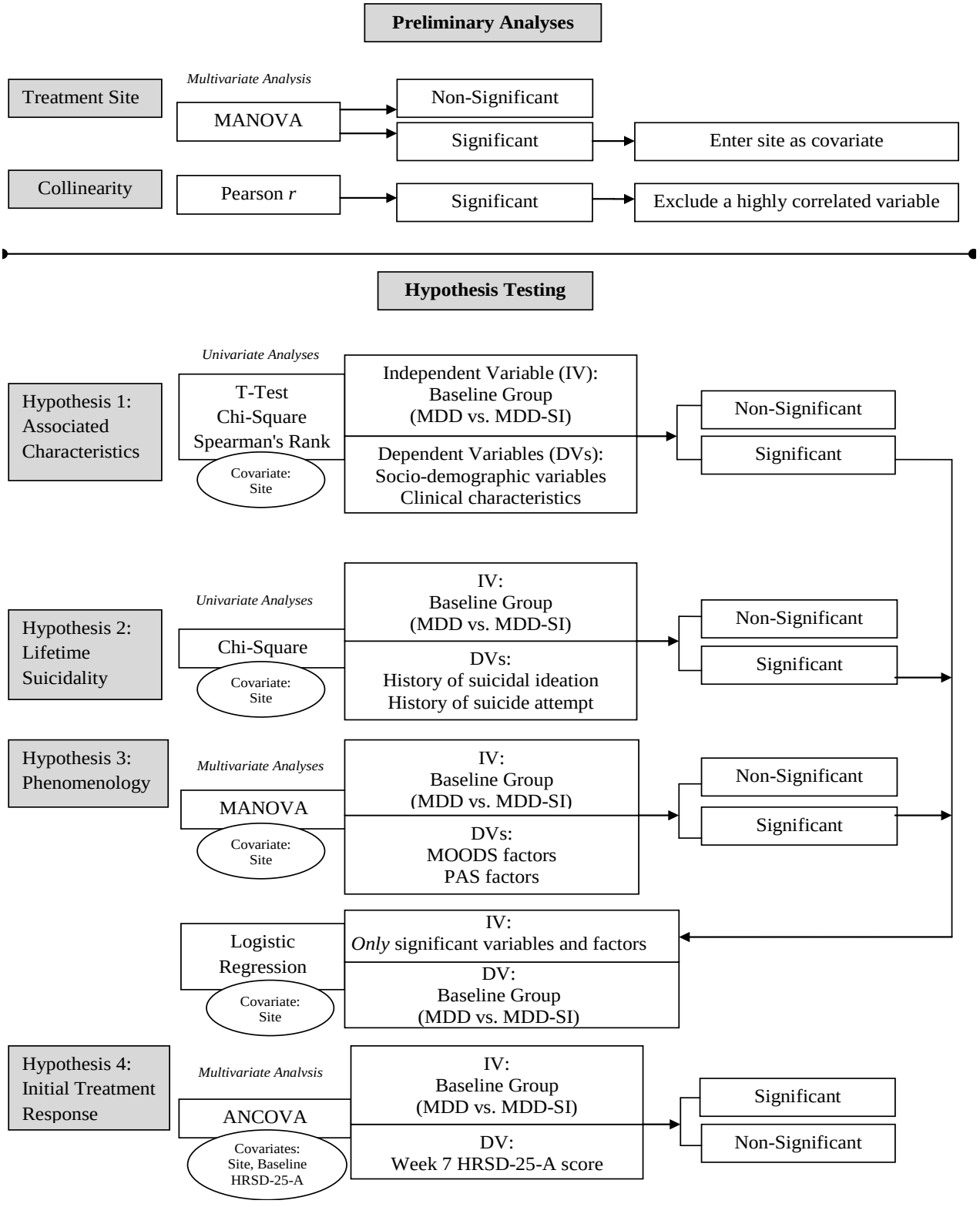
testing included a range of statistical techniques, and statistical techniques vary in robustness to modest violations of these assumptions, we tested assumptions for each hypothesis. We manipulated the data when the statistical technique warranted. Mainly, this included censoring outliers when Mahalanobis distances exceeded the critical value, or standardized residual or z-score values were greater than +/- 3.3 (Tabachnick & Fidell, 2007). Since the univariate analyses were only preliminary steps for evaluating the relationships among variables and suicidal ideation, we included all variables that were significant at $p = 0.05$, unless otherwise noted, in the logistic regression models.

To determine whether we should enter site as a covariate, we evaluated differences in ten socio-demographic variables and baseline clinical characteristics between sites with a one-way between-groups multivariate analysis of variance (MANOVA). The dependent variables were: age, HRSD-25-A, Q-LES-Q score, ISF score, MOODS-Lifetime score, PAS-Lifetime score, MOODS-PM score, PAS-PM score, total number of past month anxiety diagnoses, and total number of lifetime anxiety diagnoses. An overview of our analytical strategy is depicted in Figure 1.

3.3.2 Hypothesis 1: Associated characteristics of MDD-SI

To test Hypothesis 1, that individuals with MDD-SI and individuals with MDD will differ in pre-treatment socio-demographic variables and baseline clinical characteristics, we first examined the relationships among socio-demographic variables and baseline clinical characteristics using Pearson product-moment correlation coefficients. Then, we calculated Chi-square tests of independence with Yates Continuity Correction or Spearman's rank correlation coefficients for

Figure 1. Overview of Analytical Strategy for Hypothesis Testing



categorical socio-demographic variables and baseline clinical characteristics. Non-ranked categorical socio-demographic variables included: gender, marital status, employment status, and current smoking status. Non-ranked categorical baseline clinical characteristics included: lifetime diagnosis of alcohol or substance abuse or dependence disorder, any anxiety disorder, generalized anxiety disorder, panic disorder with or without agoraphobia, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, post-traumatic stress disorder, and anxiety not otherwise specified. Ranked categorical socio-demographic variables included: educational attainment, body mass index (BMI), and number of current medical conditions. Ranked categorical baseline clinical characteristics included: age of first MDE and number of previous MDEs (including current MDE). Next, we conducted independent-samples t-tests for age and continuous baseline clinical characteristic, including HRSD-25-A score, QIDS-16-A score, and Q-LES-Q score.

3.3.3 Hypothesis 2: Lifetime suicidality

To test Hypothesis 2, that individuals with MDD-SI and individuals with MDD will differ in lifetime experience of suicidal ideation and history of suicide attempts, we calculated Chi-square tests of independence with Yates Continuity Correction. To determine the relationships among self-report ratings (QIDS, MOODS-Lifetime, and MOODS-PM) and interviewer-ratings (HRSD, ISF) of suicidality, we calculated Pearson product-moment correlation coefficients.

3.3.4 Hypothesis 3: Phenomenology of MDD-SI

To test Hypothesis 3, that individuals with MDD-SI and individuals with MDD will differ in lifetime and past month spectrum assessment total and factor scores, we first examined the relationships among the factor scores using Pearson product-moment correlation coefficients. Next, we conducted independent-samples t-tests for lifetime and past month MOODS total scores, MOODS adjusted scores (scores without suicide items), and PAS total scores. Then, we used MANOVAs to test for differences between groups on the combined factor scores and, if statistically significant, to consider the factor scores separately. Finally, with logistic regression, we assessed the impact of the factor scores that significantly distinguished the MDD and MDD_SI groups in the multivariate analyses, with and without pre-treatment socio-demographic variables and baseline clinical characteristics that significantly distinguished the MDD and MDD-SI groups in univariate analyses, on the likelihood that participants would report baseline suicidal ideation.

3.3.5 Hypothesis 4: Initial treatment response

To test Hypothesis 4, that current suicidal ideation is a non-specific predictor of initial treatment response, we conducted a two-way between-groups analysis of covariance (ANCOVA) to compare the efficacy of initial treatment strategy in reducing depression severity for individuals with MDD-SI and individuals with MDD. The independent variables were initial treatment strategy (SSRI or IPT) and baseline group (MDD or MDD-SI). We ran analyses with site and then site and baseline HRSD-25-A scores as covariates. The dependent variable was HRSD-25-

A scores after six weeks of treatment (Week 7 scores). We considered the main effect for baseline group, the main effect for initial treatment strategy, and the interaction between baseline group and initial treatment strategy.

4.0 RESULTS

4.1 SAMPLE CHARACTERISTICS

A total of 368 outpatients with non-psychotic unipolar depression enrolled in the study; 182 participants were randomly allocated to an initial treatment strategy of SSRI and 186 participants were randomly allocated to an initial treatment strategy of IPT. Baseline data was analyzed for the entire sample. As detailed in Figure 1, complete data was unavailable for 23 participants.

Participants had a mean age of 39.44 years (SD = 12.17). Participants mostly were female (71.74%), Caucasian (91.03%), not married (61.14%), and employed at least part-time (64.67%). The majority had at least some college or advanced training (78.53%), BMI either in the normal range (43.75%) or overweight to severely obese range (48.37%), and either no medical conditions (46.74%) or one to two medical conditions (34.78%).

Using study criteria, 85 (23.10%) participants were classified as experiencing MDD-SI and 283 (76.90%) participants were classified as experiencing MDD. Means, standard deviations, and percentages within each group for lifetime and current suicidality at baseline are presented in Table 1.

