The Impact of Efficacious Treatments for Major Depressive Disorder on Remission Rates of Specific Symptoms: A Re-Analysis of the Treatment of Depression Collaborative Research Program

by

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Abstract

Major Depressive Disorder (MDD) is a highly prevalent mental disorder that will affect 12.2% of Canadians over the course of their lifetimes, and 4.8% annually (Patten, et al., 2006). One of the most robust findings in the MDD literature is that the gold-standard treatments – Cognitive-Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), and anti-depressant medications - are equal in their efficacy, and superior to placebo. However, it is unclear whether rates of remission for certain types of symptoms differ among treatments with theoretically different mechanisms. This study re-analyzed data from the Treatment of Depression Collaborative Research Program, which included 158 adults with MDD randomized to CBT, IPT, imipramine or placebo. We statistically derived 4 factors from the baseline Hamilton Depression Rating Scale. We hypothesized that the rate of remission of somatic factors (sleep and appetite) would be most rapid in the group receiving imipramine plus clinical management (IMI-CM), and that the rate of remission for cognitive-affective factors would be fastest in IPT and CBT. Hierarchical regression analyses predicted the sum of symptom scores corresponding to each factor using linear and quadratic time (measured in weeks). Treatment-by-time interactions were entered in a stepwise fashion. There were no significant interactions found in the appetite factor, suggesting that all therapies acted on these symptoms at similar rates. Consistent with hypotheses, IMI-CM produced more rapid remission in sleep symptoms compared to psychotherapy. Surprisingly, IMI-CM was also more rapid at relieving cognitive-affective symptoms. The results lend partial support to the idea that different treatments for MDD may target specific symptoms at different rates according to their underlying mechanisms of action. The findings present some exciting possibilities for elevating response rates through empirically-based “tailored treatments”.

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Chapter 1

Introduction

Unipolar Major Depressive Disorder (MDD) is a mood disorder characterized by intense feelings of sadness and despair and/or a loss of interest in almost all usual activities or pastimes. These are accompanied by a number of additional symptoms that can include diminished energy, mental slowing and loss of concentration, feelings of worthlessness, inappropriate guilt, recurrent thoughts of death and suicide, sleep disturbances and appetite disturbances. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association, 2000), an individual needs suffer from 5 of 9 possible symptoms for a minimum duration of 2 weeks to meet criteria for a MDD.

Depression is a highly prevalent mental disorder that has serious consequences for individuals and society as a whole. It ranks fourth highest in the global burden of disease (Murray & Lopez, 1997) and will affect 12.2% of Canadians over the course of their lifetimes, and 4.8% annually (Patten, et al., 2006). Given its prevalence, it is not surprising that depression incurs such great costs to society – it is the main source of disability in the Canadian workplace (Dewa, Lesage, Goering, & Craveen, 2004) and significantly impairs general workforce function in adults (McIntyre et al., 2008), which results in an estimated cost of approximately 1.4 billion dollars per year due to lost time alone (Stephens & Joubert, 2001). Depressed Canadians are also at increased risk of mortality, particularly due to unnatural causes (e.g., suicide) and cardiovascular disease (Wulsin, Vaillant, & Wells, 1999). Attempted and/or completed suicide are amongst the most serious consequences of untreated MDD – it is estimated that the lifetime mortality

risk by suicide by individuals with a history of MDD is approximately 15% (Guze & Robins, 1970) and approximately 60% of suicide victims suffered from MDD or another major mood disorder (Cavanagh, Carson, Sharpe, & Lawrie, 2003)

Statistics such as the above led some countries to identify the detection and treatment of depression as a national health priority (Kessler et al., 2003). Currently in Canada, 63.9% of depressed Canadians seek some form of help, and most (52.9%) choose conventional (i.e., psychologists, psychiatrists, etc.) resources (Wang et al., 2005). Not surprisingly then, a large body of research has focused on the overall efficacy and specific utility of the most common treatments for major depression so as to ensure that those who seek treatment get the best available. Unfortunately, there are indications that much more of this research is needed – a large study conducted in the United States indicates that of the individuals suffering from depression who seek treatment (50% of all cases), only 42% receive adequate treatment (Kessler et al.). Thus, only 21% of all depressed individuals in the United States receive adequate treatment.

There are currently three primary gold-standard approaches to the treatment of MDD that have been found to be similarly efficacious: Cognitive-Behavioural Therapy (CBT), Interpersonal Psychotherapy (IPT) and anti-depressant medications. However, response rates across these treatments remain unacceptably low. In most studies, approximately 40% (at best) of patients remain unremitted at termination of acute phase treatment. When remission is defined as a nearly complete remission of *all* symptoms and a return to full functioning in all areas of life, no more than one third of patients meet the criteria (e.g., Thase, 2003). Furthermore, the typical length of the acute phase in these studies is 16 weeks, which is far longer than most would receive in more naturalistic

settings. Thus, the rate of remission might be considered an over-estimate of actual effectiveness.

The need to improve upon our current gold-standard treatments becomes even more clear when their efficacy is compared to a placebo control group. One recent study conducted a meta-analysis of randomized control trials of antidepressant medications submitted to the U.S. Food and Drug Administration (these included published and unpublished trials). The authors found that 82% of the antidepressant drug response was duplicated by placebo, and that the difference between drugs and placebo was 1.8 points on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960; 1967) (Kirsch, Moore, Scoboria, & Nicholls, 2002). The effects reported were large ($d = 2.36$) and statistically significant, but the clinical relevance of such small differences in symptom scores is questionable. In another large meta-analysis of 58 studies on the efficacy of a variety of psychotherapies (Robinson, Berman, & Neimeyer, 1990), effect sizes for comparisons between psychotherapy and placebo ($d = .28$) did not differ reliably from zero. The above studies indicate the need for research into how active treatments are working in the treatment of major depression, so as to better understand and improve upon them.

One explanation for the low remission rates is that one treatment may work better for certain individuals and another treatment may be most effective for a different group of individuals. When these patients are randomized to treatments without regard to individual difference characteristics, the average effect may be the same, but the process masks differences in patterns of response that could be very useful in matching the treatment to the patient. If so, then treatments for MDD could be used selectively for

certain symptom profiles that they are theoretically most effective at treating according to their proposed methods of action. However, the relative strengths of particular treatments for specific symptoms or groups of symptoms has yet to be thoroughly explored. The current study will begin to fill this crucial gap in the MDD treatment literature. Specifically, the focus will be upon different types of symptoms within the depressive syndrome (e.g., cognitive-affective, appetite disturbances) and whether these remit at differential rates across CBT, IPT and imipramine hydrochloride (an antidepressant medication).

To do so, the current study will use the data from the above mentioned Treatment for , a large, multi-site randomized controlled trial of IPT, CBT, and imipramine sponsored by the National Institute of Mental Health (NIMH) in the United States. These data are ideal for addressing the present question of rates of symptom remission over time across treatments because they include (a) random assignment of patients to treatment condition, (b) a conservative (i.e., stringent) placebo control group, (c) well-controlled, manualized treatments, and (d) multiple informants for the key measures of depressive symptoms collected at 5 time points over the course of the 16-week treatment trial. A series of hierarchical regression analyses will be used to characterize the shape of remission for symptom factors across the 4 treatment groups and to test hypotheses about the differences between symptom factors on their mean rate of change over the acute phase.

Treatments for Major Depression

A brief discussion of three of the treatments for MDD – anti-depressant medications, CBT and IPT - will be presented below. CBT and IPT both meet the criteria set out by The Task Force on Promotion and Dissemination of Psychological Procedures (American Psychological Association, 1993) for empirically-validated treatments, and they are both commonly used in practice. They have well-established guidelines for their use, which are detailed in treatment manuals (e.g., Beck, Rush, Shaw, & Emery, 1979; Klerman, Weissman, Rounsaville, & Chevron, 1984). A large amount of literature, dating back 50 years documents the efficacy of the anti-depressant medications, and, again, well-established guidelines exist for their use, which include monitoring dosage and blood drug levels (Fawcett, Epstein, Fiester, Elkin, & Autry, 1987). Importantly for the current study, the three treatments were assessed head-to-head in the TDCRP (Elkin, et al., 1989).

Anti-depressant medications. The first treatments found to reliably relieve the symptoms of major depression in the 1950s were anti-depressant medications. Currently, antidepressant medications are used by approximately 30% of depressed Canadians and their usage is rising (Patten & Beck, 2004). Tricyclic antidepressants (TCAs) were the first class of medications developed to alleviate depression, and they do so by inducing neurochemical changes in the individual. Classically, depression has been conceptualized as a disorder involving deficiencies of, or problems with, specific neurotransmitters (e.g., serotonin). Neurotransmitters such as serotonin play a role not only in affective states, but also in sleep, libido and the regulation of body temperature.

The current understanding of the pathophysiology of depression suggests that it is characterized not only by deficiencies in neurotransmitters such as norepinephrine, serotonin and dopamine, but also by deficiencies in certain tropic hormones that maintain cell survival and health. Deficiencies in these hormones result in neuronal atrophy and neuronal loss which presents itself phenotypically as structural and neurochemical changes in particular areas of the brain, the frontal cortex, hippocampus and other subcortical areas (see Julien, 2005 for a review). TCAs such as imipramine hydrochloride (Tofranil) act at the level of the limbic system, blocking both the norepinephrine and serotonin reuptake transporter (Baldessarini, 1983), as well as stimulating the needed adaptive changes in neuronal systems that have lost cellular plasticity (Santarelli et al., 2003). Along with inhibiting effects listed above, TCAs also block postsynaptic histamine and acetylcholine receptors. These latter two pharmacologic actions account for the bevy of side effects associated with the use of these medications.

The focus of this study are the TCAs, but given that the data were collected in the 1970s and 1980s, several additional families of anti-depressant medications have come into common use, including Monoamine Oxidase Inhibitors (MAOIs), Selective Serotonin Reuptake Inhibitors (SSRIs), and Selective Norepinephrine Reuptake Inhibitors (SNRIs). All of the newer medications have demonstrated comparable overall efficacy and onset of action to TCAs when treating adult outpatient depression (Frank, Karp, & Rush, 1993; Kennedy, Lam, Cohen, Ravindran, & the CANMAT Depression Workgroup, 2001), although specific medication rubrics have been developed to manage particular subtypes of MDD (e.g., MDD with melancholic features). Currently, most TCAs are considered third line treatments of MDD (Kennedy et al.), but this is mostly due their

higher occurrence of nuisance side effects (e.g., dry mouth, blurry vision, constipation, and light headedness) and safety issues (i.e., lethal in overdose versus the notable safety of most SSRIs in overdose) rather than efficacy.

Turning to the evidence for the efficacy of TCAs, a large body of research beginning in the late 1950s has demonstrated their superiority to placebos in double-blind studies. For example, TCAs were found to be superior to placebos in 63 out of 91 controlled studies in a large, comprehensive literature review of published research (Morris & Beck, 1974). In another review, examining both inpatient and outpatient samples, the authors reported a 21.3% and 18.0% advantage over placebo, in these respective samples (Frank et al., 1993). Similarly, a range of approximately 20% to 40% for drug-placebo differences was reported in a review of randomized controlled trials (RCTs) by the Depression Guideline Panel (1993).

Evidence from both preclinical studies and research on human samples indicates that antidepressant medications create changes in brain function and structure. They have been shown to produce rapid extracellular increases in serotonin and/or norepinephrine (Nierenberg et al., 2007), and effective treatment with antidepressant medications correlates with the down-regulation of serotonin receptors (Sheline & Minyun, 2003). Emerging evidence from preclinical studies has shown higher level structural changes in the brain after effective treatment with antidepressants. For example, one study demonstrated that atrophy and loss of neurons in the prefrontal cortex and hippocampus may be reversed by administering a modified TCA (Czeh et al., 2001) and may also reverse the "negative plasticity" brought on by stress and other factors by normalizing the functioning of the hypothalamo-pituitary-adrenocortical (HPA) axis and stimulating long-

term potentiation in the synapses of neurons in affected neural areas such as the hippocampus and prefrontal cortex (see Garcia, 2002 for a review).

Given the actions that antidepressant medications have on the serotonin, norepinephrine and other neurotransmitter symptoms, it follows that these medications would have a preferential impact on somatic symptoms. As well as being involved in the regulation of mood, neurotransmitters such as serotonin and norepinephrine also play a role in regulating key bodily functions such as sleep, appetite, and sexual arousal. Thus, through actions on the above neurotransmitter systems, antidepressants may act at a more rapid rate, or preferentially, on the somatic symptoms of depression, such as sleep disturbances, appetite disturbances, reduced energy, and loss of libido.

Cognitive-behavioural therapy. Dr. Aaron T. Beck's Cognitive Behavioural Therapy (CBT) has been the most widely studied and disseminated psychological treatment for major depression (Beck, et al., 1979). CBT is founded on the idea that depressed individuals possess thought processes that are logically flawed, and that are manifested in the individual's interpretation and organization of the world (Beck, 1976). CBT uses both behavioural and cognitive techniques to facilitate coping, to help the individual develop new strategies for dealing with life problems, and, most importantly, to alter patterns of thinking, beliefs and responses theorized to underlie the maintenance of the disorder. The cognitive model makes four main assumptions about depression (Kuyken, Watkins, & Beck, 2005). The first is that a biopsychosocial model is implicated in both the etiology and maintenance of MDD. The second is that the maladaptive beliefs about the self, the world and the future are shaped in early developmental experiences. Third, maladaptive beliefs remain dormant until they are activated by impactful

situations. Finally, negative situations interact with the underlying beliefs through selective attention and interference, generating negative mood and patterns of behaviours that maintain this lowered mood.

When treating depression, the cognitive-behavioural therapist first seeks to identify and operationalize current problems and to set goals to be worked towards, as well as acclimatizing the client to the cognitive model of depression (i.e., the idea that there are bidirectional relationships between thoughts, moods, behaviours and bodily sensations). Sessions proceed with the therapist seeking to build a strong relationship with the client through the use of empathy and a collaborative approach while drawing upon a wide range of cognitive and behavioural techniques, including thought records, behavioural experiments and action plans. CBT is designed as a short- to medium-term treatment, with typical patients attending 16 to 20 meetings.

In a large number of trials, CBT has shown equal efficacy to TCAs and other antidepressant medications in the treatment of non-bipolar, non-psychotic, outpatient depression of mild to moderate severity (Beck, Hollon, Young, Bedrosian, & Budenz, 1985; Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Elkin, et al., 1989; Hollon et al., 1992; Murphy, Simons, Wetzel, & Lustman, 1984). These findings have also been confirmed in meta-analyses (Hollon, Shelton, & Loosen, 1991; Robinson et al., 1990). Within the meta-analyses, effect sizes for CBT and related psychotherapies ranged from .28 to 1.02, depending on the type of therapy and whether the studies compared the active treatment to no treatment, wait-list control or placebo group.

Additionally, CBT may be as effective as antidepressant medications in treating moderate to severe depressed outpatients (DeRubeis, Gelfand, Tang, & Simons, 1999), although this issue remains a contentious one. CBT also has long-term, prophylactic (i.e., relapse prevention) effects that are superior to medications and have been documented by several research groups over 1- and 2-year follow-up periods (Evans et al., 1992; Kovacs, Rush, Beck, & Hollon, 1981; Shea et al., 1992; Simons, Murphy, Levine, & Wetzel, 1986).

Research has also examined whether CBT indeed works by inducing changes in cognition. For example, using the TDCRP dataset, investigators found that patients successfully treated with CBT scored lower than those treated with IPT, imipramine, and placebo on the Need for Social Approval factor of the Dysfunctional Attitudes Scale (DAS; Weissman & Beck, 1978) (Imber et al., 1990). Studies have also found that changes on measures of depression-related cognitions from pre-treatment to mid-treatment (6 weeks) predicted change in depression from mid-treatment to post-treatment (12 weeks) in those receiving CBT but not in those receiving pharmacotherapy (DeRubeis et al., 1990). Similarly, Kwon and Oei (2003) more recently used Structural Equation Modeling to show that CBT was associated with a reduction in negative automatic thoughts early in treatment, which then led to a reduction in dysfunctional attitudes and depressive symptoms. Similar results have been found with hopelessness, such that changes in hopelessness within the first four weeks predicted improvement in depression symptoms at termination (Kuyken, 2004).

The research above on the mechanisms of change in CBT indicates that CBT produces improvements in cognition early in treatment that then leads to alleviation of the

depressive syndrome overall. While the above studies were not assessing cognition in terms of symptoms, many of the cognitive constructs measured, including hopelessness and dysfunctional attitudes, are also symptoms of depression (e.g., feelings of worthlessness, inappropriate guilt and hopelessness). It is possible, therefore, that CBT targets the cognitive symptoms of MDD more rapidly and effectively than other depressive symptoms, and more efficiently than other depression treatments.

Interpersonal psychotherapy. Interpersonal Psychotherapy (IPT) was developed by Gerald Klerman and Myrna Weissman for the treatment of MDD. IPT considers the interrelationships among symptoms, social and interpersonal and personality problems. IPT only attempts to intervene at the level of symptom function and social and interpersonal relationships, positing that, as symptoms lift, patients will gain a degree of control over personality patterns. Unconscious factors and past experiences (e.g., early childhood experiences) are often recognized but are not addressed directly, with the focus instead turning to helping individuals in the 'here and now'.

