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Residual Symptoms after Treatment of Chronic Depression: A Comparison across Treatment Modalities

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

RESIDUAL SYMPTOMS AFTER TREATMENT OF CHRONIC DEPRESSION: A COMPARISON ACROSS TREATMENT MODALITIES

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Despite the development of several effective treatments for depression, symptoms often persist in a number of individuals. Unfortunately, these residual symptoms are associated with several negative outcomes, including persistence of depressive illness. Few studies have examined the exact nature of individual residual symptoms across specific treatment modalities, and studies have failed to distinguish between depression courses. The current study expands on previous findings by examining, among a chronically depressed population, differences in individual residual symptoms and clusters between treatment modality (medication, psychotherapy, combination) and treatment response (full response, partial response). Five hundred and nineteen chronically depressed participants completed the study. Participants were randomly

assigned to receive treatment with nefazodone, CBASP, or the combination of both. Residual symptoms were assessed with two depression severity ratings, a clinician administered interview and a self-report questionnaire. The frequency and severity of individual residual symptoms and clusters were examined between treatment and response groups. The emergence of symptoms after treatment was compared between treatment groups. Residual symptoms were common, reported in over 90% of the sample. The most common residual symptoms reflected both core depressive symptoms and co-morbid symptoms not specific to depression. In general, similar residual symptoms were reported among partial and full responders. The only individual residual symptoms that differed between treatment groups were early insomnia, OCD symptoms, hopelessness, hypersomnia, concentration, and decreased libido. Treatment groups also differed on two factors of the HDRS. The Nefazodone group reported a greater number of Disturbed Thinking items than the CBASP group. The CBASP group reported more items on the Psychic Depression factor compared to the Nefazodone group for full responders only. Analyses revealed that the Nefazodone group was more likely to report the emergence of guilt and psychic anxiety after treatment than the CBASP and Combination group, and the emergence of weight loss occurred more frequently among participants in the Nefazodone and Combination groups when compared with the CBASP group. Results suggest residual weight loss may be a side effect of medication and CBASP may offer protection against the development of guilt and anxiety

Introduction

Depression is one of the most common psychiatric disorders present in the general population, affecting approximately 17 percent of American adults (Kessler, et al., 1994). Despite the development of several treatments for depression, including psychotropic medication and psychotherapy, symptoms often persist in a significant number of individuals (Fava, Grandi, Zielezny, Canestrari, & Morphy, 1994; Nierenberg et al., 1999; Paykel, et al., 1995; Thase et al., 1992). However, research investigating the efficacy of depression treatment generally report only response and remission rates related to treatment outcome, ignoring the frequency and nature of residual or "left over" symptoms. Unfortunately, residual symptoms are prevalent not only in non-responders and partial responders, but even in full responders who achieve remission from depression (Nierenberg et al., 1999; Ogrodiczuk, Piper, & Joyce, 2004).

Despite positive response to treatment, seemingly mild symptoms appear to have a potentially negative effect on long-term outcomes (Mintz, Mintz, Arruda, & Hwang, 1992). Residual symptoms have been found to be related to negative consequences, both in terms of overall functioning and persistence of depressive illness. Residual symptoms are consistently a major predictor of relapse of depression, and compared with asymptomatic remission, are associated with shorter time between episodes, more

symptomatic weeks during follow-up (Judd, et al., 1998a, 1998b, 2000), more frequent depressive episodes over time if untreated, (Fava, Rafanelli, Grandi, Canestrari, et al 1998; Fava, Rafanelli, Grandi, Conti, et al., 1998) and a decreased likelihood of recovery over time (Judd, et al., 1998b, 2000). Further, the presence of residual symptoms after response to treatment has been found to contribute to worse occupational and psychosocial functioning (Ogrodiczuk, et al., 2004), greater health care utilization psychiatric hospitalizations, emergency room use, public assistance, disability benefits, and suicidal thoughts and behaviors (Judd, Akiskal, Paulus, 1997. Chronicity is increased in patients with residual symptoms (Judd, et al., 2000) and residual symptoms are believed to represent the most common expressions of illness activity during the long-term course of unipolar depression (Judd & Akiskal, 2000).

Based on the profound negative outcomes associated with residual symptoms, researchers and clinicians have emphasized that the goal of treatment outcome should be a full treatment response with an asymptomatic state (Keller, 2003; Rush & Trivedi, 1995). However, debate ensues as to whether the alleviation of all symptoms is possible and a reasonable goal for treatment, as non-clinical community samples often report some level of depressive symptoms (Fava, Fabbri, Sonino, 2002, Fava, et al., 1986). In the spirit of achieving an asymptomatic full remission state, current research has focused on the treatment of residual symptoms. The major questions being examined are based on the underlying theoretical deliberation as to what residual symptoms represent (Menza, Marin, Sokol-Opper, 2003). Specifically whether they are part of a prolonged illness, represent a different phase of the illness, are independent of the depressive

episode and represent a different psychiatric or medical disorder, or develop as a result of treatment.

While the focus on treatment implications is relevant and important, the nature of residual symptoms with specific treatment approaches should first be examined to guide treatment planning. Few studies have examined the specific symptoms that are "left over" after treatment and most studies simply report the presence or absence of symptoms (Ogrodiczuk, et al., 2004; Simon, 2000; Thase et al., 1992). Also, many studies examining residual symptoms do not distinguish between episodic and chronic depression, resulting in mixed findings. A chronic course compared to episodic depression has unique developmental and interpersonal characteristics associated with greater negative outcomes, and calls for specific treatment approaches, therefore illustrating the importance of making this course distinction (McCullough, 2000; Riso, Miyatake, & Thase, 2002; Schaefer, Vrana, McCullough, Williams, et al., 2004).

The few studies that have examined the nature of individual residual symptoms have focused primarily on pharmacotherapy (Nierenberg, et al., 1999; Paykel, et al., 1995) with less emphasis on the residual symptoms after psychotherapy (Karp, et al., 2004; Thase, et al., 1992), and no study known to date has compared the frequency and nature of residual symptoms across treatment modality. Because treatment approaches differ widely regarding their mechanism of change, targeting distinct processes, (i.e. neurotransmitters vs. cognitions, emotions, and behavior), it is reasonable to expect that residual symptoms are not uniform across treatments. If the residual symptom clusters can be identified with particular approaches, then the development or modification of

treatments to address these symptoms can take place. Further, although research demonstrates a therapy's efficacy to treat depression, little is known about which symptoms are most affected.

The following is a more comprehensive review of the literature, examining in greater detail the conceptualization of treatment outcome and residual symptoms. Further, the existing literature examining the prevalence and consequences of residual symptoms and the relationship between treatment approach and the nature of individual residual symptoms will be presented.

Literature Review

Depression is one of the most common psychiatric disorders present in the general population. Data collected from the National Comorbidity Survey (NCS) between 1990 and 1992 indicated that approximately 17 percent of American adults between the ages of 15 to 54 years of age experienced a major depressive episode in their lifetime (Kessler, et al., 1994). Further, in the United States about 19 million people (9.5% of the population) experience depression each year, and nearly two thirds do not get the help they need (Robins & Reiger, 1990). Unfortunately, rates of major depression are rising and depression is occurring at younger ages (Bland, 1997), and even higher rates have been consistently found with women compared to men, at roughly twice the rate (Blehar & Oren, 1997; Weissman, et al., 1996). Throughout the world, affective disorders present major public health problems (Bland, 1997). In the United States, depression is the leading cause of disability, with associated costs averaging more than $30 billion per year (NIMH, 1999). Further, depressed patients face an increased risk of morbidity and mortality from general medical conditions, and use health care services three times more often than do non-depressed patients (Zajecka, 2003). These extraordinary economic and emotional costs associated with depression highlight the importance of effective treatment.

Treatment of Depression

Due to the extreme negative outcomes associated with depression, several promising treatments have been developed and evaluated, including both pharmacotherapy and psychotherapy approaches. Below is a brief summary of the most common approaches to treat depression and their demonstrated efficacy.

Pharmacotherapy

The four most frequently used classes of antidepressant medications are tricyclics (TCAs; i.e. imipramine, desipramine, amitriptyline, nortriptyline), atypical or second generation antidepressants (i.e. serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, Trazodone, and bupropion), selective serotonin reuptake inhibitors (SSRIs; i.e. fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), etc), and serotonin antagonist and reuptake inhibitor (SARIs, i.e. nefazodone (Serzone)). The precise mechanism of action of antidepressants has been an ongoing subject of intensive research and is beyond the scope of this paper. Interested readers are encouraged to consult Julien (2001) for further review.

Tricyclic antidepressants. Tricyclic antidepressants are older medications, and due to their unpleasant side effects (such as blurred vision, dry mouth, constipation, difficulty urinating, drowsiness, weight gain and sexual dysfunction), have increasingly been replaced by newer generations of medications such as SSRIs, SNRIs, and SARIs. Up to forty percent of patients stop taking TCAs due to these side effects. While new medications have a more favorable profile of side effects than the older medications, they are not necessarily more efficacious, and TCAs remain the standard against which other

antidepressants are compared (Hirschfeld, 1999). TCAs block multiple receptors including presynaptic serotonin, dopamine, and norepinephrine receptors, which likely accounts for their efficacy and toxicity. However there are substantial disadvantages of TCAs, including a slow onset of action, bothersome side effects and if overdose occurs, they can be lethal.

Atypical/second generation. Atypical or second-generation antidepressants were developed to provide an alternative treatment without the negative side effects. These medications include trazodone (Desyrel), bupropion (Wellbutrin), and venlafaxine (Effexor). While these medications vary in the specific neurotransmitters they act on, commonly prescribed SNRIs (venlafaxine), typically inhibit both serotonin and norepinephrine reuptake.

Selective Serotonin Reuptake Inhibitors. SSRIs have been used to treat depression for more than 15 years. These drugs block the presynaptic transporter from serotonin reuptake, therefore temporarily increasing the levels of serotonin at the receptor site. Side effects differ between medications, but commonly include anxiety, agitation, insomnia and sexual dysfunction. Most studies have found SSRIs to be as effective as TCAs and atypical antidepressants (Julien, 2001; Keller et al., 1998).

Serotonin Antagonist Reuptake Inhibitor. The development of nefazodone (Serzone; Bristol-Myers Squibb) was originally believed to be a particularly advantageous antidepressant medication and is the medication investigated in the current proposal. It has a unique structure, differing from the SSRIs by encompassing a dual action on the serotonin synapse. Nefazodone acts as a serotonin 5-HT_2 antagonist and

reuptake inhibitor, thus providing therapeutic effect without the side effects commonly found in SSRIs (most notably the absence of sexual side effects). Nonetheless, some common side effects were found and included sedation, nausea, dry mouth, dizziness, and light-headedness. It was taken off the market in the US by Bristol-Myers Squibb because of the potential for liver dysfunction. Nefazodone has been found to be as effective as TCAs and SSRIs, but not of therapeutic superiority.

Psychotherapy

Although medication has demonstrated effectiveness in alleviating depressive symptoms, a substantial number of patients are either unwilling to take medication, or have an adverse reaction, thus discontinuing treatment. Therefore, the identification of effective psychotherapy approaches is imperative. Two psychotherapy treatments have received the most attention and have demonstrated the most empirical support; these include Cognitive-Behavioral Therapy (CBT; Beck, Rush, Shaw, & Emery, 1979) and Interpersonal Psychotherapy (IPT; Klerman, Weissman, Rounsaville, & Chevron, 1984). A brief description of both approaches is warranted as the psychotherapy approach employed in the current proposal integrates principles from both perspectives.

Cognitive Behavioral Therapy. Cognitive behavioral therapy is an active, directive, time-limited structured approach based on an underlying theoretical rationale that depression is related to maladaptive cognitions or schemas. Techniques of cognitive therapy are designed to teach patients to identify and monitor negative automatic thoughts, recognize the connection between thoughts, feelings and behavior, challenge the validity of these thoughts, and develop and utilize more reality-oriented

interpretations. Behavioral techniques are also incorporated to change behavior and elicit more appropriate cognitions. The patient develops and works towards a sequence of tasks to reach a goal and to test certain maladaptive assumptions. Homework between sessions is an important component of CBT, as it is used to transfer what is learned in therapy to patients' outside lives. Patients who complete homework make greater progress in therapy and maintain their gains after termination of treatment.

Interpersonal Psychotherapy. Interpersonal Psychotherapy (ITP) is a focused, short-term, time-limited therapy that emphasizes the current interpersonal relations of the depressed patient, since it is believed that depression occurs in an interpersonal context (Klerman, Weissman, Rounsaville, & Chevron, 1984). IPT is based on the premise that focusing on the interpersonal relationships will facilitate the patients' recovery. Four common problems are believed to be associated with the onset of depression and are a focus of treatment, including grief and loss, role disputes, role transitions and interpersonal deficits. The therapist and patient focus on the problem most salient to the patient. IPT attempts to change cognitions and behaviors within the context of the interpersonal relationship. Behaviors and cognitions outside the scope of the interpersonal relationship are not a focus of therapy.

While several treatment approaches have been developed and are viewed as promising interventions in alleviating depressive symptoms, their ability to offer treatment gains is most important.

Empirical support

The support for the above treatment approaches have been based primarily on randomized clinical trials, in which treatment efficacy is often reported in terms of the percent of patients who respond to treatment and the percentage of change from baseline at treatment completion. Table One provides a summary of response rates for various treatment approaches.

Table 1 *Sample of outcome studies for treatment of depression as a function of treatment modality.*

Study and Treatment Types	*Population*	*Definition of Response*	*Response Rate (% patients responding)*	*Response Rate (% of change from baseline)*	*Remission Rate (% of patients remitted)*
Elkins, et al. (1989)					
CBT	250 Outpatients with MDD	HDRS < 6	N/A	N/A	51.4%
IPT					55.3%
Imipramine					56.8%
Placebo					29.4%
Hollon et al. (1992)					
CBT	107 Outpatients with MDD	BDI ≤ 9	62%	N/A	N/A
TCA			56%		
Murphey, et al. (1984)					
CBT	87 Outpatients with MDD	BDI ≤ 9	53%	65%	N/A
Nortriptyline			56%	64%	
Combination				67%	
Rush et al. (1977)					
CBT	32 Outpatients with MDD	BDI ≤ 9	83%	73%	N/A
Imipramine			36%	58%	
DeRubeis, et al. (2005)	240 Outpatients with moderate to severe MDD	Response: HDRS ≤ 12 Remission: HDRS ≤ 7	N/A		
CBT				58%	40%
Paroxetine				58%	46%
Casacalenda, et al. (2002)	Meta analysis of six randomized control trials (RCTs)- Completers 489 Outpatients	HDRS ≥6 or ≥ 7 Raskin ≤ 5 (Depression Scale)	N/A	N/A	
Amitriptyline					62.5%
Imipramine					56.8%
Nortriptyline					66.7%
IPT					50-71.8%
CBT					51.4%

Casacalenda, et al. (2002)	Meta analysis of six RCTs	HDRS ≥6 or ≥ 7 Raskin Depression ≤	N/A	N/A	
Amitriptyline	-Intent to treat	5			35%-57.7%
Imipramine	883 Outpatients				42.1%
Nortriptyline	with mild to				48.4%
Phenelizine	moderate MDD				41.4%
IPT					41.2 %-46.2%
CBT					35.6%-44.4%
Star*D Study Group[a]	2876	Response:	(Based on		(Based on
Level 1: (n=2876)	Outpatients	HDRS & QUIDS	QUIDS)		QUIDS)
Citalapram	Diagnosed with	>50% improvement	48.6%		33.0%
Level 2	MDD	Remission:			
(augmentation)		HDRS ≤ 7	31.8%	25.3%	39%
Bupropion SR		QUIDS[b] ≤ 5	34.1%		29.4%
(n=279)			26.9%	17.1%	32.9%
CBT (n=85)					
Buspirone (n=286)			26.1%		25.5%
Level 2 (switching)			26.7%		26.6%
Bupropion (n=239)			28.2%		25.0%
Sertraline (n=238)			30.6%		41.9%
Venlafaxine (n=250)					
CBT (n=62)			16.1%		14.5%
Level 3			24.3%		25.7%
(augmentation)					
Lithium+level 2 med.			17.2%		12.9%
T_3 + level 2 med.			13.9%		8.3%
Level 3 (switching)					
Nortriptyline (n=116)					
Mirtazapine (n=110)					

Note: a Star*D study group references: Fava, et al. (2006); Rush et al. (2006a, 2006b); Trivedi et al. (2006).

[b] QUIDS=Quick Inventory of Depressive Symptomotology.

Although there has been considerable variability in improvement rates from study to study, several conclusions have been drawn and include 1) the rate of symptom improvement with either medication or psychotherapy is around 50% (Young, Weinberger, & Beck, 2001), 2) the percentage of patients that respond to a particular treatment is around 50%, 3) no significant differences between treatments have been found in terms of efficacy (Elkin, et al., 1989; Scott, 2001), and 4) psychotherapy and medication treatment are usually more effective than placebo (DeRubeis, et al., 2005). In order to evaluate potential differences between treatments, NIMH launched the "Treatment of Depression Collaborative Research Program" (TDCRP), a landmark study investigating the effectiveness of interpersonal psychotherapy, CBT, imipramine hydrochloride plus clinical management, and placebo plus clinical management (Elkin, et al., 1989). Patients in all treatments showed significant improvement in functioning over the course of treatment. Overall, none of the active treatment groups were significantly more or less effective than the other.

When comparing overall rates of response, there are modest differences between an approach that uses either medication or psychotherapy alone from one that combines medication and therapy (Young, Weinberger, & Beck, 2001). However, Scott (2001) argues that in severe recurrent depressive disorders the combination of medication and therapy offers significant benefit. For example, in a sample of severely depressed patients, the overall response rate to combined therapy was 63% and three times higher than brief psychotherapy alone (20%) (Thase et al, 1997).

Although, treatment for depression is a well-researched area, inconsistencies in treatment outcome data are prevalent and hinder our ability to make accurate conclusions regarding treatment effectiveness. Only slightly more than half of depressed patients respond well to treatment, and a substantial number of patients carry residual symptoms after treatment (Durand & Barlow, 2000). Residual symptoms are the "left over" symptoms that carry over after treatment response, and are associated with significant negative outcomes. When patients are evaluated beyond immediate remission the outcome of depression is not as promising as previously thought (Paykel, 1994). Common outcomes after treatment include failure to remit, delayed remission, partial remission, relapse and recurrence.