Figure 2. CONSORT 2010 Flow Diagram for Pilot and Full Study

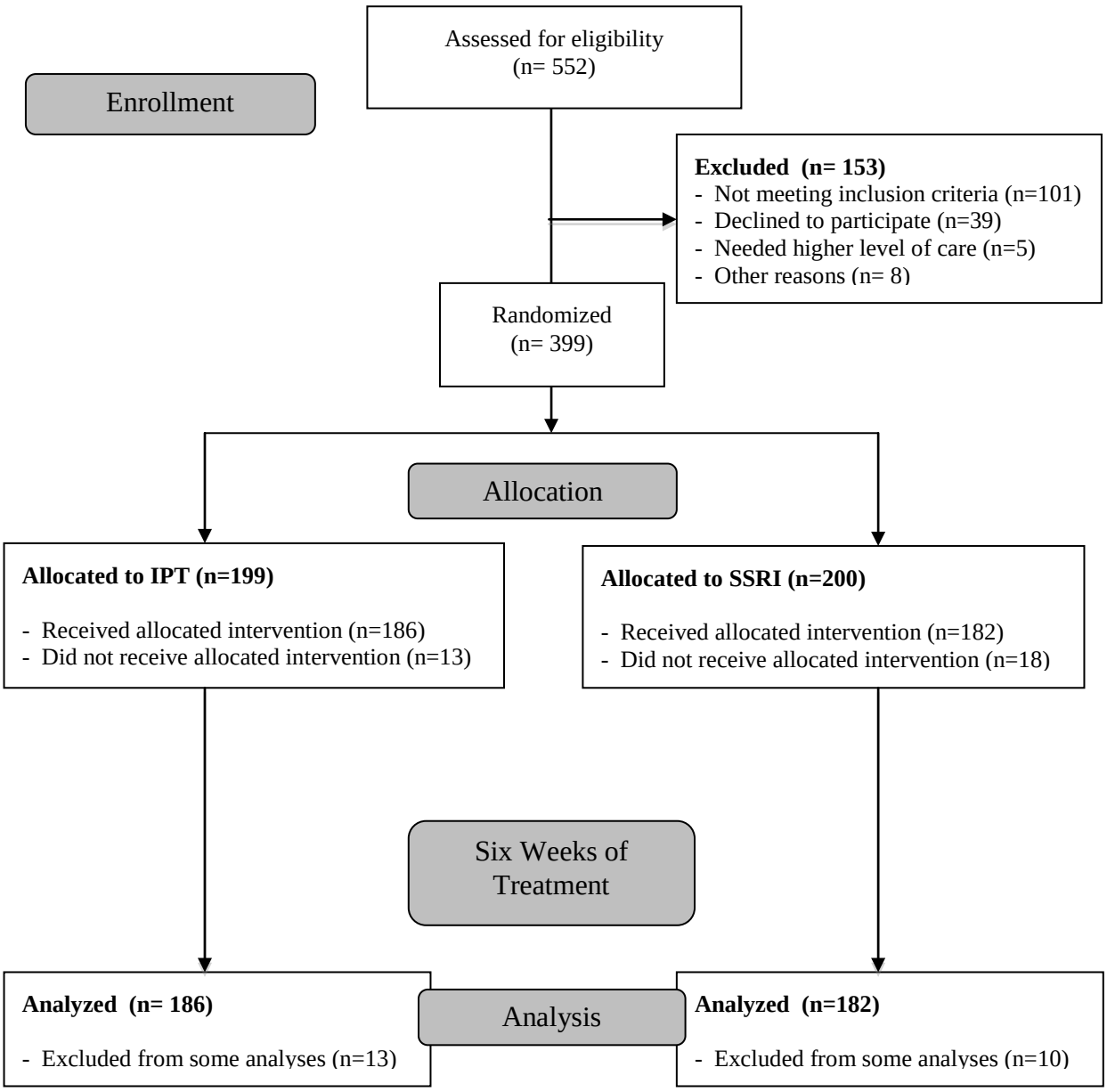


Table 1. Lifetime and Current Suicidality at Intake to Treatment

Assessment Item	Group				Total N	X^2	p
	MDD N = 283		MDD-SI N = 85		368		
	N	%	N	%			
History of suicidal ideation[a]	91	23.4	67	78.8	158	56.00	.00
History of suicide attempt[b]	20	7.1	25	29.4	45	28.36	.00
HRSD Suicide							
0 Absent	195	68.9	15	17.6	210	-	
1 Doubtful or trivial	88	31.1	33	38.8	121		
2 Mild	0	0	37	43.5	37		
3 Moderate	0	0	0	0	0		
4 Severe, attempted	0	0	0	0	0		
QIDS Thoughts of death or suicide							
0 Absent	196	69.3	6	7.1	202	-	
1 Life is empty	83	29.3	49	57.6	132		
2 Several times a week	0	0	25	29.4	25		
3 Several times a day	0	0	3	3.5	3		
ISF Thought to attempt	105	37.1	70	82.4	175	-	
Past week	0	0	34	40.0	34		
Two weeks to 12 months ago	56	19.8	29	34.1	85		
More than a year ago	46	16.3	7	8.2	53		
ISF Seriously thought to attempt	30	10.8	39	45.9	69	-	
Past week	0	0	4	4.7	4		
Two weeks to 12 months ago	8	2.8	16	18.8	24		
More than a year ago	22	7.8	19	22.4	41		
ISF Attempted suicide	18	6.4	21	24.7	39	-	
Past week	0	0	0	0	0		
Two weeks to 12 months ago	3	1.1	0	0	3		
More than a year ago	15	5.3	21	24.7	36		
ISF Total score	1.50	$\pm$1.44	3.31	$\pm$1.28	364		

Notes. [a]Does not include baseline ideation; [b] Data obtained from *Lifetime Mood Spectrum* and *Interview of Suicidal Feelings* (ISF); (-) Analysis not completed; HRSD = *Hamilton Rating Scale for Depression*; QIDS = *Quick Inventory of Depressive Symptoms*

4.2 TREATMENT SITE

A one-way between-groups MANOVA indicated that there was a statistically significant difference between the Pittsburgh and Pisa samples on the combined dependent variables, $F(10, 323) = 28.74$, $p = .00$; Pillai's trace = .47; partial eta squared = .47. When the results for the dependent variables were considered separately, using a Bonferroni adjusted alpha level of .005, five variables reached statistical significance: Q-LES-Q score $F(1, 332) = 44.59$, $p = .000$; ISF score, $F(1, 332) = 8.24$, $p = .003$; MOODS-Lifetime score, $F(1, 332) = 9.18$, $p = .003$; PAS-Lifetime score, $F(1, 332) = 40.37$, $p = .000$; and PAS-PM score, $F(1, 332) = 113.20$, $p = .000$. Compared to the Pisa sample, the Pittsburgh sample had higher scores on the Q-LES-Q, ISF, and MOODS-Lifetime, and lower scores on the PAS-Lifetime and PAS-PM. Based on these differences, all hypothesis testing was conducted with site as a covariate.

4.3 HYPOTHESIS 1: ASSOCIATED CHARACTERISTICS OF MDD-SI

The strength of the relationships among socio-demographic variables and baseline clinical characteristics are presented in Table 2 and Table 3, respectively. There were strong, positive correlations between age and marital status ($r = .56$) and HRSD-25-A and QIDS-16-A ($r = .56$). As shown in Table 4 and Table 5, chi-square tests of independence and independent-samples t-tests indicated few differences in pre-treatment socio-demographic and baseline clinical characteristics between the MDD and MDD-SI groups. The MDD-SI group included

significantly more participants from Pittsburgh than from Pisa, 63.5% versus 36.5%, respectively. In the Pittsburgh sample (data was not available for the Pisa sample), the MDD-SI group was significantly more likely than was the MDD group to smoke, 16.5% versus 9.2%, respectively. This difference remained significant after controlling for site differences (e.g., Q-LES-Q, MOODS-Lifetime, PAS-Lifetime, and PAS-PM scores) The MDD-SI group had significantly greater baseline depression severity, as indicated by higher HRSD-25-A scores (M = 25.85, SD = 5.53 versus M = 23.53, SD = 4.54) and QIDS-16-A scores (M = 15.24, SD = 4.15 versus M = 11.99, SD = 4.09), and lower baseline life satisfaction and enjoyment, as indicated by lower Q-LES-Q scores (M = 33.59, SD = 8.18 versus M = 37.04, SD = *0*.49). These group differences remained significant when site was entered as a covariate. As detailed in Table 6, there were no significant differences in the lifetime diagnosis of alcohol use, substance use, or anxiety disorders.

Table 2. Correlations among Socio-Demographic Variables

Variable	1	2	3	4	5
1 Gender	1.00	.09	-.15 *	.11	-.04
2 Age		1.00	-.11 **	.12	.16 *
3 Educational attainment			1.00	-.06	.08
4 Smoker status				1.00	-.09
5 Body mass index					1.00

Notes. * Significant at 0.01 level (two-tailed); ** Significant at 0.05 level (two-tailed); Male = 0, female = 1; Non-smoker = 0, smoker = 1

Table 3. Correlations among Baseline Clinical Characteristics

Variable	1	2	3	4	5	6
1 HRSD-25-A score[a]	1.00	.56 *	-.34 *	-.00	.01	.04
2 QIDS-16-A score[a]		1.00	-.40 *	.00	.02	.02
3 Q-LES-Q score			1.00	-.09	-.02	.09
4 Age of first MDE				1.00	-.37 *	-.07
5 Number of MDEs					1.00	.14 **
6 Number of current medical conditions						1.00

Notes. [a]Adjusted score does not include suicide items; HRSD-25 = *Hamilton Rating Scale for Depression, 25-item*; QIDS-16 = *Quick Inventory of Depressive Symptoms, 16-item*; Q-LES-Q = *Quality of Life Enjoyment and Satisfaction Questionnaire*; MDE = Major depressive episode; * Significant at 0.01 level (two-tailed); ** Significant at 0.05 level (two-tailed)

Table 4. Socio-Demographic Characteristics

Variable	Group				Total N	Stat[a]	p
	MDD N = 283		MDD-SI N = 85		368		
	N	%	N	%			
Study site						4.16	.04
Pittsburgh, USA	142	50.2	54	63.5	196		
Pisa, Italy	141	49.8	31	36.5	172		
Gender						2.27	n.s.
Male	74	26.1	30	35.3	104		
Female	209	73.9	55	64.7	264		
Age	39.67	± 12.33	38.68	± 11.70	368	t = 0.66	n.s.
Race and ethnicity							
Caucasian	257	90.8	78	91.8	335	-	
African-American	17	6.0	1	1.2	18		
Asian	3	1.1	2	2.4	5		
Other or declined	6	2.1	4	4.7	10		
Marital status						4.80	n.s.
Never married	117	41.3	40	47.1	157		
Married or living with	115	40.6	28	32.9	143		
partner	38	13.4	16	18.8	54		
Separated or divorced	13	4.6	1	1.2	14		
Widowed							
Educational attainment						ρ = 0.03	n.s.
Less than HS diploma	48	17.0	9	10.6	57		
HS diploma or GED	14	4.9	8	9.4	22		
Some college or adv. train.	127	44.9	37	43.5	164		
College degree	30	10.6	14	16.5	44		
Advanced degree	64	22.6	17	20.0	81		

Notes. [a]X^2 test statistic presented unless otherwise noted; (-) = Analysis was not conducted.

Table 4. Socio-Demographic Characteristics (con't)

Variable	Group				Total N	Stat [a]	p
	MDD N = 283		MDD-SI N = 85		368		
	N	%	N	%			
Employment status						7.21	n.s.
Full-time	157	55.7	38	44.7	195		
Part-time	35	12.4	8	9.4	43		
Homemaker or retired	30	10.6	9	10.6	39		
Student	26	9.2	13	15.3	39		
Unemployed, laid off, disabled, on leave, or other	34	12.1	17	20.0	51		
Smoking status (Pittsburgh, only)						3.96	.05
Current smoker	26	9.2	14	16.5	53		
Body mass index (BMI)						ρ =	n.s.
Under-weight, < 18.5	12	4.4	3	3.6	15	-0.01	
Normal, 18.5 – 24.9	120	44.3	41	49.4	161		
Overweight, 25.0 – 29.9	83	30.6	18	21.7	101		
Obese, 30.0 – 34.9	29	10.7	10	12.0	39		
Severely obese, > 35.0	27	10.0	11	13.3	38		
Number of current medical conditions						ρ = -0.04	n.s.
No conditions	127	49.8	45	56.3	172		
1 or 2 conditions	102	40.0	26	32.5	128		
3 or more conditions	26	10.2	9	11.3	35		

Notes. [a]X^2 test statistic presented unless otherwise noted; (-) = Analysis was not conducted.