Unlike CBT, IPT emphasizes adopts the medical model of depression, legitimizing the 'sick role' of the patient and providing them with an explanation for their symptoms. The early sessions of IPT are devoted to describing depression in terms of the medical model. Then the patient and therapist together define the patient's interpersonal issue that will provide the focus for intervention in the remaining sessions in terms of one of four interpersonal problems: grief, role transition, role dispute, or interpersonal deficit. In the intermediate phase of treatment, a collaborative problem solving approach is adopted by client and therapist to target the identified interpersonal problem(s). IPT assigns 2 to 4 sessions to termination issues, including the experience of grief and anxiety

in response to termination and a discussion of the client's independent competence. IPT, like CBT, is also a time-limited therapy lasting 20 sessions or less in most cases.

Relatively speaking, there are few thorough evaluations of the efficacy of IPT for treating depressed outpatients. Studies have consistently found shown an advantage for IPT above placebo controls for the acute treatment of MDD (DiMascio et al,, 1979; Elkin, et al., 1989; Markowitz et al., 1998; O'Hara, Stuart, Gorman, Wenzel, 2000). The effect sizes for these studies ranged from modest (d = .33) to large (d = 1.21) depending on the nature of the comparison group. A meta-analysis comparing a combination of antidepressant medications and IPT to both treatments alone found an advantage for the combination over IPT alone, but not over medication alone (de Mello, de Jesus Mari, Bacaltchuk, Verdeli, & Neugebauer, 2005). Another meta-analysis reported no significant difference in remission rates between IPT and TCA monotherapy over acute treatment (Weissman & Markowitz, 1994). Finally, researchers have failed to find the same prophylactic effects in IPT as have been found for CBT, finding no advantage of IPT over maintenance antidepressant medications in preventing recurrence (Frank et al., 1990; Reynolds, et al., 1999).

There has also been very little research investigating the mechanisms of action in IPT. In one study, the authors found that IPT worked more effectively in individuals with lower levels of social functioning, as might be predicted by the focus of IPT on improving interpersonal relationships (Feske, Frank, Kupfer, Shear, & Weaver, 1998). However, in the TDCRP data (Imber et al., 1990), there was no statistically significant advantage of IPT over CBT and IMI treatments on measures of social adjustment. Further, in this

dataset, higher levels of social adjustment predicted of superior treatment response preferentially in the *CBT* condition (Sotsky et al., 1991).

The absence of concrete theoretical underpinnings of IPT, along with a paucity of research into the mechanisms of change in IPT make it difficult to develop hypotheses regarding the specific symptoms that IPT might target. Additionally, a study by Ablon and Jones (2002) revealed that CBT and IPT may not have been firmly differentiated in the TDCRP. The authors used the transcripts of therapies recorded in the study, scored them, and compared them to independently derived prototype descriptions of each therapies. The authors found that both therapies were most strongly associated with the CBT prototype, and adherence to this prototype correlated with positive outcome for both of the therapies. Thus, CBT and IPT may not be able to be discriminated in the TDCRP. Therefore, the hypotheses below will pertain to both therapies together as differentiated from the medication condition.

Background of the NIMH Treatment of Depression Collaborative Research Program

In 1977, the staff at the Psychotherapy and Behavioural Intervention Section of the Clinical Research Branch of the NIMH reviewed the current status of the field of psychotherapy research in MDD and determined that a large-scale collaborative study was both necessary and feasible. And so was born the TDCRP – the first large-scale, multisite collaborative model in the field of psychotherapy research, and the first attempt to directly compare the efficacy of TCAs, CBT and IPT in any disorder, and in MDD in

particular. The "outcome" phase of the study began in May 1982, and the 18-month "follow-up" phase was completed for all patients in 1986.

The initiative was undertaken in response to the paucity of adequate evidence demonstrating the overall efficacy of psychotherapies and the limited understanding of the differential changes that may occur as a result of different therapies and the variables that moderate efficacy (e.g., therapist, patient and setting variables). Several collaborating investigators at different sites adopted a standard protocol and set of measures for assessing depression, the characteristics of the treatment interventions, and various aspects of patient change. The qualities above allowed the researchers to assess generalizability across sites, explore various predictors of successful outcomes, and identify methodological and substantive issues relevant to psychotherapy research.

Briefly, 239 patients entered treatment and were randomly assigned to receive imipramine plus clinical management (IMI-CM), IPT, CBT or pill placebo plus clinical management (PLA-CM). A total of 162 patients completed the acute treatment phase (32% attrition). For those who completed treatment, the remission rates for IMI-CM, IPT, CBT and PLA-CM were 57%, 55%, 51% and 29%, respectively.

In their primary analyses, the authors found that none of the active treatments differed in terms of their efficacy in the treatment of depression after the 16 weeks, but that all were significantly superior to placebo (Elkin, et al., 1989). These results were unexpected because all three treatments have a different theorized mechanism of action – TCAs are believed to work at the level of an individual's neurochemistry, CBT is theorized to act primarily at the level of dysfunctional thoughts and attitudes about the

self, others and the world and IPT was developed to target maladaptive behaviours in social and interpersonal relationships.

It is critical to note that efficacy in previous research using TDCRP data was defined in terms of remission of the overall *syndrome* of depression. As defined above, depression is a phenotypically diverse syndrome – that is, individuals vary greatly in terms of the constellation of symptoms that they may present with. Indeed, it is it is even possible for 2 people to meet criteria for MDD and have no overlapping symptoms. Partly due to this heterogeneity, researchers have difficulty agreeing on the true nature of depression and thus it becomes difficult to interpret conclusions base on, and correlates of, the syndrome as a whole.

Examining treatment response at the level of symptom clusters is potentially useful because particular constellations of symptoms have specific prognostic implications. For instance, individuals who present with primarily somatic and vegetative symptoms, such as sleep and appetite disturbances, psychomotor disturbance, and anhedonia (i.e., a 'melancholic/endogenous' subtype) tend to have a greater magnitude of biological disturbance, including hypercorticolism and dexamethasone non-suppression, a superior and differential response to physical treatments, such as antidepressant medications and electroconvulsive therapy, and a lowered response rate to placebo (see Parker, Hadzi-Pavlovic, & Boyce, 1996, for a review). These symptoms are also associated with increased severity, inpatient status and psychotic features (APA, 2000). The group of symptoms described above are also heritable, whereas other depressive symptoms are not, suggesting a genetic basis for the subtype (Jang, Livesley, Taylor, Stein, & Moon, 2004).

In addition, sleep disturbances alone may have a particular robust relationship to negative outcomes. These symptoms (e.g., insomnia, hypersomnia, excessive sleepiness) are reported in approximately 90% of depressed patients and sleep disturbance is very frequently the symptom that makes patients seek medical help (Tsuno, Besset, & Ritchie, 2005). Sleep disturbances and early morning awakening are associated with increased global severity and increased probability of suicidal ideation (Thase, 1998), and, if persistent after successful treatment, may reflect incomplete remission and signal relapse (Perlis, Giles, Buysse, Tu, & Kupfer, 1997). Thus, this group of symptoms provides clinically relevant information that would be unavailable were the focus to be solely on the overall syndrome measure.

The literature above illustrates the utility of considering depression at the level of symptoms when considering etiology, course, treatment and prognosis. The symptoms of depression fall into categories, which include somatic symptoms (appetite and sleep disturbances, loss libido, fatigue/lack of energy), cognitive symptoms (hopelessness, helplessness/pessimism, worthlessness, concentration difficulties) and affective symptoms (sadness, depressed mood, crying). Measures such as the HDRS also include symptoms reflecting anxiety and anxiety-related afflictions (e.g., psychic anxiety, somatic anxiety), and thus this can be considered another group of symptoms. The current study will examine the depression syndrome and its treatments at this level of detail to obtain a more clinically relevant picture of treatment efficacy.

Symptom Specificity and Depression Treatment

Despite the theoretical importance of studying the differential patterns of individual symptom remission in treatments of depression, very few studies have done so, and most of these have done so in the context of pharmacological treatments. Consistent with theory that a biological treatment should work best on the somatic symptoms of MDD, one early study examined depressed women treated with amitriptyline over a 4 week period. The authors found that sleep disturbances (initial and delayed insomnia), suicidal feelings, appetite loss, and psychomotor retardation were most responsive (i.e., improved the most) to treatment in the first 4 weeks. Importantly, most of the improvement in sleep disturbances and suicidal feelings occurred in the first week of treatment. In contrast, anxiety, pessimism and hopelessness, and irritability were most resistant to treatment (Haskell, DiMascio, & Prusoff, 1975).

Other research has also found that sleep disturbances responded most quickly to treatment with TCAs versus placebo (Kupfer, Foster, Reich, Thompson, & Weiss, 1976; Raskin, Schulterbrandt, Reatig, & McKeon, 1970). However, Raskin et al. found evidence for preferential remission of a different constellation of additional symptoms than those found by Haskell et al., including feelings of guilt and worthlessness, depressive mood, and hostility. Other early studies took a different approach and investigated the issue of individual symptom response by comparing those who responded to TCAs versus those who did not on symptom scores at various points in treatment. Again, sleep disturbances distinguished the groups as early as the first couple of weeks of treatment, while the results were inconsistent in terms of which cognitive and

affective symptoms differentiated the two groups (Casper et al., 1994; Katz et al., 1987; Katz et al., 1991).

Patterns of symptom improvement in depression have also been studied using the more recently developed medications. For example, a study comparing nefazodone (an atypical anti-depressant) to a modified version of CBT in chronic depression confirmed early reports by demonstrating superior improvements on sleep disturbances in the medication condition compared to CBT after 2 weeks, and this effect was sustained over 12 weeks (Thase et al., 2002). However, a meta-analysis of 6 double-blind, placebo controlled studies of fluoxetine (an SSRI) found that cognitive and psychomotor symptoms, assessed by the HDRS (Hamilton, 1960; 1967) showed the most rapid improvement in the active medication group (Tollefson & Holman, 1994).

One research group tested a sample of patients with melancholic depression used the HRSD and divided the symptoms into subfactors corresponding to cognitive disturbance, psychomotor retardation, sleep disturbance, anxiety/somatization and melancholia. They compared an active SSRI treatment to a placebo group and found that the SSRI group had significantly greater improvement on all the subfactors except the anxiety/somatization factor (Mendels, Kiev & Fabre, 1999). Although the authors do not specify the items that make up their "subfactors", it is possible that the anxiety/somatization subfactor was composed of Psychic Anxiety, Somatic Anxiety and perhaps Somatic (General).

Some research has approached the question of symptom specificity within antidepressant medication as a predictor of course. For instance, one study examined a

large sample of patients with MDD treated acutely with nefazodone, and specified subgroups of late responders and non-responders. The authors specified clusters of symptoms within the HDRS-17: they had a mood cluster (depressed mood, guilt, suicide, work and interests, psychomotor retardation, somatic energy and libido), a sleep/psychic anxiety cluster (initial insomnia, middle insomnia, delayed insomnia, agitation and psychic anxiety) and a somatic anxiety/weight cluster (somatic anxiety, hypochondriasis and weight loss). Results showed that non-responders and late responders had identical patterns of improvement on all symptom clusters up until week four, but then their patterns diverged. Specifically, non-responders stopped improving, or got worse, between weeks 3 and 4 of treatment on the three symptom clusters whereas responders continued to improve over the same time frame (Trivedi, Morris, Grannemann, & Mahadi, 2005). The study above suggests that groups of symptoms may play an important role in predicting course and outcomes in depression treatments.

The studies described above are heterogeneous in their methods, and their findings are somewhat inconsistent. Nevertheless, one relatively consistent finding is that antidepressant medications act early (within the first three weeks) on sleep disturbances relative to both pill placebo and CBT. The timing of the effects of medication on the other somatic, cognitive, and affective symptoms, however, shows no consistent pattern.

Relatively little attention has been given to the effects of CBT or IPT on specific symptoms. An early study by DiMascio et al. (1979) was probably the most direct examination of this question. In this study, 96 inpatients with MDD were randomized to receive amitriptyline (a TCA) plus IPT or amitriptyline alone or IPT alone. Those receiving medication (either alone or in combination with IPT) scored lower on the sleep

disturbances symptoms of the HDRS than those in the IPT alone group after 1 week and this was sustained throughout treatment. In contrast, those receiving IPT (either alone or in combination with amitriptyline) scored lower than those receiving amitriptyline alone on suicidal ideation, depressed mood, lack of interest, and guilt at week 4, and this effect was also sustained throughout treatment. However, these results are somewhat difficult to interpret because the data were collected primarily to measure the effects of combining psychotherapy and medications. Thus, there were no direct comparisons of the two monotherapies. Nevertheless, the results of this study are consistent with theory that medication works preferentially on somatic symptoms of the syndrome, whereas psychotherapy would work preferentially on the cognitive and affective symptoms.

Most of the work on the specific effects of CBT has focused on how it brings about change in cognitive symptoms. For example, an early study that compared CBT to imipramine used a cross-lagged panel design to examine the patterns of symptom improvement over time, as measured by scores on scales constructed from the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Symptom Checklist 90 (SCL-90; Derogatis, Lipman, & Covi, 1973), and the Hopelessness Scale (HS; Beck, Weissman, Lester, & Trexler, 1974). The authors found that early improvements in views of self, hopelessness, and depressed mood preceded changes in vegetative (e.g., sleep, appetite, energy) and motivational symptoms in the CBT group. In contrast, the authors found no specific pattern of improvement for the medication group. Both treatments produced statistically significant changes on all scales between weeks 1 and 4, but between treatment differences were non-significant (Rush, Kovacs, Beck, Weissenburger, & Hollon, 1981). This same research group also found

that CBT improved scores on hopelessness and self-concept to a significantly greater degree than imipramine, and that the major difference between the treatments occurred within the first 5 weeks (Rush, Beck, Kovacs, Weissenburger, & Hollon, 1982). In contrast to these studies reviewed above, however, Simons, Garfield, and Murphy (1984) found no significant differences in the pattern of improvement in mood, and cognition between their patients randomized to CBT versus medication. In summary, there is some limited evidence that both IPT and CBT act preferentially and early on the cognitive and affective symptoms of depression.

The proposed study will address the limitations of the earlier studies reviewed above. The TDCRP was a very structured, well-controlled study that included manualized treatment procedures and highly trained practitioners. The dataset allows for the direct comparison of both psychotherapies and a common TCA (imipramine) and includes reliable and valid clinician-rated measures of symptoms. The clinicians were blind to the type of treatment the patient was receiving, as well as other treatment variables, making relevant clinician-rated measures less likely to be impacted by expectancy or other systematic biases.

Unlike many of the studies reviewed above, the TDCRP also includes a placebo condition. A placebo is not necessary to answer research questions regarding differential patterns of symptom remission across treatments; that is, we already know these treatments work, we are now interested in fine-grained differences among these efficacious treatments in the *way* they work. However, inclusion of the placebo group in the current analyses will enable me to compare the time course of symptom remission in active treatment to that seen in a non-active treatment. This is an interesting and

important question in itself as it will shed more light on the mechanism of action of the placebo. Finally, my analyses will be conducted using sophisticated statistical methods designed to maximize power for questions about hierarchical data (such as the TDCRP data). These methods are more powerful compared to those used in most studies conducted in the 1980s and 1990s (see below).

Objectives

To date, there has been little well controlled research that has compared the efficacy of treatments for depression on specific symptoms of the disorder over the course of treatment. Additionally, to our knowledge, there have been no studies that have directly compared the different slopes of remission of groups of symptoms in CBT, IPT, and medication. The primary goal of the study, then, is to describe and compare the slopes of empirically derived depressive symptom factors across three efficacious treatments of depression.

To test our hypotheses, we will derive symptom factors from scores on the HDRS using exploratory and confirmatory factor analytic procedures. A series of hierarchical regression analyses will be used to predict scores on these symptom factors from time (measured in weeks) and dummy-coded treatment variables. This will allow us to specify both linear and quadratic terms and to test time by treatment interactions. Follow-up simple slopes analyses will be used on significant interaction terms

To our knowledge, there have not been any factor analyses conducted on the 23-item version of the HDRS used in the current study, but a number of studies *have*

investigated the structure of the 17-item version. To summarize, studies on the HDRS have found evidence for anywhere between 2 and 8 factors and most have used the same general approach. The typical study uses the Eigenvalues > 1 rule to determine the number of factors, employs principal components analysis as the method of extraction and applies orthogonal rotation (usually Varimax). Variability may be attributed to differences in the samples used and minor differences in method.