Before I discuss in greater detail the prevalence and implications of these negative course outcomes, a discussion of how treatment outcome has been typically defined across studies is warranted and should provide a framework for the remaining literature review.

Defining Treatment Outcome

Due to the high rates of negative outcomes after treatment (i.e., failure to remit, partial remission, residual symptoms and relapse) and the inconsistency in response rates, researchers have begun to focus on how treatment outcome is defined across studies.

Keller (2003) argues that depression is a chronic disorder similar to other chronic medical disorders; however, unlike other chronic disorders, a measurable end point of treatment for depression has yet to be clearly established. Further, with other chronic medical conditions treatment is continued until the outcome criteria has been met and the

risk of recurrence is minimal. Keller additionally suggests that wellness must be determined by evaluating a combination of three key domains, including symptoms, functional status, and pathophysiological changes. Unfortunately, these three domains are rarely discussed or evaluated in the outcome research described above. Instead, descriptions of outcomes include terms such as full or partial response, remission, and recovery.

The MacArthur Foundation Research Network on the Psychobiology of Depression convened a task force to examine ways in which change points in the course of depressive illness had been described and the extent to which inconsistency in definitions might impede research of depression (Frank et al., 1991). The MacArthur Foundation found that the way these terms were often defined frequently vary across studies in terms of the assessment scales used, criteria for significant improvement, and length of improvement. However, one consistency across studies has been the way response has been defined. Typically response is described as more than a 50% reduction in symptoms from baseline to treatment completion. Therefore, when studies report the rate of response they often report the rate of improvement, or the percentage of patients that demonstrated a 50% reduction in symptoms. The way response is typically measured often varies across studies, but is frequently assessed through the use of depression severity rating scales, with the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) as the most commonly used tool. Other frequently employed rating scales in treatment outcome studies are the Montgomery & Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), Beck Depression Inventory (BDI; Beck,

1996), Research Diagnostic Criteria (RDC, Spitzer, Endicott, Robins, 1978), and the Paykel Clinical Interview for Depression (Paykel, 1985). However, since the 1990's, the goal of treatment is remission with an asymptomatic state, and simply a "response" to treatment is not sufficient. Unfortunately, studies that do report outcomes in terms of full response or remission have not been consistent in their operational definitions, using a variety of assessment measures with varying cutoffs. The most common cutoffs are scores of six or less or seven or less on the HDRS, designating a full response or remission. Subsequently, there is currently no universal definition for remission or specific criteria for when treatment goals are met (Frank et al., 1991). In an attempt to provide consistency in defining treatment response, the McArthur task force developed guidelines for operational definitions of treatment outcome (See Table 2). They concluded only five terms were needed to designate the relevant change points in the course of a depressive illness, which included response or partial remission, full remission, recovery, relapse, and recurrence. These terms are defined by the level of severity and duration of the symptoms or lack there of. Frank et al. (1991) suggest that partial response and partial remission have both been used to describe identical treatment outcomes and can therefore be used interchangeably. Hence, for the purpose of the proposed study, both terms are used similarly to describe incomplete response.

Table 2 *Definitions of outcomes in depression*

Term	*Definition*
Response/Partial Remission	Patient no longer fully symptomatic but evidence of more than minimal symptoms
Remission	Patient no longer meets syndromal criteria and has no or minimal symptoms
Relapse	Return to fully symptomatic state that occurs during remission; reemergence of current episode
Recovery	Extended period of remission; indicates the end of the current episode
Recurrence	Appearance of new episode of major depression; only occurs during recovery

Note. Taken from Frank et al., 1991

Operational criteria for outcomes in depression were also suggested based on selected rating scales. Table 3 illustrates the proposed criteria based on the HDRS.

Table 3 *Operational criteria for outcomes in depression based on the HDRS*

Clinical Ranges	*HDRS Total Score*
Asymptomatic	Score of ≤ 7
Fully Symptomatic	Score of ≥ 15
Partial remission/response	Score between 8 and 14
Durations	
Episode	≥ 2 weeks of fully symptomatic
Full remission	≥ 2 weeks to ≤ 6 months of being asymptomatic
Recovery	≥ 6 months of being asymptomatic

Note. Taken from Frank et al., 1991

The guidelines in Table 3 suggest that using a 50% reduction in symptom severity based on rating scales is insufficient in defining treatment outcome and has many drawbacks. For example, a 50% reduction on the HDRS in a patient with mild depression may leave them asymptomatic, but a patient with moderate to severe depression may end up with a score between 10 and 15, suggesting that significant symptoms are still present (Cornwall & Scott, 1997). Both patients may be improved but are not in similar stages of recovery.

According to the criteria defined by Frank et al. (1991), the first patient would be deemed asymptomatic and depending on the duration of improvement, may be in full remission or recovery. The second patient would be only partially remitted or even fully symptomatic. Many of the efficacy studies described above use response as the primary outcome, and thus have not stated clearly the number or percent of subjects fulfilling the criteria for partial response verses full remission.

Since the useful definition of partial remission has been developed and is now recognized in the DSM-IV as a course specifier (APA, 1994), research has begun to focus on partial remission and its implications in depression course. Partial remission has gained attention as a significant contributor to relapse and recurrence of depression and researchers have begun to evaluate the prevalence of partial response and residual symptoms. A review of the literature on the prevalence of incomplete response is important in understanding the magnitude of residual symptoms after treatment response, and is thus provided in the next section.

Prevalence of Incomplete Response

Partial Response

Although complete remission has been the ultimate goal for treatment since the early 1990s, only recently have outcome studies focused on differentiating between partial and full response. However, because criteria for partial remission vary across studies, comparisons of prevalence rates remain difficult. Regardless, the research investigating the prevalence of partial remission is quite compelling. In a review by Cornwall and Scott (1997), rates of partial remission widely varied, ranging from 4.9% to

42% of patients identified as partially remitted. However, this range is based on varying criteria of partial remission, patient samples, settings, and treatment approaches.

In a sample of 114 treatment resistant patients, 60% showed complete remission of symptoms (mean HRSD score of 5.9), while 18% achieved partial remission (final mean HDRS of 15.9) (MacEwan & Remick, 1988; as cited in Cornwall & Scott, 1997). After 25 weeks of acute and continued treatment of the combination of nortriptyline and IPT, 79% of elderly patients with recurrent depression met criteria for full remission (HRSD score of < 11), while 4.9% met the criteria for partial remission (HRSD score between 11 and 14) (Reynolds et al., 1992; as cited in Cornwall & Scott, 1997). Van Londen, Molenaar, Goekoop, Zwinderman, and Rooijmans (1998) found that after 9 months of combination psychotherapy and medication, 49% of patients with Major Depressive Disorder had reached full remission and 45% were partially remitted (MADRS < 10 with only one symptom at most a three). Further, the length of time to reach full remission was extensive, with 16 percent of patients requiring at least two years of treatment in order to reach full remission. Paykel et al. (1995) found partial response (HDRS = 8-18) occurred in 32% of responders after treatment with a variety of antidepressant medications.

Using the recommendations delineated by Frank et al. (1991), rates of partial remission (HDRS between 8 and 14) typically become higher, while rates of full remission (HDRS $\leq$ 7) become lower. For example, in a sample of inpatients with Major Depressive Disorder, only 21% of patients met full recovery criteria after 2 years of treatment, while 36% met criteria for partial remission (Scott, Tacchi, Jones, Scott, 1997).

Thase et al. (1992) found that in a sample of patients who responded to treatment with CBT (50% reduction of symptoms), 54 percent of patients partially remitted (defined as a HDRS score between 7 and 10), while only 46 percent achieved full remission.

In the follow-up phase of the NIMH TDCRP study comparing CBT, IPT, imipramine and placebo for treatment of major depression, Shea, et al. (1992) looked at recovery rates after treatment and found that a low prevalence of patients fully recovered after treatment (8 weeks of minimal or no depressive symptoms following the end of treatment) and remained recovered at follow-up after 6, 12, and 18 months. Specific percentages of patients who achieved full recovery for each treatment were 30% for CBT, 26% for IPT, 19% for imipramine, and 20% for the placebo group. These rates did not significantly differ between treatments groups or with the placebo group.

Residual Symptoms

Residual symptoms are similar to partial response in that they both represent incomplete recovery, but they also differ in that residual symptoms are common both in partial responders and full responders. They are the symptoms that are "left over" after treatment and represent a common outcome. The prevalence of residual symptoms is similar to rates of partial response described above. In a sample of patients that fully remitted from depression after treatment with Prozac, only 17.6% were free of all symptoms of depression, while 25.9% had one symptom, 23.3% had two symptoms, 18.5% had 3 symptoms, and about 15% of patients had at least 4 symptoms of depression (Nierenberg, et al., 1999). Fava, et al. (1994) found that residual symptoms were present in 87.8% of patients who fully responded to antidepressant treatment. Residual

symptoms have also been found after treatment with psychotherapy. For example, Ogrodniczuk, et al. (2004) found that 55% of patients responded fully to psychotherapy, with residual symptoms present in 82% of the patients that responded.

Longitudinal studies have demonstrated the longevity of subthreshold and residual symptoms after treatment. Data from a 12 year, longitudinal, prospective study suggested that patients manifested symptoms of depression at least 60% of the time during follow-up weeks after treatment, and a significant number of patients (23%) never experienced a symptom-free week in the long-term course of their illness (Judd & Akiskal, 2000). Further, the course of the depressive illness was dominated primarily by subsyndromal symptoms (43% of weeks) than symptoms at a major depression level (15% of weeks), suggesting that minor or residual symptoms may represent the most common expression of illness activity during the long-term course of unipolar depression (Judd & Akiskal, 2000). It is important to note that this study did not control for treatment of depression and the results may reflect particular treatment approaches rather than the natural course of depression if left untreated.

Summary

It should be clear from the above review that partial remission and residual symptoms are prevalent regardless of the treatment approach used, and despite the varying definitions of partial remission. Overall in clinical trials, approximately one-third of patients achieve full remission, one-third experience a response, and one-third are non-responders (Tranter, O'Donovan, C., Chandarana, P., Kennedy, S., 2002), with lower rates of full remission found in managed care settings (27% to 39%; Cuffel, et al., 2003).

Therefore, approximately 70% of patients do not meet the criteria for full remission, which has become the optimal outcome of treatment (Keller, 2003). The finding that residual symptoms may represent the most common presentation of depression course is also compelling and highlights the importance of focusing on residual symptoms as a significant treatment outcome. Recently, researchers have begun to investigate the consequences of residual symptoms on long-term outcomes. Below is a review of their findings.

Consequences of Residual Symptoms

Several negative consequences have been found to be associated with residual symptoms in terms of psychosocial functioning, risk of social and occupational impairment, suicidal contemplation (Boulenger, 2004), chronicity of symptoms, and progression of depression.

Functional Impairment

Treatment outcome studies often focus on symptom reduction and report response rates based on symptom presentation, ignoring the impact on psychosocial and functional impairment. While it is important to examine how well a treatment approach impacts depressive symptoms, it is equally important to evaluate their additional impact on psychosocial functioning (Judd & Akiskal, 2000; Papakostas, et al., 2004). A meta-analysis by Mintz et al. (1992) found higher rates of work impairment among unremitted patients with a range of 18 to 79% of patients demonstrating post treatment work impairment compared to remitted patients, in which 8% to 57% had evidenced work impairment. Residual symptoms are also associated with impairment in social

functioning. Patients with residual symptoms have been found to have greater marital difficulties (Kennedy & Paykel, 2003), impaired extended family relationships, and economic problems (Papakostas et al., 2004). Further, a greater number of residual symptoms and greater severity of depressive symptoms predicts poorer overall psychosocial functioning in responders to treatment, regardless the degree of psychosocial impairment at baseline (Papakostas, et al., 2004). Patients with residual symptoms compared to asymptomatic patients are associated with a past history of major depressive episodes and more lifetime suicide attempts (Judd & Akiskal, 2000). Ogrodniczuk, et al. (2004) found that residual symptoms were associated with less favorable psychosocial functioning at post treatment and 6 month follow-up. Specifically, patients with residual symptoms after responding to psychotherapy reported greater general distress, interpersonal dysfunction, and self-esteem compared to asymptomatic patients, even after accounting for pre treatment levels.

Residual symptoms are also associated with thoughts of suicide and suicidal attempts (Judd & Akiskal, 2000). Several symptoms of depression have been found to predict suicide in depressed patients, and include anhedonia, psychic anxiety, panic attacks, diminished concentration and global insomnia (Fawcett, 1994). These are the same symptoms that commonly persist after partial and sometimes full response to treatment; thus becoming a potentially major source of suicide risk for these patients.

In addition to the psychosocial and work impairments associated with residual symptoms, greater health care utilization; including more frequent medical and psychiatric visits, emergency room use, psychiatric hospital admissions, public

assistance, and disability benefits have also been found be related to residual symptoms when compared to asymptomatic patients (for review, see Tranter et al., 2002).

Progression of Depression

The long term effects of residual symptoms on depressive course has been examined by Judd et al. (1998b), in a seminal study as part of the NIMH Collaborative Depression Study (CDS), where patients who recovered from a unipolar Major Depressive Disorder were followed prospectively for 10 years. During recovery, 86.6 percent of patients with residual symptoms relapsed, compared to 65.8 percent of asymptomatic patients. Relapse was more than three times faster for patients with residual symptoms (68 weeks or 1.4 years) than asymptomatic patients (231 weeks or 4.4 years). In fact, residual symptoms predicted relapse over and above the well-documented contribution of recurrent major depressive episodes (Keller, Lavori, Lewis, Klerman, 1983). The importance of residual symptoms on future depression course is even apparent during one's first major depressive episode. Using the CDS longitudinal sample, patients with residual symptoms after treatment of a first episode of depression have a significantly more severe and chronic course of illness than do patients who are treated to remission (Judd, et al., 2000). Specifically, the initial relapse or recurrence of a depressive episode occurred more than 12 times faster for patients with subthreshold depressive symptoms than for asymptomatic patients. Also, after recovery from their major depressive episode, only 7.7 percent of patients with residual symptoms remained free of a depressive episode during the remainder of the follow-up (up to 12 years), compared to 34 percent of the asymptomatic patients. Residual symptoms also predicted

more frequent recurrences, shorter intervals of wellness with fewer symptom-free weeks during follow-up, and more chronic major depressive episodes (lasting more than 2 years). Thus, not treating even the first depressive episode to an asymptomatic state may contribute to the development of treatment resistance. The influence of residual symptoms on long-term negative outcomes remains strong even when accounting for other factors associated with greater severity such as, psychotic features, lower anti-depressant doses, and comorbidity of mental and substance use disorders.

Other longitudinal studies provide further evidence of residual symptoms' influence after treatment on adverse outcomes, regardless of treatment approach employed (Ogrodniczuk, et al., 2004; Paykel, 1998; Simon, 2000; Thase, et al., 1992). In a longitudinal study using a primary care sample, Simon (2000) found that patients with subsyndromal symptoms after antidepressant medication treatment were less likely to remit after six months when compared to patients without residual symptoms. Also, the impact of residual symptoms on prognosis was even stronger than the influence of baseline severity of depression. A longitudinal study of 64 inpatients with Major Depressive Disorder treated with medication and followed up until remission, found a strong correlation between residual symptoms and the risk of relapse (Paykel, 1998; Paykel et al., 1995). Specifically, 76% of patients with residual symptoms (HDRS = 8-18) relapsed over 10 months following remission compared to only 25% of patients without residual symptoms (HDRS $\leq$ 7). Further, when residual symptoms were separated by severity, 57% of the patients with more severe symptoms (HDRS > 12)

relapsed compared to 90% of patients with mild residual symptoms (HDRS =8 - 12). Thus, seemingly mild symptoms are powerful predictors of relapse.

A longitudinal study in the Netherlands found that patients who partially remitted from unipolar or bipolar depression were at significantly greater risk of relapse during the subsequent 12 months than patients in full remission, even despite continuing treatment. Patients with residual symptoms typically relapsed in the first four months after remission, while patients without residual symptoms experienced a recurrence of depression primarily more than 12 months after remission (Van Londen, et al., 1998). This suggests that residual symptoms not only are associated with risk for relapse, but also a quicker relapse rate than asymptomatic patients.

The presence of residual symptoms after successful psychotherapy also has been shown to predict relapse (Ogrodniczuk, et al., 2004). Thase et al., (1992) found that after response to psychotherapy, 32% of patients relapsed during a one-year follow-up, with 52% of patients who had partially responded (HDRS between 7-10) relapsing compared to 9% of patients who fully responded (HDRS < 7).

Recently it has been suggested that greater variability in the frequency of residual symptoms may also predict a more severe and chronic course of depression (Karp, et al., 2004). Patients who experienced recurrences of depression had higher levels of residual symptoms and greater variability in symptoms over time compared to patients who remained well over a three-year maintenance period regardless of receiving psychotherapy or medication treatment.

Summary

The above review highlights the substantial impact of residual symptoms on both psychosocial functioning and progression of depression course. It is apparent that residual symptoms are not benign and underlie much of the impairment associated with depression. Thus, even mild depressive symptoms cannot be equated with an asymptomatic state, and, independent of treatment modality, are associated with more psychosocial dysfunction and a chronic course, characterized by relapses, recurrences, subsequent chronic episodes, and possibly treatment resistance. Because residual symptoms are associated with great risk of a chronic depression course, the current study proposes to examine the frequency and nature of residual symptoms in a sample of chronically depressed patients. Chronically depressed patients are most expected to experience residual symptoms. The importance of treating residual symptoms is heightened due to the tremendous negative implications of chronic depression. A review of the characteristics and treatment of chronic depression will be discussed below, as the current proposal represents a chronically depressed sample, and a chronic course is associated with substantial negative outcomes.

Chronic Depression

Chronic depression is characterized by either persistent or recurrent episodes. According to the National Institute of Mental Health Collaborative Study of the Psychobiology of Depression, approximately 15 to 20 percent of patients with a major depressive episode develop a chronic course (Mueller et al., 1996). Further, the longer the episode, the lower the chances for recovering in each subsequent year, with 12 percent of patients not

recovered after five years and seven percent still not recovered after 10 years. Fifty percent of patients who recover from a major depressive episode with an underlying chronic disorder experience a recurrence of the major depressive episode within the next year (Keller, Lavori, Endicott, Coryell, and Klerman, 1983; for review see Belsher & Costello, 1988 and Coryell & Winokur, 1992). The risk of relapse is strongly related to the number of episodes a patient has had and the time between relapses seems to be shorter with each ensuing episode (Keller et al., 1983). Specifically, the probability of recurrence after one episode is less than 50%, after two episodes between 50% and 90%, and with more than three episodes greater than 90%. Also, the longer the prior episodes, the more likely the subsequent episode will maintain a chronic course (Keller, et al., 1986).