Table 5. Baseline Clinical Characteristics

Variable	Group				Total N	Stat[a]	p
	MDD N = 283		MDD-SI N = 85		368		
	M N	SD %	M N	SD %			
HRSD-25 score	23.84	± 4.57	27.27	± 5.80	368	-	
HRSD-25-A score[b]	23.53	± 4.54	25.85	5.53	367	t = -3.50	.00
QIDS-16 score	12.29	± 4.24	16.54	± 4.46	362	-	
QIDS-16-A score[b]	11.99	± 4.09	15.24	± 4.15	362	t = -6.34	.00
Q-LES-Q score	37.04	± 0.49	33.59	± 8.18	352	t = 3.52	.00
Age of first MDE						ρ =	n.s.
Before age 12	18	6.5	11	12.9	29	-0.08	
Between age 13 and age 18	50	18.1	21	24.7	71		
After age 18	209	75.5	53	62.4	266		
Number of MDEs						ρ =	n.s.
1 MDE	91	32.5	24	28.6	115	0.04	
2 to 3 MDEs	99	35.4	30	35.7	129		
4 to 5 MDEs	41	14.6	12	14.3	53		
6 or more MDEs	49	17.5	18	21.4	67		

Notes. [a] X^2 test statistic presented unless otherwise noted; [b] Adjusted score does not include suicide items; (-) = Analysis was not conducted. HRSD-25 = *Hamilton Rating Scale for Depression, 25-item*; QIDS-16 = *Quick Inventory of Depressive Symptoms, 16-item;* Q-LES-Q = *Quality of Life Enjoyment and Satisfaction Questionnaire;* MDE = Major depressive episode

Table 6. Alcohol, Substance, and Anxiety Comorbidity

Variable	Group				Total N	X^2	p
	MDD N = 283		MDD-SI N = 85		368		
	N	%	N	%			
Alcohol abuse or dependence							
Lifetime [a]	23	8.1	12	14.1	35	2.07	n.s.
Drug abuse or dependence							
Lifetime	18	6.4	8	9.4	26	0.52	n.s.
Any comorbid anxiety disorders							
Past month	125	44.2	42	50.0	167	0.69	n.s.
Lifetime	139	49.1	47	55.3	186	0.77	n.s.
Generalized anxiety							
Past month	55	19.4	22	25.9	77	1.23	n.s.
Lifetime	58	20.5	22	25.9	80	0.82	n.s.
Panic with or without agoraphobia							
Past month	38	13.4	11	12.9	49	0.00	n.s.
Lifetime	57	20.1	15	17.6	72	0.12	n.s.
Agoraphobia							
Past month	14	4.9	7	8.2	21	0.77	n.s.
Lifetime	19	6.7	8	9.4	27	0.36	n.s.
Social phobia							
Past month	19	6.7	12	14.1	31	3.74	n.s.
Lifetime	21	7.4	12	14.1	33	2.82	n.s.

Note. [a] Lifetime totals include past month cases.

Table 6. Alcohol, Substance, and Anxiety Comorbidity (con't)

Variable	Group				Total N	X^2	p
	MDD N = 283		MDD-SI N = 85		368		
	N	%	N	%			
Specific phobia							
Past month	17	6.0	4	4.7	21	0.04	n.s.
Lifetime	18	6.4	5	5.9	23	0.00	n.s.
Obsessive compulsive							
Past month	7	2.5	4	4.7	11	1.28	n.s.
Lifetime	9	3.2	4	4.7	13	0.11	n.s.
Post-traumatic stress							
Past month	5	1.8	5	5.9	10	2.78	n.s.
Lifetime	8	2.8	5	5.9	13	1.01	n.s.
Anxiety not otherwise specified							
Past month	4	1.4	2	2.4	6	0.01	n.s.
Lifetime	4	1.4	2	2.4	6	0.01	n.s.

Note. [a] Lifetime totals include past month cases.

4.4 HYPOTHESIS 2: LIFETIME SUICIDALITY

As detailed in Table 1, chi-square tests of independence demonstrated statistically significant differences between the MDD and MDD-SI groups for lifetime experience of suicidal ideation and history of suicide attempts. The MDD-SI group was significantly more likely than was the MDD group to report a lifetime experience of suicidal ideation (80.7% versus 23.4%,

respectively) and history of suicide attempts (29.4% versus 7.1%, respectively). When site was entered as a covariate, the relationship between group and suicidal ideation remained significant. There was insufficient power to test for site effects on history of suicide attempts.

The correlations among self-report (QIDS, MOODS-Lifetime, and MOODS-PM) and interviewer ratings of suicidality (HRSD, ISF) are presented in Table 7. There were strong, positive correlations between the HRSD and QIDS (r = .58), ISF Thought to attempt and MOODS-Lifetime Wanted to die, (r = .53), and MOODS-Lifetime Made plan to die and MOODS-Lifetime Required medical attention after attempt (r = .63). There was a strong, negative correlation between the MOODS-Lifetime Wanted to die and MOODS-Lifetime Made plan to die, (r = -.54).

Table 7. Correlations among Interviewer and Self-report Ratings of Suicidality

	1	2	3	4	5	6	7	8	9
1 HRSD Suicide	1.0	.58**	.31**	.33**	.20**	.35**	-.25**	.14**	-.04
2 QIDS Thoughts of death or suicide		1.0	.35**	.27**	.05	.44**	-.34**	.06	-.00
3 ISF Thought to attempt			1.0	.46**	.28**	.53**	-.39**	.28**	-.15**
4 ISF Seriously thought to attempt				1.0	.63**	.47**	-.25**	.55**	-.24**
5 ISF Made attempt					1.0	.34**	-.20**	.81**	-.36**
6 MOODS-L Wanted to die/hurt self						1.0	-.54**	.34**	-.15**
7 MOODS-L Made plan to die							1.0	-.17**	.46**
8 MOODS-L Made attempt								1.0	-.41**
9 MOODS-L Required medical attention after attempt									1.0

Notes. HRSD = *Hamilton Rating Scale for Depression*; QIDS = *Quick Inventory of Depressive Symptoms*; ISF = *Interview of Suicidal Feelings;* MOODS-L = *Lifetime Mood Spectrum*
* Significant at 0.01 level (two-tailed); ** Significant at 0.05 level (two-tailed)

4.5 HYPOTHESIS 3: PHENOMENOLOGY OF MDD-SI

The strength of the relationships among MOODS-Lifetime, PAS-Lifetime, MOODS-PM, and PAS-PM factor scores are presented in Table 8, Table 9, Table 10, and Table 11, respectively. There were multiple moderate and strong correlations.

As shown in Table 12, independent-samples t-tests indicated significant differences between the MDD and MDD-SI groups for lifetime and past month MOODS total scores,, such that the MDD-SI group had significantly higher scores.

One-way between-groups MANOVAs were performed to investigate differences between groups on the lifetime and past month MOODS and PAS factor scores. Site was entered as a covariate in each MANOVA. As reported in Table 13 and Table 14, there were statistically significant differences between the groups on the combined MOODS-Lifetime factor scores, $F(14, 355) = 8.29$, $p = .00$; PAS-Lifetime factor scores, $F(10, 362) = 1.91$, $p = .04$; MOODS-PM factor scores, $F(14, 356) = 9.54$, $p = .00$; and PAS-PM factor scores, $F(10, 356) = 1.72$, $p = .05$. When the results for the dependent variables were considered separately, eleven factors reached statistical significance: MOODS-Lifetime: depressive mood, psychomotor retardation, psychotic features, and euphoria; PAS-Lifetime: depersonalization; MOODS-PM: depressive mood, psychomotor retardation, and psychotic features; and PAS-PM: separation anxiety, agoraphobia, and depersonalization.

Four logistic regression analyses were performed to determine the impact of the eleven spectrum factors on the likelihood that participants would report baseline suicidal ideation. The

first model, shown in Table 15 (Model 1), included only site and lifetime spectrum factor scores. As a whole, Model 1 explained between 6.8% (Cox and Snell R square) and 10.3% (Nagelkerke R squared) of the variance in baseline ideation status. The sensitivity of the model (true positives) was 2.4%; the specificity (true negatives) was 98.2%. Overall, Model 1 correctly classified 76.2% of cases. None of the variables made a unique statistically significant contribution to the model.

The second model, presented in Table 16 (Model 2), included site, significant socio-demographic variables and baseline clinical characteristics, and lifetime spectrum factor scores. This model was an improvement over the first model; it explained between 22.5% (Cox and Snell R square) and 34.6% (Nagelkerke R squared) of the variance in baseline ideation status. The sensitivity of the model was 38.2%; the specificity was 93.7%. Correct classification was 81.4%. Four of the variables made statistically significant and unique contributions to Model 2: site, Q-LES-Q score, lifetime experience of suicidal ideation, and MOODS-Lifetime euphoria.

The third model, reported in Table 17 (Model 3), included only site and past month spectrum factor scores. This model explained between 9.4% (Cox and Snell R square) and 14.2% (Nagelkerke R squared) of the variance in baseline ideation status. The sensitivity of the model was 4.8%; the specificity was 98.9%. Correct classification was 76.7%. Only MOODS-PM depressive mood made a statistically significant and unique contribution to Model 3.

The fourth model, detailed in Table 18 (Model 4), included site, significant socio-demographic variables and baseline clinical characteristics, and past month spectrum factor scores. As a whole, the model explained between 23.7% (Cox and Snell R square) and 36.2% (Nagelkerke R squared) of the variance in baseline ideation status. The sensitivity of the model was 47.4%; the specificity was 93.5%. The model correctly classified 83.1% of cases. Only site

and lifetime experience of suicidal ideation made statistically significant and unique contributions to Model 4. This was the best fitting model.

4.6 HYPOTHESIS 4: INITIAL TREATMENT RESPONSE

Controlling for site, an ANCOVA indicated a significant main effect for baseline group, $F(1, 340)=14.77$, $p =. 000$, no main effect for initial treatment strategy, $F(1, 340)=0.11$, $p =.744$, and no group-treatment interaction effect, $F(1, 340)=0.06$, $p =.810$. The effect size for baseline group was small; baseline group explained 4.2% of the variance in HRS-D-25-A scores after six weeks of treatment.

Controlling for site and baseline depression severity, an ANCOVA indicated a significant main effect for baseline group, $F(1, 338)=6.10$, $p =.014$, no main effect for initial treatment strategy, $F(1, 338)=0.31$, $p =.580$, and no group-treatment interaction effect, $F(1, 338)=0.88$, $p =.349$. The effect size for baseline group was small; baseline group explained 1.8% of the variance in HRS-D-25-A scores after six weeks of treatment.

As detailed in Table 19, after six weeks of treatment, the MDD-SI group continued to have significantly higher scores compared to the MDD group on assessments of suicidality and depression severity. Means and standard deviations for baseline group (MDD or MDD-SI) by initial treatment strategy (SSRI or IPT) are presented in Table 20.