Despite the inconsistencies across studies in the exact number of factors, some general trends appear. Most studies find that the sleep disturbances (initial, middle and late insomnia and hypersomnia) items group together as a single factor (e.g., Fleck, Poirier-Littre, Guelfi, Bourdel, & Loo, 1995; Marcos & Salamero, 1990; Pancheri, Picardi, Pasquini, Gaetano, & Biondi, 2002). There is also some evidence that the cognitive-affective items (e.g., worthlessness, depressed mood, hopelessness, helplessness) of the HDRS tend to hang on the same factors – one group of researchers reviewed 15 large factor analysis studies of the HDRS-17 and found that depressed mood, guilt and suicide appeared together in the same factor in 6 datasets, while the combination of depressed mood, suicide and psychic anxiety occurred in seven datasets (Bagby, Ryder, Schuller, & Marshall, 2004). Despite the fact that the exact factor structure of the HDRS remains unclear, somatic/vegetative symptoms, such as sleep disturbances, eating disturbances and genital symptoms typically occur on the same factor(s), whiles cognitive-affective symptoms occur on separate factor(s).

The current study will improve upon previous factor analyses of the HDRS primarily by enhancing the process of factor determination and specification. This will be done by examining scree plots, model fit (determined using Maximum Likelihood as the

extraction method), and parallel analyses to inform decisions. It is unclear how many factors will be obtained, given the heterogeneity of previous findings and the use of the 23-item HDRS, but we expect a general somatic-vegetative/cognitive-affective distinction, and thus, hypotheses are made with this in mind.

Along with examining symptoms at the level of derived factors, the current study will also examine between-treatment differences in rates of remission for the overall syndrome (i.e., the HDRS-17). Previous research on the TDCRP data used a repeated measures approach to analysing between-treatment differences over time and found that IMI-CM had significantly superior symptom remission compared to the other treatments at week 8 and week 12, but that the active treatments did not differ by week 16 (Watkins et al., 1993). Thus, we hypothesize that IMI-CM will have a more rapid rate of remission through the earlier weeks of the study than the other treatments.

Consistent with the research reviewed above, we hypothesize that the slope for remission for somatic/vegetative symptoms (e.g., sleep disturbances and appetite disturbances) will be significantly more rapid (steeper) in the TCA group than in the CBT or IPT groups. This effect is likely to be most pronounced for sleep disturbances factor. we hypothesize that the slope for cognitive-affective symptoms will be significantly steeper in the CBT and IPT groups than in the TCA group. Any differences between IPT and CBT will be described in an exploratory fashion because there is evidence for the parity of their administration in the TDCRP (Ablon & Jones, 2002) and as such, there are no hypotheses for the separate effects of the treatment types. Finally, we hypothesize that all three active treatments will have steeper slopes than that of the placebo group in all four symptom factors.

Chapter 2

Method

Participants

Recruitment took place at three research sites - University of Pittsburgh (Pa), George Washington University (Washington, DC) and the University of Oklahoma (Oklahoma City). The major sources of referral for the original TDCRP included self-referrals, psychiatric outpatient services at the three research sites and other mental health facilities. Prospective participants underwent a pre-screening to ensure that they met participation criteria (e.g., between 21 and 60 years old, minimum grade 8 education and sufficient literacy to read the questionnaires) and to obtain informed consent. Five hundred and sixty potential participants passed pre-screening and were interviewed by a clinical evaluator using the Schedule of Affective Disorders and Schizophrenia (SADS) interview (Endicott & Spitzer, 1978) to determine whether they met Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) for a current episode of MDD for at least 2 weeks prior to screening. Participants also needed to score 14 or higher on an amended version of the 17-item HDRS (Hamilton, 1960; 1967).

Participants were excluded if they met criteria for specific additional psychiatric diagnoses which included definite bipolar II, probable or definite bipolar I, panic disorder, alcoholism, drug use disorder, antisocial personality disorder, Briquet's syndrome, and RDC diagnosis of major depressive disorder, psychotic subtype. Participants were also excluded if they showed two or more schizotypal features or if they had a history of schizophrenia, organic brain syndrome or mental retardation. Participants

could not be involved in any concurrent treatment and could not suffer from any specific physical illnesses or conditions that were medical contraindications for the use of imipramine. Finally, participants were excluded if they were acutely suicidal or displayed some other clinical state inconsistent with participating in the research protocol (e.g., clear need for immediate treatment).

After screening, participants were given a 7- to 14- day wait and drug washout period and then were rescreened by the clinical evaluator using the same criteria as above. The 250 patients who passed rescreening and who had consented to all study procedures (45% of all individuals screened) were randomly assigned to one of the four treatment groups (CBT, IPT, IMI-CM or PLA-CM) using a separate computer-generated random order for each site.

Attrition

For the acute phase of the TDCRP, patients received assessments by a clinical evaluator on the measures of interest to the current study (see below) at rescreening (wk 0) and after 4, 8, 12 and 16 (termination) weeks of treatment. Eleven participants (4.4%) dropped out before their first session (3 in CBT, 2 in IPT and 6 in IMI-CM), and thus, 239 patients entered treatment. Of those participants, 77 (32%) did not complete treatment (i.e., received less than 15 weeks and/or 12 sessions of treatment). There were 19 early terminators in the CBT group (32%), 14 (23%) in IPT, 19 (33%) in IMI-CM and 25 (40%) in PLA-CM. The treatment groups did not significantly differ in terms of the number of individuals who dropped out early, $\chi^2(3) = 3.16$, $p = .37$.

The primary analyses for the current study will focus exclusively on the 162 individuals who completed at least 15 weeks and/or 12 sessions of treatment. The hypotheses for the current study are based on the empirically demonstrated and/or hypothesized impacts of *full treatments* – the current study has not included any expectations for the differential impacts of certain component parts of treatments.

Of the 162 individuals who completed acute phase treatment, 20 (12.3%) had missing symptom data for at least one of the time points. To calculate total scores for each group of symptoms, complete listwise data for each subject was required. Rather than using statistical estimation procedures for missing value replacement, the missing entries from the Clinical Evaluator data could often be replaced by the HDRS data supplied by the treating clinician.

Between the 20 individuals who were missing data, there were a total of 38 pieces of symptom information that were unavailable (i.e., some participants had data that was missing at more than one point over time). Of these missing points, 6 (15.8%) were because the evaluator forgot, 8 (20.1%) were due to patient refusal, 20 (52.6%) were because the patient was unavailable for evaluation, 1 (2.6%) was because the patient was not testable or unable to answer the questions, 2 (5.3%) were because the evaluation was not required and 1 (2.6%) was because the record was lost. Twenty-seven (71.1%) of the missing clinical evaluator assessments were replaced using data from the clinicians – some data points could not be recovered because the data were missing from both the CE *and* the clinician delivering treatment. In the end, only 3 (1.9%) individuals were removed from further analyses.

The final sample of 159 cases used in the primary analyses did not differ from the non-replaced (142 cases) sample on age, sex, occupation, education level, ethnicity, marital status, index of social position, initial depression severity (indexed by HDRS-17 score), number of previous episodes of depression, age of first onset of depression or the presence of comorbidity (for continuous variables, all *p*s > .45; for categorical variables, all *z*s > -.637 and < .407, all *p*s > .10). Additionally, the four treatment groups did not differ in terms of number of cases missing (all *z*s > -.132 and < .00, all *p*s > .10).

The final sample of 159 individuals (after attrition and missing values) did not differ from the rescreening sample in terms of the percentage of cases falling into each of the four treatment groups (all *z*s < .72 and > .08, all *p*s < .10). Furthermore, they did not differ from the rescreen sample on any demographic or clinical characteristics of interest (for continuous variables, all *p*s > .29; for categorical variables, all *z*s > -.41 and < 1.25, all *p*s > .10).

Therapists

A different group of therapists conducted treatment for each of the conditions, with the exception of IMI-CM and PLA-CM, which were carried out double-blind by the same therapists. Initially, 27 therapists, 9 at each site (i.e., 3 for each active treatment), underwent training while pilot testing for the project was being carried out (i.e., beginning in July, 1980). Seven additional therapists needed to be trained afterwards to replace 4 who were not certified to participate and three who left the program.

To be a part of the TDCRP, therapists needed to have at least two years of full-time clinical work following the completion of their professional training, treatment of at least 10 depressed patients and a special interest in and commitment to the approach in which they chose to be trained. Thus, therapists required a baseline level of professional maturity and familiarity with the population before training even began. Therapists were rigorously trained by experts in the relevant treatment modalities. Following the training, all therapists were evaluated by experts, who were not involved in the actual training program, on their performance in carrying out their respective treatments as specified by carefully delineated protocols.

In the end, 28 therapists (10 psychologists and 18 psychiatrists) took part in the outcome study: 8 CBT therapists and 10 each for IPT and pharmacotherapy. These therapists averaged 41.5 years old and had an average of 11.4 years of clinical experience ranging from 2 to 27 years. Twenty of the 28 therapists (71%) were male.

Treatments

CBT. CBT was conducted according to the manual written by Beck et al. (1979). Therapists focused on correcting the negative, distorted views that their patients had about themselves, the future and the world, and ultimately, targeting the underlying maladaptive beliefs theorized to give rise to the above thoughts. Patients in this group were expected to receive 12 sessions over the first 8 weeks, followed by one per week over the next 8 weeks, for a total of 20 sessions, in accordance with the usual practice of the time. All sessions were 50 minutes in length.

IPT. IPT was set out in accordance with procedures set out by Klerman, et al. (1984). Briefly, IPT therapists focused on the interpersonal problems of their patients, helping them better understand how they relate to others and facilitating the development of more adaptive ways of interacting with others. Patients in this group received one session per week for all 16 weeks, with the option of scheduling up to 4 additional sessions, which involved a spouse or other relevant person in the patient's life. Again, this was consistent with usual practice at the time of the study, and all IPT sessions were 50 minutes in length.

IMI-CM. The CM component for both the IMI-CM and PLA-CM groups provided guidelines not only for the administration of medications, management of side effects and review of client status, but also for providing the client with support, encouragement and advice. The CM component has been referred to as a "mini supportive therapy" elsewhere (Elkin, et al., 1989) and is a relatively stringent control condition, by the standards then and now.

Imipramine was administered double blind during CM sessions using a flexible dose schedule. By the third week of treatment, therapists sought to achieve a dose of 200 mg/day unless impeded by side effects. Median plasma concentrations of imipramine and desmethylimipramine at 4, 8, 12 and 16 weeks were 164 ng/ml, 239 ng/ml, 202 ng/ml, and 198 ng/ml, respectively.

PLA-CM. Pill placebos were also administered double blind in the context of CM sessions. Both pharmacotherapy groups received 16 weekly sessions, all of which were 20 to 30 minutes long, except the initial session, which was 45 to 60 minutes long. Both

the IMI-CM and the PLA-CM sessions were carried out in accordance with the guidelines established by Fawcett et al. (1987).

Assessment Measures

Demographic Variables. Several sociodemographic variables of interest to the current study were collected by Clinical Evaluators (CEs) and Research Assistants. These included sex, age, ethnicity, participant occupation (ranging from 0 – not gainfully employed – to 7 – higher executives and major professionals), participant education level (ranging from 7 – under 7 years of schooling – to 1 – completed graduate / professional training), and marital status. In addition, the TDCRP dataset includes an index of social position for the patient, which was calculated by first reversing the patient's scores for occupation and then applying the following formula: (7 * patient occupation) + (4 * patient education).

Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967). In the TDCRP, the HRSD was filled out by both the clinicians who were responsible for the treatment of the client (after the first session, week 4, 8, 12 and 16) and by independent CEs (at rescreening, week 4, 8, 12 16). The CEs were PhD level psychologists experienced in diagnostic assessment who were "blind" to treatment conditions. In the current study, we opted to employ CE data as the HDRS is largely made up of subjective clinical impressions and the CEs were free of the bias of administering treatment and having the expectations that could potentially come along with that process.

Each HDRS item consists of a particular depression symptom that is rated on a scale of 0-3 or 0-5 where higher scores indicate greater severity of the symptom. The clinician chooses the possible response by observation of symptoms during the interview and the patients's own self-report of his or her symptoms.

Different versions of the HDRS have been used in research and clinical practice. The most commonly reported version of the HDRS includes the first 17 items. The psychometric properties of the 17-item HDRS have been most thoroughly investigated, and it is the version most readily interpretable as an index of depression severity. In particular, in treatment outcome studies for depression, a score of 16 or greater on the 17-item HDRS is required as a standard inclusion criterion for participants. Further, a score of 8 or less is a generally accepted definition of treatment response. A large meta-analysis of studies investigating the psychometric properties of the HDRS, the measure had Chronbach's alpha values of between .46 and .92, interrater reliability values (Pearson's r) of between .65 and .98, and the authors concluded that the measure meets established criteria for convergent, discriminant, and predictive validity (Bagby et al., 2004). As reported in Table 1, patients in the present sample had a mean intake HDRS-17 score of 19.03 (*SD* = 4.08).

When it came to conducting the factor analyses on Hamilton items with the goal of obtaining symptom factors to address the study's hypotheses, however, a broader range of potential symptom items was deemed preferable. Therefore, the 23-item HDRS was used for this purpose. The HDRS-23 includes the first 17 items plus items assessing hypersomnia, increased appetite, weight gain, worthlessness, hopelessness, and helplessness. These latter 3 items were deemed particularly important to include as they

are cognitive symptoms of depression that are not well represented in the basic HDRS-17.

See Appendix A for a copy of the HDRS items used in the TDCRP.

Schedule of Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978). The SADS is a semi-structured interview designed to assess the presence of both current and past RDC criteria for major depression and other psychiatric disorders (e.g., manic syndrome, generalized anxiety disorder, antisocial personality disorder). The measure provides a description of the current episodes of illnesses when they were at their most severe and a detailed description of past psychopathology and functioning. The SADS was administered at the initial screening by the CE.

Schedule of Affective Disorders and Schizophrenia – Change Version (SADS-CV; Endicott, Cohen, Nee, Fleiss, & Sarantakos, 1981). The SADS-CV is a semi-structured interview used to assess change in depressive symptomatology at rescreening. Administered by the CE and is composed solely of the items assessing the symptoms of major depression. Thus, it was used to confirm the continued presence of the disorder at entry into treatment.

Data Analysis

The first step of the data analysis process was to determine the factor structure of the items that make up the TDCRP's 23-item HDRS. Although there have been several previous factor analyses of 17-item Hamilton data in depressed adult outpatient samples (see Bagby et al., 2004 for a review), the factor structure of the 23-item Hamilton remains

unknown. Thus, an exploratory factor analysis (EFA) of the 250 individuals who were rescreened was deemed appropriate.

The rescreen sample was used instead of the final sample to increase the subject to item ratio from approximately 5:1 up to over 10:1. Although absolute cut-off rules for the subject to item ratio in EFA have mostly disappeared, the consequences of low subject to item ratio in most datasets (exceptions might be made for structures with uniformly high communalities with no cross loadings) include decreased chances of obtaining the "correct" factor structure (i.e., identical to population parameters), increased chances of misclassified items and increased chances of obtaining Heywood cases (see Costello & Osborne, 2005 for a review).

The EFA was conducted according to the suggestions made by Fabrigar, Wegener, MacCallum, & Strahan (1999) and was primarily performed using SPPS version 17.0 (SPSS, Inc., Chicago, IL). Maximum Likelihood Estimation (MLE) with a Direct Oblimin rotation was used to determine the number and nature of the factors. MLE was chosen because it allows for the computation of goodness of fit indices (specifically, in this case, Root Mean Square Error of Approximation - RMSEA) that contributed to settling on the appropriate number of factors. The EFA procedure began by determining the lower and upper limits for the number of factors by examining the scree plot associated with the analysis. We also conducted a parallel analysis which compared the obtained Eigenvalues to a set of Eigenvalues that were produced using 100 samples of random data. It should be noted that SPSS defaults to produce the Eigenvalues based on the sample correlation matrix which is a misapplication of the rule – Eigenvalues based

on the reduced correlation matrix were computed before performing producing the scree plot or performing the parallel analysis.

Arriving at the factor structure involved an examination the fit of models with different numbers of factors (using RMSEA values calculated in FITMOD; Browne, 1992) and a consideration of the pattern of loadings itself. To maximize the power of our main analyses and reduce the unique variance associated with our derived factors, we only included items with loadings above .35 on at least one factor and excluded items that loaded complexly (i.e., any item where the loading on the primary factor was less than two times the loading on some other factor). The structure and fit of the model were then reassessed based on the remaining items.

The obtained factor structure was then subjected to a Confirmatory Factor Analysis (CFA) using LISREL 8.80 (Joreskog & Sorbom, 2006) for both the rescreen (n = 250) and completer (n = 159) samples. Each item was restricted to loading on only one of the factors, and the loadings were standardized by fixing the diagonal values of the Phi matrix at 1. Factors were allowed to correlate with one another and this was accomplished by allowing the off-diagonal values of the Phi matrix to be freely estimated. The solutions for the rescreen and completer samples were compared to ensure that the factor structure held equally well in the latter.

Four aggregate variables were created for each of the symptom factors. These simply corresponded to the sum of the items that loaded on to each particular factor. Thus, a shift was essentially made towards a causal indicator conceptualization of the measurement of symptoms whereby a group of symptoms (e.g., various problems with

under-sleeping or over-sleeping) collectively form a logical group (i.e., Sleep Disturbances). This is opposite the effects indicator model that was assumed in the CFA conducted above (see Bollen & Lennox, 1991 for a discussion of these indicator models). The study aimed to create scales that defined a certain category of symptom, and sometimes this could mean bipolar items composed the same group. For this reason, traditional scale reliabilities were not computed for the four symptom groups[1].