Different forms of chronic depression have been identified and include the following: (1) chronic major depression, (2) recurrent major depression without interepisode recovery (3) dysthymia (4) double depression, and (5) double depression/chronic major depression (for review see McCullough, et al., 2000, McCullough, et al., 2003). Minimal differences have been found between the types of chronically depressed individuals in terms of demographic variables, clinical characteristics, social adjustment, comorbidity, family history of psychopathology, and response to treatment (McCullough et al., 2000; McCullough, et al., 2003). Because no significant differences have been demonstrated between the types of chronic depression, the current study will collapse these forms of chronic course patterns under the heading, chronic depression.

Compared to episodic major depression, poorer treatment outcomes are associated with chronic depression. Chronic depression has been described as one of the most difficult disorders to treat in psychotherapy (McCullough, 2000) and often times is treatment resistant (Keller, 1990, Akiskal, 1997). Because chronic depression frequently goes unrecognized and misdiagnosed, patients with chronic forms of depression are often mistreated. When depression is left untreated, the cost of depression exceeds $40 billion annually in the United States alone (Greenberg, Stiglin, Finkelstein, & Berndt, et al., 1993). Of this $40 billion, 28 percent is attributable to direct costs of medical, psychiatric and pharmacological care, 17% to mortality costs relating to lost capital due to depression-related suicides, and 55% to morbidity costs such as financial loss due to worker absenteeism and a reduction in productive capacity due to depression. While the financial cost of depression is extreme, the emotional costs associated with chronic depression are even greater and of grave concern. Chronic forms of major depression are associated with more frequent suicide attempts and hospitalizations when compared to episodic depression (Klein et al., 1998). In addition, a large proportion of health care services are utilized by chronically depressed adults (Howland, 1993; Weissman & Klerman, 1977). Due to the substantial emotional and economic burden of chronic depression, researchers have directed their attention on developing treatments for chronic or treatment resistant depression. The following is a review of treatments for chronic depression.

Chronic Depression Treatment

A variety of approaches to treat chronic forms of depression have been implemented and include adapting existing treatments, such as IPT and CBT, augmenting treatment with medications, or developing a new treatment specific to chronic depression. As with non-chronic depression, inconsistencies in operationalizing treatment outcome data hinder our ability to make accurate conclusions regarding treatment effectiveness. However, the efficacy of using traditional approaches to treat chronically depressed patients is even more discouraging, with the percentage of patients significantly responding typically around or below 50% (Browne, et al. 2002; de Jong, Treiber, Henrich, 1986; Fennell & Teasdale, 1986; Gonzoles, Lewinsohn, & Clarke, 1985; Harpin, Liberman, Marks, Stern, Bohannon, 1982; Hellerstein et al., 1993; Keller, Hanks, & Klein, 1996; Keller et al., 1998; Kornstein et al., 1998; Mercier, Stewart, Quitkin, 1992; Stravynski, Shahar, Verreault, 1991).

The research presented thus far has focused primarily on the application or modification of existing psychotherapeutic modalities to chronic depression. Only one psychotherapeutic treatment to date has been developed specifically for meeting the unique needs of the chronically depressed patient. Cognitive-Behavioral Analysis System of Psychotherapy (CBASP) was developed and introduced in the 1980s by McCullough (1984) to treat chronically depressed patients and is the psychotherapeutic approach investigated in the current proposal. CBASP (McCullough, 2000) is a time-limited, manualized treatment that integrates elements of cognitive-behavioral therapy and interpersonal psychotherapy and is based on social learning principles described by

Bandura (1977), cognitive-emotional development proposed by Piaget (1954/1981), operant psychology of B.F. Skinner (1953) and the interpersonal theory of Kiesler (1996). The primary components are the "therapist role enactment" and situational analysis. McCullough (2006) describes the "therapist role enactment" as containing principles of learning theory, with behavioral contingencies and modeling as central components. It is comprised of the choreography of therapists' personal reaction contingencies (contingent personal responsivity) and the interpersonal discrimination exercise (IDE), a discrimination task to enable patients to discriminate between problematic past relationships and the therapeutic relationship (McCullough, 2000; Riso, McCullough, & Blandino, 2003). Situational analysis is a social problem-solving algorithm that helps patients recognize their influence on their environment (perceived functionality). It consists of three phases: elicitation, remediation and generalization. The elicitation phase involves the patient describing an interpersonal situation in which they identify the event, their interpretation of the event, their behavior, the actual outcome of the event, their desired outcome, and finally whether their desired outcome was achieved. The next phase, remediation, involves revising their interpretations, behaviors, and/or desired outcomes to facilitate the achievement of a favorable outcome. The final stage is the generalization phase, in which the patient and therapist explore what was learned and its applicability to other situations. Situational analysis is completed at every session beginning with the third session.

Since its introduction, CBASP has undergone two studies evaluating its effectiveness, one preliminary trial (McCullough, 1991) and one large-scale randomized

clinical trial using the same dataset as in the current study (Keller et al., 2000). The first study investigated CBASP's effectiveness with 10 dysthymic patients, which found that 90% of patients were remitted after a two-year follow-up. These encouraging results prompted the inclusion of CBASP in a large-scale randomized clinical trial for the treatment of chronic depression, comparing nefazodone, CBASP and the combination of both. Results suggested that CBASP and medication alone were equally effective in treatment outcomes, as 55% of the patients in the nefazodone group and 52% of the patients in the CBASP group significantly responded to treatment. Most impressive was the advantage of a combined treatment approach over the single-modality approach, where 85% of patients who completed combination treatment significantly improved. These findings are notable in that within chronically depressed samples, response rates rarely rise above 50% regardless of treatment approach.

Although the above study demonstrates promise in the treatment of chronic depression, the rates of residual symptoms were not clearly identified. Based on the profound negative outcomes associated with residual symptoms, researchers and clinicians have emphasized that the goal of treatment outcome should be a full treatment response with an asymptomatic state (Keller, 2003; Rush & Trivedi, 1995). Rush (1996) states, "We have grown too accustomed to accepting an improved status as good enough and no longer require a true clinical remission". In the spirit of achieving an asymptomatic full remission state, current research has focused on the treatment of residual symptoms, and major questions regarding the underlying theoretical deliberation as to what residual symptoms represent are being asked (Menza, Marin, Sokol-Opper,

2003). Specifically whether they are part of a prolonged illness, represent a different phase of the illness, are independent of the depressive episode and represent a different psychiatric or medical disorder, or develop as a result of treatment. While the focus on treatment implications is relevant and important, the nature of residual symptoms with specific treatment approaches should first be examined to guide treatment planning.

As reviewed previously, most outcome studies only report global response rates to treatment, rather then answering questions at the molecular level or symptom profile. Furthermore, few studies have examined the specific symptoms that are "left over" after treatment and most studies simply report the presence or absence of symptoms (Ogrodiczuk, et al., 2004; Simon, 2000; Thase et al., 1992). Also, studies examining individual residual symptoms have not distinguished between an acute verses chronic depression course and inconsistently define treatment response and residual symptoms across studies. The studies that have examined the nature of individual residual symptoms associated with particular treatments have either focused on residual symptoms present among partial responders or full responders to treatment. Therefore, the following review of these studies is organized by degree of response.

Individual Residual Symptoms

Partial response

An essential aspect of the definition of partial remission is that not all symptoms fully resolve and instead the patient only partially responds to treatment. Therefore, it is reasonable to suspect a high prevalence of residual symptoms among this population. In a longitudinal study examining residual symptoms after treatment with various anti-

depressant medications, Paykel, et al. (1995) found partial remission rates of 32% as defined by a post treatment score between 8 and 18 on the HDRS (below the level of definite research diagnostic criteria for major depression, but still experiencing symptoms). Residual symptoms were deemed present when the total depression score assessed by the HDRS was eight or greater. Based on this definition, 47 percent of the patients with residual symptoms reported moderate or greater depressed mood, impairment in work and activities, psychic anxiety, and genital symptoms. The following symptoms were present to at least a mild degree in almost half of the partial responders: guilt, suicidal thoughts, middle insomnia, and general somatic symptoms. The symptoms that either were less common or absent were associated with more severe depression and included somatic or "biological" symptoms such as late insomnia, psychomotor and cognitive retardation, agitation, hypochondriasis, weight loss, and loss of insight. When compared with patients defined as "without residual symptoms" (HDRS = 1-7), patients with residual symptoms had higher mean ratings on all individual symptoms except the less common symptoms listed above. When individual symptoms were measured by the Clinical Interview for Depression, a similar pattern emerged, as the most common residual symptoms were depressed mood, guilt, hopelessness, work and interests, psychic anxiety, phobic and somatic anxiety, and anorexia.

Full response

While it would be expected to uncover residual symptoms among partial responders, it is more compelling that residual symptoms are also common among full responders. In fact, Fava, Grandi, Zielezny, Canestrari, and Morphy (1994) found a high

prevalence of residual symptoms in a sample of 49 depressed outpatients who fully responded (no longer met syndromal criteria and had no more than minimal symptoms) to three to five months of antidepressant medication treatment. All but six of the patients (87.8%) who successfully responded to treatment continued to have residual symptoms when assessed with the Paykel Clinical Interview for Depression, with a mean of 2.7 symptoms per patient. The most prominent residual symptoms were generalized anxiety (72.5%), somatic anxiety (55%), and irritability (40%).

Nierenberg et al. (1999) further examined the nature of residual symptoms in a sample of 108 depressed outpatients who were considered full responders (HRSD < 7) after treatment with fluoxetine for 8 weeks. Only 19 patients (17.6%) who fully responded were without residual symptoms after treatment. The most common symptoms were sleep disturbances (44%), fatigue (38%), and diminished interest or pleasure (27%). Over 20% of patients also had "left over" symptoms of guilt and concentration problems. However, depressed mood and suicidal ideation were rarely reported post treatment.

The frequency and severity of residual symptoms comparing the SSRI, fluoxetine, with the SNRI, reboxetine, was examined by Nelson, Portera, Leon (2005). No distinction of depression course was reported for this sample; therefore the sample likely consisted of both acute and chronically depressed participants. Among responders, defined by a 50% improvement on the HDRS, the most frequent symptoms present after eight weeks of treatment were psychic anxiety, lack of interest, somatic anxiety and depressed mood, occurring in over 40% of the sample. No residual symptom differed

significantly between treatment groups in prevalence or severity. However, greater decreased libido was found after treatment with fluoxetine compared to roboxetine, which was interpreted as a side effect associated with the use of an SSRI.

Although residual symptoms have been found to be highly prevalent after both medication treatment and psychotherapy (Thase et al., 1992), no known study to date has reported on individual residual symptoms after response to psychotherapy. Because various treatments target different mechanisms of action, it is reasonable to expect diverse clusters of residual symptoms resulting from different treatments. Paykel et al.'s study found that after medication treatment, residual symptoms were more commonly of a psychosocial or "psychic" rather than "biological" nature, thus suggesting that psychosocial aspects of depression were not as affected by treatment as somatic symptoms (Paykel, 1998; Paykel et al., 1995). Therefore, medication may adequately target the symptoms that are thought to be more biologically based since the mechanism of change is a biological approach. A psychotherapeutic approach may produce a greater impact on psychosocial or psychic symptoms compared to somatic symptoms.

Only one study known to date examined the relationship between individual symptoms of depression and treatment modality (Karp, et al., 2004). However, this study did not compare residual symptoms as a function of treatment modality, but instead examined the relationship between treatment approach and the variability of symptoms throughout the course of maintenance treatment of residual symptoms. One hundred and twenty-eight patients with recurrent depression who were currently in remission after treatment with imipramine and interpersonal psychotherapy were randomized to receive

either Interpersonal Psychotherapy, Imipramine, the combination of both, or placebo as maintenance treatment. The variability in symptom presentation did not differ between treatment groups; each treatment group had similar rates of residual symptom variance. The items on the HDRS that showed the greatest variability were loss of energy, loss of libido, initial, middle and delayed insomnia, psychological and somatic anxiety, depressed mood and weight loss. Further, patients who exhibited greater variability in residual symptoms were at greater risk to experience a recurrence than those with less symptom variability. This study implies that an aim of treatment is not only full recovery, but to reduce the variability of residual symptoms in order to prevent recurrences.

When comparing these studies, inconsistent results in the types of residual symptoms emerge. Discrepancies in findings may be due to several reasons, including variability of definitions of treatment response, medications used, and patient populations. Although recommendations have been published regarding the definition of treatment outcome and response, studies continue to vary in operationalizing the presence of residual symptoms and response criteria. Also, the measures used to identify individual symptoms vary between studies. For example, Paykel et al. (1995) defined partial response as between 8-18 on the HDRS, which yields a wide range of severity. Also, the presence of residual symptoms was defined as a score of 8 or greater, while participants with a score of less than 8 were considered "without residual symptoms." However, Nierenberg et al. (1999) defined the presence of residual symptoms as subthreshold symptoms based on SCID-P criteria. Also, the samples of the studies

differed in terms of depression course, severity, and type of responders. Most studies did not differentiate patients with a chronic course from those with episodic or acute depression (Fava, et al., 1994; Nierenberg et al., 1999; Paykel, et al., 1995). This distinction is important as a chronic course has unique developmental and interpersonal characteristics associated with greater negative outcomes, and calls for specific treatment approaches (McCullough, 2000; Riso, Miyatake,& Thase, 2002; Schaefer, et al., 2004). Patients with chronic depression are at great risk of having residual symptoms. Further, some populations consisted of primarily inpatients (Paykel et al., 1995), a potentially more severely depressed population, while others were primarily outpatients (Fava, et al, 1994; Nierenberg, et al, 1999).

Statement of the Problem

While extant research has demonstrated that residual symptoms are associated with a chronic course (Judd et al., 2000), characterized by relapse and poor long term outcomes, there is a dearth of research investigating the type of residual symptoms associated with different treatment modalities. Considering the goal of treatment is full remission without residual symptoms, it is important to examine which symptoms or symptom clusters are "left over" after completion of acute treatment. Identifying these symptoms that are not targeted by a particular treatment is an essential step in treatment planning and maintenance therapy. Residual symptoms carry many treatment implications, which provide challenges to the existing medical model approach of treating depression as a syndrome rather than treating individual symptoms.

When comparing studies examining the nature of individual residual symptoms, inconsistent results emerge (Fava et al, 1994; Nierenberg et al., 1999; Paykel et al, 1995). Discrepancies in findings may be due to several reasons, including the variability of definitions of treatment response, medications used, and patient populations. Some of the most common symptoms that have been identified after response to pharmacotherapy are depressed mood, impairment in work and activities, psychic, somatic and generalized anxiety, genital symptoms, and irritability. Currently, no study has identified or examined the nature of individual residual symptoms after psychotherapy treatment.

Although research on residual symptoms has bourgeoned in recent years, important questions remain. First, little attention has been given to identifying what individual symptoms persist after specific treatments and whether these symptoms cluster into related symptomatic groups (Menza, Marin, & Sokol-Opper, 2003). Second, the etiology of residual symptoms continues to be unclear. Residual symptoms are generally assumed to be core depressive symptoms that have not resolved after treatment. However, there may be many contributing factors for the development of residual symptoms, such as the result of treatment (i.e. medication side effect) or psychiatric or medical comorbidities independent of depression (Menza, Marin, & Sokol-Opper, 2003). Unfortunately, research focusing on residual symptoms has not directly examined this relationship. One study by Nierenberg et al. (1999) evaluated whether medication side effects were misinterpreted as residual symptoms, by looking at the prevalence of pre treatment fatigue and insomnia in patients who exhibited residual symptoms of fatigue and insomnia. It was found that in many of these patients, sleep dysfunction (91.7%) and fatigue (92.7%) were common also during pre treatment. Thus, results suggest that these symptoms should be considered residual symptoms rather than medication side effects. Although the distinction between depressive symptoms and medication reactions continues to be vague, this study advances our knowledge of the nature of residual symptoms.

The current study examined among a chronically depressed population, differences in individual residual symptoms and clusters between treatment modality

(nefazodone, CBASP, and the combination of both) and treatment response (full responders, partial responders, non-responders). The following hypotheses were tested:

1) Residual symptoms will differ in frequency and severity between types of treatment response (non-responders, partial responders and full responders). Non-responders are expected to be more likely to report the presence of residual symptoms compared to partial and full responders. Further, it is predicted that partial responders, compared to full responders, will be more likely to report the presence of residual symptoms and demonstrate greater severity of symptoms.

2) Residual symptoms will differ in frequency and symptom clusters between types of treatments, with fewer symptoms with the combination treatment group than the CBASP alone or medication alone groups. Residual symptoms of a psychosocial nature (i.e. guilt, psychic anxiety, irritability, anhedonia, helplessness, hopelessness, suicidal ideation, worthlessness, rejection sensitivity) are predicted to occur more frequently and at a higher severity in the Nefazodone group compared to the CBASP group. Alternatively, individual residual symptoms that are of a somatic nature (i.e. insomnia, somatic anxiety, psychomotor agitation/retardation, loss of libido, fatigability, appetite/weight) are predicted to occur more frequently and at greater severity among the CBASP group when compared to the Nefazodone group. Symptom clusters are also expected to differ between the

CBASP and Nefazodone group. Based on the five factor model of the HDRS found by Grunebaum et al. (2005) and the three factor model of the IDS-SR (Rush, 1996), it is predicted that the Nefazodone group compared to the CBASP group will report a greater number of residual symptoms on the following factors: Psychic Depression and Disturbed Thinking on the HDRS and Cognitive/mood on the IDS-SR, as these factors are of a psychosocial and cognitive nature. Conversely, the CBASP group is expected to report a greater number of residual symptoms represented by the Sleep Disturbance and Loss of Motivated Behavior factors of the HDRS and IDS-SR, as these factors represent somatic symptoms.

3) Due to potential side effects of medication, it is hypothesized that the medication and combination group will demonstrate an emergence of somatic symptoms (i.e. sedation, nausea, dry mouth, dizziness, and light-headedness), whereas the psychotherapy group would demonstrate no change in type of symptoms from pre to post treatment.