Table 8. Correlations among Lifetime Mood Spectrum Factors

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Depressive mood	1.0	.62**	.41**	.35**	.37**	.49**	.25**	.31**	.21**	.10	.09	.34**	.26**
2 Psych. retardation		1.0	.39**	.25**	.44**	.50**	.38**	.31**	.29**	.13*	.22	.41	.29**
3 Suicidality			1.0	.12*	.29**	.24**	.17**	.13*	.11*	.01	.06	.21**	.08
4 Drug or illness related depression				1.0	.13*	.30**	.12*	.40**	.14**	.19**	.07	.33**	.19**
5 Psychotic features					1.0	.28**	.47**	.25**	.27**	.09	.26**	.44**	.41**
6 Neurovegetative						1.0	.29**	.32**	.23**	.14**	.10	.36	.19**
7 Psych. activation							1.0	.30**	.53**	.44**	.40**	.45**	.54**
8 Creativity								1.0	.38**	.40**	.21**	.36**	.34**
9 Mixed instability									1.0	.52**	.34**	.34**	.44**
10 Sociability and extroversion										1.0	.24**	.28**	.36**
11 Spirituality											1.0	.30**	.39**
12 Mixed irritability												1.0	.43**
13 Inflated self-esteem													1.0
14 Euphoria													
15 Recklessness													

Notes. Psych = psychomotor; * Significant at 0.01 level (two-tailed); ** Significant at 0.05 level (two-tailed)

Table 9. Correlations among Lifetime Panic-Agoraphobic Spectrum Factors

	1	2	3	4	5	6	7	8	9	10
1 Panic symptoms	1.0	.58	.65	.36	.30	.70	.40	.61	.66	.26
2 Separation anxiety		1.0	.61	.33	.41	.50	.42	.54	.58	.41
3 Agoraphobia			1.0	.33	.33	.60	.32	.62	.70	.28
4 Medical reassurance				1.0	.27	.30	.23	.48	.43	.20
5 Rescue object					1.0	.24	.27	.33	.34	.27
6 Depersonalization						1.0	.30	.55	.53	.27
7 Family reassurance							1.0	.33	.30	.21
8 Drug phobia								1.0	.54	.28
9 Claustrophobia									1.0	.22
10 Loss sensitivity										1.0

Note. All correlations are significant at the 0.01 level (two-tailed).

Table 10. Correlations among Past Month Mood Spectrum Factors

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Depressive mood	1.0	.74**	.43**	.32**	.54**	.57**	.30**	.07	.15**	-.03	.11*	.49**	.16**	.04	.21**
2 Psych. retardation		1.0	.37**	.29**	.51**	.55**	.37**	.10	.14**	.00	.12*	.51**	.18**	.05	.20**
3 Suicidality			1.0	.17**	.28**	.26**	.16**	.05	.10	.01	.11*	.20**	.09	-.02	.18**
4 Drug or illness related depression				1.0	.24**	.21**	.14**	.08	.24**	.01	-.01	.32**	.13*	.02	.08
5 Psychotic features					1.0	.34**	.46**	.19**	.23**	.06	.27**	.50**	.35**	.12*	-.24**
6 Neurovegetative						1.0	.22**	.11*	.10	.04	.08	.38**	.14*	-.05	.23**
7 Psych. activation							1.0	.33**	.34**	.25**	.23**	.54**	.45**	.26**	.24**
8 Creativity								1.0	.30**	.48**	.30**	.23**	.32**	.40**	.20**
9 Mixed instability									1.0	.27**	.26**	.20**	.23**	.24**	.30**
10 Sociability and extroversion										1.0	.12*	.18**	.22**	.51**	.19**
11 Spirituality											1.0	.21**	.23**	.12*	.22**
12 Mixed irritability												1.0	.33**	.19**	.27
13 Inflated self-esteem													1.0	.26**	.19**
14 Euphoria														1.0	.17**
15 Recklessness															1.0

Notes. Psych = psychomotor * Significant at 0.01 level (two-tailed); ** Significant at 0.05 level (two-tailed)

Table 11. Correlations among Past Month Panic-Agoraphobic Spectrum Factors

	1	2	3	4	5	6	7	8	9	10
1 Panic symptoms	1.0	.58	.66	.28	.36	.71	.48	.60	.59	.34
2 Separation anxiety		1.0	.60	.32	.29	.51	.44	.50	.50	.34
3 Agoraphobia			1.0	.27	.43	.61	.36	.60	.65	.29
4 Medical reassurance				1.0	.26	.26	.26	.39	.26	.08
5 Rescue object					1.0	.33	.21	.39	.39	.25
6 Depersonalization						1.0	.38	.58	.49	.32
7 Family reassurance							1.0	.40	.37	.27
8 Drug phobia								1.0	.50	.18
9 Claustrophobia									1.0	.28
10 Loss sensitivity										1.0

Note. All correlations are significant at the 0.01 level (two-tailed).

Table 12. Mood and Panic-Agoraphobic Spectrum Total Scores

Score	Group				t	p
	MDD N = 283		MDD-SI N = 85			
	M	SD	M	SD		
MOODS Lifetime	63.71	23.39	74.29	20.91	-3.75	.00
MOODS Lifetime-Adjusted[a]	64.42	22.80	71.07	20.44	-3.14	.00
PAS Lifetime	31.14	18.94	33.54	22.44	-0.89	n.s.
MOODS Past Month	40.63	19.49	52.12	18.44	-4.79	.00
MOODS Past Month-Adjusted[a]	40.04	19.15	49.94	17.68	-4.21	.00
PAS Past Month	16.50	15.11	18.31	16.64	-0.93	n.s.

Notes. [a]Score does not include suicide items

Table 13. Lifetime Spectrum Factor Scores

Variable	Group				F[a]	p
	MDD N = 283		MDD-SI N = 85			
	M	SD	M	SD		
Depressive mood	14.46	6.05	17.24	4.11	11.64	.00
Psychomotor retardation	8.05	4.30	9.84	3.57	9.41	.00
Drug or illness related depression	0.78	1.11	0.96	1.18	0.68	n.s.
Psychotic features	2.65	1.49	2.94	1.40	3.75	.05
Neurovegetative symptoms	6.13	2.58	6.40	2.71	0.02	n.s.
Psychomotor activation	4.94	3.23	5.41	3.38	2.28	n.s.
Creativity	1.51	1.50	1.86	1.83	1.71	n.s.
Mixed instability	4.07	3.01	4.39	2.86	0.37	n.s.
Sociability and extroversion	2.11	1.86	2.39	1.99	1.37	n.s.
Spirituality	0.55	0.95	0.73	1.20	2.26	n.s.
Mixed irritability	2.48	1.59	2.78	1.64	2.00	n.s.
Inflated self-esteem	1.39	1.51	1.58	1.52	0.87	n.s.
Euphoria	2.04	1.64	2.53	1.80	6.26	.01
Recklessness	1.53	1.32	1.62	1.28	0.00	n.s.

Notes. [a]A one-way between-groups multivariate analysis of variance with site as a covariate indicated a statistically significant difference between groups on the combined Mood Spectrum Lifetime factor scores

Table 13. Lifetime Spectrum Factor Scores (con't)

Variable	Group				F^a	p
	MDD N = 283		MDD-SI N = 85			
	M	SD	M	SD		
Panic symptoms	7.72	4.81	7.93	4.98	0.98	n.s.
Separation anxiety	3.45	2.70	3.71	3.30	2.22	n.s.
Agoraphobia	4.24	3.96	4.59	4.46	1.06	n.s.
Medical reassurance	0.85	1.24	0.74	1.22	0.01	n.s.
Rescue object	0.59	0.93	0.50	0.82	0.03	n.s.
Depersonalization	3.51	2.89	4.50	2.90	10.49	.00
Family reassurance	1.57	1.21	1.49	1.17	0.06	n.s.
Drug phobia	2.95	2.66	2.71	2.73	0.06	n.s.
Claustrophobia	2.37	2.35	2.43	2.69	0.77	n.s.
Loss sensitivity	1.45	1.07	1.67	1.06	2.44	n.s.

Notes. [a]A one-way between-groups multivariate analysis of variance with site as a covariate indicated a statistically significant difference between groups on the combined Panic-Agoraphobic Lifetime factor scores

Table 14. Past Month Spectrum Factor Scores

Variable	Group				Stat[a]	p
	MDD N = 283		MDD-SI N = 85			
	M	SD	M	SD		
Depressive mood	12.18	6.04	15.99	5.14	27.30	.00
Psychomotor retardation	6.56	4.31	9.07	3.95	22.70	.00
Drug or illness related depression	0.46	0.82	0.60	0.85	1.64	n.s
Psychotic features	1.87	1.43	2.35	1.44	7.00	.00
Neurovegetative symptoms	4.20	2.39	4.77	2.32	3.33	n.s.
Psychomotor activation	2.35	2.29	2.58	2.41	0.63	n.s.
Creativity	1.02	1.65	0.90	1.55	0.33	n.s.
Mixed instability	0.32	0.71	0.44	0.87	1.67	n.s.
Sociability and extroversion	0.65	1.05	0.65	1.11	0.00	n.s.
Spirituality	0.14	0.54	0.24	0.69	2.02	n.s.
Mixed irritability	1.78	1.48	2.02	1.33	1.89	n.s.
Inflated self-esteem	0.62	1.01	0.73	1.03	0.74	n.s.
Euphoria	0.69	1.15	0.71	1.14	0.04	n.s.
Recklessness	0.55	0.82	0.75	0.98	3.56	n.s.

Notes. [a]A one-way between-groups multivariate analysis of variance with site as a covariate indicated a statistically significant difference between groups on the combined Mood Spectrum Past Month factor scores

Table 14. Past Month Spectrum Factor Scores (con't)

Variable	Group				Stat[a]	p
	MDD N = 283		MDD-SI N = 85			
	M	SD	M	SD		
Panic symptoms	4.42	4.22	4.85	4.62	0.63	n.s.
Separation anxiety	1.68	2.24	2.01	2.66	1.29	.02
Agoraphobia	2.14	2.93	2.60	3.57	1.40	.05
Medical reassurance	0.33	0.85	0.26	0.73	0.50	n.s.
Rescue object	0.36	0.73	0.44	0.73	0.71	n.s.
Depersonalization	2.03	2.40	2.79	2.88	5.77	.00
Family reassurance	1.17	1.19	1.11	1.17	0.20	n.s.
Drug phobia	1.66	2.22	1.60	2.27	0.05	n.s.
Claustrophobia	1.05	1.58	1.20	2.02	0.53	n.s.
Loss sensitivity	0.78	0.86	0.90	0.90	1.33	n.s.