These aggregate variables were entered as dependent variables in a series of hierarchical within-subjects regression models. The independent variables of interest were time (measured in weeks, with the rescreening representing 0 weeks) and time squared – these variables were centered to accommodate interaction terms. The inclusion of these two variables allowed for the estimation of linear and quadratic slope terms for the aggregate symptom variables. In each of our models, individual subject dummy variables (i.e., N-1 dummy coded participant variables indicating that the individual either was – coded 1 – or was not – coded 0 – a particular subject) were included in the first step to account for the lack of independence of observations (i.e., each participant has scores at 5 time points).

In the second step of the model, the time and timesquared terms were entered on their own. These can be considered the 'main effects' of time in the analysis and the changes in R^2 and F were evaluated to determine whether these effects were statistically significant. Finally, to examine whether there were differences in the linear and/or

[1] Two of the symptom clusters, Cognitive-Affective and Somatic, do not contain bipolar items and thus it is possible to compute the scale reliability values over time. Chronbach's alpha values for the Cognitive-Affective items were .69, .82, .81, .88, and .86 over the five time points, while the alpha values for Somatic were .51, .61, .68, .67, and .74 over the same time frame. It would have been possible to define a coherent scale with the other two symptom clusters by recoding some of the items so that they all evaluated the construct in one direction (i.e., a measure that ranged from over-sleep to lack of sleep). However, measuring the scale in such a manner ran counter to the goals of the study and would produce results that would not speak to the effects of treatments on the specific symptoms of depression as well as the chosen method.

quadratic terms by treatment group, 3 dummy-coded treatment variables were created (PLA-CM served as the reference group). Linear and quadratic interaction terms (6 terms in total) were entered in the third step of the model. Significant treatment-by-time interactions were examined using simple slopes analyses, which allowed for the comparison of the slope terms (both linear and quadratic) between the treatment groups.

Chapter 3

Results

Sample Characteristics

Table 1 presents the demographic and clinical characteristics of the final sample of 159 individuals used in the primary analyses. There were no statistically significant differences among treatment groups on any of these demographic and clinical characteristics, all *p*s > .08.

Table 1

Demographic and clinical characteristics of final (n = 159) sample.

		M	SD	n	%
Age		35.39	8.10		
Sex (Female)				105	66.5
Occupation	Unskilled			4	2.5
	Semi-Skilled			7	4.4
	Skilled manual workers			10	6.3
	Clerical / sales workers			62	39.2
	Administrative personnel etc			40	25.3
	Business managers, proprietors etc			25	15.8
	Higher executives, etc			10	6.3
Education	Graduate/professional training			31	19.6
	College/university graduate			38	24.1
	Partial college training			51	32.3
	High school graduate			32	20.3
	Partial high school			5	3.2
	< 7 years of schooling			1	.6
Marital Status	Single			36	22.8
	Married			56	35.4
	Living in permanent relationship			8	5.1
	Separated			23	14.6
	Divorced			33	20.9
	Widowed			2	1.3
Ethnicity	White			138	87.3
	Black			16	10.1
	Hispanic			3	1.9
	Other			1	.6
Social Position		34.91	12.16		
Initial HDRS17		19.03	4.08		
Age of First Onset		27.02	10.21		
Number of Previous Episodes		2.25	4.99		
Comorbid Diagnosis (present)				62	39.2

Note. Social Position = patient index of social position; HDRS 17 = 17-item Hamilton Depression Rating Scale

Exploratory Factor Analysis (EFA)

An EFA was conducted on the 23 items that made up the TDCRP's 23-item HDRS total score. Using Maximum Likelihood Estimation (MLE) with a Direct Oblimin rotation and setting the factor identification rule to Eigenvalues greater than 1, six factors were extracted which accounted for 43.58% of the variance in items. A scree plot of the first 13 reduced correlation matrix Eigenvalues is given in Figure 1. Based on a visual examination of the slope of the curve, the last *major* drop occurs after 3 factors are extracted, indicating that a three-factor solution might be most appropriate. However, the curve does not entirely flatten out until after 7 factors, indicating that 7 factors might be an appropriate upper limit to examine.

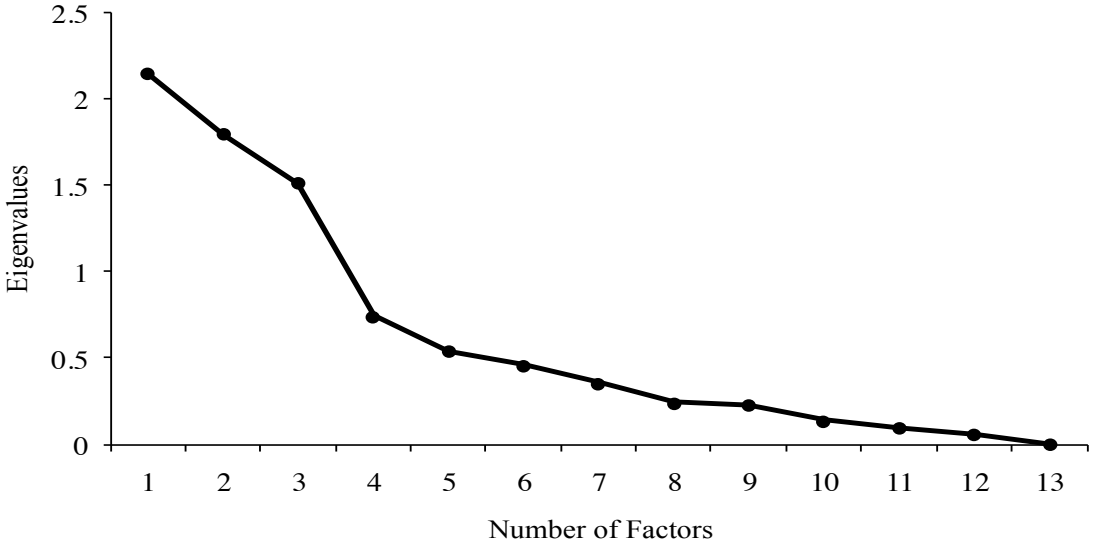

Figure 1. Scree plot using reduced correlation matrix Eigenvalues for the exploratory factor analysis on the HDRS-23 data.

Next a parallel analysis was conducted to compare the Eigenvalues from the reduced correlation matrix of the sample to the Eigenvalues that would be obtained from

completely random data. The number of random datasets to be computed was set to 100. The results of the parallel analysis are given in Table 2. The actual Eigenvalue is greater than the upper bound (95th percentile) of the completely random data up until an 8 factor solution, which again indicates that 7 factors is an appropriate upper bound for the EFA.

Table 2

Eigenvalues Obtained Using Exploratory Factor Analysis and Eigenvalues Estimated from 100 Samples of Random Data

Factor	Actual	Predicted	Upper Bound (95th %ile)
1	2.14	.69	.80
2	1.79	.59	.67
3	1.51	.51	.59
4	.74	.44	.50
5	.54	.38	.44
6	.46	.33	.38
7	.35	.28	.33
8	.24	.23	.28
9	.23	.18	.22
10	.14	.14	.18

Note. 95th %ile = Value represents the upper limit of the confidence interval

We next conducted a series of EFA runs using MLE with a Direct Oblimin[2] rotation and specifying 1, 2, 3, 4, 5, 6 and 7 factor solutions. RMSEA values with 90% confidence intervals were calculated from given chi-square values using FITMOD (Browne, 1992). RMSEA values and their associated confidence intervals are presented in Table 3 (note – the 7 factor solution was not included because it failed to converge). Based on the substantial improvement in fit between 1 and 2 factors and 2 and 3 factors, the 1 and 2 factor solutions were eliminated from consideration. The improvement in fit

[2]Given the relatively low correlations between our factors, the same series of analyses were run a second time, specifying an orthogonal (Varimax) rotation. This did not change the pattern of results in any way that would affect further analyses. These analyses are available from the author by request.

between 3 and 4 factors was much more modest and that same amount of improvement occurred on all other factor solutions considered (i.e., an improvement of about .08). The 4 factor solution was deemed the best combination of parsimony, relative fit and ease of interpretation. The 3 factor solution was rejected partly based on fit, but mostly for a high number of complex loading items and a factor that included theoretically distinct items. By the time problematic items were removed, a large amount of the symptom information (i.e., items) were lost. The 5 factor solution was rejected because it had one factor where only one item loaded heavily enough to be interpreted.

Table 3

Root Mean Squared Error of Approximation Values for Various Factor Solutions and their Confidence Intervals

Factor #	RMSEA	90% CI
1	.130	.120 - .141
2	.106	.094 - .118
3	.054	.043 - .063
4	.045	.033 - .056
5	.038	.023 - .050
6	.030	.007 - .045

Note. RMSEA = Root Mean Squared Error of Approximation; 90% CI = 90% Confidence Interval

For the purpose of minimizing unique variance and thus enhancing the power of our main analyses, only non-complex (i.e., the main loading is at least 2 times greater than any other loading) loadings of above .35 were rerun in the final EFA. In total, 7 Hamilton items were removed (Work and Activities, Retardation, Agitation, Anxiety Psychic, Genital Symptoms, Hypochondriasis and Insight), leaving 16 items.

The pattern matrix of factor loadings for the remaining items is presented in Table 4 and the associated factor correlation matrix is presented in Table 5. The final solution explained 37.70% of the variance in the included items and converged in 4 iterations. The four factors were named 'Appetite Disturbances', 'Sleep Disturbances', 'Cognitive-Affective' and 'Somatic'.

Table 4

Factor Loadings for HDRS 23 Items for the Final Four-Factor Solution Derived Using MLE with a Direct Oblimin Rotation

Item	Factor			
	Appetite Disturbances	Sleep Disturbances	Cognitive-Affective	Somatic
Increased Appetite	-.83			
Somatic Symptoms Gastrointestinal	.67			
Weight Gain	-.65			
Loss of Weight	.45			
Hypersomnia		.76		
Insomnia Middle		-.64		
Insomnia Late		-.56		
Insomnia Early		-.52		
Hopelessness			.67	
Worthlessness			.65	
Helplessness			.55	
Depressed Mood			.53	
Suicide			.41	
Feeling of Guilt			.36	
Anxiety Somatic				.68
Somatic Symptoms General				.50

Note. Factor loadings less than .30 are not shown. HDRS 23 = 23-item Hamilton Depression Rating Scale; MLE = Maximum Likelihood Estimation

Table 5

Intercorrelations Between Four Factors Derived from the HDRS-23

Factor	Appetite Disturbances	Sleep Disturbances	Cognitive-Affective	Somatic
Appetite Disturbances	----			
Sleep Disturbances	-.042	----		
Cognitive-Affective	.041	.015	----	
Somatic	.119	-.051	.064	----

Note. HDRS 23 = 23-item Hamilton Depression Rating Scale

Confirmatory Factor Analysis (CFA)

A CFA was conducted to confirm the 4 factor structure above both in the explored sample (i.e., the 250 rescreened patients) and in the final sample (159 patients). For both models, covariances amongst factors were freely estimated, as well as the unique variances associated with the manifest variables. Solutions were standardized by specifying values of 1 on the diagonal of the Phi matrix.

The factor structure was a close fit to the data in the initial rescreen sample, $\chi^2(98) = 154.74$, $p < .001$; RMSEA = .048 (90% CI: .033 - .062). An identical factor structure was specified for the final sample of 159, with the same specifications as above, and the model was actually a slightly better relative fit to the data, $\chi^2(98) = 126.81$, $p = .03$; RMSEA = .044 (90% CI: .017 - .064). The general structural model for the CFA that was used in both groups is presented in Figure 2, along with the factor loadings and factor covariances for each of the two solutions. It is clear from the diagram that the pattern and magnitude of the factor loadings is quite similar.

For both models, all the factor loadings were statistically significant (all ts < -5.68 or > 2.20, all ps < .05). For both of the models, none of the factor covariances reached statistical significance, -1.28 > ts < 1.88. All the unique variances associated with the

manifest variables reached statistical significance in both models (ts > 2.13, ps < .05), with the exception of the unique variance associated with Somatic General in the 250 patient model, $t = 1.47$, $p > .05$. Thus, it can be concluded relatively confidently that the structure of the model held equally well in both of the samples.

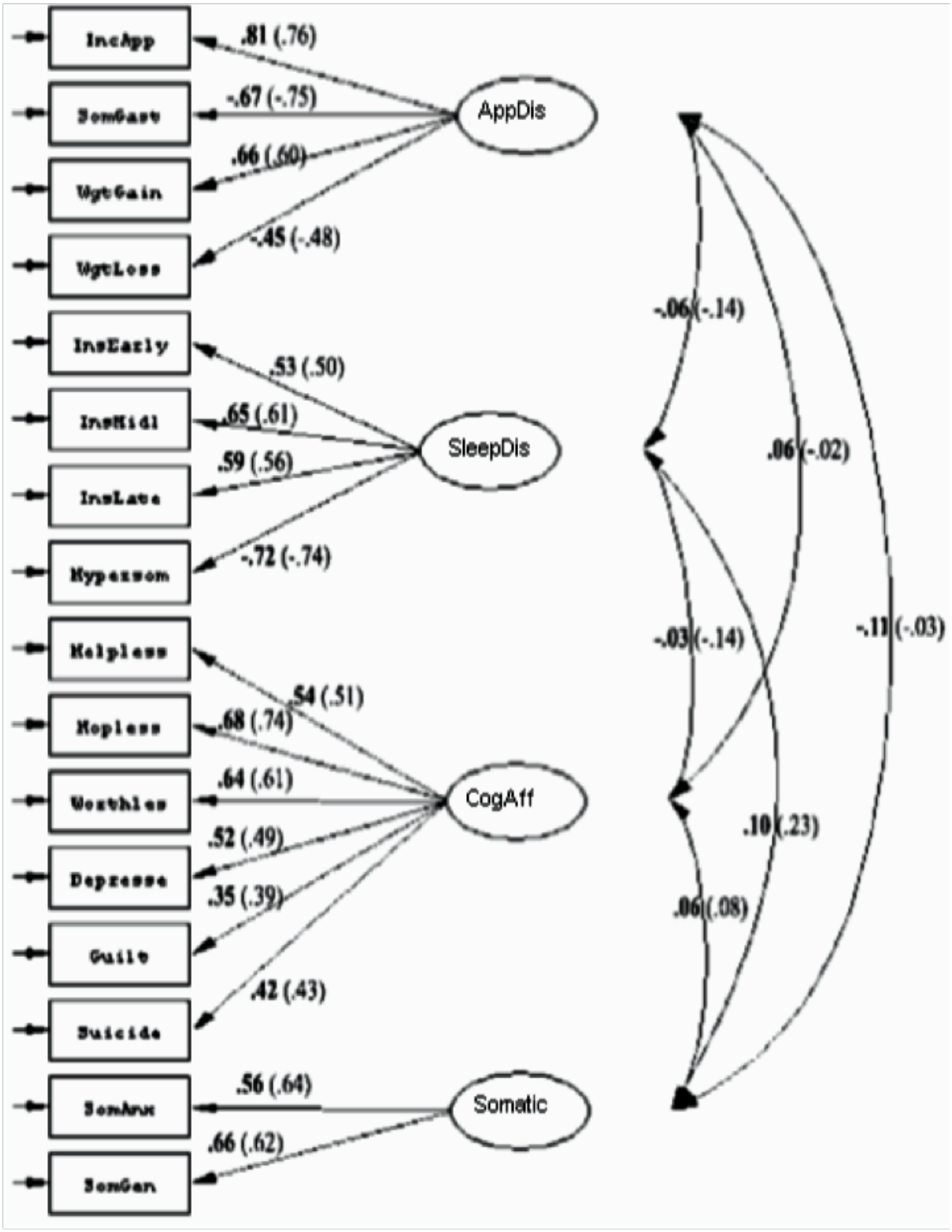

Figure 2. Structural model for CFA conducted on the rescreening (n = 250; loadings indicating in bold) and final (n = 159; loadings indicated in brackets) samples. AppDis = Appetite Disturbances. SleepDis = Sleep Disturbances. CogAff = Cognitive-Affective.

Primary Analyses

Five hierarchical regression models were specified to test the linear and quadratic main effects of time, as well as all treatment by time interactions, in predicting overall HDRS-17 scores and scores on each of the 4 symptom factors. The results of the omnibus regression analyses are presented in Table 6. As was expected, the addition of the linear and quadratic time terms to the model in the second step resulted in a significant increment in R^2 in all five of the models. Three of the models – HDRS-17, Sleep Disturbances and Somatic – also improved significantly with the addition of the treatment by time interaction terms. The interaction terms of the Cognitive-Affective factor resulted in an increment in R^2 that did not reach statistical significance, but was considered a significant trend effect (i.e., $p < .10$). Thus, follow up analyses were also conducted on the Cognitive-Affective symptom factor[3].