Method

Participants

Six hundred and eighty-one adults meeting DSM-IV criteria for chronic depression were recruited from 12 academic centers between June 1996 and December 1997. Chronic depression was defined as encompassing the following course trajectories: (1) chronic major depressive disorder (at least 2 years duration), (2) recurrent major depression without inter-episode recovery with a total duration of continuous illness of at least two years, (3) double depression (a current major depression superimposed on a preexisting dysthymic disorder, and (4) double depression/chronic major depression (chronic major depressive episode with antecedent dysthymia) (for review see McCullough, et al., 1996, McCullough, et al., 2000). Minimal differences have been found between the types of chronically depressed individuals in terms of demographic variables, clinical characteristics, social adjustment, comorbidity, family history of psychopathology, and response to treatment (McCullough et al., 2000; McCullough, et al., 2003). Because no significant differences have been demonstrated between the types of chronic depression, the current proposal will collapse these forms of chronic course patterns under the heading, chronic depression.

To be eligible for the study, patients had to be between the ages of 18 and 75 years and have had a score of at least 20 on the 24-item Hamilton Rating Scale for

Depression (HRSD) at screening and, after a two-week period without antidepressant medication, at baseline. Laboratory tests, electrocardiography (if clinically indicated), and physical examinations were performed at the time of screening. Patients were required to discontinue taking monoamine oxidase inhibitors and fluoxetine at least four weeks before study entry, neuroleptic agents at least six months before entry, and other psychotropic medications at least two weeks before entry.

Participants were excluded from the study if they had any of the following: a history of seizures, abnormal findings on electroencephalography, severe head trauma, or stroke; evidence suggesting they were at high risk for suicide; a history of psychotic symptoms or schizophrenia, bipolar disorder, an eating disorder (if it had not been in remission for at least one year), obsessive compulsive disorder, dementia; antisocial, schizotypal, or severe borderline personality disorder; a principal diagnosis of panic, generalized anxiety disorder, social anxiety disorder, or posttraumatic stress disorders or any substance-related abuse or dependence disorder (except involving nicotine) within six months before the study began; an absence of a response to a previous adequate trial of nefazodone or Cognitive Behavioral Analysis System of Psychotherapy; an absence of a response to three previous adequate trials of at least two different classes of antidepressants or electroconvulsive therapy or to two previous adequate trials of empirical psychotherapy in the three years preceding the study; a serious, unstable medical condition; or a positive urine screen for drugs of abuse. Women of child bearing potential had to agree to use adequate contraception during the study. Patients were not

allowed to take anxiolytic agents, sedatives, hypnotic agents, or any others types of sleep aids (pharmacologic or behavioral) during the study.

Design and Procedure

The study design was a single-blind, randomized clinical trial. All patients provided written informed consent. Patients who were eligible based on the above inclusion/exclusion criteria were randomized to receive nefazodone (Serzone, Bristol-Myers Squibb), Cognitive Behavioral Analysis System of Psychotherapy, or the combination of nefazodone and psychotherapy. Randomization was completed by a central computerized randomization schedule in a 1:1:1 ratio by the sponsor, Bristol Myers Squibb.

The measures were administered by clinical raters certified to have a high rate of inter-rater reliability and level of procedural integrity. Attempts to mask the patient's treatment assignment from the clinical raters were made at all sites, in which the rater was located at a separate location so that he or she could not see patients attending treatment sessions.

Treatment Groups

Nefazodone. The initial dose of nefazodone was 200 mg per day (100mg twice per day) and was increased to 300 mg per day during the second week. Thereafter, the dose was increased by 100 mg per day to a maximum of 600 mg per day, to maximize the efficacy of the drug without producing intolerable side effects. To remain in the study, patients had to be receiving a dose of at least 300 mg per day by week three. Visitations for medications were 15 to 20 minutes long. Psychopharmacologists followed a

published manual for clinical management, consisting of an evaluation of concomitant use of medications and symptoms, side effects, and illnesses between sessions. Side effects that were reported in this sample were consistent with the known side effects of the drug, and included headache, somnolence, dry mouth, nausea, and dizziness.

Cognitive behavioral-analysis system of psychotherapy (CBASP). CBASP is a structured, time-limited psychotherapy approach that uses a social problem solving algorithm that teaches patients "perceived functionality", where the patient understands the interpersonal effect of their behavior. CBASP also followed a manual specifying twice-weekly sessions during weeks one through four, and weekly sessions during weeks five through 12. Twice weekly sessions were allowed until week eight if the patient was not adequately performing a learned social problem solving procedure. A total of 16-20 individual 45-60 minute sessions were conducted. CBASP was conducted by psychotherapists with at least two years experience after earning a degree of either M.D. or Ph.D. or at least five years experience after earning an M.S.W., who attended a two-day training workshop and me mastery of treatment procedures. Each psychotherapist was required to conduct two pilot cases, in which their sessions were videotaped and their performance was evaluated. In the current study all psychotherapy sessions were videotaped and reviewed by supervisors weekly to assess the psychotherapists' adherence to the treatment procedures.

Combination group. All of the above principles were followed with the patients receiving the combination of nefazodone and CBASP.

Measures

Structured Clinical Interview for Axis I DSM-IV Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1995). The SCID was administered at the first screening visit to diagnose Axis I disorders according to the criteria of the DSM-IV.

Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First, Spitzer, Gibbon, Williams, & Benjamin, 1994). Selected sections of the SCID-II were conducted to assess exclusion Axis II diagnoses, including antisocial, avoidant, borderline, dependent, obsessive-compulsive and schizotypal.

Depression Course Timeline. The Depression Course Timeline is a collateral visual-graphing timeline procedure to trace the longitudinal course of depression (McCullough, Klein & Holzer, as described in McCullough et al., 1996). The depression course timeline was used to diagnose a chronic course. The timeline measures the course of depression by assessing the individual's current mood, based on the following scale: normal, mild, moderate, severe. The participant then retrospectively graphed their mood intensity level each month over the course of the previous three years, with their current mood acting as a comparison or anchor point. This graphing procedure is recommended by researchers and clinicians to aid in the differentiation of depressive course and diagnosis of chronic depression (McCullough et al., 1996; Schaefer et al., 2004).

Hamilton Depression Rating Scale (HDRS; Hamilton, 1967). The HDRS-24 was conducted as an interview to assess the severity of depression. Items are presented as a Likert-type scale, ranging from 0-4, with a few items ranging 0-2. Zero represents the absence of the symptom, one equals mild severity, and two or greater reflects moderate to

severe impairment. The HDRS was administered by an independent rater at screening, baseline (week 0), and at weeks 1 through 4, 6, 8, 10, and 12. Inconsistent results have emerged regarding the number and type of factors yielded by the HDRS. Ranges between two and eight have been found across studies and with a variety of populations and three to five factors have been reported among samples of depressed patients. In a review of 15 studies reporting factor analysis of the HDRS, Bagby, Ryder, Schuller, and Marshall (2004) found consistent support for an insomnia factor and the presence of general depression and anxiety/agitation factors. However, the multidimensionality of the HDRS remains unclear. In the current study, a five-factor structure of the HDRS (Psychic Depression, Anxiety, Sleep Disturbance, Loss of Motivated Behavior, and Disturbed Thinking) was tested as a function of treatment modality (Grunebaum et al., 2005) (See Appendix A for five-factor structure). This model was used for a number of reasons. First, it is based on the HDRS-24, which was used in the current study, rather than the 17-item HDRS, on which other factor structures have been based (Pancheri et al., 2002; Brown et al, 1995; Gibbons et al., 1993). Second, the five-factor structure was found with a sample of depressed inpatients, which may better represent a chronic population than other structures found with episodically-depressed outpatients (Arnow & Constantino, 2003; Klein & Santiago, 2003; Klein et al., 1999). Lastly, the factors represent clusters of affective, cognitive, and somatic symptoms that theoretically correspond with the current study's hypotheses; thus this factor model allows a much closer test of the study's hypotheses than other models.

The HDRS has adequate psychometric properties (Bagby et al., 2004). In depression samples, the internal reliability was adequate, with Cronbach's alpha coefficients ranging from .48 to .86. Inter-rater reliabilities ranged from .90 to .97. The HDRS also demonstrated adequate convergent, divergent and predictive validity, specifically for the total HDRS score.

Inventory for Depressive Symptomatology-Self-report (IDS-SR; Rush et al., 1986, 1996). The IDS-SR is a self-report measure used to assess the severity of depression consisting of 30 items that span the DSM-III-R and DSM-IV criterion symptoms. A factor analysis of the IDS-SR revealed the following three factors: cognition/mood, anxiety/arousal, and sleep disturbance (Rush et al., 1996). These three factors were tested in the current study across treatment modality. The IDS-SR was administered at the baseline (week 0), and at weeks 2, 4, 6, 8, 10, 12. Items are presented as a Likert-type scale, of which 28 items range from zero to three. Item-total correlations, Cronbach's alpha, and measures of concurrent validity have established acceptable psychometric properties (Rush et al., 2005). Concurrent validity has been found to be high ($r = .81$ to .84) (Corruble, Legrand, Duret, Charles, & Guelfi, 1999). This scale has been noted to be sensitive to change over time and closely paralleled the HDRS in the current sample (Rush et al., 2005).

Personal Information Questionnaire (PIQ). The PIQ was developed by the sponsor specifically for use in the current study in order to obtain demographic information and psychiatric history. The PIQ consists of items measuring demographic information, such as age, gender, education, ethnicity, employment, relationship status,

etc. The PIQ also contains items related to the receipt of previous and current treatment for mental health problems, such as medication and psychotherapy.

Response Groups

The following definitions of treatment outcome were based on recommendations provided by Frank et al. (1991). See Table 4 for the number of subjects in each response group by treatment group. The current study's definitions of response groups are listed below and derived from the baseline visit and the last three assessment visits (visit 10, visit 12, and the final visit). After twelve weeks of treatment, some completers were brought back for further assessment if needed because they did not get their minimum number of sessions in by visit 12. Thirty percent (n=150) of patients were brought back for another assessment visit, which did not differ across treatment groups. This final assessment visit was held usually between one and four weeks after visit 12, with the exception of two patients whose last visits were 38 and 62 days after visit 12. Then, out of the last three data points (visit 10, 12 or last visit) patients had to demonstrate $\geq$ 50% improvement from baseline and a score of 15 or less on at least two visits to be considered a responder.

Non-responders. Patients were categorized as non-responders if their total HDRS score was greater than 14 and they did not demonstrate $\geq$ 50% improvement on two out of the three last visits (visit 10, 12 or final visit).

Partial responders. Partial responders were operationalized as no longer meeting syndromal criteria for major depressive disorder but continuing to evidence more than minimal symptoms. Therefore, out of the last three data points (visit 10, 12 or last visit)

patients had to have demonstrated a greater than or equal 50 percent improvement from baseline and a score of between 8 and 14 on at least two visits to be considered a partial responder.

Full responders. Patients who responded to treatment with at least a 50% reduction in their total HDRS score from baseline *and* a score of seven or less on at least two out of the final three visits were classified as full responders.

Statistical Analyses

First, baseline demographic variables were compared across treatment and response groups using an analysis of variance for continuous variables and chi-square analyses of categorical variables. Second, in order to compare residual symptom prevalence rates across response groups (Hypothesis 1), the presence or absence of each symptom on the HDRS and IDS-SR was examined as a function of Response group (No Response, Partial, Full) using chi-square analyses. The analyses were conducted for both the HDRS and the IDS-SR in order to examine residual symptom data identified both through a clinician-administered interview and self-report modality. Although many symptoms overlap across measures, each measure also has unique items that are not shared by both.

Third, in order to test treatment group comparisons of residual symptom prevalence (Hypothesis 2), the presence or absence of each symptom on the HDRS and

IDS-SR was examined as a function of Treatment group (CBASP Only, Nefazodone Only, Combination) using chi-square analysis.[1]

Fourth, a 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) analysis of variance (ANOVA) for each HDRS and IDS-SR factor was conducted to compare clusters of residual symptoms among treatment and response groups (Hypothesis 2), with the number of residual symptoms endorsed within each factor as the dependent variable. Non-responders were excluded since residual symptoms are defined as symptoms that remain after responding to treatment, and the Combination group was excluded because the primary interest is in the differences between pharmacotherapy and psychotherapy. This approach also allowed for the identification of interactions between treatment and response groups on residual symptom clusters. For the HDRS, items were grouped into factors based on a five-factor model (Factor 1: Psychic Depression, Factor 2: Anxiety, Factor 3: Sleep Disturbance, Factor 4: Loss of motivated behavior, and Factor 5: Disturbed Thinking) found by Grunebaum et al. (2005) (See Appendix A for the five-factor structure). For the IDS-SR, the well-established three-factor model of the IDS-SR (Factor 1: Cognitive/mood, Factor 2: Anxiety/arousal, Factor 3: Sleep Disturbance) was examined (Rush et al., 1996) (See Appendix B for the three-factor structure).

In order to further understand whether treatment groups not only differed in the prevalence of specific residual symptoms and clusters of symptoms, but also in their

[1] Chi-square analyses were also completed for each HDRS and IDS-SR item using a cutoff of two or greater (moderate degree) to classify the symptom as present. No differences were found between treatment groups for all of the items.

severity of individual symptoms (Hypothesis 2), mean differences were compared for individual HDRS and IDS-SR items among response and treatment groups using 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) ANOVAs. Next, in order to test whether residual symptoms emerged after treatment (Hypothesis 3), pre treatment prevalence rates (presence, absence) of each item of the HDRS and IDS-SR were compared to post treatment (presence, absence) using chi-square analyses for responders regardless of treatment group. Finally, in order to examine treatment group differences in the emergence of residual symptoms, the presence or absence of each symptom on the HDRS and IDS-SR at pre treatment was examined as a function of treatment group (CBASP, Nefazodone, Combination) using chi-square analyses for those participants who reported the symptom at post treatment.

It is important to note that due to the multiple independent analyses conducted, there is an increased risk for making a Type I error (falsely finding significant differences). Due to our primary interest in describing the nature of residual symptoms across response and treatment groups, the following analyses should be interpreted in a descriptive manner, so that a $p < .05$ criterion for alpha is used as a way to help identify symptoms that may differ across groups, rather than in a strict hypothesis-testing way.

Results

Baseline Demographic Characteristics

The sample consisted of 681 participants who were randomized to one of the three treatment conditions: nefazodone only (n = 226, 33.2%), CBASP only (n = 228, 33.5%), or the combination of nefazodone and CBASP (n = 227, 33.3%). Of the 681 participants who underwent randomization, a total of 519 participants completed the study. The present study is focused on residual symptoms in those participants who completed the study; therefore, no further analyses were conducted with non-completers. Among the 519 completers, 167 (32.2%) participants had received nefazodone alone, 173 (33.3%) underwent CBASP alone, and 179 (34.5%) received the combination of both nefazodone and CBASP. Of completers, 183 (35.3%) participants did not respond to treatment, 203 (39.1%) partially responded, and 131 (25.2%) participants fully responded based on the criteria recommended by Frank et al. (1991).[2] A 3 X 3 chi-square analysis of treatment response (No Response, Partial, Full) by treatment group (CBASP Only, Nefazodone Only, Combination) was completed and is represented in Table 4. Significant differences in treatment response were found between treatment groups, X^2

[2] These results differ from those presented in the original article by Keller et al. (2000) (No response = 183 (35.4%), Satisfactory response = 182 (35.2%), remission = 152 (29.4%) due to different cutoff requirements for remission status. The original paper used a cutoff of 8 or less on the HDRS to be classified as achieving remission, while the present study required a cutoff of 7 or less on the HDRS. Therefore, when using stricter criteria, 21 participants' status changed from full remission to partial remission.

(4,517) = 52.86, $p < .001$). The rates of full response and partial response among the Combination group were higher than the CBASP alone and nefazodone alone treatment groups. There were no significant differences in treatment response between the CBASP only and Nefazodone only group.[3]

Table 4. *Rates of response as a function of treatment group*

Group	Nefazodone	CBASP	Combination	Significance		
	Number of Participants (%)			CBASP vs. Nefazodone	Combo vs. CBASP	Combo vs. Nefazodone
No. of pts.	167	173	179		X^2	
Response	92 (55.8)	90 (52)	152 (84.9)	.47	44.30***	35.40***
Full	30 (18.2)	35 (20.2)	66 (36.9)	.23	11.91**	14.91***
Partial	62 (37.6)	55 (31.8)	86 (48)	1.25	9.68**	3.84*
No response	73 (44.2)	83 (48)	27 (15.1)			

Note. *** $p < .001$, ** $p < .01$, * $p = .05$

Demographic characteristics of completers are presented in Table 5. The average age of completers was 43.84 years. Three hundred thirty-five (64.5%) were female. The majority were Caucasian (91.9%), followed by African American (2.9%), Hispanic (2.5%), and Asian (1.2%). Three hundred and eighty-eight participants (74.8%) reported being employed either part time or full time. A large segment of the sample was currently married (n = 204, 39.3%). One hundred and thirty-nine participants were single/never married (26.8%), 138 participants were divorced or separated (26.6%), 29 were in a relationship or co-habitating (5.6%), and nine were widowed (1.7%). No significant differences were found between treatment groups or between response groups with respect to baseline demographics.

[3] Rates of full and partial response differ slightly with the results presented in the original paper by Keller, et al. (2000) (Combination: Full response=42%, partial=43%; Nefazodone: Full=22%, partial=34%; CBASP: Full=24, partial=28); however, the pattern of significance is consistent with the original paper.

Table 5: *Demographics of treatment groups and response groups of completers*

	Treatment Group			*Significance*	*Response Group*			*Significance*	
	CBASP	*Nefazodone*	*Combo*		*No response*	*Partial response*	*Full response*		
Demographics	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*F*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*F*	*Totals (N=519)*
Age	43.89 (10.58)	42.81 (10.53)	44.76 (9.85)	1.55	43.42 (11.17)	43.64 (9.66)	44.80 (10.20)	.75	43.84 (10.33)
	Percent	*Percent*	*Percent*	X^2	*Percent*	*Percent*	*Percent*	X^2	
Female	63.0%	62.3%	68.2%	1.58	65.6%	66.5%	59.5%	1.85	64.5%
Male	37.0%	37.7%	31.8%		34.4%	33.5%	40.5%		35.5%
Ethnicity				15.42				8.70	
White	90.8%	91.0%	93.9%		90.7%	90.6%	95.4%		91.9%
Black	4.0%	1.8%	2.8%		2.7%	3.9 %	1.5%		2.9%
Asian	2.3%	1.2%	0.0%		2.2%	.5%	.8%		1.2%
Hispanic	1.2%	5.4%	1.1%		2.2%	3.9%	.8%		2.5%
Other	1.7%	0.6%	2.2%		2.2%	1.0%	1.5%		1.5%
Marital Status				7.36				7.96	
Single	31.8%	25.7%	22.9%		30.1%	26.6%	22.1%		26.8%
Married	36.4%	38.9%	42.5%		38.3%	38.4%	42.7%		39.3%
Widowed	1.2%	2.4%	1.7%		2.2%	1.5%	1.5%		1.7%
Divorced	19.1%	22.8%	25.1%		20.2%	22.7%	24.4%		22.4%
Separated	4.6%	4.2%	3.9%		3.3%	6.4%	2.3%		4.2%
Co-habitating	6.9%	6.0%	3.9%		6%	4.4%	6.9%		5.6%
Employment				5.11				2.11	
Unemployed	17.9%	18.6%	18.4%		18.0%	19.2%	16.0%		18.3%
Employed	75.7%	76.6%	72.1%		73.8%	74.4%	77.9%		74.8%
Retired	2.9%	3.0%	6.7%		4.9%	3.4%	4.6%		4.2%
Student	3.5%	1.8%	2.8%		3.3%	3.0%	1.5%		2.7%
Totals	173	167	179	519	183	203	131	517[a]	N=519

Note. [a] The responses of two participants in the Nefazodone group could not be determined because no scores were available for the HDRS at week 10 or 12.