Notes. [a]A one-way between-groups multivariate analysis of variance with site as a covariate indicated a statistically significant difference between groups on the combined Panic-Agoraphobic Past Month factor scores

Table 15. Model 1: Logistic Regression Predicting Baseline Suicidal Ideation from Lifetime Spectrum Factors

Predictor	*B*	*S.E.*	Wald $_X^2$	p	Odds Ratio	
Site	0.39	0.31	1.48	.211	0.80	2.73
MOODS-Life Depressive mood	0.06	0.04	1.07	.071	1.00	1.14
MOODS-Life Psychomotor retardation	0.03	0.04	1.03	.528	0.94	1.12
MOODS-Life Psychotic symptoms	-0.07	0.11	0.94	.549	0.76	1.16
MOODS-Life Euphoria	0.11	0.08	1.12	.141	0.96	1.30
PAS-Life Depersonalization	0.10	0.05	1.10	.058	1.00	1.22

Notes. MOODS-Life = *Mood Spectrum, Lifetime*; PAS-Life = *Panic-Agoraphobic Spectrum, Lifetime*

Table 16. Model 2: Logistic Regression Predicting Baseline Suicidal Ideation from Lifetime Spectrum Factors, Socio-Demographic Variables, and Baseline Clinical Characteristics

Predictor	*B*	S.E.	Wald $_{\chi}^{2}$	*p*	Odds Ratio	
Site	1.21	0.42	3.36	.00	1.46	7.71
Baseline HRSD-25-A score[a]	0.04	0.03	1.05	.19	0.98	1.12
Q-LES-Q score	-0.07	0.02	0.93	.00	0.89	0.98
Age of first MDE	0.07	0.53	1.07	.90	0.38	3.02
History of suicidal ideation	-1.97	0.38	0.14	.00	0.07	0.29
History of suicide attempt	-0.75	0.43	0.47	.08	0.20	1.10
MOODS-Life Depressive mood	0.02	0.04	1.02	.63	0.94	1.11
MOODS-Life Psychomotor retardation	-0.03	0.05	0.97	.54	0.87	1.07
MOODS-Life Psychotic symptoms	-0.08	0.13	0.92	.53	0.71	1.19
MOODS-Life Euphoria	0.19	0.09	1.21	.04	1.01	1.44
PAS-Life Depersonalization	-0.03	0.07	0.97	.63	0.85	1.10

Notes. [a]Score does not include suicide items; HRSD-25 = *Hamilton Rating Scale for Depression, 25-item*; QIDS-16 = *Quick Inventory of Depressive Symptoms, 16-item;* Q-LES-Q = *Quality of Life Enjoyment and Satisfaction Questionnaire;* MDE = Major depressive episode; MOODS-Life = *Mood Spectrum, Lifetime*; PAS-Life = *Panic-Agoraphobic Spectrum, Lifetime*

Table 17. Model 3: Logistic Regression Predicting Baseline Suicidal Ideation from Past Month Spectrum Factors

Predictor	*B*	S.E.	Wald $_{X}^{2}$	*p*	Odds Ratio	
Site	0.63	0.33	1.88	.06	0.98	3.62
MOODS-PM Depressive mood	0.09	0.04	1.09	.02	1.02	1.18
MOODS-PM Psychomotor retardation	0.05	0.05	1.06	.26	0.96	1.16
MOODS-PM Psychotic symptoms	0.01	0.12	1.01	.94	0.80	1.27
PAS-PM Separation anxiety	0.06	0.08	1.06	.44	0.92	1.23
PAS-PM Agoraphobia	-0.05	0.06	0.95	.36	0.85	1.06
PAS-PM Depersonalization	0.06	0.07	1.06	.38	0.93	1.22

Notes. MOODS-PM = *Mood Spectrum, Past Month*; PAS-PM = *Panic-Agoraphobic Spectrum, Past Month*

Table 18. Model 4: Logistic Regression Predicting Baseline Suicidal Ideation from Past Month Spectrum Factors, Socio-Demographic Variables, and Baseline Clinical Characteristics

Predictor	*B*	S.E.	Wald $_X^2$	*P*	Odds Ratio	
Site	1.20	0.43	3.00	.01	1.28	7.00
Baseline HRSD-25-A score[a]	0.00	0.04	1.00	.97	0.94	1.07
Q-LES-Q score	-0.05	0.03	0.95	.04	0.90	1.00
Age of first MDE	-0.06	.536	.938	.905	.328	2.68
History of suicidal ideation	-1.75	0.36	0.17	.00	0.09	0.35
History of suicide attempt	-0.75	0.44	0.47	.09	0.20	1.12
MOODS-SR-PM Depressive mood	0.07	0.05	1.07	.12	0.98	1.17
MOODS-PM Psychomotor retardation	0.04	0.06	1.04	.52	0.93	1.16
MOODS-PM Psychotic symptoms	0.02	0.14	1.02	.86	0.78	1.33
PAS-PM Separation anxiety	0.11	0.09	1.12	.24	0.93	1.34
PAS-PM Agoraphobia	-0.11	0.07	0.90	.10	0.78	1.02
PAS-PM Depersonalization	0.02	0.08	1.02	.82	0.87	1.20

Notes. [a]Score does not include suicide items; HRSD-25 = *Hamilton Rating Scale for Depression, 25-item*; QIDS-16 = *Quick Inventory of Depressive Symptoms, 16-item;* Q-LES-Q = *Quality of Life Enjoyment and Satisfaction Questionnaire;* MDE = Major depressive episode; MOODS-PM = *Mood Spectrum, Past Month*; PAS-PM = *Panic-Agoraphobic Spectrum, Past Month*

Table 19. Suicidality and Illness Characteristics after Six Weeks of Treatment

Assessment Item	Group				Total N	Stat[a]	p
	MDD N = 283		MDD-SI N = 85		368		
	N M	% SD	N M	% SD			
HRSD Suicide						72.89	.00
0 Absent	253	93.4	40	54.1	293		
1 Doubtful or trivial	17	6.3	27	36.5	44		
2 Mild	1	0.4	7	9.5	8		
3 Moderate	0	0	0	0	0		
4 Severe, attempted	0	0	0	0	0		
QIDS Thoughts of death or suicide						48.46	.00
0 Absent	235	90.7	42	57.5	277		
1 Life is empty	23	8.9	26	35.6	49		
2 Several times a week	1	0.4	4	5.5	5		
3 Several times a day	0	0	1	1.4	1		
ISF Thought to attempt	79	32.9	53	76.8	132	-	
Past week	6	7.6	9	17.0	15		
Two weeks to 12 months ago	38	48.1	37	69.8	75		
More than a year ago	35	44.3	7	13.3	42		
ISF Seriously thought to attempt	32	13.3	33	47.8	65	-	
Past week	0	0	2	6.1	2		
Two weeks to 12 months ago	12	37.5	14	42.4	26		
More than a year ago	20	62.5	17	51.5	37		
HRSD-25 score	11.63	6.73	16.16	8.74	345	t = -4.14	.00
QIDS-16	6.64	4.19	9.99	5.67	334	t = -5.55	.00
Q-LES-Q score	42.79	9.63	40.03	9.93		t = 2.03	.04

Notes. [a]X^2 test statistic presented unless otherwise noted; HRSD = *Hamilton Rating Scale for Depression*; QIDS = *Quick Inventory of Depressive Symptoms;* Q-LES-Q = *Quality of Life Enjoyment and Satisfaction Questionnaire*

Table 20. Depression Severity after Six Weeks of Treatment

Score	Group							
	MDD				MDD-SI			
	SSRI		IPT		SSSI		IPT	
	M	SD	M	SD	M	SD	M	SD
HRSD-25	11.70	7.17	11.57	6.30	16.46	9.07	15.86	8.51
HRSD-25-A	11.64	7.12	11.49	6.22	15.92	8.69	15.30	8.02
QIDS-16	6.57	4.32	6.72	4.07	9.14	5.06	10.81	6.17
QIDS-16-A	6.37	4.22	6.52	3.95	8.75	4.71	10.19	5.57

Notes. HRSD = *Hamilton Rating Scale for Depression, 25-item;* HRSD-25-A = *Hamilton Rating Scale for Depression, 25-item* adjusted to exclude suicide item; QIDS-16 = *Quick Inventory of Depressive Symptoms, 16-item;* QIDS-16-A = *Quick Inventory of Depressive Symptoms, 16-item* adjusted to exclude suicide item

5.0 DISCUSSION

The goal of this investigation was to broaden our understanding of non-psychotic, unipolar major depression with current suicidal ideation (MDD-SI). We sought to document the associated features of MDD-SI, understand the phenomenology of MDD-SI, develop a clinical phenotype of MDD-SI, and discern whether the MDD-SI phenotype is associated with an unfavorable or differential initial response to treatment. We conceptualized this work as a preliminary investigation of the specific treatment needs of individuals with MDD-SI and potential identification of one subset of individuals who fail to experience an initial response to first-line monotherapies for major depression. To this end, we completed a secondary analysis of data from a two-site, cross-national clinical trial in which individuals presenting in an episode of major depression were randomly allocated to an initial treatment protocol consisting of SSRI antidepressant pharmacotherapy (SSRI) or interpersonal psychotherapy (IPT).

In comparisons between individuals with MDD-SI and individuals without current, baseline suicidal ideation (MDD), we found that (1) few pre-treatment socio-demographic or baseline clinical characteristics significantly distinguished MDD-SI and MDD, (2) lifetime experiences of suicidal ideation and suicidal behavior were significantly different between MDD-SI and MDD, and (3) lifetime history and past month experiences of some mood and panic-agoraphobic spectrum symptoms were significantly different between MDD-SI and MDD.

In addition, we demonstrated that MDD-SI is negatively associated with initial treatment response, such that individuals with MDD-SI were significantly more depressed after six weeks of treatment than were individuals with MDD. Nonetheless, after six weeks of treatment, interviewer-rated suicidal ideation resolved for over 90% of individuals with MDD-SI and self-reported suicidal ideation resolved for all but about 11%. Notably, baseline group (MDD or MDD-SI) explained minimal between group variance in depression severity (when excluding suicidality) after six weeks of treatment. Below, we discuss our main findings in detail, then the limitations and strengths, implications, and future directions of this work.

5.1 TREATMENT SITE

Preliminary analyses revealed significant differences between the Pittsburgh and Pisa samples. Therefore, we entered site as a covariate into all analyses for hypothesis testing. Yet, one supposition of using site as a covariate is that site is somehow causative. Rather, site might be a measure of unmeasured cultural factors or illness characteristics. To extend our understanding of these differences, we conducted unplanned, exploratory analyses. These post-hoc analyses indicated that the Pittsburgh and Pisa samples differed on a number of characteristics. Indeed, in all analyses, site had a significant effect on the dependent measure(s). For example, compared to the Pisa sample, the Pittsburgh sample reported a longer duration of their index episode and a higher number of previous MDEs. Compared to the Pittsburgh sample, the Pisa sample was more likely to be married and to be experiencing their first MDE. Notably, there were no site by treatment interaction effects. These findings suggest that, despite identical inclusion criteria and

multiple efforts to minimize site differences in the study populations recruited, the Pittsburgh and Pisa samples were somewhat different clinical samples. Accordingly, some of the variance explained by site likely is better explained by illness features.