[3] For two of the models – Cognitive-Affective and Somatic – the results of the omnibus test using the 4 treatment groups did not reach statistical significance but were at a trend level (i.e., *p*s ~ .10). The analyses were redone collapsing the two psychotherapy groups as this did not change the hypotheses and increased power. The results of those models are presented here, and the results using all treatment groups are available from the author.

Table 6

Omnibus Results for Regression Models for the overall HDRS-17 Scores, and Scores on the 4 Symptom Factors.

	Model R^2	Δ R^2	Δ *F*	df 1	df 2	*P* (Δ F)
Model 1: HDRS-17						
Step 1: Individual Level	.356	.356	2.23	158	636	< .001
Step 2: Main Effects	.678	.321	316.07	2	634	< .001
Step 3: Interaction Terms	.691	.013	4.37	6	628	< .001
Model 2: Appetite Disturbances						
Step 1: Individual Level	.328	.328	1.97	158	636	< .001
Step 2: Main Effects	.425	.097	53.36	2	634	< .001
Step 3: Interaction Terms	.428	.003	.479	6	628	.825
Model 3: Sleep Disturbances						
Step 1: Individual Level	.373	.373	2.39	158	636	< .001
Step 2: Main Effects	.537	.165	112.33	2	634	< .001
Step 3: Interaction Terms	.552	.015	3.56	6	628	.002
Model 4: Cognitive Affective						
Step 1: Individual Level	.426	.426	2.99	158	636	< .001
Step 2: Main Effects	.697	.271	283.54	2	634	< .001
Step 3: Interaction Terms	.701	.004	2.07	4	630	.083
Model 5: Somatic						
Step 1: Individual Level	.377	.377	2.43	158	636	< .001
Step 2: Main Effects	.463	.086	51.06	2	634	< .001
Step 3: Interaction Terms	.472	.009	2.71	4	630	.030

Note. 'Individual Level' represents all dummy-coded participant variables alone. 'Main Effects' indicates the addition of Time and Time Squared. 'Interaction Terms' indicates the addition of all time by treatment interactions and all time squared by treatment interactions

The slope characteristics for the second step of each model are presented in Table 7. For all five models, both terms are significant within the step of the model, and the general pattern is for a large negative linear term and a relatively smaller, positive, quadratic term. This generally described a curve that has a relatively rapid descent earlier on in time but becomes flatter at later time points.

Table 7

Slope Characteristics for Linear and Quadratic Terms within the Second Step of the Omnibus Models

	B	SE	*t*	*p*
Model 1: HDRS-17				
Step 2: Centered Time	-1.11	.081	-13.74	< .001
Centered Time Squared	.027	.004	6.53	< .001
Model 2: Appetite Disturbances				
Step 2: Centered Time	-.111	.018	-6.20	< .001
Centered Time Squared	.003	.001	3.33	.001
Model 3: Sleep Disturbances				
Step 2: Centered Time	-.201	.023	-8.57	< .001
Centered Time Squared	.005	.001	4.32	< .001
Model 4: Cognitive Affective				
Step 1: Centered Time	-.672	.049	-13.65	< .001
Centered Time Squared	.018	.003	6.91	< .001
Model 5: Somatic				
Step 1: Centered Time	-.119	.021	-5.71	< .001
Centered Time Squared	.003	.001	2.84	.005

Note. B = Beta (slope); SE = Standard Error associated with slope; *t* = *t*-value associated with slope

Follow Up Analyses

For each of the models (excluding the Appetite Disturbances factor), simple slopes values were computed by conducting regression analyses separately for each treatment group. In these analyses, dummy coded participant variables, linear and quadratic terms were entered simultaneous to predict the four different outcome variables. The values for each of these slope terms are presented in Table 8.

Table 8.

Values for Linear and Quadratic Terms, by Treatment Group, for the HDRS-17 and the three Symptom Clusters

	CBT	IPT	IMI-CM	PLA-CM	Therapy
HDRS-17					
Linear	-.746 (.158)	-.943 (.136)	-1.681 (.175)	-1.191 (.177)	
Quadratic	.006 (.008)	.019 (.007)	.054 (.009)	.038 (.010)	
Sleep					
Linear	-.058 (.048)	-.177 (.040)	-.319 (.052)	-.281 (.047)	
Quadratic	-.003 (.002)	.004 (.002)	.011 (.003)	.010 (.003)	
Cog-Aff					
Linear			-.890 (.100)	-.697 (.111)	-.581 (.066)
Quadratic			.029 (.005)	.021 (.006)	.012 (.003)
Somatic					
Linear			-.226 (.045)	-.109 (.047)	-.082 (.027)
Quadratic			.008 (.002)	.004 (.003)	.001 (.001)

Note. Values represent Beta (slope) associated with each treatment and the standard error of the slope in brackets. HDRS-17 = 17-item Hamilton Depression Rating Scale. Cog-Aff = Cognitive-Affective. Sleep = Sleep Disturbances

Pairwise differences between slopes were analyzed using a test of differences between coefficients from independent samples (Cohen & Cohen, 1983), an equation that yields a t-value with N-4 degrees of freedom. Within each dependent variable, the p-value required for statistically significance was determined using a Bonferroni correction. Thus, $p < .0083$ was considered statistically significant for the HDRS-17 and Sleep calculations, while $p < .0125$ was considered significant for the Cognitive-Affective and Somatic calculations.

HDRS-17. A visual depiction of the overall HDRS-17 trends by treatment group is presented in Figure 3 (for a plot of actual HDRS-17 means, see Appendix B). This was produced by entering the non-centered linear and quadratic time variables as predictors of

the HDRS-17 symptom scores alone for each treatment group, and then substituting the mean time and time squared values into the regression equation to produce mean values for each of the five time points in the study (the same procedure will be used below for the four symptom clusters).

It is evident from the figure that the significantly greater magnitude of the linear trend in the IMI-CM group incurs an advantage over the two psychotherapies through the first two time points. However, the effect of the quadratic term is to reduce the rate of change of the medication group with time (both IMI-CM and PLA-CM show a flattening of the curve) while the psychotherapies continue to improve in the later weeks (at the fourth and fifth measurement points) . The CBT group, especially, displayed a nearly completely linear trajectory.

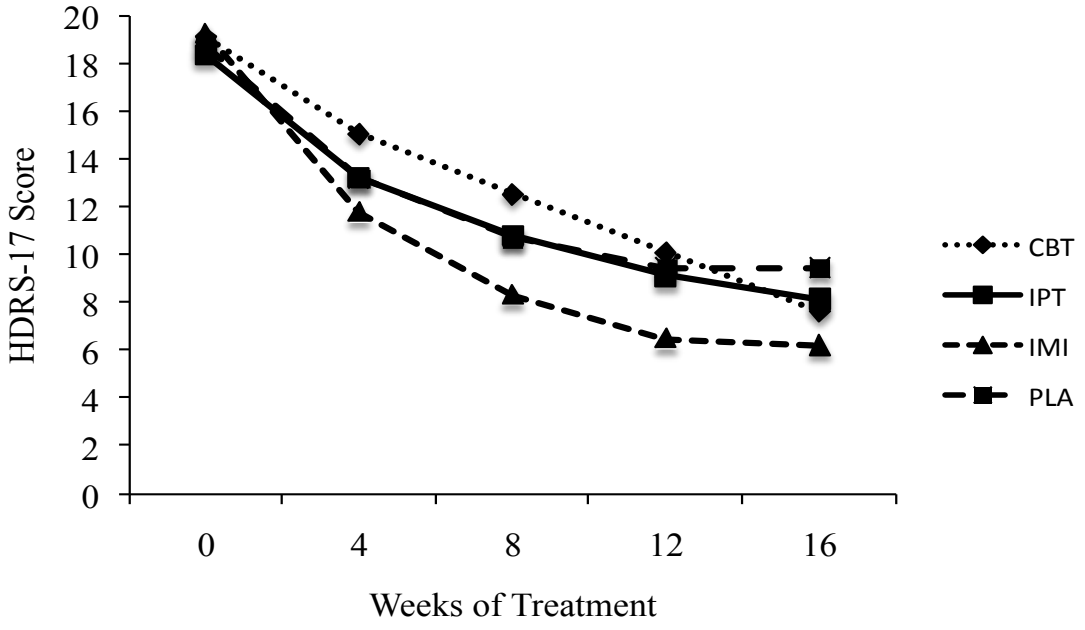

Figure 3. Plot of total HDRS-17 scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI = Imipramine plus clinical management. PLA = Placebo plus clinical management.

For the overall HDRS-17 score, the magnitude of the negative slope for both CBT and IPT was significant smaller than that of IMI-CM, $t(376) = 3.97$, $p < .001$, $d = .41$ and $t(416) = 3.33$, $p < .001$, $d = .33$ respectively. There were no other significant differences in any of the pairwise comparisons of the linear terms (all ps > .049).

For the quadratic terms, the magnitude of the IMI-CM positive term was significantly larger than both the CBT and IPT quadratic terms, $t(376) = 3.99$, $p < .001$, $d = .41$ and $t(416) = 3.07$, $p = .002$, $d = .30$. Additionally, the CBT quadratic term was smaller than the PLA-CM term at a trend level of statistical significance, $t(371) = 2.50$, $p = .013$, $d = .26$. There were no other significant differences in any of the pairwise comparisons of the quadratic terms for the HDRS-17 total (all ps > .12).

Sleep Disturbances. As is clear in Figure 4 (for a plot of actual Sleep Disturbances means, see Appendix C), IMI-CM, PLA-CM and IPT all show very similar trajectories for the Sleep cluster in the first 12 weeks (i.e., rapid early reduction in symptoms followed by more modest reductions after week 8). The strong positive quadratic term in IMI-CM and PLA-CM leads to a trend towards *increasing* symptom scores between week 12 and week 16. The negative quadratic term for Sleep symptoms in CBT causes a greater rate of improvement to occur *later* on in treatment as opposed to earlier – the reverse of every single other quadratic term under study. Thus, the CBT group experiences substantially less reduction in Sleep symptoms earlier on in treatment but achieves reduction of symptoms that is nearly identical to the other treatments by week 16.

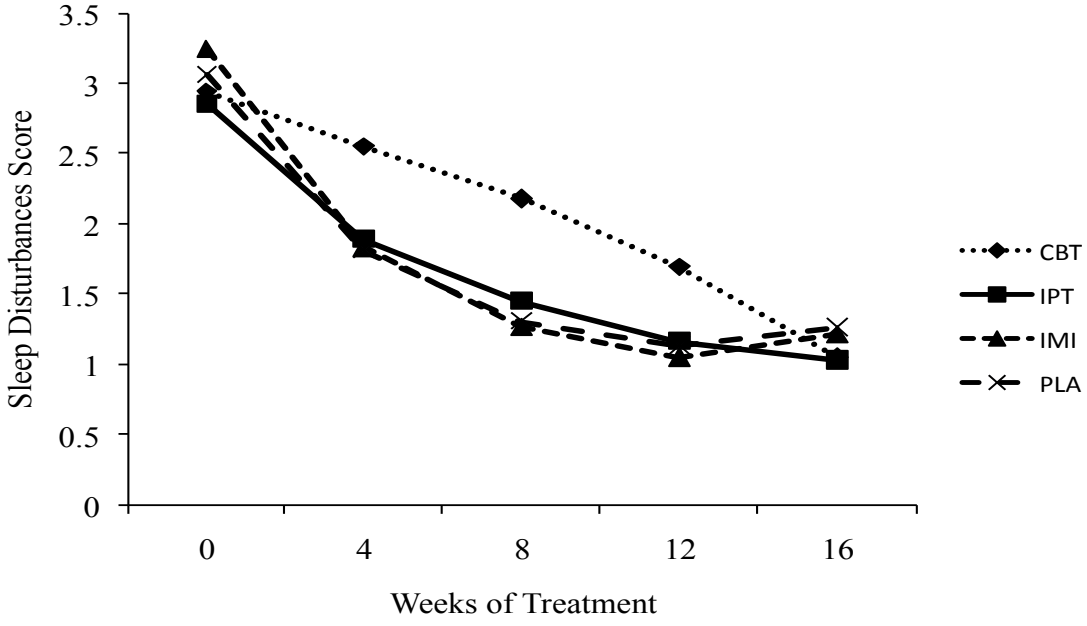

Figure 4. Plot of Sleep Disturbances scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI = Imipramine plus clinical management. PLA = Placebo plus clinical management.

In this factor, the magnitude of the negative slope for IMI-CM *and* PLA-CM were both significantly larger than that of CBT, $t(376) = 3.67$, $p < .001$, $d = .38$ and $t(371) = 3.32$, $p < .001$, $d = .34$, respectively. Additionally, IMI-CM showed a larger magnitude of negative slope than IPT that was significant at a trend level, $t(416) = 2.16$, $p = .031$, $d = .21$. There were no other significant differences in any of the pairwise comparisons of the linear terms (all ps > .057).

For the quadratic terms, the magnitude of the positive acceleration for IMI-CM and PLA-CM were both significantly larger than that of CBT, which actually had a *negative* quadratic term (see Table 8), $t(376) = 3.88$, $p < .001$, $d = .40$ and $t(371) = 3.60$, $p < .001$, $d = .37$, respectively. IPT also had a positive quadratic term of greater magnitude than CBT, and this was significant at a statistical trend, $t(416) = 2.47$, $p = .014$, $d = .24$. There were no other significant differences in any of the pairwise comparisons of the quadratic terms for the Sleep cluster (all ps > .053).

Cognitive-Affective. Figure 5 (for a plot of actual Cognitive-Affective means, see Appendix D) demonstrates that the combined therapy group has a nearly identical trajectory to the PLA-CM group when it comes to the remission of the Cognitive-Affective Symptom cluster. This is consistent with the fact that no significant differences were found between the treatments on either the linear or quadratic terms. Cognitive-Affective symptoms improve most rapidly in the IMI-CM group at the beginning of treatment, and flatten out more than Therapy by the end. However, these differences are modest, and the overall significance of the interaction is only significant at a trend level.

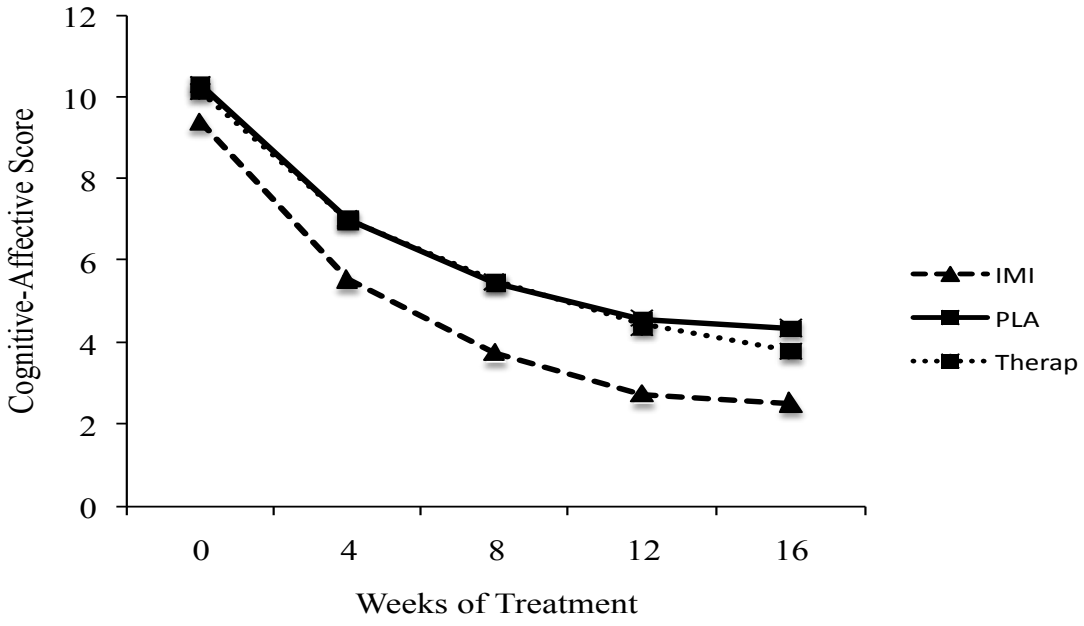

Figure 5. Plot of Cognitive-Affective scores over the 16 week treatment period by treatment group. Therap = Combined therapy group. IMI = Imipramine plus clinical management. PLA = Placebo plus clinical management.

For the Cognitive-Affective cluster, the magnitude of the negative linear slope for IMI-CM was significantly larger than that of the combined therapy group, $t(606) = 2.56$, $p = .010$, $d = .21$. There were no significant differences between therapy and PLA-CM, or between IMI-CM and PLA-CM (all *p*s > .197).

For the quadratic terms, the magnitude of positive acceleration for IMI-CM was significantly larger than that of the combined therapy group, $t(606) = 2.92$, $p = .004$, $d = .24$. There were no significant differences between therapy and PLA-CM, or between IMI-CM and PLA-CM (all *p*s > .180).