Residual Symptoms

Prevalence

The presence of residual symptoms after treatment was a common occurrence in all treatment and response groups (See Tables 6 through 9). Given that the mere presence of residual symptoms is associated with negative outcomes (Paykel, 1998), and that even mild residual symptoms appear to be associated with powerful consequences (e.g. increased work and social impairment, suicide risk, health care utilization, risk for chronicity) (Judd et al., 1997; Mintz et al., 1992; Ogrodiczuk, et al., 2004) and represent the most common expression of illness activity in depression course (Judd & Akiskal, 2000), it was decided to examine the presence versus absence of a reported residual symptom, regardless of severity. The presence of a residual symptom was defined as at least a mild (>0) level on each HDRS and IDS-SR item at treatment completion.

Based on the HDRS, 98 percent of the sample reported at least one symptom still present at least to a mild degree after treatment completion, with no significant differences between response groups or between treatment groups. Overall, the most commonly reported residual symptoms on the HDRS were depressed mood (N=333, 64.4%), psychic anxiety (n=331, 64%), decreased energy (n=326, 63.1%), somatic anxiety (n=293, 56.7%), decreased interest in work/activities (n=286, 55.3%), decreased libido (n=284, 54.9%) and hopelessness (n=278, 53.8%).

As with the HDRS, the IDS-SR revealed a high rate of residual symptoms, with 98.2% of the sample reporting at least one residual symptom after treatment. The most common symptoms were concentration problems (n=365, 71.9%), future pessimism

(n=363, 71.7%), somatic complaints (n=345, 69.4%), middle insomnia (n=340, 66.9%), and sad mood (n=318, 62.7%).

Response groups

Clinician Administered Interview (HDRS). In order to test Hypothesis One, that residual symptoms would differ in frequency between response groups, the presence or absence of each item on the HDRS was examined as a function of response group (No Response, Partial, Full) using chi-square analyses. Results suggested that even among full responders, 90.8% (n=119) reported experiencing at least one residual symptom to a mild degree (see Table 6). The most common symptoms reported among full responders were psychic anxiety (n=51, 38.1%), somatic anxiety (n=39, 29.8%), depressed mood (n=37, 28.2%), decreased libido (n=35, 26.7%), and decreased energy (n=34, 26%). These same symptoms were the most common among partial responders, with over 50% of participants reporting each symptom at treatment completion.

When comparing response groups, significant differences in the presence of residual symptoms emerged. As expected, a greater percentage of participants in the non-response group reported the presence of residual symptoms when compared to responders on every HDRS-24 symptom with the exception of lack of insight, which none of the participants in the sample reported, psychomotor agitation, and weight loss. Within responders, significantly more partial responders than full responders endorsed symptoms of depressed mood, guilt, suicide, early and middle insomnia, decreased work and activities, psychomotor retardation, psychic anxiety, somatic anxiety, decreased appetite, decreased energy, genital symptoms, diurnal variation, depersonalization,

helplessness, hopelessness, and worthlessness. Partial and full responders did not differ in endorsement of late insomnia, psychomotor agitation, hypochondriasis, weight loss, paranoid symptoms, and obsessive/compulsive symptoms. It is also important to identify differences in symptom prevalence at baseline when examining residual symptoms. There were no differences at baseline between response groups for all HDRS items, with the exception of suicide and worthlessness. At baseline, full responders were significantly less likely to endorse suicidal ideation (X^2 (4, 517) = 9.17, p = .01) and worthlessness (X^2 (4, 517) = 8.66, $p < .05$) than both non-responders and partial responders.

Table 6. *Presence of HDRS items (>0) as a function of response group at treatment completion*

HDRS Item	Response Group No. of participants (%)			Total	Overall Significance
	Non-Response (n=183)	Partial Response (n=203)	Full Response (n=131)	N=517	X^2
1. Depressed Mood	177 (96.7)[a]	119 (58.6)[b]	37 (28.2)[c]	333 (64.4)	161.06***
2. Guilt	154 (84.2)[a]	76 (37.4)[b]	23 (17.6)[c]	253 (48.9)	151.18***
3. Suicide	87 (47.5)[a]	13 (6.4)[b]	2 (1.5)[c]	102 (19.7)	139.55***
4. Early Insomnia	79 (43.2)[a]	44 (21.7)[b]	16 (12.2)[c]	139 (26.9)	41.84***
5. Middle Insomnia	124 (67.8)[a]	67 (33)[b]	22 (16.8)[c]	213 (41.2)	91.13***
6. Late Insomnia	95 (51.9)[a]	35 (17.2)[b]	23 (17.6)[b]	153 (29.6)	67.73***
7. Work/Activities	169 (92.3)[a]	96 (47.3)[b]	21 (16)[c]	286 (55.3)	188.63***
8. Psychomotor Retardation	76 (41.5)[a]	24 (11.8)[b]	5 (3.8)[c]	105 (20.3)	81.91***
9. Psychomotor Agitation	53 (29)[a]	43 (21.2)[ab]	21 (16)[b]	117(22.6)	7.69*
10. Psychic Anxiety	157 (85.8)[a]	123 (60.6)[b]	51 (38.9)[c]	331 (64)	74.50***
11. Somatic Anxiety	150 (82)[a]	104 (51.2)[b]	39 (29.8)[c]	293 (56.7)	88.74***
12. Appetite	67 (36.6)[a]	28 (13.8)[b]	4 (3.1)[c]	99 (19.1)	61.73***
13. Energy	174 (95.1)[a]	118 (58.1)[b]	34 (26)[c]	326 (63.1)	160.10***
14. Decreased Libido	146 (79.8)[a]	103 (50.7)[b]	35 (26.7)[c]	284 (54.9)	89.21***
15. Hypochondriasis	64 (35)[a]	38 (18.7)[b]	17 (13)[b]	119 (23)	24.33***
16. Weight Loss	30 (16.4)[a]	20 (9.9)[ab]	6 (4.6)[b]	56 (10.8)	11.36**
17. Insight	0	0	0	0	----------
18. Diurnal Variation	85 (46.4)[a]	72 (35.5)[b]	20 (15.3)[c]	177 (34.2)	33.19***
19. Depersonalization	22 (12)[a]	6 (3)[b]	0 (0)[c]	28 (5.4)	25.49**
20. Paranoid Symptoms	17 (9.3)[a]	3 (1.5)[b]	0 (0)[b]	20 (3.9)	22.85**
21. Obsessive/ Compulsive	13 (7.1)[a]	5 (2.5)[b]	1 (.8)[b]	19 (3.7)	10.06**
22. Helplessness	128 (69.9)[a]	45 (22.2)[b]	6 (4.6)[c]	179 (34.6)	167.02***
23. Hopelessness	163 (89.1)[a]	93 (45.8)[b]	22 (16.8)[c]	278 (53.8)	168.97***
24. Worthlessness	146 (79.8)[a]	78 (38.4)[b]	26 (19.8)[c]	250 (48.4)	123.02***

Note. Different letters indicate significantly different frequencies using Chi-square analyses.

* $p < .05$, ** $p < .01$, *** $p < .001$

Self-Report (IDS-SR). Chi-square analyses were conducted to examine the presence or absence of each of the 30 IDS-SR item as a function of response group (No Response, Partial, Full). Similar to the HDRS data, results suggested that even among full responders, 93.7% (n=118) reported experiencing at least one residual symptom to a

mild degree (see Table 7). The most common symptoms reported among full responders were middle insomnia (n=67, 51.5%), future pessimism (n=54, 41.5%), concentration problems (n=53, 41.1%), mood variation (n=48, 37.2%), anxiety/tension (n=43, 33.1%), rejection sensitivity (n=40, 30.8%), irritability (n=36, 27.7%), decreased libido (n=37, 28.7%), and somatic complaints (n=34, 26.2%). Also consistent with HDRS results, these same symptoms were the most common among partial responders along with sad mood and fatigability, with over 50% of participants reporting these symptoms at treatment completion. When comparing response groups, significant differences in the presence of residual symptoms emerged. As expected, a greater percentage of participants in the non-response group reported the presence of residual symptoms when compared to responders on every IDS-SR item with the exception of mood variation, in which non-responders did not differ from partial responders, X^2 (1, 376) = 2.14, p = .14. Similarly, within responders, most of the IDS-SR items were reported more frequently by partial responders than full responders, with the exception of 6 out of 30 items: hypersomnia, appetite increase, weight decrease, weight increase, concentration and suicidal thoughts. We also examined pre treatment differences between response groups on each IDS-SR item. There were no differences at baseline between response groups for all IDS-SR items, with the exception of irritability, decreased libido, and panic/phobic symptoms.[4] When taking into account baseline prevalence of each IDS-SR item, the above results remained.

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[4] At baseline, full responders (n=123, 97.6%) were significantly more likely to report irritability (X^2 (4, 502) = 5.22, p < .05) than both non-responders (n=164, 92.1%) and partial responders (n=181, 91.4%). However, baseline panic/phobic symptoms (X^2 (4, 504) = 6.78, p < .05) were less frequently reported among full responders (n=48, 37.8%) compared to non-responders (n=94, 52.5%) and partial responders

Table 7. *Endorsement of IDS-SR items as a function of response group at treatment completion*

	Response Group No. of participants (%)			Total	Overall Significance
IDS-SR Item	No response	Partial response	Full response	N=518	X^2
1. Initial Insomnia	97 (53.9)[a]	57 (28.8)[b]	24 (18.5)[c]	178 (35)	47.19***
2. Middle Insomnia	148 (82.2)[a]	125 (63.1)[b]	67 (51.5)[c]	340 (66.9)	34.22***
3. Early Awakening	85 (47.2)[a]	36 (18.2)[b]	14 (10.8)[c]	135 (26.6)	63.12***
4. Hypersomnia	60 (33)[a]	48 (23.8)[b]	28 (21.2)[b]	136 (26.4)	6.60*
5. Sad Mood	174 (97.2)[a]	114 (57.6)[b]	30 (23.1)[c]	318 (62.7)	180.67***
6. Irritability	150 (83.8)[a]	108 (54.3)[b]	36 (27.7)[c]	294(57.9)	98.98***
7. Anxiety/Tension	150 (83.8)[a]	108 (54.3)[b]	43 (33.1)[c]	301 (59.3)	83.61***
8. Mood Reactivity	157 (88.2)[a]	64 (32.2)[b]	20 (15.5)[c]	241 (47.6)	189.93***
9. Mood Variation	111 (62.7)[a]	110 (55.3)[a]	48 (37.2)[b]	269 (53.3)	20.03***
10. Mood Quality	168 (93.9)[a]	80 (40.2)[b]	16 (12.4)[c]	264 (52.1)	217.79***
11. Appetite Decrease	58 (31.9)[a]	39 (19.3)[b]	8 (6.1)[c]	105 (20.3)	31.66***
12. Appetite Increase	45 (24.7)[a]	23 (11.4)[b]	17 (12.9)[b]	85 (16.5)	14.05**
13. Weight Decrease	53 (29.1)[a]	36 (17.8)[b]	22 (16.7)[b]	111 (21.5)	9.71**
14. Weight Increase	51 (28.0)[a]	38 (18.8)[b]	23 (17.4)[b]	112 (21.7)	6.69*
15. Concentration	168 (93.3)[a]	144 (72.4)[b]	53 (41.1)[b]	365 (71.9)	101.47***
16. Self Criticism/ Blame	138 (76.7)[a]	50 (25.1)[b]	16 (12.3)[c]	204 (40.1)	160.61***
17. Future Pessimism	170 (95.0)[a]	139 (70.6)[b]	54 (41.5)[c]	363 (71.7)	106.28***
18. Suicidal Thoughts	96 (53.6)[a]	16 (8.1)[b]	5 (3.8)[b]	117 (23.1)	145.84***
19. Interest In Activities	162 (90.5)[a]	83 (42.1)[b]	18 (13.8)[c]	263 (52.0)	189.81***
20. Energy/Fatigability	166 (92.2)[a]	102 (51.3)[b]	30 (23.3)[c]	298 (58.7)	154.79***
21. Pleasure/Enjoyment	157 (87.2)[a]	92 (46.2)[b]	24 (18.6)[c]	273 (53.7)	149.72***
22. Decreased Libido	153 (85.0)[a]	108 (54.3)[b]	37 (28.7)[c]	298 (58.7)	100.89***
23. Psychomotor Retardation	132 (73.3)[a]	56 (28.1)[b]	15 (11.5)[c]	203 (39.9)	139.01***
24. Agitation	91 (50.8)[a]	51 (25.6)[b]	19 (14.6)[c]	161 (31.7)	51.20***
25. Somatic Complaints	125 (69.4)[a]	86 (43.2)[b]	34 (26.2)[c]	345 (69.4)	59.83***
26. Sympathetic Arousal	86 (47.8)[a]	57 (28.8)[b]	20 (15.4)[c]	163 (32.1)	37.97***
27. Panic/Phobic Symptoms	57 (31.8)[a]	33 (16.6)[b]	9 (6.9)[c]	99 (19.5)	31.57***
28. Constipation/Diarrhea	84 (46.7)[a]	50 (25.1)[b]	18 (13.8)[c]	152 (29.9)	42.32***
29. Rejection Sensitivity	142 (79.3)[a]	106 (53.5)[b]	40 (30.8)[c]	288 (56.8)	73.79***
30. Leaden Paralysis	122 (68.2)[a]	85 (42.9)[b]	22 (16.9)[c]	229 (45.2)	80.47***

Note. Different subscripts represent significant differences
*$p < .05$, **$p < .01$, ***$p < .001$

(n=97, 49.0%). Also, full responders (n=97, 77.0%) were less likely to report decreased libido (X^2 (4, 503) = 6.05, $p < .05$) at baseline compared to partial responders (n=173, 87.4%), but not non-responders (n=150, 83.8%).

Treatment groups

Clinician Administered Interview (HDRS). In order to test Hypothesis Two, that residual symptoms would differ in frequency between treatment groups, the presence or absence of each symptom on the HDRS was examined as a function of treatment group (CBASP Only, Nefazodone Only, Combination) using chi-square analyses for responders (N=334) with each of the 24 HDRS items (See Table 8). Partial and full responders were combined in these analyses due to 1) the possible risk of significantly losing power as a result of a reduced sample size in each group, and 2) although fewer full than partial responders reported residual symptoms, the most common symptoms appeared to be similar between response groups. For most items, the treatment groups did not significantly differ in their report of the presence of individual residual symptoms. Only three of the HDRS items differentiated treatment groups: early insomnia, obsessive/compulsive symptoms and hopelessness (see Figure 1 for illustration of significant results). Early insomnia was more frequently reported by participants in the CBASP group than the Nefazodone and Combination groups, X^2 (2, 336) = 11.26, $p <$ .01. However, obsessive/compulsive symptoms were more common within the Nefazodone group compared to the CBASP and Combination groups, X^2 (2, 336) = 15.73, $p < .001$. Finally, the CBASP and Nefazodone groups were significantly more likely to endorse hopelessness than the Combination group. In general, the Combination group was less likely to report residual symptoms than the other groups. Baseline comparisons between treatment groups revealed no significant differences regarding the presence of baseline symptoms for all HDRS items, with the exception of psychic

anxiety.[5] After controlling for baseline psychic anxiety, the results continued to support no significant differences between treatment groups for post treatment psychic anxiety.

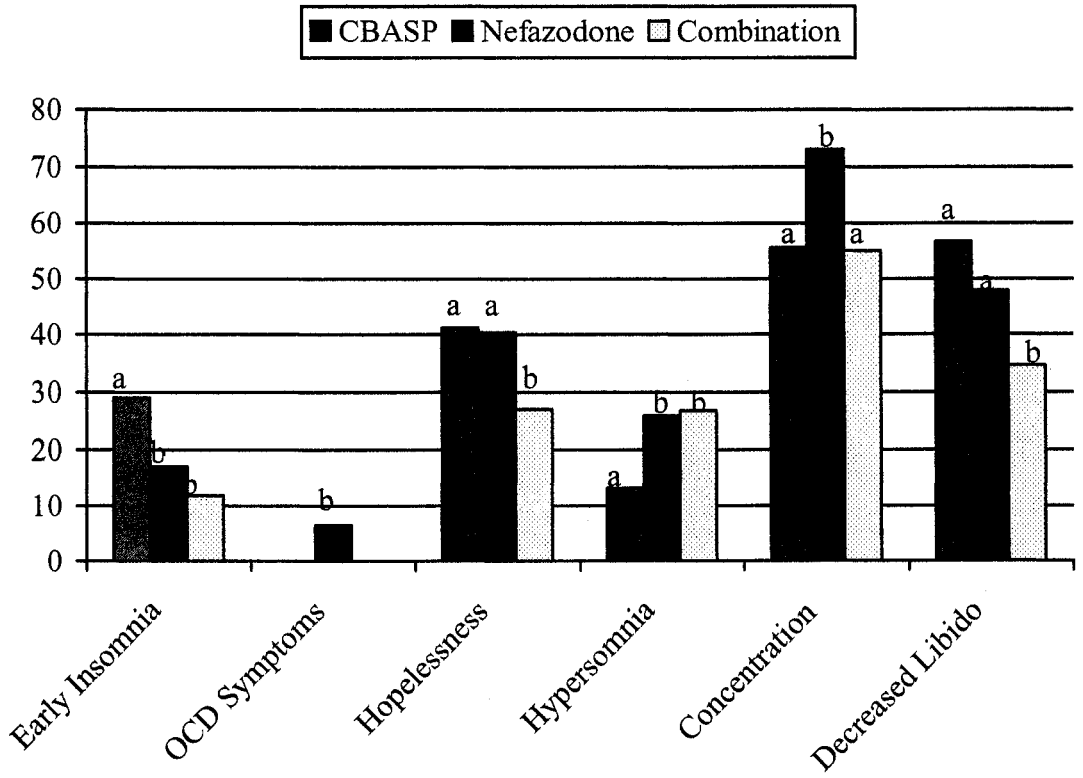
[5] The Combination group (n=151, 99.3%) was significantly more likely to report psychic anxiety at baseline than the Nefazodone group (n=83, 90.2%) and CBASP group (n=86, 95.6%), X^2 (2, 334) = 11.90, $p < .01$.