5.2 PRE-TREATMENT SOCIO-DEMOGRAPHIC VARIABLES AND BASELINE CLINICAL CHARACTERISTICS

Contrary to our expectations, only a few pre-treatment socio-demographic or baseline clinical characteristics significantly distinguished MDD-SI and MDD. These included study site, depression severity, and current smoking status. First, the Pittsburgh site recruited more individuals with MDD-SI than did the Pisa site, even after controlling for treatment site differences. This is consistent with epidemiological data demonstrating strong cross-national differences in the prevalence of suicidal ideation between the US and Italy (Bernal et al., 2007; Kessler et al., 1999, 2005; Nock et al., 2008; Scocco et al., 2008). The point prevalence rates of suicidal ideation, however, among study participants at the Pittsburgh site (27.6%) and Pisa site (18.0%) are inconsistent with previous reports. For example, in the STAR*D study, 63% of the participants reported baseline suicidal ideation.

One explanation of the low point prevalence might be our strict definition of MDD-SI. Whereas we categorized participants who experienced passive death ideation as MDD, other investigators have classified individuals with either death ideation or specific suicidal ideation as MDD-SI. Had we expanded our operational definition of MDD-SI to include death ideation,

54.6% of our entire sample would have meet criteria for MDD-SI. This revised point prevalence rate more closely approximates the prevalence of baseline suicidal ideation reported in other depression trials (e.g., STAR*D).

Another explanation might be our study inclusion and exclusion criteria. Specifically, while we purposely limited the number of study exclusion criteria in an attempt to capture the "real world" heterogeneity of individuals experiencing unipolar major depression, we excluded individuals who reported alcohol and drug abuse or dependence during the preceding three months because substance use may initiate, maintain, or exacerbate mood symptoms. Considering the high rates of alcohol and drug use associated with MDD-SI (SAMHSA, 2006), we likely excluded a percentage of individuals with MDD-SI.

Second, as we predicted, individuals with MDD-SI were significantly more severely depressed at intake than were individuals with MDD. This was consistent between interviewer-rated (HRSD-25-A) and self-reported (QIDS-16-A) depression severity, and is consistent with past research (Goldney et al., 2000; Sokero, 2006). Although statistically significant, the difference between the two groups' baseline depression severity scores lacks clinical importance (e.g., HRSD-25-A: 23.53 versus 25.85). The absence of a clinically meaningful difference, however, is noteworthy. Using standard assessments of depressive symptomatology, and excluding suicidality scores, the groups' severity of depression is nearly identical. When suicidality is included, however, the difference in illness severity reaches clinical importance (e.g., HRSD-25: 23.84 versus 27.27). On one hand, suicidal ideation is an indicator of disease severity (Minnix et al., 2007; Williams et al., 2006). If suicidal ideation denotes depression severity, then the presence of suicidal ideation might indicate a more severe subjective experience of the disease. That is, this cognitive symptom of depression might be a proxy for

certain personality and psychological dimensions co-occurring with and key to the development of suicidal ideation, such as hopelessness, pessimism, low self-directedness, and depressogenic thinking. For example, Beck and colleagues (1990) assert that if an individual is depressed and believes that there is no solution to his or her problems, then suicide emerges as a possible solution to the hopeless situation. Although we did not measure hopelessness, some of our findings are compatible with this theory. First, we demonstrated significantly lower ratings of life satisfaction and enjoyment in MDD-SI compared to MDD at intake to treatment. Second, we found that these ratings improved after six weeks of treatment, at which time over 90% of interviewer-rated suicidal ideation and almost 90% of self-reported suicidal ideation had resolved. Conceivably, as life satisfaction and enjoyment increase, the cognitive substrate changes and suicidal ideation remits, or vice versa.

On the other hand, the absence of *apparent* clinically important differences in depression severity might be misleading. As we argued in our research review, standard assessments of depressive symptomatology fail to capture a broad array of manifestations of major depression, including subsyndromal or temperamental features. As we discuss later, lifetime and current subsyndromal and syndromal symptomatologic experiences, as measured by the more sensitive indicator of the disease process, the Spectrum Assessment Method, were different. Accordingly, suicidal ideation might reflect both a more severe subjective *and* objective experience of depression.

Third, with the Pittsburgh sample only (data were not available for the Pisa sample), smoking was associated with MDD-SI. This is compatible with findings from other studies indicating a high rate of smoking among mood disorder populations (Murphy et al., 2003), and potentially suggestive of attempts to self-medicate, engagement in risk-taking behaviors, or

fewer positive coping skills (Oquendo et al., 2004). Of note, there is some evidence that chronic smoking creates an antidepressant-like effect in some neurons implicated in major depression (Klimek et al., 2001).

Finally, we were unable to confirm prior findings of associations between suicidal ideation and age, marital status, educational attainment, employment status, BMI, number of medical conditions, age of illness onset, number of MDEs, lifetime alcohol or substance abuse or dependence, or the presence of any or a particular lifetime or past month anxiety disorder. One explanation is that our failure to replicate previous findings is reflective of the homogeneity of our sample. For example, of the entire sample, fewer than 15% were separated or divorced and almost 43% were not married or living with a partner. About 85% were an employee, homemaker, or student, and 22% held advanced educational degrees. Almost 47% reported at least one current medical condition.

Another explanation is that these socio-demographic variables and baseline clinical characteristics have limited utility for predicting current liability for suicidal ideation *during* major depression. For instance, major depression often co-occurs with at least one other Axis I disorder (Feske et al., 1998; Frank et al., 2000; Sokero, 2006). Additionally, previous studies indicate that a syndromal anxiety disorder comorbid with major depression increases the likelihood of MDD-SI (Norton, Temple, & Pettit, 2008). Yet, of the entire sample, almost 46% met criteria for a past month and almost 51% met criteria for a lifetime syndromal DSM-IV-TR anxiety disorder.

Of note, the absence of differences in the number of current medical conditions was surprising, as poor physical health is consistently associated with suicidal ideation (Alexopoulos et al., 2009; Russell, Turner, & Joiner, 2009). One explanation might be our methodology for

coding medical conditions. During the screening and intake process, evaluators asked potential participants about current and lifetime medical history. Additionally, they completed a medical examination, complete with blood work. We entered any self-reported or examiner-noted medical condition, regardless of severity, chronicity, or associated impairment. While it was beyond the scope of this investigation to objectively classify conditions, we anecdotally observed substantial variance in the elaboration of the self-reports. For example, one individual reported current medical conditions to be sinusitis and tendonitis. Another individual reported Crohn's disease and chronic pain. Yet, we coded both as having two medical comorbidities. Clearly, these medical comorbidities have different implications for the affected individual's functioning and health status. Nonetheless, some researchers (Dennis et al., 2007; Goodwin & Olfson, 2002) have demonstrated that simply reporting poor physical health, in spite of actual health status, increased risk of suicidal ideation – hence, our interest in looking at non-coded medical conditions. For future studies, it might be informative to investigate the relationships among self-reported medical conditions, severity of such conditions, and MDD-SI.

To summarize, few pre-treatment socio-demographic or baseline clinical characteristics significantly distinguished MDD-SI and MDD. MDD-SI was associated with the US treatment site, higher depression severity, and current smoking. The practical utility of these variables for predicting liability for suicidal ideation during major depression is minimal.

5.3 LIFETIME EXPERIENCE OF SUICIDAL IDEATION AND SUICIDE ATTEMPTS

As expected, lifetime experience of suicidal ideation and suicide attempts significantly distinguished current MDD-SI and MDD. In fact, lifetime experience of suicidal ideation consistently made statistically significant and unique contributions to logistic models predicting current, baseline suicidal ideation. First, on the MOODS-Lifetime, almost 80% of individuals with MDD-SI but only about 23% of individuals with MDD indicated a previous experience of suicidal ideation for at least one three to five day period. Thus, less than 60% of our sample had *never* experienced suicidal ideation. Importantly, less than 20% of the MDD-SI sample were experiencing suicidal ideation for the first time and about 32% reported a history of making a plan or attempt. These results are compatible with previous findings documenting the consistency of suicidal ideation across depressive episodes (Antypa, Van der Does, & Pennix, 2010; Williams et al., 2006). Joiner and colleagues (2003) assert that experiences with suicidal ideation habituate an individual to the fear, pain, and taboo associated with self-harm. Consequently, these previous experiences increase an individual's risk for more severe forms of suicidality. If previous or worst-point suicidal ideation are indicators of risk, then our MDD-SI sample is a moderate-to-high risk population. Therefore, our findings may be generalizable to other at-risk samples.

Second, almost 30% of individuals with current MDD-SI and 7% of individuals with current MDD reported that they had previously attempted suicide. This overall rate of 12.2% is somewhat lower than that of other reports, including the 16.5% reported by Zisook and colleagues (2009) for STAR*D study participants. Similar to other reports, however, in our

sample, as severity of suicidality increased, prevalence also decreased (Kessler et al., 1999, 2005).

Third, similar to previous investigations (Nock et al., 2010; Valtonen et al., 2009), we found that the prevalence of suicidal ideation depends on the definition of suicidal ideation and method for assessing it. Specifically, there were some disagreements between self-report and interviewer ratings of suicidality, such that interviewer ratings were higher than were self-report ratings. These findings are consistent with previous reports (Bridge et al., 2005; Joiner et al., 1999; Nock et al., 2010; Valtonen et al., 2009). For example, almost 33% of the MDD-SI sample indicated suicidal ideation on the QIDS, whereas interviewers coded almost 44% of the MDD-SI sample as experiencing suicidal ideation on the HRSD. Yet, it is unlikely that this reflects individuals' concealment of suicidality because of fear and stigma associated with suicidality: about 25% of the MDD-SI sample reported a previous suicide attempt to an evaluator, but only around 15% indicated a previous suicide attempt on a self-report. Rather, the observed discrepancies may reflect evaluators' assessment of certain cognitions and behaviors as suicidal, whereas the individual does not. Of note, interviewer-rated suicidal *ideation* (HRSD) correlated moderately with self-reported suicidal *ideation* (QIDS) ($r = 0.58$), and interviewer-rated suicidal *behaviors* (ISF) correlated strongly with self-reported suicidal *behavior*s (MOODS) ($r = 0.81$).

To summarize, current MDD-SI was associated with lifetime experiences of suicidal ideation and suicidal behaviors. Interviewer ratings of suicidality were higher than were self-report ratings of suicidality, for both lifetime and current assessments. Taken together, our findings underscore the importance of incorporating a lifetime assessment of suicidality into routine clinical practice.