Somatic. Figure 6 (for a plot of actual Somatic means, see Appendix E) shows that the combined therapy group has a nearly completely linear pattern of symptom remission for the Somatic cluster. This is in stark contrast to the IMI-CM, where there is rapid remission in symptoms over the first 8 weeks of treatment, followed by a flattening

between week 8 and 12, then a slight increase in symptoms in the last 4 weeks. The absence of a strong linear term in the PLA-CM group creates a relatively flat profile of remission.

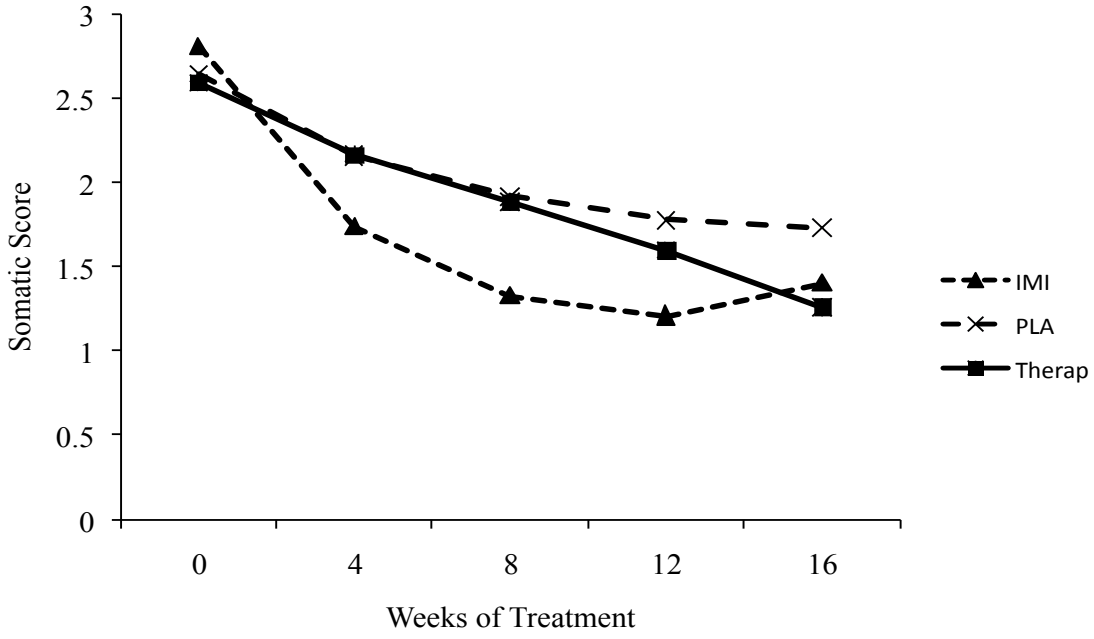

Figure 6. Plot of Somatic scores over the 16 week treatment period by treatment group. Therap = Combined therapy group. IMI = Imipramine plus clinical management. PLA = Placebo plus clinical management.

For the Somatic cluster, the magnitude of the negative linear slope for IMI-CM was significantly larger than that of the combined therapy group, $t(606) = 2.74$, $p = .006$, $d = .22$. There were no significant differences between therapy and PLA-CM, or between IMI-CM and PLA-CM (all ps > .073).

For the quadratic terms, the magnitude of the positive acceleration for IMI-CM was significantly larger than that of the combined therapy group, $t(606) = 3.13$, $p = .002$, $d = .25$. There were no significant differences between therapy and PLA-CM, or between IMI-CM and PLA-CM (all ps > .267).

Chapter 4

Discussion

The present study set out to investigate a question that has yet to receive thorough attention in the literature on MDD: do specific groups of symptoms (e.g., sleep disturbances, cognitive-affective symptoms) respond at differential rates depending on the treatment the individual receives? This question is of crucial importance to our understanding of the differential theoretical mechanisms that underlie efficacious treatments for MDD, and emerging evidence that certain symptoms of the disorder may be preferentially related to clinical variables such as severity, course and mortality risk.

Our results show that, overall, at the syndrome level and for specific symptom clusters, treatment with IMI-CM results in more rapid remission rates compared to psychotherapy and PLA-CM. For all outcome measures, the active medication group experienced substantial decline in symptoms up to week 8 followed by a relatively flatter pattern for the remainder of treatment. In contrast, psychotherapy (and particularly, CBT), usually produced a more gradual pattern of remission that continued over the entire treatment period.

This general pattern of results has been documented in previous literature examining treatment of the overall depression syndrome (i.e., HDRS-17 scores). Using TDCRP completers, one group of researchers found that the most rapid changes in depressive symptoms occurred in IMI-CM and that this treatment achieved significantly greater results than the other treatments at week 8 and week 12, along with non-significantly different results at completion (Watkins, et al., 1993). More recent research

has also replicated this pattern. For instance, a study on individuals with chronic MDD showed more rapid remission in HDRS-17 scores in a group receiving nefazadone compared to a group receiving a form of cognitive therapy after up to 8 weeks of treatment (Keller et al., 2000). A more pronounced negative linear slope in an antidepressant medication group compared to a group receiving cognitive therapy was also found in another study, but only for a high severity subset of the overall sample (Dimidjian, Hollon, Dobson, Schmaling, Kohlenberg, Addis, et al., 2006). When considering time to remission (defined as minimal or no symptoms of depression, often HDRS-17 scores of less than or equal to 6), pharmacotherapy typically achieves remission between 4 and 12 weeks of treatment, while psychotherapy is slower, achieving remission between 6 and 10 weeks of treatment (Rush et al., 2006).

Our analyses on the overall depression syndrome extend previous research by explicitly examining both the linear and quadratic time terms of the HDRS-17. To our knowledge, only Keller and colleagues (2000) have reported and tested slope terms of depression symptoms, although they did not test the quadratic shape of the data. Our analyses characterize the shape of the data in a more fine-grained manner – specifically, IMI-CM has a stronger downward linear effect than psychotherapy and a strong quadratic effect that produces early acceleration and the flattening at later time points, while psychotherapy has a smaller downward linear slope, but also a smaller, flattening quadratic term. Our analysis also benefits from treating time as a continuous variable measured in weeks, which differs from previous repeated measures approaches (e.g., Watkins et al., 1993), which assume that the time in weeks between assessments is the same for each individual.

The present study also extends previous research by examining the time course of remission of not only the overall depression syndrome, but also of specific symptom factors within the syndrome. The temporal advantage of IMI-CM over psychotherapy in the Sleep Disturbances and Somatic symptom factors is consistent with our hypotheses. For Sleep Disturbances, we found a more rapid rate of remission in the early weeks (i.e., a more substantial negative linear term) in the IMI-CM group compared to the CBT group, but not the IPT group. Remission in CBT was relatively gradual over the first 8 weeks and became more rapid for the second half of treatment. For the Somatic factor, remission occurred more rapidly in the early weeks then plateaued after week 8 for IMI-CM, while psychotherapy exhibited a much more linear, steady remission rate for the factor. The early improvements on Sleep Disturbances found in the IMI-CM group are consistent with literature showing the relatively immediate action of medications on subcortical areas involved in the regulation of autonomic processes, such as sleep (a "bottom up" process; see Derryberry & Tucker, 1992).

In contrast to our hypotheses, however, our results showed that the same pattern as above held for Cognitive-Affective symptoms, which we hypothesized would be more strongly affected by psychotherapeutic treatments with a "top-down" neural mechanism (Derryberry & Tucker, 1992). Instead, IMI-CM had a significantly stronger negative linear trend than the combined psychotherapy group, coupled with a significantly larger positive quadratic trend, leading to rapid improvement in the early weeks followed by a flattening of improvement later on. We expected that CBT, in particular, might act on cognitive symptoms (e.g., worthlessness) rapidly in the early stages of treatment because of the explicit attention paid to negative automatic thoughts and dysfunctional attitudes

that, presumably, directly underlie the cognitive symptoms of depression. However, were not able to test differences between the psychotherapy groups due to the need to collapse across these groups to increase power in our omnibus analysis.

It is unclear from the present results *why* psychotherapy worked more slowly than IMI-CM across symptoms. One possibility is that the actual implementation of the "active ingredients" in psychotherapy does not occur until later sessions. Specifically, in CBT the first several sessions are spent in educating the client about the cognitive model and introducing them to the techniques of treatment (e.g., thought records). The actual implementation of these techniques to achieve cognitive and behavioural change does not occur until after this first phase of treatment. Similarly, IPT devotes early sessions to providing information to the client about their disorder within a medical model, and to leading the patient to an acceptance of the "sick role". Early sessions are also spent identifying the interpersonal target of the interventions that are to come later on. The initial acclimatization stage of IPT is not as long as for CBT, which might account for our findings for the overall HDRS-17 showing findings for IPT on the Sleep Disturbances symptom cluster that were closer to IMI-CM.

In contrast, anti-depressant medications work on brain chemistry immediately and it is generally accepted that they begin to show effects above placebo by the third week of treatment (Quitkin et al., 1987; Quitkin, Rabkin, Ross, & Stewart, 1984). Indeed, a recent meta-analysis found no evidence for a delayed antidepressant effect, concluding that many patients demonstrate a true effect within the first 1 to 2 weeks of treatment (Posternak & Zimmerman, 2005). Regardless of the exact timing of antidepressant effect,

it is clear that antidepressant medications take their effect much more rapidly than current psychotherapeutic interventions.

As such, the present results suggest a problem with RCTs that measure the effects of psychotherapies and medications concurrently. That is, if medications are expected to work within 8 weeks, but psychotherapies are not expected to have their full effect until 16 weeks, this makes comparison of these two treatments head-to-head somewhat artificial. Indeed, when antidepressant medications are tested for efficacy in clinical trials in the absence of psychotherapy, the trials are usually no more than 8 weeks, and can sometimes be as short as 4 weeks. As such, anything after 8 weeks in the medication condition is better conceptualized as 'continuation' or 'maintenance' treatment, as the acute effects have already been seen and one would not expect to see any further improvements.

For many of the primary analyses, the trends suggested that IMI-CM and PLA-CM no longer appear to be producing improvement symptoms of depression for the sample, while, in many cases, the psychotherapy conditions appear as though they would continue to produce improvement were the acute phase treatment period to be extended. It is possible that the "active ingredients" to psychotherapy would continue to lead to individuals remitting past the 16 week cut-off. However, extending time in psychotherapy would no doubt lead to diminishing returns – there would be fewer and fewer individuals achieving remission for the weeks of treatment added. Extending the acute phase for psychotherapy also runs counter to the time-limited nature of these psychotherapies – the "real world" practitioner would try an alternative approach to treatment were he or she unable to see substantial improvement in a client by the end of 16 weeks of therapy.

Nonetheless, the end of the acute phase of treatment in most RCTs to date may not lend full justice to psychotherapeutic interventions.

The unexpected advantage of IMI-CM over psychotherapy in the rate of remission for Cognitive-Affective symptoms should also be considered in light of some of the methodological characteristics of the current study. The HDRS only contains three cognitive items that are relevant to MDD (i.e., hopelessness, helplessness, and worthlessness) and these are the symptoms upon which our hypotheses were based. However, our cognitive-affective factor was comprised of several additional symptoms (e.g., depressed mood, guilt, etc.). It is possible that psychotherapy does not work selectively more rapidly on these 'affective' symptoms (although some early studies found that this does occur; DiMascio et al., 1979). Indeed, guilt is a symptom of the melancholic / endogenous subtype of MDD, which has been shown to be more efficaciously treated with pharmacological approaches (Parker et al., 1996). Some diagnostic (i.e., concentration difficulties, indecisiveness) and non-diagnostic (e.g., pessimism, self-criticalness, feelings of being punished) cognitive symptoms are not assessed by the HDRS. Therefore, hypotheses related to the rate of symptom remission across therapeutic modalities of the cognitive symptoms of MDD may be better testing using other depression measures that present a broader and more representative array of these symptoms (e.g., the BDI; Beck et al., 1961).

It is also important to note IMI-CM was not a 'drug-only' condition as it involved "clinical management". The TDCRP included manualized guidelines for the psychiatrists who were administering medications for how to support and encourage clients in the IMI-CM and PLA-CM groups. Clinicians were trained not only to maximize the participants'

medication compliance, but also to help them deal with set backs in general (i.e., support) and to motivate them. Thus, the IMI-CM may be thought of as a combined medication/supportive psychotherapy group that is capitalizing on some of the nonspecific factors psychotherapy (i.e., client-therapist rapport, source of social support, unconditional positive regard). Therefore, it is possible that the CM component of the active medication group is contributing the temporal advantage of this condition over psychotherapy.

The inclusion of the clinical management condition in the imipramine and placebo conditions brings up the issue of generalizability of the findings. The CM component stipulates that the pharmacotherapist spend approximately 20 minutes with the patient reviewing their status and providing them general support in the event of setbacks. This may be slightly different than what occurs in naturalistic settings. Although responsible psychiatrists spend up to 15 minutes with patients reviewing medication side-effect and compliance issues and tracking symptoms, they are not explicitly trained in the effective ways of delivering support and encouragement to their patients. Furthermore, a large portion of antidepressant medications are prescribed by general practitioners who may not be as diligent as physicians with explicit mental health training, which might further reduce the amount of "face time" patients receive. It would be important in future research to determine whether the effects seen here generalize to treatment with medications in naturalistic settings such as hospitals and outpatient clinics.

As potential support for the above suggestion, research has investigated differences across the treatment conditions in the TDCRP on the relation of therapeutic alliance (i.e., the bond between the therapist and patient) to overall symptom outcomes at

the end of treatment. The researchers reviewed videotaped sessions from the study and scored these sessions using a measure of therapeutic alliance. They found that all four conditions, including PLA-CM, did not differ in terms of therapeutic alliance and that the amount of therapeutic alliance was uniformly high. Patient therapeutic alliance accounted for 21% of the variance in final HDRS-17 scores in their regression models (Krupnik et al., 1996). One would not expect therapeutic alliance to be equally strong in all groups given that therapists conducting CBT and IPT are specifically instructed to foster these factors. These results suggest that IMI-CM may be better seen as a combined treatment, thus potentially giving it an unfair advantage over IPT and CBT that may not exist in other studies, and that is unlikely to correspond to naturalistic conditions.

Our results did not show any significant treatment by time interactions for Appetite Disturbances. One reason for the lack of significant findings may have been that, compared to other symptom clusters, participants did not report severe appetite symptoms. The mean for the sample on the Appetite Disturbance symptom cluster at intake was 1.70, and 88% of the sample scored 3 or less at this time (50.3% scored a 1 or 0). Thus, there was little room for improvement over 16 weeks of treatment on this factor, which may have contributed to the lack of a significant interaction effect amongst the treatment groups. The low mean may be a product of the bipolarity of the group of items – the appetite symptoms essentially measure disturbances of eating in the upward and downward direction. Barring irresponsible clinician ratings, it is not possible to score high on both increases and decreases of appetite. Thus the effective range of the symptom factor was 4 as opposed to 8.

There is also evidence to suggest that weight / appetite items may not be as useful as other items when defining a coherent dimension of depression liability. One group of researchers used two parameter logistic item response models and compared these to a binary diagnosis of MDD to determine how the diagnostic criteria performed. The analysis revealed that the weight / appetite criterion in the MDD diagnostic criteria showed the poorest discrimination, the greatest misfit and was the least useful in defining a coherent dimension of liability out of all the criteria (Aggen, Neale, & Kendler, 2005). For the purposes of this study, the Appetite Disturbances group of symptoms may be the least clinically relevant of the four empirically derived factors when it comes to its response to treatments.

One final finding worthy of mention in our data was the efficacy of PLA-CM compared to the active treatments, whether it was in the overall HDRS or the separate symptom factors. Only one of the PLA-CM versus active treatment differences in our study was statistically significant (PLA-CM versus CBT in the Sleep Disturbances factor) and this was to the advantage of PLA-CM. The response pattern of PLA-CM is very close to that of IMI-CM in all of our outcome measures, and there were no statistically significant differences. The parity of overall effect is consistent with literature that that finds modest effect sizes (.50 on average) of pharmacological treatments over placebo in producing overall response in outpatients with MDD (see Hollon, Thase, & Markowitz, 2002).

Implications

This study tested hypotheses derived from the theoretical mechanisms of action for treatments of MDD. Contrary to our predictions, the data displayed an overall speed of remission rate advantage of IMI-CM over psychotherapy regardless of the outcome measure examined. In particular, across all symptoms, IMI-CM achieved the bulk of its remission by week 8, whereas the time course of remission in the psychotherapies was more gradual, catching up by week 16. There are a number of implications of these results for the treatment of MDD.

First, our results may point to a need to develop shorter psychotherapeutic interventions, and contribute to a growing consensus that psychotherapeutic interventions need to be distilled into their most salient active ingredients. When it comes to treating patients in "the real world", 16 sessions of CBT is a luxury that the vast majority of individuals cannot afford. Furthermore, results indicate that 16 sessions of psychotherapy is a standard that is largely reserved for RCTs. In a large sample of individuals receiving psychotherapy for MDD, the mean number of sessions attended was 8.7 (Olfson et al., 2002). Furthermore, in another study, 76.2% of individuals who visited a psychiatrist for mental health services only attended between 2 and 4 sessions (Wang et al., 2005). The median number of psychotherapy sessions reported across mental health conditions has traditionally been between 4 and 8 sessions (e.g., Olfson & Pincus, 1994).