Table 8. *Endorsement of HDRS items (>0) as a function of treatment group at time of treatment completion*

	Treatment Group No. of participants (%)[a]			Total	Overall Sig.	CBASP vs. Nef.	CBASP vs. Combo	Nef. vs. Combo
HDRS Item	CBASP	Nefazodone	Combo	N=334	X^2	X^2	X^2	X^2
1. Depressed Mood	50 (55.6%)	40 (42.6%)	68 (44.7)	158 (47.6)	3.70			
2. Guilt	29 (32.2%)	25 (26.6%)	47 (30.9%)	101 (30.1)	.79			
3. Suicide	2 (2.2%)	6 (6.4%)	7 (4.6%)	15 (4.5%)	1.88			
4. Early Insomnia	26 (28.9)	16 (17)	18 (11.8)	60 (17.9)	11.26**	3.68*	11.04**	1.31
5. Middle Insomnia	24 (26.7)	27 (28.7)	40 (26.3)	91 (27.1)	.18			
6. Late Insomnia	20 (22.2)	14 (14.9)	25 (16.4)	59 (17.6)	1.94			
7. Work/Activities	29 (32.2)	31 (33)	57 (37.5)	117 (34.8)	.89			
8. Psychomotor Retardation	7 (7.8)	10 (10.6)	12 (7.9)	29 (8.6)	.67			
9. Psychomotor Agitation	12 (13.3)	23 (24.5)	29 (19.1)	64 (19)	3.70			
10. Psychic Anxiety	51 (56.7)	45 (47.9)	79 (52)	175 (52.1)	1.43			
11. Somatic Anxiety	33 (36.7)	37 (39.4)	74 (48.7)	144 (42.9)	3.99			
12. Appetite	8 (8.9)	8 (8.5)	16 (10.5)	32 (9.5)	.33			
13. Energy	33 (36.7)	43 (45.7)	77 (50.7)	153 (45.5)	4.46			
14. Decreased Libido	44 (48.9)	41 (43.6)	54 (35.5)	135 (41.4)	4.43			
15. Hypochondriasis	16 (17.8)	14 (14.9)	25 (16.4)	55 (16.4)	.28			
16. Weight Loss	6 (6.7)	8 (8.5)	12 (7.9)	26 (7.7)	.23			
17. Insight								
18. Diurnal Variation	29 (32.2)	22 (23.4)	41 (27)	92 (27.4)	1.82			
19. Depersonalization	0	3 (3.2)	3 (2)	6 (1.8)	2.73			
20. Paranoid Symptoms	0	0	3(2)	3 (.9)	3.66			
21. Obsessive/ Compulsive	0	6 (6.4)	0	6 (1.8)	15.73***	5.94*	-------	9.95**
22. Helplessness	9 (10)	16 (17)	26 (17.1)	51 (15.2)	2.56			
23. Hopelessness	37 (41.1)	38 (40.4)	41 (27)	116 (34.5)	7.01*	.009	5.17*	4.84*
24. Worthlessness	27 (30)	30 (31.9)	47 (30.9)	104 (31)	.08			

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

[a] Responders only (partial and full combined



* Different letters indicate significant differences.

Figure 1. Significant differences in prevalence between treatment groups

Self-Report (IDS-SR). In order to compare self-reported prevalence rates of residual symptoms between treatment groups, the presence or absence of each symptom on the IDS-SR was examined as a function of treatment group (CBASP Only, Nefazodone Only, Combination) using chi-square analyses. As with the HDRS analyses, partial and full responders were combined, and the presence of a residual symptom was defined as at least a mild (>0) level on each IDS-SR item at treatment completion. For most items, the treatment groups did not significantly differ in their report of the presence of individual residual symptoms. Only three of the IDS-SR items differentiated treatment

groups: hypersomnia, concentration, and decreased libido (see Figure 1 for illustration of significant results). Consistent with the HDRS data that the CBASP Only group was more likely to report early insomnia than the Nefazodone Only and Combination groups, hypersomnia (increased sleep) was more frequently reported by participants in the Nefazodone and Combination groups than the CBASP group X^2 (2, 334) = 6.54, p <.05. There were no differences between Nefazodone and the Combination groups for hypersomnia. Difficulty concentrating was more common within the Nefazodone group compared to the CBASP and Combination groups, X^2 (2, 328) = 8.58, p < .05. Decreased libido was more frequently reported among the CBASP and Nefazodone groups when compared to the Combination group, X^2 (4, 328) = 11.83, p < .01). Baseline comparisons between treatment groups revealed significant differences in the presence of baseline symptoms for appetite increase, self-criticism/blame, and energy.[6] After controlling for baseline prevalence for these items, the results continued to support the above findings.

[6] The Combination group was significantly more likely to report appetite increase (n=68, 45.0%) at baseline than the CBASP group (n=27, 29.7%, X^2 (1, 242) = 5.62, p < .05). Baseline self-criticism/blame was less frequently reported among the Nefazodone group (n=70, 78.7%) than the CBASP (n=79 (90.8%) and Combination group (n=129, 87.8%), X^2 (2, 323) = 6.06, p < .05. Lastly, the Nefazodone group (n=84, 94.4%) was less likely to report fatigability compared with the Combination group (n=145, 99.3%), X^2 (1, 235) = 5.41, p < .05.

Table 9. *Presence of IDS-SR items as a function of treatment group at treatment completion*

	Treatment Group No. of participants (%)			Total	Overall Significance
IDS-SR Item	CBASP	Nefazodone	Combo	N=334	X^2
1. Initial Insomnia	28 (31.1)	23 (25.6)	30 (20.3)	81 (24.7)	3.59
2. Middle Insomnia	57 (63.3)	48 (53.3)	87 (58.8)	192 (58.5)	1.86
3. Early Awakening	16 (17.8)	11 (12.2)	23 (15.5)	50 (15.2)	1.09
4. Hypersomnia	12 (13.2)[a]	24 (25.8)[b]	40 (26.7)[b]	76 (22.8)	6.54*
5. Sad Mood	41 (45.6)	39 (43.8)	64 (43.0)	144 (43.9)	.16
6. Irritability	42 (46.7)	37 (41.1)	65 (43.6)	144 (43.8)	.57
7. Anxiety/Tension	46 (51.1)	41 (45.6)	64 (43.0)	151 (45.9)	1.51
8. Mood Reactivity	25 (27.8)	24 (26.7)	35 (23.6)	84 (25.6)	.57
9. Mood Variation	42 (46.7)	49 (54.4)	67 (45.3)	158 (48.2)	2.00
10. Mood Quality	29 (32.2)	26 (28.9)	41 (27.7)	96 (29.3)	.56
11. Appetite Decrease	8 (8.8)	17 (18.3)	22 (14.7)	47 (14.1)	3.50
12. Appetite Increase	13 (14.3)	6 (6.5)	21 (14.0)	40 (12.0)	3.74
13. Weight Decrease	15 (16.5)	14 (15.1)	29 (19.3)	58 (17.4)	.80
14. Weight Increase	14 (15.4)	16 (17.2)	31 (20.7)	61 (18.3)	1.16
15. Concentration	50 (55.6)[a]	65 (73.0)[b]	82 (55.0)[a]	197 (60.1)	8.58*
16. Self Criticism/ Blame	22 (24.4)	16 (17.8)	28 (18.8)	66 (20.1)	1.52
17. Future Pessimism	58 (65.2)	53 (59.6)	82 (55.0)	193 (59.0)	2.38
18. Suicidal Thoughts	6 (6.7)	10 (11.2)	5 (3.4)	21 (6.4)	5.78
19. Interest In Activities	30 (33.7)	34 (38.2)	37 (24.8)	101 (30.9)	5.12
20. Energy/Fatigability	34 (37.8)	35 (38.9)	63 (42.6)	132 (40.2)	.63
21. Pleasure/Enjoyment	36 (40.0)	34 (37.8)	46 (31.1)	116 (35.4)	2.26
22. Decreased Libido	51 (56.7)[a]	43 (47.8)[a]	51 (34.5)[b]	145 (44.2)	11.83**
23. Psychomotor retardation	17 (18.9)	26 (28.9)	28 (18.8)	71 (21.6)	3.91
24. Agitation	18 (20.0)	23 (25.6)	29 (19.5)	70 (21.3)	1.36
25. Somatic Complaints	34 (37.8)	32 (35.6)	54 (36.2)	120 (36.5)	.10
26. Sympathetic Arousal	19 (21.1)	19 (21.1)	39 (26.4)	77 (23.5)	1.24
27. Panic/ Phobic Symptoms	13 (14.4)	11 (12.2)	18 (12.1)	42 (12.8)	.31
28. Constipation/ Diarrhea	16 (17.8)	21 (23.3)	31 (20.8)	68 (20.7)	.85
29. Rejection Sensitivity	44 (48.9)	36 (40.0)	66 (44.6)	146 (44.5)	1.44
30. Leaden Paralysis	26 (28.9)	28 (31.1)	53 (35.8)	107 (32.6)	1.35

Note. Different subscripts represent significant differences

*$p < .05$, **$p < .01$

Residual Symptom Clusters

Clinician Administered Interview (HDRS). In order to investigate clusters of residual symptoms across response and treatment groups, items were grouped into factors based on a five-factor model (Factor 1: Psychic Depression, Factor 2: Anxiety, Factor 3: Sleep Disturbance, Factor 4: Loss of motivated behavior, and Factor 5: Disturbed Thinking) found by Grunebaum et al. (2005) (See Appendix A for the five-factor structure). We computed the factor scores by totaling the number of items that were reported to be present at treatment completion within each factor, generating a total number of residual symptoms for each factor.

A series of 2 Response (partial, full) X 2 Treatment (CBASP only, Nefazodone only) analyses of variance was used to explore mean differences in residual symptom factor scores between response groups and between treatment groups. Non-responders were excluded since residual symptoms are defined as symptoms that remain after responding to treatment, and the Combination group was excluded because the primary interest is in the differences between pharmacotherapy and psychotherapy. The results are presented in Table 10.

Table 10. *Mean number of items endorsed per HDRS factor as a function of response and treatment group at treatment completion*

	Treatment Group Mean (SD)		Response Group Mean (SD)		Total	Treatment M.E. [a] (df = 1, 178)		Response M.E. [b] (df = 1, 178)		Interaction (df = 1, 178)	
HDRS Factor[c]	CBASP (n=90)	Nef. (n=92)	Partial (n=117)	Full (n=65)	N=182	F	ES	F	ES	F	ES
Psychic Depression	1.79 (1.40)	1.74 (1.60)	2.17 (1.56)	1.03 (1.07)	1.76 (1.50)	1.29	.01	28.80***	.14	3.97*	.02
Anxiety	1.24 (.96)	1.27 (1.02)	1.45 (1.02)	.91 (.82)	1.26 (.99)	.02	.00	13.49***	.07	.13	.00
Sleep Disturbance	.78 (.95)	.59 (.70)	.79 (.89)	.48 (.69)	.68 (.83)	1.26	.01	6.72*	.04	3.83	.02
Loss of motivated behavior	.97 (.81)	.95 (.82)	1.15 (.81)	.62 (.70)	.96 (.81)	.40	.00	19.75***	.10	.40	.00
Disturbed Thinking	00 (.00)	.10 (.33)	.07 (.29)	.02 (.12)	.05 (.24)	4.91*	.03	1.71	.01	1.71	.01

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

[a]Tx M.E.=Treatment Main Effect

[b]Response M.E. = Response Main Effect

[c]The number of items represented by each factor: Psychic Depression (n=7), Anxiety (n=4), Sleep Disturbance (n= 3), Loss of Motivated Behavior (n=4), Disturbed Thinking (n=4)

As expected, there was a significant main effect of response group on residual symptom clusters for all but one of the HDRS factors. Overall, partial responders reported a greater mean number of residual symptoms represented by the psychic depression, anxiety, sleep disturbance, and loss of motivated behavior factors than full responders. No response group main effects were found for the disturbed thinking factor.

There was a significant treatment group main effect for only one of the HDRS factors: Disturbed thinking. The Nefazodone group demonstrated a significantly higher mean number of residual symptoms on the disturbed thinking factor than the CBASP group. There were no other treatment group main effects for any of the other HDRS factors.

A significant interaction between response group and treatment group was found for psychic depression. Post-hoc analyses using an independent samples t-test was conducted to examine the specific nature of the interaction. Figure 2 illustrates that for partial responders no differences in mean number of items reported on the psychic depression factor emerged between the Nefazodone (M=2.26, SD=1.60) and CBASP (2.07, SD=1.51) group, t (115) = .64, p =.52. However, in full responders the CBASP group (M=1.34, SD=1.08) reported significantly more items compared to the Nefazodone group (M=.67, SD=.96), t (63) = -2.64, p <.05. No other significant interactions were found.[7]

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[7] The above analyses were repeated at baseline in order to control for pre treatment differences in clusters of symptoms. A response group main effect was found for the psychic depression factor (F (1, 178) = 6.36, p <.05) and loss of motivated behavior factor (F (1, 178) = 3.24, p <.10), in which full responders reported fewer symptoms in each factor at baseline then partial responders. A treatment group main effect was found for the anxiety factor (F (1, 178) = 3.18, p <.10) and loss of motivated behavior factor (F (1, 178) =

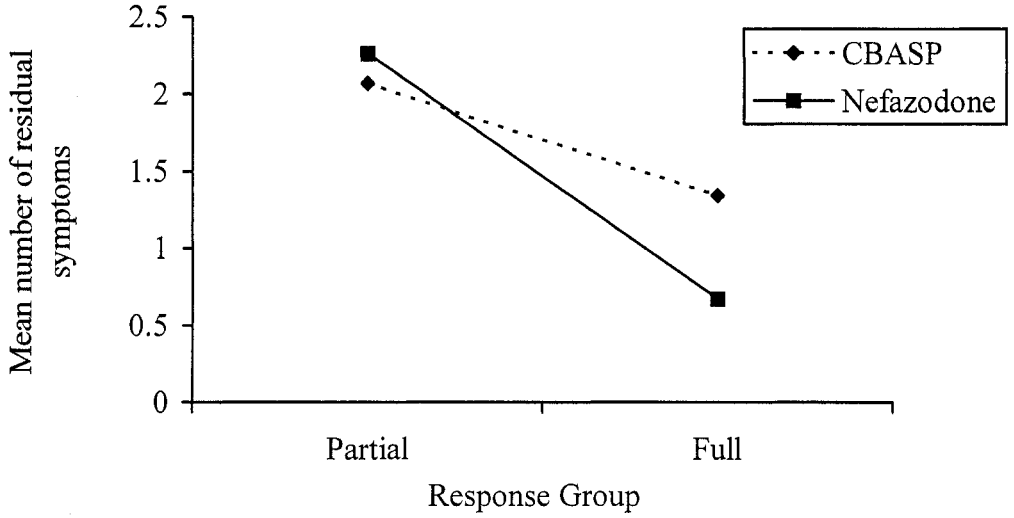

Figure 2. Response by treatment interaction of mean number of items reported in HDRS psychic depression factor.

Self-Report (IDS-SR). Clusters of self-reported residual symptoms between treatment groups and response groups were evaluated using the well-established three-factor model of the IDS-SR (Factor 1: Cognitive/mood, Factor 2: Anxiety/arousal, Factor 3: Sleep Disturbance; Rush et al., 1996). As with the HDRS factors, the IDS-SR factor scores were computed by totaling the number of items that were reported to be present at treatment completion within each factor. The factor structure of the IDS-SR items is presented in Appendix B.

3.21, $p < .10$), in which the Nefazodone group reported fewer baseline symptoms in each factor than the CBASP group. Using baseline factor scores as covariates, post treatment results were sustained.

A series of 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) analyses of variance was used to explore mean differences in residual symptom factor scores between response groups and treatment groups. Consistent with the HDRS analyses, only responders (partial and full) and those participants treated with CBASP only and nefazodone only were included in subsequent analyses. The results are presented in Table 11.

Table 11. *Mean number of items present per IDS-SR factor as a function of response and treatment group at treatment completion*

	Treatment Group Mean (SD)		Response Group Mean (SD)		Total	Tx M.E. [a]			Response M.E. [b]			Interaction		
IDS-SR Factor[c]	CBASP (n=90)	Nef. (n=92)	Partial (n=117)	Full (n=65)	N=182	F	df	ES	F	df	ES	F	df	ES
Cognitive/ Mood	5.28 (3.29)	5.24 (3.70)	6.31 (3.34)	3.42 (2.95)	5.26 (3.49)	.25	1, 172	.00	33.02***	1, 172	.16	.08	1, 172	.00
Anxiety/ Arousal	3.99 (2.92)	4.16 (2.76)	4.84 (2.78)	2.69 (2.39)	4.07 (2.84)	.04	1, 175	.00	26.56***	1, 175	.13	.17	1, 175	.00
Sleep Disturbance	1.46 (1.04)	1.41 (1.23)	1.59 (1.20)	1.15 (.96)	1.43 (1.13)	.04	1, 176	.00	6.29*	1, 176	.04	.48	1, 176	.00

Note. * $p < .05$, *** $p < .001$

[a]Tx M.E.=Treatment Main Effect

[b]Response M.E. = Response Main Effect

[c]The number of items represented on each factor: Cognitive/Mood (n=16), Anxiety/Arousal (n=12), Sleep Disturbance (n=5)

Similar to the HDRS data, there was a significant response group main effect of residual symptom clusters for all of the IDS-SR factors. Overall, partial responders reported a higher mean number of residual symptoms represented by the cognitive/mood, anxiety/arousal, and sleep disturbance factors than full responders. However, in contrast to the HDRS, no main effects for treatment group or interactions were found for the IDS-SR factors. Baseline analyses revealed no significant main effects or interactions between treatment and response groups.