5.4 LIFETIME AND PAST MONTH SPECTRUM CONDITIONS

As predicted, the lifetime history and past month experience of mood and panic-agoraphobic spectrum symptoms were significantly different between MDD-SI and MDD. First, MDD-SI was associated with significantly higher scores on the lifetime and past month MOODS and PAS. Second, MDD-SI was associated with higher factor scores, including (1) MOODS-Lifetime depressive mood, psychomotor retardation, psychotic features, and euphoria; (2) MOODS-PM depressive mood, psychomotor retardation, and psychotic features; (3) PAS-Lifetime depersonalization; and (4) PAS-PM separation anxiety, agoraphobia, and depersonalization. Whereas these factors contributed to the sensitivity and specificity of logistic regression models predicting baseline suicidal ideation, only two spectrum factors made statistically significant and unique contributions to any one of the four models. These were the MOODS-Lifetime euphoria (Model 2) and MOODS-PM depressive mood (Model 3). Of note, the other variables that uniquely and independently contributed to at least one model were site (Model 2 and Model 4), Q-LES-Q score (Model 2 and Model 4), and history of suicidal ideation (Model 2 and Model 4). Importantly, whereas only the spectrum factors which significantly distinguished MDD and MDD-SI in multivariate analyses were entered into the logistic regression models, few made statistically significant and unique contributions to the logistic regression models. One explanation for this discrepancy might be the *Wald* statistic. The *Wald* statistic is a measure of the significance of each independent variable's ability to contribute to the logistic regression model, and is quite conservative (Tabachnick & Fidell, 1996). Had we adopted a more liberal significance value, as some recommend, more spectrum factors likely would have made unique contributions to the models. Fourth, contrary to our predictions, there

were no between group differences for MOODS-Lifetime or MOODS-PM neurovegetative symptoms, spirituality, or recklessness, or for PAS-Lifetime or PAS-PM panic symptoms. Taken together, these findings corroborate previous reports that individuals who experience suicidal ideation concurrent with a major depressive episode are distinct from those who do not. Moreover, these findings support the conceptualization of MDD-SI as phenomenologically distinct from MDD on a number of illness severity indices.

First, the higher lifetime and past month MOODS and PAS total scores associated with MDD-SI indicate that, compared to individuals with MDD, individuals with MDD-SI experience a greater array of core mood and anxiety symptoms, as well as related prodromal, subsyndromal, attenuated, residual symptoms, and temperamental features (Cassano et al., 1997, 2009, 2010). Notably, these score differences remained significant even with the suicidality items excluded. Chiefly, this finding supports and extends the documented connection between MDD-SI and illness severity (Minnix et al., 2007; Williams et al., 2006). Likewise, it provides credence to our speculation that suicidal ideation reflects both a more severe subjective and objective experience of depression. Importantly, these findings confirm Cassano et al. (2004) and Balestrieri et al. (2006)'s findings that the more mood spectrum items an individual endorses, the greater the likelihood he or she is to endorse suicidal ideation. Interestingly, the mean MOODS-Lifetime score of the MDD-SI sample, 74.29, is higher than Cassano et al.'s (2004) recurrent unipolar depression sample mean but lower than their bipolar sample mean, 64.8 and 83.7, respectively.

Second, the higher lifetime and past month depressive mood factor scores associated with MDD-SI supports the connection between suicidal ideation and personality and psychological dimensions (Cassano et al., 2004, 2009; Cox, Enns, & Clara, 2004). The depressive mood factor reflects core symptoms of depression, including anhedonia, and its temperamental correlates.

Individuals scoring high on this factor may have a reduced capacity for experiencing pleasure and affectively responding to the anticipation of pleasure. They may also have high levels of neuroticism. The inability to experience or anticipate pleasure might establish vulnerability to suicidal ideation by cultivating hopelessness and pessimism, particularly in the context of poor health, negative life events, or psychosocial problems.

Third, the higher lifetime and past month psychomotor retardation factor scores associated with MDD-SI support and extend previous results demonstrating that depression severity is intimately connected to suicidal ideation (Goldney et al., 2000). The psychomotor retardation factor is an indicator of severity and psychomotor changes representative of the melancholic subtype of major depressive episodes in DSM-IV-TR (Cassano et al., 2009). Specifically, melancholic depressions are characterized by severe anhedonia, loss of mood reactivity, psychomotor disturbances, sleep continuity disturbances and early morning awakenings, diminished appetite with weight loss, diurnal variation with signs and symptoms being worse in the morning, and guilty ruminations (APA, 2000).

Fourth, the higher lifetime and past month psychotic features factor scores associated with MDD-SI is a novel, and particularly interesting, finding. For this investigation, we defined MDD-SI as a non-psychotic unipolar major depressive episode with current, baseline suicidal ideation. We excluded potential participants who reported a history of manic or hypomanic episodes, schizophrenia or schizoaffective disorder, and current psychotic symptoms. Thus, we would expect minimal endorsement of psychotic symptoms, particularly past month experiences. The psychotic feature factor scores imply that whereas individuals with MDD-SI did not experience syndromal psychosis, they did experience subtle, sub-syndromal, and less severe aspects of psychosis. These may include core symptoms of psychosis, as well as paranoid

thoughts, sensing hostility from others, feeling very vulnerable, guilty or remorseful, and being preoccupied with one's own problems, thoughts and feelings.

Fifth, the higher lifetime, but not past month, euphoria factor scores associated with MDD-SI corroborate previous findings that the lifetime experience of manic/hypomanic symptoms, in the context of a "unipolar" mood disorder, increases likelihood of suicidal ideation (Akiskal & Benazzi, 2005; Balestrieri et al., 2006; Cassano et al., 2004, 2009). The euphoria factor scores reveal positive experiences of mood elevation associated with pure mania or "sunny" hypomania. This finding underscores the importance of incorporating a lifetime assessment of subsyndromal mood pathology – some individuals experiencing MDD-SI may not have a "pure" unipolar disorder.

Sixth, the higher lifetime and past month depersonalization factor scores associated with MDD-SI corroborates previous findings of a connection between symptoms of depersonalization and suicidal ideation (Michal et al., 2010; Yoshimasu et al., 2007). The depersonalization factor reflects an individual's subjective sense of detachment from one's own being and a sense of unreality. It frequently is conceptualized as a nonspecific response to anxiety (Mula, Pini, & Cassano, 2007). Researchers have documented an increased risk for depersonalization symptoms during adulthood among individuals with histories of childhood trauma and bipolar mood disorders (Mula et al., 2010). Furthermore, researchers have evidenced the utility of depersonalization in mood disorders as a clinical index of disease severity, high level of comorbidity, and poor response to treatment (Cassano et al., 2010; Michal et al., 2010).

Finally, the higher past month separation anxiety factor and agoraphobia factor scores associated with MDD-SI support previous results that anxiety is related to suicidal ideation (Benvenuti et al., 2010; Norton, Temple, & Pettit, 2008; Sareen et al., 2005). Both factors reflect

an individual's fear and avoidance of being alone. Importantly, in separation anxiety the focus of the fear is danger to a significant other, whereas in agoraphobia the fear is panic (Aaronson et al., 2008). The presence of co-occurring anxiety and panic symptoms is consistently related to less favorable outcomes to psychotherapy, pharmacotherapy, or their combination, to more severe symptom profiles, greater depression severity, and poorer quality of life (Benvenuti et al., 2010; Frank et al., 2000; Michal et al., 2010).

In sum, using the Spectrum Assessment Method, we documented that the lifetime and concurrent syndromal, subsyndromal, and trait-level symptomatologies associated with MDD-SI are significantly different from those related to MDD. Chiefly, by exploring a broad array of manifestations of mood and anxiety disorders, we captured group differences that standard assessments of depressive symptomatology have not. Mainly, our findings confirm the relationship between severity of depression and suicidal ideation. They also add to the accruing body of evidence connecting sub-syndromal hypomanic and manic symptoms to increased liability for suicidal ideation.

5.5 INITIAL TREATMENT RESPONSE

Consistent with our hypothesis, response to an initial treatment strategy of either SSRI or IPT significantly distinguished MDD-SI and MDD. Specifically, compared to individuals with MDD, individuals with MDD-SI were significantly more depressed after six weeks of treatment. Overall reductions in depression severity, as indicated by the change in HRSD-25 scores from baseline thru week six of treatment, were somewhat less dramatic for individuals with MDD-SI

compared to individuals with MDD, 40.7% versus 51.2%, respectively. Despite this diminished response to treatment, after six weeks of treatment, among individuals with MDD-SI, over 90% of interviewer-rated suicidal ideation and almost 90% of self-reported suicidal ideation resolved. These findings are notable in three respects.

First, our results indicate that baseline suicidal ideation is a nonspecific predictor and not a moderator of initial treatment response (Kraemer et al., 2001, 2002). That is, the presence of suicidal ideation at start of treatment is related to a less favorable but not a differential initial treatment response to SSRI versus IPT. Thus, the presence of suicidal ideation does not appear to indicate that treatment should be initiated with SSRI versus IPT. Individuals with MDD-SI may represent one subset of individuals who experience a diminished initial response to first-line treatment for major depression, accounting for some of the previously reported variance in initial treatment response rates (Kessler et al., 2003a; Trivedi et al., 2006; WHO, 2005).

Importantly, although we found that baseline suicidal ideation is a nonspecific predictor of initial treatment response, effect size analyses demonstrated that baseline suicidal ideation accounted for little of the between group variance. One explanation might be that by entering baseline depression severity and treatment site as covariates, we not only partialed out the effects of these concomitant variables on initial treatment response, but also partialed out important between group differences. For example, whereas the effect size for baseline suicidal ideation was 0.18, the effect sizes for site and baseline depression severity were 0.12 and 0.07, respectively.

Second, our results demonstrate that suicidal ideation resolves with empirically-supported monotherapies for major depression. This is compatible with previous reports documenting remission of MDD-SI with antidepressant pharmacotherapy, with or without an adjunctive

psychosocial intervention (Mulder et al., 2008; Tondo, Hennen, & Baldessarini, 2001; Tondo et al., 2008; Zisook et al., 2009; Alexopoulos et al., 2009). The treatment effectiveness and efficiency we observed, however, is considerable, particularly compared to other studies. For example, in STAR*D, 75% of individuals with MDD-SI experienced *improvements* in suicidal ideation following 12 to 14 weeks of treatment with citalopram (Zisook et al., 2009). Similarly, in the PROSPECT study, older individuals with MDD-SI enrolled in the collaborative care arm experienced a 12.8% *decline* in suicidal ideation after 16 weeks of algorithm-driven treatment (Alexopoulos et al., 2009). In our study, only about 10% of individuals with MDD-SI had *any* suicidal ideation after six weeks of treatment.

One explanation for this finding might be our strict definition of MDD-SI. Again, we did not classify death ideation as suicidal ideation. After six weeks of treatment, a proportion of individuals with MDD-SI did report death ideation. If we considered these individuals to be experiencing suicidal ideation, then our treatment response rates might be more like previous reports. Yet, our separation of death ideation and suicidal ideation is consistent with the new CDC Classification System of Self-directed Violence (Brenner et al., 2010).

Another explanation for the rapid resolution of suicidal ideation might be the level of care study participants received. Participants in our study were engaged in a comprehensive treatment protocol at an academic research clinic specifically established for the conduct of research. Providers were solely focused on providing care to study participants, and were free to provide such care without distractions or barriers, as clinically indicated. Then again, study participants in the STAR*D and PROSPECT trial also received a higher-level of care than is usual. In fact, a substantial proportion of participants in these two studies also received care at

outpatient research clinics associated with the Department of Psychiatry at the University of Pittsburgh.