Shortening psychotherapeutic interventions may give practitioners more impact for their time – one study found that the progression toward more positive sessions (i.e., session depth and smoothness, relationship with the therapist, feelings of understanding

and problem solving, post-session positive mood) was more rapid in an 8-session cognitive therapy versus a 16-session cognitive therapy (Reynolds et al., 1996). A naturalistic pilot study of brief (8 week) IPT found that a group of depressed women receiving the psychotherapy improved more rapidly than a group receiving an antidepressant medication for the same period (Swartz et al., 2004).

Achieving distilled versions of psychotherapies depends upon the identification of the components of therapies that are most responsible for bringing about change (the "active ingredients"). One example of a potential active ingredient that has received research attention is behavioural activation (BA). An initial study by Neil Jacobson and his colleagues isolated a BA component in CBT to determine whether simply encouraging people to make contact with potentially reinforcing experiences could account for the treatment effects of CBT. The BA component was equally efficacious as the full CBT protocol at the termination of acute treatment and at 6-month follow-up, and was also equally effective at altering negative thinking and dysfunctional attributional styles (Jacobson et al., 1996). Subsequent studies of BA have also demonstrated equal efficacy of BA and antidepressant medications in the treatment of outpatient MDD (Dimidjian et al., 2006). It is noteworthy that in the TDCRP patients would not have received a BA component in the CBT condition until week 12.

Achieving a more condensed, faster-acting psychotherapeutic intervention may impact the treatment-seeking trends of depressed individuals. For example, research has shown that depressed patients' treatment-seeking is driven primarily by sleep disturbance (Tsuno et al., 2005) and this study clearly illustrates the more rapid relief of this key cluster of symptoms for IMI-CM compared to psychotherapy (specifically, CBT). Indeed,

in Canada, a large percentage of individuals who seek treatment for depression receive medications (Patten & Beck, 2004) and this may at least partially be due to the fact that they bring about relatively rapid relief of sleep disturbance. This immediate gratification effect may propagate a bias toward medication use despite evidence for the equal effectiveness of psychotherapeutic interventions for MDD in the long run.

Our results point to the a need to further delineate and understand the precise mechanisms of action of our gold-standard treatments for MDD. Experts in the area typically concede that we are far from achieving a full understanding of the actions of antidepressant medications on neurobiology (e.g., Garcia, 2002) and some continue to contend that antidepressant medications do not have any true pharmacological effects (i.e., real advantages over placebo; Kirsch et al., 2002). Similarly with CBT, there continues to be debates over what exactly the necessary ingredients are for effective administration of the treatment. Of particular relevance to the current study is the role that the behavioural activation component of CBT (e.g., behavioural experiments, action plans, etc) plays and the fact that is may be equally effective as the entire protocol (Jacobson, et al., 1996). The role of nonspecific factors (e.g., emotionally charged, confiding therapeutic relationship, a rationale to explain patients symptoms, an organized treatment procedure, etc.) may be particularly important for symptom relief in the early stages of psychotherapy (Ilardi & Craighead, 1994) and these have yet to be described in such a way that meaningful predictions may be made about their impact on specific symptoms of depression.

Given that PLA-CM has a similar time course to IMI-CM (at least over the first 12 weeks of acute treatment), it brings into question the actual clinical utility of placebo

treatments. Research has shown that placebo treatments for MDD can be quite powerful – for instance, one group of researchers conducted a meta-analysis of *all* trials for antidepressant medications submitted to the FDA (which included published and unpublished data) and found that 82% of response to antidepressant medications was duplicated by placebo (Kirsch et al., 2002). Furthermore, there is growing evidence of anatomically concordant metabolic changes associated with treatment response to antidepressant medications and placebo (see Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005 for a review). Clearly then, the *expectation* of improvement is a therapeutic tool that warrants careful study, both for pharmacological and psychotherapeutic interventions.

Finally, our results raise some interesting questions about the time courses of symptom factors in aspects of treatment that were not under study. Specifically, our results do not pertain to the maintenance of remission and/or recurrence over periods following efficacious acute-phase treatments. There is well-documented evidence that indicates that treatment with psychotherapy results in lower rates of relapse in long-term follow-up periods (Dobson et al., 2008; Evans, et al., 1992; Kovacs, et al., 1981; Shea, et al., 1992; Simons et al., 1986). However, it is yet unclear whether the re-emergence of different symptom factors is associated with differential acute treatments. A systematic investigation of symptom specificity for those who relapse during follow-up periods may shed light upon the mechanisms behind the efficacy of continuation and sequential treatments for MDD.

Limitations and Future Directions

The current study has several key strengths, which include a strong theoretical foundation, a rigorous statistical approach, especially when it came to determining the factor structure of the data and the use of time in treatment as a continuous variable in weeks, and the contribution of a relatively novel approach to the study of the treatments for MDD. Nonetheless, the results of this study need to be taken in the context of the limitations below.

First, there are several limitations that are inherent to the TDCRP dataset that warrant consideration. One issue is that HDRS symptoms were not rated by the clinical evaluator immediately before the commencement of treatment, and thus, data from rescreening were used. Rescreening occurred an average of approximately 2 weeks before most participants began treatment. Although overall rescreening HDRS-17 scores (rated by the clinical evaluator) did not differ from scores measured after the first session of treatment by the treating clinician in any of the treatment groups (all ps > .05), the magnitude of the slope between the beginning of treatment and the week 4 assessment is not properly estimated. It is possible that the initial decline between the beginning of treatment and the first assessment is actually steeper than we estimated. In this case, we nonetheless opted to use the clinical evaluator data as the issue above was not deemed important enough to put the unbiased nature of symptom assessment into question.

The TDCRP dataset also represents an outlier in the CBT treatment literature in terms of how poorly it worked overall for treating depression. This is most clear when considering an earlier controversy where the results from the TDCRP initially seemed to

indicate that CBT was no better than PLA-CM for the treatment of more severely depressed outpatients (Elkin et al., 1989). However, this finding was later debunked through an examination of other studies of CBT and antidepressant medications from around the same time, where two out of the three (Hollon et al, 1992; Rush, Beck, Kovacs, & Hollon, 1977) reported a slight advantage in CBT for treating severe depression and the other (Murphy et al., 1984) showed no difference between the two (DeRubeis, Gelfand, Tang, & Simons, 1999). Since the TDCRP, it has generally been accepted that the CBT condition was not administered in an optimal fashion.

The information above makes some of our findings difficult to interpret. Specifically, it is hard to know whether the differences seen between CBT and IMI-CM on the Sleep Factor, for instance, were due to core differences in the mechanisms of the two treatments or due to the relatively poor execution in the CBT group. The fact that each pharmacotherapy condition also came with a "mini-supportive therapy" further clouds the issue in a similar fashion – as discussed above, this is particularly relevant when considering the advantage of IMI-CM over psychotherapy. Future research would benefit from working with "purer" forms of each treatment (i.e., no clinical management augmentation in the case of medications) and more modern datasets or newly collected treatment data – the fact that CBT and IPT were relatively new treatment options also contributes to the risk that they, and CBT in particular, were not operating the way in which they are known to currently.

The current study was also limited by the relatively small number of symptom items that were under study, and the lack of inclusion of some of the core symptoms of depression (e.g., anhedonia, psychomotor disturbances) within the symptom groups. We

chose to focus on empirically-derived symptom groups for the purposes of the current project, but the result was that many items did not load significantly within the factor structure and were thus not part of the analyses. Were these items to be included in meaningful way within factor groupings, there may be a different pattern of results across the different treatments.

One possibility for future research might be to move away from only including items that work within an empirically derived factor structure and instead use theoretically-motivated symptom groupings. One possibility might be to group all the diagnostic symptoms corresponding to depression subtypes (e.g., melancholic, atypical) and determine whether different treatments act on these symptom groups. Another possibility might be to compute an aggregate score for all of the somatic items (this would include symptoms that weren't included such as Genital Symptoms and Hypochondriasis) and examine these based on the same set of hypotheses. Using theoretically derived symptom groupings may afford some advantage over the factor approach as scales would likely include more item (increased reliability) and may be more readily interpretable (especially in the case of using symptoms that correspond to different subtypes of the disorder).

A theoretically-motivated approach to symptom groupings may even be more appropriate for the type of data used in our study. The use of CFA in our study made the assumption of an effects-indicator model – that is, the indicators (i.e., individual symptoms) *depend* on the underlying latent variable (e.g., Appetite Disturbances). However, as Bollen and Lennox (1991) note, we would expect an increase in a particular latent symptom variable to *require* an increase in all of its indicators. Thus, a causal-

indicator model may be more appropriate in this case – such a model would posit that a group of indicators (i.e., symptoms) determine the latent variables. Thus, for example, if Hypersomnia increases, Sleep Disturbances also increases, even if there is no change in any other symptom. Future research may consider this distinction and use methods such as Structural Equation Modeling (SEM) to create causal-indicator models for groups of depressive symptoms. Causal-indicator models would yield regression weights for each individual symptom that could be used as an alternative method for computing scores on symptom clusters.

As mentioned above, the HDRS is considerably limited in the range of cognitive symptoms that it assesses. Given that the specific actions of psychotherapies (especially on CBT) are most likely to rapidly treat the cognitive pathology of MDD from the start of treatment, measures of depression symptoms with a greater range of cognitive symptoms may allow future studies to detect the hypothesized effects. An obvious candidate is the BDI which covers a broader range of cognitive symptoms, but future studies might also attempt to integrate several measures of depression symptoms (e.g., HDRS, BDI along with other measures such as the SCL-90) to produce a more reliable construct that lends a richer representation of a type of symptom.

Related to the above, some research has indicated that the HDRS may not be an optimal measure of depression. The primary issue for the current study is at the level of item content. To summarize some insightful observations made by Bagby and colleagues (2004), it is clear that many items of the HDRS do not measure single symptoms along a continuum of severity per se – for instance, within depressed mood there is a combination of affective (e.g., sadness), behavioural (e.g., tendency to weep), and cognitive (e.g.,

pessimism about the future) features that could potentially be rated. In fact, the depressed mood item includes hopelessness, helplessness and worthlessness (three separate HDRS symptoms) as features. Another example of this sort of HDRS symptom is general somatic symptoms, which includes a heterogeneous group of features that are essentially separate symptoms (i.e., feelings of heaviness, diffuse backache, loss of energy).

As Bagby and colleagues (2004) note, it is sometimes unclear whether the anchors of some HDRS items actually assess the same underlying construct. For instance, the most severe anchor of the guilt item mentions guilt themed visual and auditory hallucinations. As the above authors note, a patient who scores a 4 on this item may be more severely ill than patients who do not present with these symptoms, but does this really mean an increase in guilty feelings or is it actually a marker of a more severe subtype (i.e., MDD with psychotic features) of the overall syndrome? Unfortunately, problems such as those mentioned above reduce the potential meaningfulness of the items and cloud the interpretability of the derived symptom groups in this study. This may be particularly true of the Cognitive-Affective symptom cluster, which includes both depressed mood and guilt, which clearly measure a kaleidoscope of different constructs.

Research that has examined the HDRS from an item response standpoint also has implications for our use of the measure in the current study. In a series of studies, Santor and Coyne (2001a, b) used item response analyses to determine whether the HDRS was composed of items that cover a range of symptoms that are consistently associated with the syndrome over a range of severity. Unfortunately, the authors found that 12 of the HDRS items had at least one problematic response option. For instance, the likelihood of receiving a 1 on the three insomnia items was nearly the same regardless of overall

depression severity, while the likelihood of receiving a 4 on somatic anxiety was very low, even in severe depression. When items aren't sensitive over a range of severity, this impacts the ability to detect change on these symptoms – in clinical trials, patients are expected to move along the severity continuum as they improve and items that are not sensitive at all levels of severity lead to an underestimation of the strength of actual treatment effects (Bagby et al., 2004). This phenomenon would only be amplified when examining smaller clusters of items, and thus it is possible that the nature of these items masked some effects that may really be there.

As was discussed briefly above, the current study may be improved upon by adjusting the way in which we approach the measurement of symptoms. This could be accomplished by employing questionnaires, such as the BDI, which may be particularly useful because, unlike the HDRS, each item focuses explicitly on a single construct, and a single construct alone. Another frontier, which may apply particularly to the somatic symptoms of MDD, might be to examine change in some of the biological correlates of depression. Some possible candidates include changes in basal cortisol, as hypercortisolemia is a well-documented correlate of MDD (e.g., Holsboer, 1995), and neurophysiological correlates of sleep abnormalities (often measured using electroencephalograms). The later would be useful as MDD has been associated with premature loss of slow wave sleep and an early onset of the first period of rapid eye movement (see Thase, Jindal, & Howland, 2002 for a review).

Although the current study examined the remission rates for different clusters of symptoms between treatments, another way to examine the question at hand would be to focus on how symptoms remit within each treatment. That is, although IMI-CM generally

works faster than psychotherapy regardless of the symptoms under study, perhaps IMI-CM produces more rapid remission in sleep symptoms compared to its remission rate for cognitive symptoms. One might hypothesize different patterns of remission speed for groups of symptoms between the different treatments for MDD. Future research is needed to examine this possibility in a systematic manner, potentially using a similar analytic approach as the current study.

Finally, future research into the development and evaluation of brief psychotherapies for MDD is crucial. Recently, a modular approach to treatment is becoming more common - this would simply supply patients with the most crucial components of a psychotherapeutic intervention (e.g., perhaps BA in CBT) over 2-4 sessions. These condensed psychotherapies need to be evaluated against current gold-standard approaches (i.e., antidepressant medications) in the acute treatment of depressed adult outpatients to determine if pharmacotherapy continues to have a more rapid rate of remission of symptoms compared to the "active ingredients" in psychotherapy. Furthermore, follow-up analyses would be required to determine whether brief psychotherapy has prophylactic effects equivalent to a full 16 weeks of CBT, for instance.

Another aspect of our current understanding of treatments for MDD that could readily be incorporated into efficacy measurement is augmentation strategies. RCTs now commonly use open label trials for antidepressant medications where a medication that is not working properly is substituted for another medication. Similarly, there may be ways in which standard CBT could be systematically augmented by the use of techniques such as motivational interviewing or aspects of mindfulness. These techniques, if used early on

or at times where therapeutic gains seemed to have slowed, may moderate the impact of standard CBT interventions.

Conclusions

The current study sought to examine whether different efficacious treatments for MDD acted on empirically derived symptom clusters at different rates over the course of acute phase treatment in adult outpatients. Our results indicate that IMI-CM acts on Sleep Disturbances, Somatic Symptoms and the overall depression syndrome rapidly early on in treatment and plateau later on, but that psychotherapeutic techniques produce gradual sustained improvement. IMI-CM appears to have an overall advantage when it comes to Cognitive-Affective symptoms as well (i.e., more rapid improvement and greater remission by the end of treatment).

It is clear that meaningful groups of symptoms may respond differently depending on which treatment is used. Further research in the area using measures of symptoms that are more tailored towards this type of project may lead to further clinically and theoretically interesting discrepancies between treatments. Given the heterogeneity inherent in individuals who suffer from MDD, it is not logical to approach every case with the same tool. The onus is on researchers in mental health to determine ways in which the information that patients bring into their clinician's office (such as their symptoms) can be used to optimize their treatment. Further research on the effects of different treatments on separate symptom profiles may eventually fuel this type of individualized approach.

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Appendix A

Hamilton Psychiatric Rating Scale for Depression

INSTRUCTIONS: Using the key beneath each symptom, please fill in the blank to the far right with the number that best describes that symptom's severity.