Severity

In order to further understand whether treatment groups not only differed in the prevalence of specific residual symptoms and clusters of symptoms, but also in their severity of individual symptoms (Hypothesis 2), a 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) ANOVA was conducted for each individual HDRS and IDS-SR item to compare mean differences between response groups and treatment groups. Also, this approach allowed for the examination of interactions between treatment and response groups.

Clinician Administered Interview (HDRS). As with the residual symptom pattern analyses, only responders (partial and full) and those participants treated with CBASP only and nefazodone only were included in the subsequent analyses. Also, two items (insight and paranoid symptoms) were not included in the analyses due to both resulting in a mean of zero across all response and treatment groups. The mean HDRS item scores as a function of response and treatment group are presented in Table 12.

Table 12. *Mean HDRS item scores as a function of response and treatment group at treatment completion*

	Treatment Group Mean (SD)		Response Group Mean (SD)		Total [a]	Treatment M.E		Response M.E.		Interaction	
HDRS Item	CBASP (n=90)	Nefazodone (n=92)	Partial (n=117)	Full (n=65)	N=182	F	ES	F	ES	F	ES
1. Depressed Mood	.62 (.61)	.51 (.69)	.68 (.68)	.37 (55)	.57 (.65)	3.62	.02	10.77**	.06	3.80	.02
2. Guilt	.38 (.59)	.28 (.52)	.40 (.60)	.20 (.44)	.33 (.56)	2.17	.01	6.11*	.03	.50	.00
3. Suicide	.02 (.15)	.07 (.25)	.06 (.24)	.02 (.12)	.04 (.20)	.63	.00	1.87	.01	2.88	.02
4. Early Insomnia	.37 (.63)	.24 (.56)	.36 (.62)	.20 (.54)	.30 (.60)	.78	.00	3.22	.02	5.05*	.03
5. Middle Insomnia	.36 (.64)	.37 (.66)	.45 (.70)	.20 (.51)	.36 (.65)	.07	.00	6.36**	.03	.97	.01
6. Late Insomnia	.31 (.63)	.18 (.49)	.25 (.57)	.25 (.56)	.25 (.57)	1.41	.01	.01	.00	.84	.01
7. Work/Activities	.44 (.74)	.50 (.85)	.65 (.90)	.15 (.36)	.47 (.79)	.04	.00	17.53***	.09	.00	.00
8. Psychomotor Retardation	.09 (.32)	.12 (.36)	.14 (.39)	.05 (.21)	.10 (.34)	.63	.00	2.75	.02	1.22	.01
9. Psychomotor Agitation	.16 (.42)	.25 (.44)	.20 (.42)	.22 (.45)	.20 (43)	2.7	.02	.16	.00	.16	.00
10. Psychic Anxiety	.74 (.74)	.76 (.89)	.91 (.83)	.48 (.73)	.75 (.82)	.19	.00	12.31**	.07	1.49	.01
11. Somatic Anxiety	.59 (.90)	.63 (.93)	.77 (1.00)	.32 (.66)	.61 (91)	.01	.00	10.41**	.06	.44	.00
12. Appetite	.10 (.34)	.09 (.28)	.13 (.36)	.03 (.17)	.09 (.31)	.08	.00	4.20*	.02	.15	.00
13. Energy	.43 (.62)	.59 (.71)	.68 (.73)	.22 (.41)	.51 (.67)	1.80	.01	20.89***	.11	.06	.00
14. Decreased Libido	.71 (.81)	.64 (.81)	.79 (.85)	.48 (.69)	.68 (.81)	.67	.00	6.54*	.04	.11	.00
15. Hypochondriasis	.19 (.42)	.15 (.36)	.19 (.41)	.14 (.35)	.17 (.39)	.30	.00	.71	.00	.15	.00
16. Weight Loss	.09 (.36)	.13 (.45)	.13 (.45)	.08 (.32)	.11 (.41)	.17	.00	.62	.00	.50	.00
18. Diurnal Variation	.37 (.57)	.29 (.57)	.39 (.60)	.22 (.48)	.33 (.57)	1.31	.01	4.49*	.03	.55	.00
19. Depersonalization	0 (0)	.03 (.18)	.00 (.00)	.03 (.16)	.02 (.13)	1.52	.01	1.52	.01	1.52	.01
21. Obsessive/Compulsive	0 (0)	.07 (.25)	.04 (.20)	.02 (.12)	.03 (.18)	4.32*	.02	.74	.00	.74	.00
22. Helplessness	.11 (.35)	.22 (.51)	.25 (.52)	.02 (.12)	.16 (.44)	.98	.01	12.09**	.06	2.03	.01
23. Hopelessness	.48 (.62)	.50 (.70)	.63 (.73)	.23 (.43)	.49 (.66)	.19	.00	16.94***	.09	1.97	.01
24. Worthlessness	.32 (.52)	.38 (.59)	.44 (.61)	.20 (.40)	.35 (.55)	.06	.00	7.75**	.04	.94	.01

Note. [a] df = 1, 178

* $p < .05$, ** $p < .01$, *** $p < .001$

As expected, there was a significant main effect of response group on residual symptom means for many of the HDRS items, including depressed mood, guilt, middle insomnia, work and activities, psychic anxiety, somatic anxiety, appetite, energy, decreased libido, diurnal variation, helplessness, hopelessness, and worthlessness. For each of these items, partial responders reported significantly higher mean severity ratings at the end of treatment than full responders. No main effects of response group were found for suicide, early insomnia, late insomnia, psychomotor retardation, psychomotor agitation, hypochondriasis, weight loss, depersonalization, or OCD symptoms.

There was a significant main effect of treatment group on residual symptom means for only one of the HDRS items: OCD symptoms. The Nefazodone group reported significantly higher mean ratings of OCD symptoms than the CBASP group. A significant interaction between response group and treatment group was found for early insomnia (see Figure 3). Post-hoc analyses using an independent samples t-test found that participants who partially responded to CBASP treatment (M=.51, SD=.69) reported higher levels of early insomnia than those partially responding to nefazodone (M=.23, SD=.53), $t(100) = -2.51$, $p<.05$; however, for full responders, the CBASP group (M=.14, SD=.43) reported similar levels of early insomnia as the Nefazodone group (M=.27, SD=.64). As Figure 3 also illustrates, the CBASP group reported significantly lower levels of early insomnia for full responders compared to partial responders, $t(88)=3.10$, $p<.01$. No other significant interactions were found.

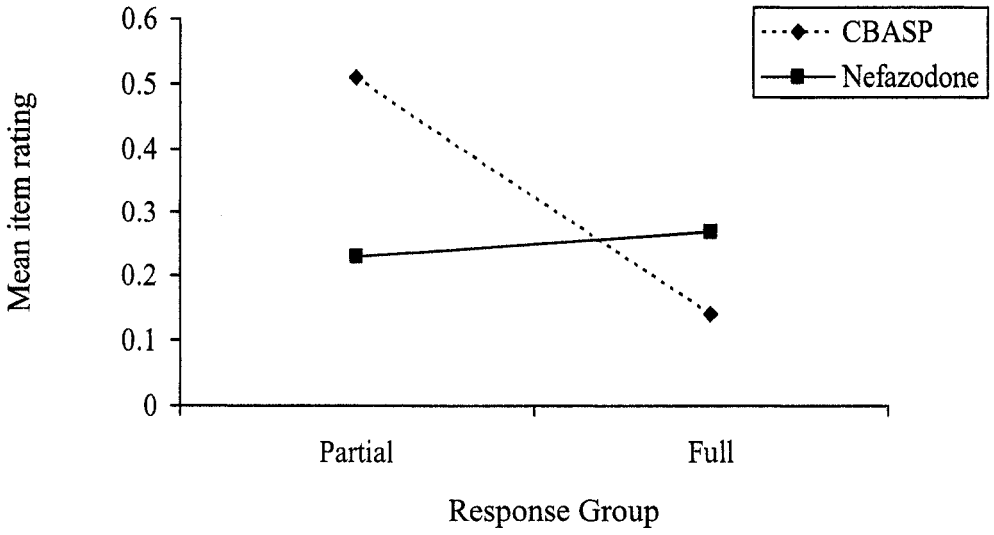

Figure 3. Response by treatment interaction of mean HDRS early insomnia rating

Baseline HDRS scores were also compared between treatment groups and response groups using a 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) ANOVA in order to control for significant baseline differences at treatment completion. Main effects were found for response group with the following items: Depressed mood, suicide, middle insomnia, work and activities, psychomotor retardation, weight loss, helplessness, and hopelessness.[8] After controlling for baseline ratings on these items all results were sustained, with the exception of psychomotor

[8] Partial responders compared to full responders reported significantly greater levels of depressed mood, work/activity impairment, psychomotor retardation, and hopelessness. However full responders reported greater levels of middle insomnia and weight loss than partial responders. Significant interactions also were found for psychomotor agitation, sexual interest, and energy items. Participants that fully responded to nefazodone reported lower levels of baseline psychomotor agitation and sexual interest than participants that fully responded to CBASP. However, there were no differences between treatment groups within the partial responders. In contrast, full responders in the CBASP group reported lower levels of baseline energy loss than full responders in the Nefazodone group, with no differences across treatment groups with partial responders.

retardation. The response group main effect found for psychomotor retardation became nonsignificant when controlling for baseline ratings ($F(1,177) = .31, p = .58$).

Self-Report IDS-SR. A 2 Response (Partial, Full) X 2 Treatment (CBASP Only, Nefazodone Only) ANOVA was used to explore mean differences in residual symptoms on each IDS-SR item between response groups and treatment groups. As with HDRS analyses, only responders (partial and full) and those participants treated with CBASP only and nefazodone only were included in the subsequent analyses. The results are presented in Table 13.

Table 13. *Mean IDS-SR item scores as a function of response and treatment group at treatment completion* [a]

	Treatment Group M (SD)		Response Group M (SD)		Treatment M.E.		Response M.E.		Interaction	
IDS-SR Item	CBASP	Nef.	Partial	Full	F	ES	F	ES	F	ES
1. Initial Insomnia	.44 (.74)	.36 (.71)	.48 (.75)	.26 (.64)	.11	.00	3.80	.02	4.41*	.02
2. Middle Insomnia	1.17 (1.04)	.97 (.99)	1.17 (1.05)	.89 (.94)	2.47	.01	3.40	.02	.49	.00
3. Early Awakening	.29 (.72)	.16 (.47)	.28 (.67)	.12 (.48)	1.29	.01	2.87	.02	1.80	.01
4. Hypersomnia[b]	.15 (.42)	.30 (.55)	.25 (.51)	.20 (.47)	4.82*	.03	.27	.00	.90	.01
5. Sad Mood	.51 (.62)	.54 (.69)	.65 (.67)	.31 (.58)	.01	.00	11.87**	.06	.47	.00
6. Irritability	.51 (.59)	.43 (.54)	.57 (.56)	.31 (.53)	.77	.00	9.26**	.05	.51	.00
7. Anxiety/Tension	.62 (.70)	.51 (.60)	.65 (.66)	.42 (.61)	1.37	.01	5.89*	.03	.07	.00
8. Mood Reactivity	.34 (.60)	.30 (.53)	.40 (.63)	.18 (.39)	.08	.00	6.15*	.03	1.76	.01
9. Mood Variation	.72 (.96)	.70 (.77)	.83 (.93)	.49 (.71)	.10	.00	6.67*	.04	.00	.00
10. Mood Quality	.56 (.91)	.53 (.94)	.70 (1.02)	.26 (.64)	.19	.00	10.09**	.05	.14	.00
11. Appetite Decrease	.09 (.29)	.20 (.45)	.20 (.44)	.05 (.21)	1.90	.01	7.21**	.04	3.29	.02
12. Appetite Increase	.20 (.56)	.13 (.54)	.13 (.48)	.23 (.65)	.57	.00	1.30	.01	.00	.00
13. Weight Decrease	.19 (.47)	.22 (.57)	.20 (.52)	.20 (.53)	.01	.00	.01	.00	2.30	.01
14. Weight Increase	.20 (.52)	.25 (.60)	.24 (.60)	.20 (.50)	.52	.00	.18	.00	.37	.00
15. Concentration	.64 (.64)	.82 (.58)	.88 (.62)	.47 (.50)	2.75	.02	19.23***	.10	.00	.00
16. Self-Criticism/Blame	.34 (.71)	.29 (.72)	.42 (.82)	.14 (.43)	.42	.00	6.67*	.04	.00	.00
17. Future Pessimism	.74 (.63)	.71 (.68)	.88 (.67)	.46 (.53)	.09	.00	18.12***	.09	1.08	.01
18. Suicidal Thoughts	.08 (.31)	.16 (.50)	.13 (.39)	.09 (.46)	1.91	.01	.28	.00	.56	.00
19. Interest In Activities	.43 (.69)	.54 (.78)	.65 (.80)	.18 (.50)	.30	.00	18.08***	.09	.39	.00
20. Energy/Fatigability	.43 (.60)	.51 (.74)	.59 (.72)	.26 (.44)	.23	.00	10.25**	.06	.15	.00
21. Pleasure/Enjoyment	.48 (.64)	.44 (.62)	.59 (.67)	.23 (.46)	.02	.00	14.57***	.08	2.29	.01
22. Decreased Libido	.89 (.98)	.78 (.98)	1.02 (1.03)	.51 (.77)	1.27	.01	12.44**	.07	.42	.00
23. Psychomotor Retardation	.20 (.43)	.32 (.54)	.33 (.53)	.14 (.39)	2.85	.02	6.05*	.03	.45	.00
24. Agitation	.29 (.67)	.28 (.50)	.33 (.66)	.20 (.44)	.02	.00	2.02	.01	.02	.00
25. Somatic Complaints	.43 (.60)	.44 (.69)	.48 (.64)	.37 (.65)	.33	.00	1.06	.00	3.47	.02
26. Sympathetic Arousal	.21 (.41)	.21 (.41)	.23 (.43)	.17 (.38)	.00	.00	1.06	.01	.00	.00
27. Panic/Phobic Symptoms	.17 (.43)	.13 (.37)	.20 (.46)	.06 (.24)	.07	.00	4.99*	.03	2.03	.01
28. Constipation/Diarrhea	.20 (.46)	.29 (.59)	.30 (.58)	.15 (.40)	1.39	.01	2.77	.02	.41	.00
29. Rejection Sensitivity	.54 (.62)	.41 (.52)	.57 (.58)	.32 (.53)	2.04	.01	8.12**	.04	.88	.01
30. Leaden Paralysis	.33 (.60)	.37 (.59)	.47 (.65)	.14 (.39)	.00	.00	13.82***	.07	.57	.00

Note. [a] df = 1, 176, [b]Treatment group main effects became non-significant after controlling for baseline ratings for these items.
* p < .05, ** p < .01, *** p < .001

As expected and consistent with the HDRS data, there was a significant main effect of response group on residual symptom means for many of the IDS-SR items, including sad mood, irritability, anxiety/tension, mood reactivity, mood variation, mood quality, appetite decrease, concentration, self-criticism/blame, future pessimism, interest in activities, energy/fatigability, pleasure/enjoyment, decreased libido, psychomotor retardation, panic/phobic symptoms, rejection sensitivity, and leaden paralysis. For each of these items, partial responders reported significantly higher mean severity ratings at end of treatment than full responders. No response group main effects were found for initial insomnia, middle insomnia, early awakening, hypersomnia, appetite increase, weight increase, weight decrease, suicidal thoughts, agitation, somatic complaints, constipation/diarrhea, and sympathetic arousal.

There was a significant main effect of treatment group on mean residual symptoms for only one of the IDS-SR items: hypersomnia. The Nefazodone group demonstrated significantly higher mean ratings than the CBASP group. However, baseline group differences were found for the hypersomnia item, in which the Nefazodone group reported higher pre treatment means than the CBASP group. When accounting for this baseline difference, the results indicated no significant differences between the CBASP and Nefazodone group at post treatment. No other treatment group main effects were found for any of the other IDS-SR items.

Consistent with the HDRS early insomnia item, a significant interaction between response group and treatment group was found for initial insomnia. Post-hoc analyses using an independent samples t-test was conducted to examine the specific nature of the

interaction. Figure 4 illustrates that participants who partially responded to CBASP treatment (M=.62, SD=.83) reported higher levels of initial insomnia than those partially responding to nefazodone (M=.35, SD=.66), t(103) = 1.91, $p<.05$; however, for full responders, the CBASP group (M=.17, SD=.45) reported similar levels of early insomnia as the Nefazodone group (M=.34, SD=.81). As Figure 4 suggests, the CBASP group reported significantly lower levels of early insomnia for full responders compared to partial responders, t(86) = -3.30, $p <.001$. No other significant interactions were found.

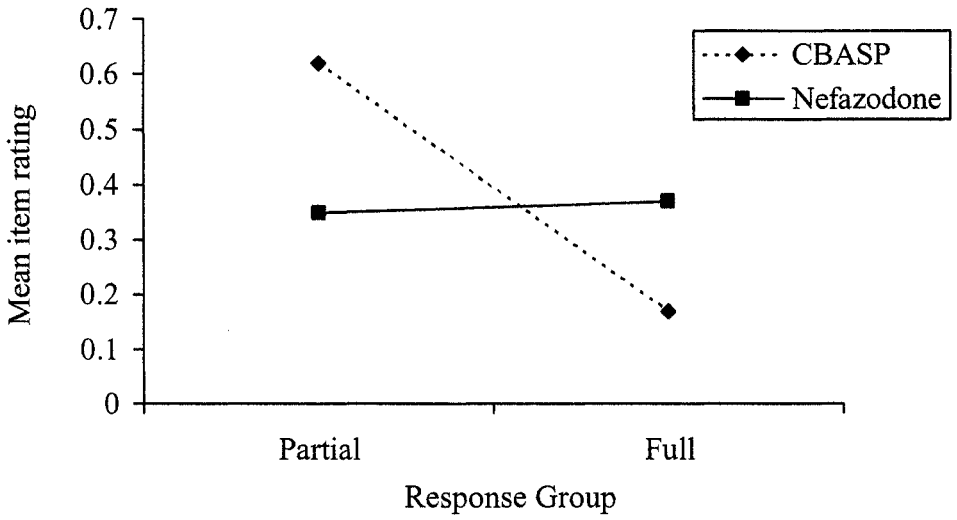

Figure 4. Response by treatment interaction of mean IDS-SR initial insomnia rating

Emergence of Residual symptoms

To further understand the nature of residual symptoms, we were interested in whether residual symptoms represented side effects of treatment rather than unresolved

core depressive symptoms. Pre treatment prevalence rates (presence, absence) of each item of the HDRS and IDS-SR were compared to post treatment prevalence rates (presence, absence) using chi-square analysis for responders only. An emergence of a residual symptom was defined as a symptom not present at pre treatment, but reported at post treatment. Only responders were included in these analyses, due to the possibility that in non-responders an emergence of a symptom may instead represent the worsening of a depressive episode rather than a side effect of treatment.