Third, our results support speculation that the resolution of suicidal ideation is intimately interwoven with the remission of major depression – alleviate the severity of the depressive episode, halt the suicidal process. With six weeks of treatment, individuals with MDD-SI had experienced not only a dramatic reduction in suicidal ideation, but also marked decreases in depression severity and increases in life satisfaction and enjoyment. This is consistent with previous reports evidencing declines in depression predict subsequent declines in suicidal ideation (Sokero, 2006). Yet, treatment of major depression in the presence of suicidal ideation is less powerful than in its absence. Does this mean treatment strategies for MDD-SI need to be more targeted and/or aggressive?

From one point of view, the answer seems to be a definite, "Yes." This is particularly true if we hope to reduce suicide-related morbidity and mortality with prevention and intervention efforts aimed at reducing suicidal ideation (van Spijker, van Straten, & Kerkhof, 2010). Whereas only a minority of individuals will transition from suicidal ideation to suicidal behaviors, a majority of these individuals will make this progression during the first year after initial onset of suicidal ideation (Kessler et al., 1999, 2005; Nock et al., 2008a). If new treatment strategies can bring about a remission sooner than do current strategies, then the faster we halt the suicidal process, the better the outcomes.

From another point of view, the answer seems to be a hesitant, "Yes." Whether (and how) treatments need to be more targeted and/or aggressive somewhat depends on whether the overall greater depression severity, phenomenological experience, or the particular psychological and biological substrate underlying MDD-SI accounts for the inferior initial treatment response. For

example, the lifetime and past month experiences of mood and panic-agoraphobic symptoms were significantly different in MDD-SI and MDD. Some of these phenomenological differences may be associated with a cascade of changes in biological processes and health behaviors (e.g., activation of the hypothalamic-pituitary adrenal axis or decreases in physical activity or sleep quality) (Dickerson & Kemeny, 2004; Motivala, Sarfatti, Olmos, & Irwin, 2005). Treatments specifically targeting these disruptions might be helpful. Then again, it might be that MDD-SI simply is a marker for a greater need for a combination pharmacological and psychosocial treatment strategy.

To summarize, we demonstrated that individuals with MDD-SI might comprise one subset of individuals who experience a diminished initial response to first-line treatment for major depression. Importantly, we found that MDD-SI is responsive to SSRI *or* IPT for major depression, just less so, and that remission of suicidal ideation is fairly rapid. Thus, for individuals with MDD-SI who decline or cannot tolerate a somatic treatment, IPT is a reasonable treatment option. MDD-SI might be a marker of greater severity on a number of levels and, in general, greater need for aggressive treatment strategies, including combination SSRI and IPT. It seems unlikely that variance in treatment response is explained solely by any one factor. Rather, it is likely that the inferior initial response associated with MDD-SI is like suicidal ideation itself – multi-dimensional. Future studies examining the role of depression severity, phenomenological experience, and the particular psychological and biological substrate underlying MDD-SI may shed further light on the multiple pathways through which MDD-SI and treatment interact.

5.6 MDD-SI: IS IT A CLINICAL PHENOTYPE?

Perlis and colleagues (2009) state that, to be clinically meaningful, an illness feature or subtype needs to improve understanding of the illness and its likely course. Clearly, our findings are preliminary, and replication is needed before we can confidently argue for or against a conceptualization of MDD-SI as a relevant subtype and clinical phenotype of major depression. With that caveat, our results do indicate that conceptualizing MDD-SI as such may be valuable. The presence of suicidal ideation appears to be a marker for a more severe form of non-psychotic unipolar major depression in several respects. Compared to individuals without baseline suicidal ideation, individuals experiencing MDD-SI reported poorer quality of life, greater depression severity, and more lifetime and past month subsyndromal and syndromal mood and panic-agoraphobic symptoms, including previous suicidality. Moreover, individuals with MDD-SI received less benefit from six weeks of either pharmacotherapy or psychotherapy, which likely reflects the complexity of MDD-SI. Noting the presence of baseline suicidal ideation in the context of non-psychotic unipolar major depression illuminated our understanding of the illness and its likely course. Accordingly, it seems reasonable to continue investigating MDD-SI as a potentially meaningful subtype and clinical phenotype of major depression.

5.7 LIMITATIONS AND STRENGTHS

The following limitations, along with aforementioned caveats, must be considered in interpreting our results. First, this study was a secondary analysis of data. We did not design the protocol,

including assessment methods, specifically to test our hypotheses. Consequently, we were limited by our data, and certain considerations and analytical strategies were not possible. For example, since study participants were randomly allocated to an initial *monotherapy* SSRI or IPT strategy, it is unclear whether initial response to a *combination* SSRI and IPT strategy would be different between MDD-SI and MDD. Similarly, because the protocol was not designed to test our hypotheses, we did not have an assessment that provided details about suicidal ideation (e.g., onset, worst point, extent of attempt planning) or one that was originally psychometrically-supported for use as an assessment of suicidality. Then again, other researchers commonly utilize suicidality ratings from depressive symptom scales to great effect, and have demonstrated good-to-excellent psychometric properties for these assessments of suicidality. Moreover, the instruments we did use were psychometrically validated in both English and Italian languages – in fact, some instruments were simultaneously developed and validated in these languages. Second, based on the extant literature, we adopted an all-inclusive, comprehensive, and structured approach to the assessment of suicidality. Although we found smaller discrepancies among interviewer-rated and self-reported ratings of suicidality than have other investigators, our discrepancies could be a function of assessment error. It is possible that the greater depression severity and overall clinical status of individuals experiencing MDD-SI affected recall or ability to complete accurately self-reports, including differentiating among past week, past month, and lifetime experiences. Third, we applied a strict operational definition for classifying major depression as MDD-SI. Whereas this somewhat hindered the comparability of our results with previous findings, it is consistent with the Classification System of Self-directed Violence (Brenner et al., 2010). Therefore, our findings are current and should remain relevant. Fourth, our operational definition of MDD-SI only included baseline suicidal ideation. We neither

censored nor distinguished those few individuals with MDD who subsequently developed treatment-emergent suicidal ideation. Fifth, we completed logistic regression analyses, which are data-driven. Therefore, it is important to replicate the logistic regression in another sample to see if the results are similar. Likewise, although we identified a set of socio-demographic, baseline clinical characteristics, and mood and panic-agoraphobic spectrum symptoms that distinguished MDD-SI and MDD, conclusions cannot be drawn concerning causation. Whether inter-related characteristics of the clinical phenotype of MDD-SI precede or are consequences of suicidal ideation is unclear. Finally, we observed significant differences between treatment sites. Based on analyses of other site differences (Frank et al., 2010), it seems very likely that some of the variance accounted for by "site" actually reflects differences in illness characteristics.

Despite these limitations, our investigation is noteworthy. To our knowledge, this is the first study to investigate the lifetime and current subsyndromal and syndromal symptomatology associated with MDD-SI. Furthermore, this is the first study to compare a psychosocial monotherapy to a pharmacological monotherapy for the initial treatment of MDD-SI. Finally, our data was a secondary analysis of data from a two-site, cross-national clinical trial, thus increasing the generalizability of our findings beyond the US.

5.8 IMPLICATIONS AND FUTURE DIRECTIONS

Our results highlight a few issues of clinical importance and areas for further exploration. One, standard assessments of depressive symptomatology failed to capture a meaningful array of manifestations of major depression, including subthreshold hypomanic, depersonalization, and

psychotic symptoms, that distinguished MDD-SI and MDD. These spectrum parameters may improve our identification and understanding of MDD-SI, including its course and treatment response (Benvenuti et al., 2010; Cassano et al., 2009; Frank et al., 2002, 2010). Moreover, they may promote the recognition of individuals at-risk for developing MDD-SI, aiding early prevention and intervention efforts. Of particular importance, individuals can generally complete the MOODS and/or PAS self-report in less than 40 minutes (Cassano et al., 2002). This is markedly less time than conventional structured clinical interviews, and provides a wealth of additional information.

Two, previous experiences with suicidality, including making a plan or attempt, was the rule for individuals experiencing current MDD-SI. The work of Joiner and colleagues (2003) suggests that these individuals are at increased likelihood for experiencing a progression of the suicidal process, including commencement of suicidal behaviors. Thus, our results support the routine clinical practice of a lifetime assessment of suicidality to capture enduring suicide risk.

Finally, the preliminary nature of our work means that there are a number of avenues for future investigations. For example, future moderator analyses might help explain the inferior initial treatment response associated with MDD-SI. Similarly, analyses of weekly symptom changes might illuminate which experiences drive the worsening or remission of suicidal ideation. Finally, comparing treatment outcomes might illuminate whether the presence of current, baseline suicidal ideation inhibits remission and recovery.

6.0 CONCLUSION

It is clear from the arsenal of empirically-supported pharmacological and psychosocial treatments for major depression that not all treatments work equally well for all individuals. Indeed, many individuals with major depression who access treatment will fail to experience an initial response. Furthermore, a minority of these individuals will experience a worsening of their illness and the initiation, maintenance, or exacerbation of their suicidal ideation. Therefore, understanding which individuals are more likely to respond to one treatment versus another would be of enormous clinical utility to mental health professionals (CDC, 2008).

Against this backdrop, we completed an investigation of MDD-SI. In part, we selected this subpopulation of major depression because suicidal ideation is multi-faceted. It is a marker for future risk (Gunnell et al., 2004), a precursor to suicidal behaviors (Kessler et al., 2005), a cognitive symptom of depression (Cox et al., 2004), and an indicator of disease severity (Minnix et al., 2007). What we did not know was whether suicidal ideation also is a predictor of who will experience an inferior response to empirically-supported pharmacological or psychosocial treatments for major depression. We reasoned that by increasing our understanding of MDD-SI and initial treatment response, we ultimately could reduce depression- and suicide-related morbidity and mortality. We could select the best treatment strategy from the start.

Similarly, we believed that one way to advance our understanding of MDD-SI was to move beyond the standard assessment of depressive symptomatology and syndromal comorbidities. Therefore, we adopted a dimensional approach to psychopathology, the Spectrum Assessment Method. With this method, we sought to capture the full range of lifetime and current mood and panic-agoraphobic symptoms associated with MDD-SI, as well as a range of behavioral traits that likely arise as a means of coping with these symptoms. We thought that this method would eventually inform treatment refinement and development projects.

We found preliminary support for our ideas. Specifically, baseline suicidal ideation, in the context of a non-psychotic unipolar major depressive episode, appears to be a predictor of initial treatment response and to be a marker for a more severe form of depression. MDD-SI is distinguished by an array of syndromal and subsyndromal mood and panic-agoraphobic symptoms. To conclude, our findings provide preliminary support for the usefulness of conceptualizing MDD-SI as a subtype and clinical phenotype of major depression. Further research, including replication of our findings, is warranted.

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