1. DEPRESSED MOOD (sadness, hopeless, helpless, worthless) . . . . . _____
   - 0 = Absent
   - 1 = These feeling states indicated only on questioning
   - 2 = These feeling states spontaneously reported verbally
   - 3 = Communicates feeling states nonverbally – i.e., through facial expression, posture, voice and tendency to weep
   - 4 = Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communications

2. FEELING OF GUILT . . . . . _____
   - 0 = Absent
   - 1 = Self reproach, feels he has let people down
   - 2 = Ideas of guilt or rumination over past errors or sinful deeds
   - 3 = Present illness is a punishment. Delusions of guilt
   - 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE . . . . . _____
   - 0 = Absent
   - 1 = Feels life is not worth living
   - 2 = Wishes he were dead or any thoughts of possible death to self
   - 3 = Suicide ideas or gestures
   - 4 = Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY . . . . . _____
   - 0 = No difficulty falling asleep
   - 1 = Complains of occasional difficulty falling asleep – i.e., more than ½ hour
   - 2 = Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE . . . . . _____
   - 0 = No difficulty
   - 1 = Patient complains of being restless
   - 2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE . . . . . _____
   - 0 = No difficulty
   - 1 = Waking in early hours of the morning but goes back to sleep
   - 2 = Unable to fall asleep again if he gets out of bed

7. HYPERSOMNIA . . . . . _____
    0 = No difficulty
    1 = Frequently sleeps at least 1 hour or more (or spends 1 hour or more in bed) than when not depressed
    2 = Frequently sleeps 2 or more hours (or spends 2 or more hours in bed) than when not depressed

8. WORK AND ACTIVITIES . . . . . _____
    0 = No difficulty
    1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities: work or hobbies
    2 = Loss of interest in activity: hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities)
    3 = Decrease in actual time spent in activities or decrease in Productivity
    4 = Stopped working because of present illness

9. RETARDATION (slowness of thought and speech; impaired ability to concentrate; decrease motor activity) . . . . . _____
    0 = Normal speech and thought
    1 = Slight retardation at interview
    2 = Obvious retardation at interview
    3 = Interview difficult
    4 = Complete stupor

10. AGITATION . . . . . _____
    0 = None
    1 = Fidgetiness
    2 = Playing with hands, hair, etc.
    3 = Moving about, can't sit still
    4 = Hand-wringing, nail-biting, hair-pulling, biting of lips

11. ANXIETY PSYCHIC . . . . . _____
    0 = No difficulty
    1 = Subjective tension and irritability
    2 = Worrying about minor matters
    3 = Apprehensive attitude apparent in face or speech
    4 = Fears expressed without questioning

12. ANXIETY SOMATIC (Physiological concomitants of anxiety such as: Gastrointestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching; Cardiovascular – palpitations, headaches; Respiratory – hyperventilation, sighing; Urinary frequency; Sweating) . . . . . _____
    0 = Absent

1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

13. SOMATIC SYMPTOMS GASTROINTESTINAL . . . . . _____
0 = None
1 = Loss of appetite but eating without encouragement. Heavy feeling in abdomen
2 = Difficulty eating without urging. Requests or requires laxatives or medication for bowels or medication for G. I. Symptoms

14. INCREASED APPETITE . . . . . _____
0 = Not present
1 = Mild to moderate increase in hunger, increased eating
2 = Hungry all the time, uncontrolled eating

15. SOMATIC SYMPTOMS GENERAL . . . . . _____
0 = None
1 = Heaviness in limbs, back or head. Backache, headaches, Muscle aches. Loss of energy and fatigability
2 = Any clear-cut symptom rates 2

16. GENITAL SYMPTOMS (symptoms such as: loss of libido, menstrual disturbances) . . . . . _____
0 = Absent
1 = Mild
2 = Severe

17. HYPOCHONDRIASIS . . . . . _____
0 = Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Frequent complaints, requests for help, etc.
4 = Hypochondriacal delusions

18. LOSS OF WEIGHT . . . . . _____
0 = No weight loss
1 = Probable weight loss associated with present illness
2 = Definite (according to patient) weight loss

19. WEIGHT GAIN . . . . . _____
0 = No weight gain
1 = Probable weight gain associated with present illness
2 = Definite (according to patient) weight gain

20. INSIGHT . . . . . _____
0 = Acknowledges being depressed and ill (or no longer depressed)
1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 = Denies being ill at all

21. DIURNAL VARIATION

A. Note whether symptoms are worse in morning or evening.
If NO diurnal variation, record "0" . . . . . _____
0 = No variation
1 = Worse in A. M.
2 = Worse in P. M.

B. When present, mark the severity of the variation.
Record "0" if no variation . . . . . _____
0 = None
1 = Mild
2 = Severe

22. DEPERSONALIZATION AND DEREALIZATION (such as: feelings of unreality; nihilistic ideas) . . . . . _____
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

23. PARANOID SYMPTOMS . . . . . _____
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference or persecution

24. OBSESSIONAL AND COMPULSIVE SYMPTOMS . . . . . _____
0 = Absent
1 = Mild
2 = Severe

25. HELPLESSNESS . . . . . _____
0 = Not present
1 = Subjective feelings which are elicited only by inquiry
2 = Patient volunteers his helpless feelings
3 = Requires urging, guidance, and reassurance to accomplish work, household, and other chores
4 = Despite urging, does not perform necessary chores because of feelings of helplessness

26. HOPELESSNESS . . . . . _____

0 = Not present
1 = Intermittently doubts that "things will improve," but can be reassured
2 = Consistently feels "hopeless" but accepts reassurance
3 = Expresses feelings of discouragement, despair, pessimism regarding the future which cannot be dispelled
4 = Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent

27. WORTHLESSNESS (ranges from mild loss of esteem, feelings of Inferiority, self-depreciation, to feelings of total worthlessness . . . . . ._____

0 = Not present
1 = Indicates feelings of worthlessness (loss of self-esteem) only on questioning
2 = Spontaneously indicates feelings of worthlessness (loss self-esteem)
3 = Different from "2" by degree: patient volunteers that he/she is "no good", "inferior," etc.
4 = Expresses feelings of total worthlessness – e.g., "I'm a heap of garbage" or its equivalent

28. HOW DEPRESSED DO YOU THINK THE PATIENT IS AT THIS TIME?

_____

0 = Not at all
1 = Slightly depressed
2 = Mildly depressed
3 = Moderately depressed
4 = Severely depressed

** NOTE: The 17-item HRSD is composed of items 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18 and 20.

Appendix B

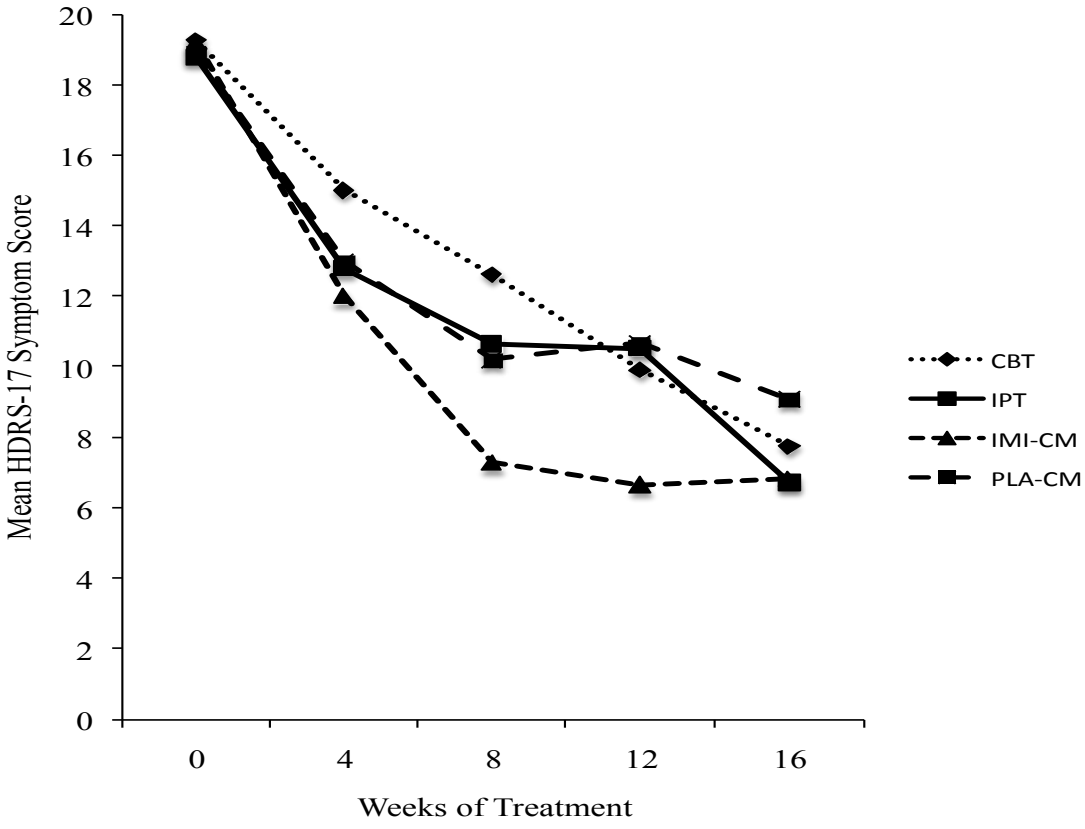

Figure 7. Plot of actual mean HDRS-17 scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI-CM = Imipramine plus clinical management. PLA-CM = Placebo plus clinical management.

Appendix C

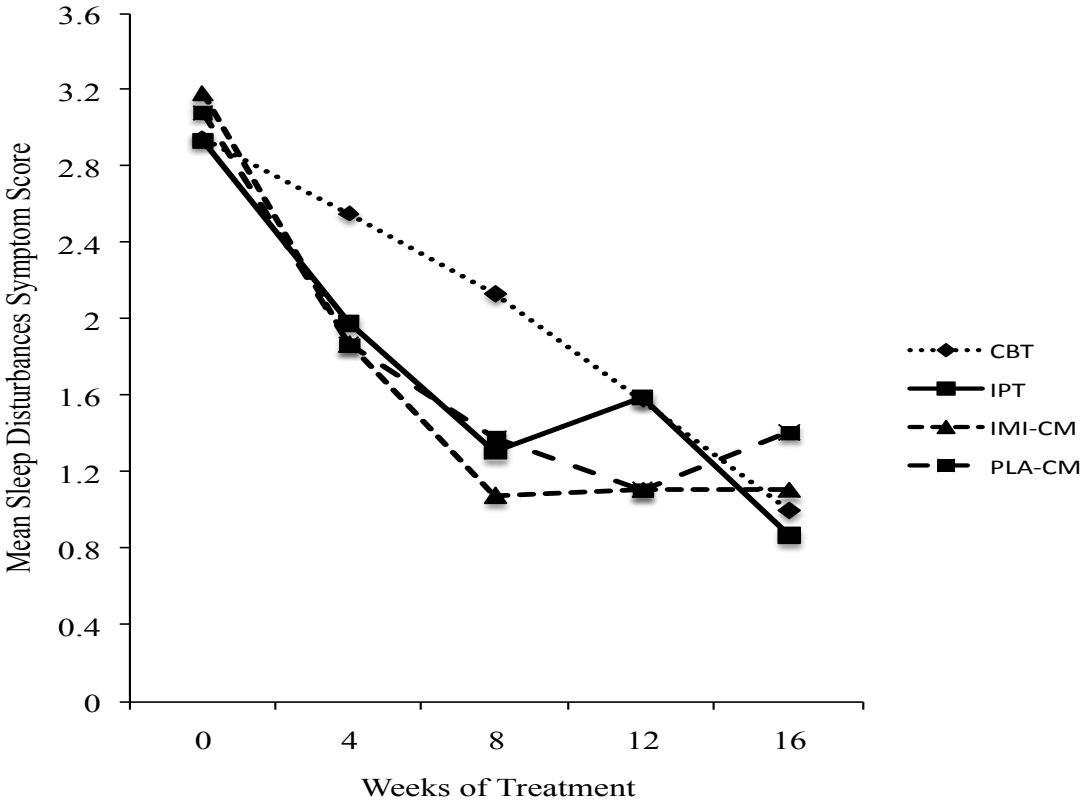

Figure 8. Plot of actual mean Sleep Disturbances scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI-CM = Imipramine plus clinical management. PLA-CM = Placebo plus clinical management.

Appendix D

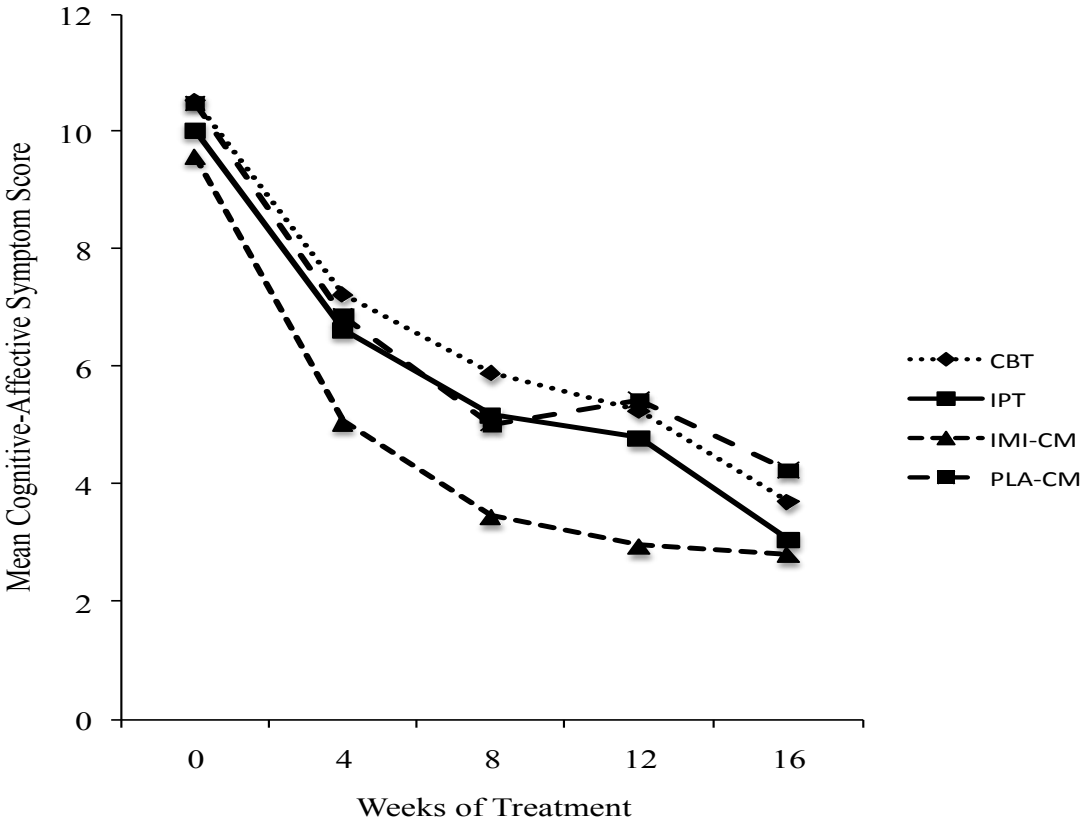

Figure 9. Plot of actual mean Cognitive-Affective scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI-CM = Imipramine plus clinical management. PLA-CM = Placebo plus clinical management.

Appendix E

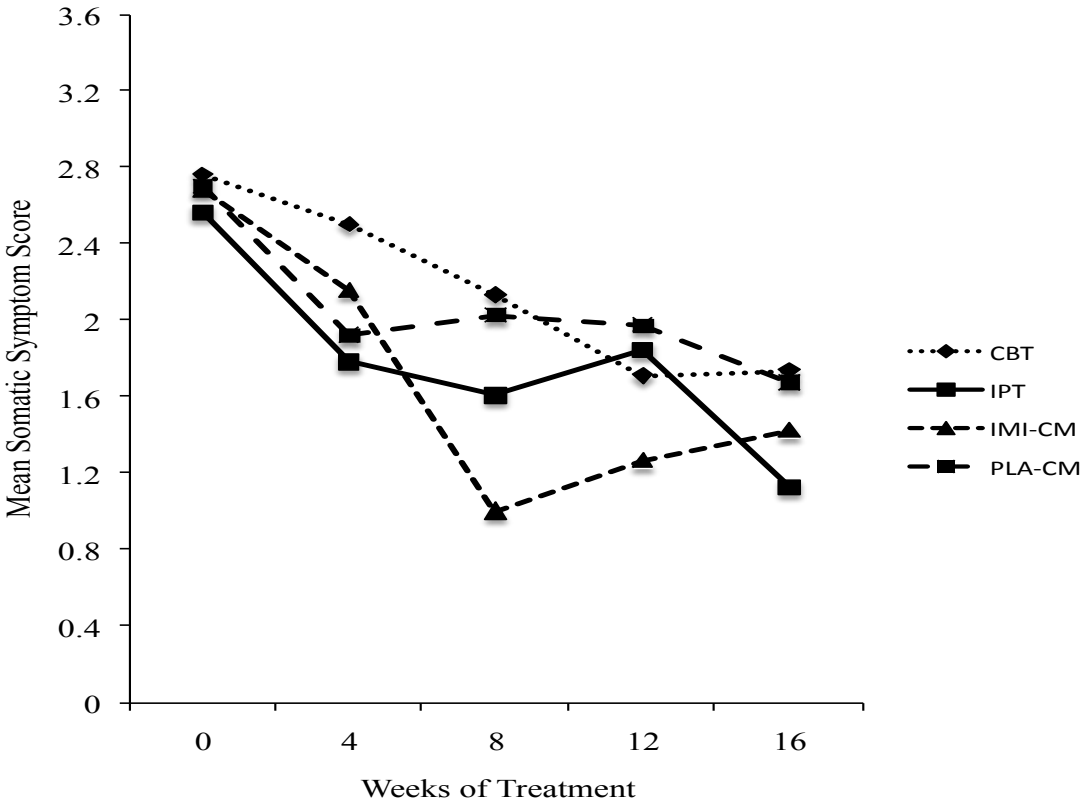

Figure 10. Plot of actual mean Somatic scores over the 16 week treatment period by treatment group. CBT = Cognitive-Behavioural Therapy. IPT = Interpersonal Psychotherapy. IMI-CM = Imipramine plus clinical management. PLA-CM = Placebo plus clinical management.