Results indicated that many of the residual symptoms reported at post treatment were also prevalent at pre treatment. Based on the HDRS, none of the participants reported an emergence of depressed mood. Furthermore, for all other HDRS residual symptoms reported, few participants (under 25 percent) who endorsed these symptoms at post treatment reported these symptoms as emerging after treatment, with the exception of weight loss, appetite loss, psychomotor agitation, late insomnia, hypochondriasis, paranoid symptoms, OCD symptoms, and depersonalization. For these items the rates of symptom emergence was quite compelling. Among participants that reported weight loss at post treatment (n=32), 88% (n=23) did not report this symptom at pre treatment. Similarly, among participants that reported appetite loss at post treatment (n=32), 31% (n=10) did not report appetite loss at pre treatment. Also, 43% (n=28) of participants who reported post treatment psychomotor agitation (n=64) did not report pre treatment agitation. Late insomnia was reported to have emerged after treatment began in 32% (n=19) of participants who reported this symptom at post treatment (n= 58), and

hypochondriasis emerged in 33% (n=18) of participants who reported residual hypochondriasis (n=55) at treatment completion.

Residual symptoms that were less prevalent at post treatment were also symptoms that were reported to have emerged after treatment began and included paranoid symptoms (n=2/3, 66.7%), OCD symptoms (n=3/6, 50%), and depersonalization (n=2/6, 33.3%). In interpreting these results, the actual number of participants that reported these symptoms should be taken into account, as some rather high percentages represent a small number of participants. For example, although 66.7% of participants who experienced post treatment paranoid symptoms reported an emergence of this item, only three participants experienced this symptom at treatment completion. Therefore, results should be interpreted with caution.

Similar results were found with the IDS-SR, in which most residual symptoms did not emerge as a result of treatment. None of the participants reported the emergence of sad mood, anxiety/tension, low energy/fatigability, and decreased pleasure or enjoyment at post treatment. Consistent with the HDRS, items representing appetite and weight were items in which the emergence rates were highest. Among participants that reported appetite increase at post treatment (n=47), 68.1% (n=32) did not report this symptom at pre treatment. Similarly, among participants that reported weight loss at post treatment (n=58), 79.3% (n=46) did not report weight loss at pre treatment. Conversely, among participants that reported appetite increase (n=39) or weight gain (n=61) at post treatment, 42.5% (n=17) did not report appetite increase at pre treatment, and 45.9% (n=28) did not report weight gain at pre treatment. Also, hypersomnia was reported to

have emerged after treatment began in 27% (n=20) of participants who reported this symptom at post treatment (n= 75). Thus, these somatic symptoms may represent symptoms associated with treatment (side effects) rather than unresolved core depressive symptoms for a large number of participants.

In order to test Hypothesis Three, that treatment groups would differ in the emergence of residual symptoms, the presence or absence of each item on the HDRS and IDS-SR at pre treatment was examined as function of Treatment group (CBASP Only, Nefazodone Only, Combination) using a chi-square analysis among participants who reported the item present at post treatment. Due to possible side effects of medication, it was predicted that the Nefazodone and Combination group would demonstrate an emergence of somatic symptoms, whereas the CBASP group would demonstrate no change in type of symptoms from pre to post treatment. Based on the HDRS treatment group differences emerged for the following items, guilt, psychic anxiety, and weight loss. The Nefazodone group was more likely to report the emergence of guilt (n=2/23, 8.7%) and psychic anxiety (n=5/44, 11.4%) than the CBASP (guilt: n=0/29, 0%, psychic anxiety: n=1/51, 2%) and Combination group (guilt: n=0/47, 0%, psychic anxiety: n=0/79, 0%) (X^2 (2, 99) = 6.75, p <.05; X^2 (2, 174) = 11.44, p <.01, respectively). The emergence of weight loss occurred more frequently among participants in the Nefazodone (n=8/8, 100%) and Combination groups (n=12/12, 100%) when compared with the CBASP group (n=3/6, 50%), X^2 (2, 26) = 11.30, p <.01. Thus, weight loss may represent a side effect of medication rather than unresolved core depressive symptoms. Inconsistent with the HDRS data, results from the IDS-SR indicated that no significant

differences in emergence of residual symptoms were found between treatment groups for all items.

Discussion

Although past research provides ample evidence for the high prevalence and negative outcomes associated with residual symptoms, only a few studies have focused on describing the specific residual symptoms that are most commonly experienced. The studies that have described the specific nature of residual symptoms have been exclusively medication efficacy studies, and included a mixed sample of episodically and chronically depressed patients. No study known to date has investigated the nature of residual symptoms in a chronically depressed sample, after psychotherapy treatment, or has compared residual symptoms across treatment modalities. Distinguishing a chronic depression course from an episodic course is important since chronic courses have distinct developmental and psychosocial characteristics. Also, given that treatment approaches differ in their mechanisms of change and target specific processes (neurotransmitters, cognitions, emotions, behavior), residual symptoms may not be uniform across treatments. The current study expands on previous findings by examining differences in individual residual symptoms and symptom clusters as a function of treatment modality and treatment response in a chronically depressed population.

Prevalence and nature of residual symptoms

The presence of residual symptoms after treatment was a common occurrence in all treatment and response groups. Even among full responders to treatment, over 90% of

participants reported experiencing at least one residual symptom to a mild degree at treatment completion. These rates are slightly higher compared to prevalence rates found in other studies of residual symptoms, in which 82.4% to 87.8% of full responders reported at least one residual symptom (Fava et al., 1994; Nierenberg et al., 1999). The difference in prevalence rates is likely due to the number of items represented on the measures. The current study measured residual symptoms using the HDRS-24 and IDS-SR-30, whereas other samples used measures with fewer items. However, differences in prevalence rates may also represent variations in sample populations, as the current study consisted exclusively of chronically depressed participants, who are at greater risk for residual symptoms, while previous studies did not differentiate between episodic and chronic depression.

The most common residual symptoms found in the current study appeared to reflect both core depressive symptoms and co-morbid anxiety and somatic symptoms. Generally, the clinician administered (HDRS) and self-report (IDS-SR) ratings appeared to converge when examining the prevalence of residual symptoms. Among the most common symptoms reported, similarities across the measures were found for items pertaining to psychic anxiety, somatic complaints, and decreased libido with both full and partial responders. Similarities across measures were found for items addressing depressed mood and energy among partial responders. Items that were not common symptoms reported on the HDRS, but occurred frequently with the IDS-SR, were middle insomnia, mood variation, and future pessimism (hopelessness). These inconsistencies may be due to the variation in scoring criteria. For example, the criterion for the presence

of middle insomnia on the IDS-SR is less rigid than with the HDRS. On the HDRS the individual is required to experience middle insomnia on at least two nights during the week for this symptom to be identified as present, whereas this requirement is not present on the IDS-SR. Another explanation for the differences across measures may involve different methods of assessment (self-report and clinician administered interview). Participants may be more likely to report hopelessness and mood variation when asked on a questionnaire than in an interview. Alternatively, these inconsistencies between measures may suggest that these items are less reliable as common residual symptoms. However, middle insomnia and hopelessness were found to be frequently reported symptoms among partial responders (Paykel, et al., 1995) and general insomnia was a common symptom among full responders in prior studies (Nierenberg et al., 1999). Common residual symptoms reported on the IDS-SR that are not represented on the HDRS were concentration problems and rejection sensitivity. However, concentration problems is a symptom that was represented in the Nierenberg et al. (1999) study but was not identified as a common residual symptom. Thus, concentration may not represent a consistent residual symptom. Nonetheless, the high occurrence of concentration and rejection sensitivity at treatment completion highlights the need for their inclusion when assessing treatment efficacy and/or residual symptoms.

The most common symptoms found among our sample after treatment with nefazodone were generally similar to residual symptoms found after response to other medications (fluoxetine, reboxetine, tricyclics: amitriptyline, desipramine, and imipramine; Fava, et al., 1994; Nelson, et al., 2005). The following residual symptoms

were the most frequently reported symptoms in the current study that were consistent with existing studies: Psychic anxiety, somatic anxiety, depressed mood, irritability, middle insomnia, general somatic symptoms, decreased libido, hopelessness, and fatigue (Nelson et al., 2005; Fava et al., 1994; Paykel, et al., 1995; Nierenberg et al., 1999). Surprisingly, the current study found that the items of decreased interest in work/activities on the HDRS and decreased interest in activities and pleasure/enjoyment on the IDS-SR were not common residual symptoms, as these symptoms were reported in less than 50% of partial responders, and in less than 20% of full responders. This finding is inconsistent with earlier studies, which found that decreased interest in activities was a common symptom, reported in 84% of partial responders and 27% of full responders (Nierenberg et al., 1999; Paykel, et al., 1995). Also inconsistent with the Paykel et al. (1995) study, which found residual guilt to be present in 68% of partial responders, the current study found lower rates of residual guilt on the HDRS among partial responders (37.4%).

Overall, it appears that the most consistent residual symptoms represent both core depressive symptoms (depressed mood, insomnia, and fatigue) and co-morbid symptoms not specific to depression (psychic anxiety, somatic anxiety, and somatic complaints, irritability, decreased libido). These co-morbid residual symptoms largely reflect common symptoms of anxiety.

Hypothesis One: Residual Symptom Differences as a Function of Response Groups

The first hypothesis, that residual symptoms would occur most frequently among non-responders, followed by partial responders, and lastly full responders, was generally

confirmed. On both the HDRS and the IDS-SR non-responders were more likely to report the presence of residual symptoms compared to responders for the majority of the items. In addition, partial responders were more likely to report the presence of most HDRS and IDS-SR items compared to full responders. Only a small number of items did not differentiate partial and full responders. The items that did not differentiate groups were generally the less frequently-reported symptoms regardless of response group, and consisted of late insomnia, psychomotor agitation, hypochondriasis, weight loss, paranoid symptoms, and OCD symptoms on the HDRS, and hypersomnia, appetite increase, weight decrease, weight increase and suicidal thoughts on the IDS-SR. Mood variation and concentration problems were also symptoms on the IDS-SR that did not differentiate partial from full responders; however, they were among the most common symptoms reported by responders, emphasizing the importance of assessing for these symptoms after treatment completion. Some of the above items on the IDS-SR that did not differentiate response groups represent atypical features of depression (hypersomnia, appetite increase, and weight increase), which is consistent with their low prevalence in the current study. Although the rate of residual symptoms reported was generally less for full than partial responders, the response groups were similar in the symptoms that were most commonly reported. As stated above, the most frequently reported symptoms were psychic anxiety, somatic anxiety, depressed mood, decreased libido, decreased energy, middle insomnia, future pessimism, concentration problems, mood variation, anxiety/tension, rejection sensitivity, irritability, and somatic complaints. Further, these

commonly reported symptoms were also the symptoms that were most severe (had the highest mean ratings).

Hypothesis Two: Residual Symptom Differences as a Function of Treatment Groups

Hypothesis two declared that residual symptoms would differ in frequency, severity and symptom clusters between types of treatments, with fewer participants in the Combination group reporting residual symptoms than the CBASP alone or medication alone groups. This hypothesis was supported for only a few items. Prevalence rates based on the HDRS differed between treatment groups on only three out of the 24 items: early insomnia, obsessive/compulsive symptoms and hopelessness. On the IDS-SR, the treatment groups differed on three different symptoms: Hypersomnia, concentration, and decreased libido. Early insomnia and hopelessness on the HDRS have symptom counterparts on the IDS-SR (initial insomnia and future pessimism); similarly, decreased libido on the IDS-SR is also a symptom on the HDRS. For these symptoms that are represented on both measures, similar patterns of results were found across measures although the symptom was significant on one measure but not the other.

As predicted, the Combination group was generally less likely to report symptoms of early insomnia, hopelessness, concentration problems, and decreased libido when compared to either the CBASP or Nefazodone group. The CBASP group was more likely to report early insomnia than the Nefazodone group. This finding is consistent with previous studies finding that nefazodone provides significant improvement in sleep symptoms associated with depression (Zajecka, 1996) whereas cognitive-behavioral therapy produces only modest improvement of insomnia (Thase et al., 1994; Thase et al.,

1998; Thase, et al., 2002). Congruent with the HDRS early insomnia item, hypersomnia was found to occur more frequently in the Nefazodone and Combination group when compared to the CBASP group. This finding may reflect a sedation side-effect that has been reported with nefazodone, or that the CBASP group was more likely to experience insomnia, thus less likely to report hypersomnia symptoms.

Further analysis of the relationship between response and treatment groups on residual insomnia revealed an interaction between response and treatment groups for the HDRS early insomnia item and the IDS-SR initial insomnia item. For partial responders only, the CBASP group reported higher levels of the early insomnia and initial insomnia items compared to the Nefazodone group. It appears that when CBASP patients are treated to remission (full response) early insomnia significantly decreases. It is possible that the rate of improvement for initial/early insomnia is related to the abatement of other depressive symptoms. Previous research has demonstrated that low mood predicts perceived lack of improvement in sleep (Vincent, Penner, & Lewycky, 2006). Since CBASP does not directly target sleep problems these symptoms may take longer to remit and be contingent on perceived improvement in other symptoms, which would be greater for full than partial responders. Nefazodone, on the other hand, is a biological approach to treatment and thus would be expected to directly target biologically-based symptoms. Therefore, the abatement of insomnia may not be contingent on the reduction of other depressive symptoms and thus not demonstrate significant differences between partial and full responders.

The Nefazodone group was more likely to report OCD symptoms and concentration problems than the CBASP group. Similarly, the Nefazodone group reported significantly higher mean ratings of OCD symptoms than the CBASP group. These items appear to reflect cognitive symptoms of depression. Given that CBASP is a cognitive-behavioral approach that targets patients' cognitive-emotional development, it would be expected that symptoms of a cognitive nature would be reported less frequently in the CBASP group when compared to medication at treatment completion. The fact that the Combination group also reported fewer of these cognitive symptoms than the Nefazodone Only group offers further support for this interpretation.

Analysis of the symptom cluster differences between treatments produced similarly mixed results. The Nefazodone group reported a greater number of items on the HDRS Disturbed Thinking factor than the CBASP group in both full and partial responders. The CBASP group reported significantly more items on the HDRS Psychic Depression factor compared to the Nefazodone group for full responders only. No differences were found between treatment groups on the HDRS Anxiety, Sleep Disturbance, and Loss of Motivated Behavior factors, or on the IDS-SR Cognitive/mood, Anxiety/arousal, and Sleep Disturbance factors.

The generally modest differences in residual symptom frequency, severity, and symptom clusters found between treatment groups may be due to insufficient power as a result of small effect sizes. The highest effect size found when comparing residual symptom severity and clusters between treatment groups was .03, which is substantially lower than the recognized moderate effect size of .30 (Cohen & Cohen, 1983). The only

other study comparing residual symptoms between treatment groups among responders did not report effect sizes (Nelson, et al., 2005), but they also found minimal differences between treatment groups, possibly as a result of small effect sizes. Since these analyses were conducted with responders only, the range of mean ratings were restricted due to the sheer definition of how responders were defined (<15 on HDRS total). Among responders, differences between treatment groups may be too small to be detected by the measures used in the current study. However, it is the residual symptoms among responders that are often undetected, ignored, and result in significant negative outcomes. Thus, identifying the leftover symptoms after a response to treatment is an important endeavor.

Hypothesis Three: Emergence of Residual Symptoms

The third hypothesis was that due to potential side effects of medication, the medication and combination group would demonstrate an emergence of somatic symptoms (i.e. sedation, nausea, dry mouth, dizziness, and light-headedness), whereas the psychotherapy group would demonstrate no change in type of symptoms from pre to post treatment. This hypothesis was partially supported. Results indicated that many of the residual symptoms reported at post treatment were also prevalent at pre treatment. The residual symptoms that were more likely to emerge after treatment were appetite increase, appetite decrease, weight loss, weight gain, and agitation. Surprisingly, the only emergent symptoms that differentiated treatment groups were weight loss, guilt, and psychic anxiety. The emergence of weight loss occurred more frequently among participants in the Nefazodone and Combination groups when compared with the CBASP

group. Thus, weight loss may represent a side effect of medication rather than an unresolved core depressive symptom. Surprisingly, weight loss is not a common side effect of nefazodone; however nausea has been identified as a side effect, which could account for decreased food intake and subsequent weight loss. Another possible explanation for these results is that participants had depression related weight gain at pre treatment, and as treatment progressed, their weight stabilized. Thus weight loss could be viewed as improvement rather than a side effect of medication.

The Nefazodone group was more likely to report the emergence of guilt and psychic anxiety than the CBASP and Combination group. This may indicate that CBASP acts as a protective factor against the development of guilt and psychic anxiety that often accompanies depression. Excessive guilt and shame typically arise in response to failures or transgressions in interactions with others, and are often related to low perceived self-efficacy in interpersonal relationships (Covert, Tangney, Maddux, Heleno, 2003; Tangney, 1991). The major components of CBASP (situational analysis and therapist role enactment) are designed to facilitate patients' perception of having efficacy (perceived functionality) in interpersonal relationships and in managing their lives. As patients learn these components it is expected that they begin to demonstrate greater effectiveness in interpersonal relationships and managing daily responsibilities, and thus are less likely to experience excessive guilt, shame and anxiety. CBASP is currently undergoing a dismantling study that may offer insight on how the components impact guilt and psychic anxiety.

Implications

The present study adds to the treatment outcome literature for depression in that it is the first study examining specific residual symptoms among responders in a chronic depression population, after treatment with psychotherapy, and between treatment modalities. Interestingly, the most common residual symptoms found with this chronically depressed sample were the same symptoms found with non-chronic or mixed samples (Fava et al., 1994; Nelson, et al., 2005; Paykel, et al., 1995). When comparing results of the current study to past research, it appears that although a larger percent of chronically depressed patients than episodically depressed patients report residual symptoms, the nature of these symptoms are similar (Fava et al., 1994; Nierenberg et al., 1999). However, no prior study has directly compared the nature of residual symptoms between episodic and chronic depression samples. Future studies directly comparing acute and chronic depression samples would further the field's understanding of the nature of residual symptoms and course outcomes.

Although differences between treatment groups were modest, our findings have important clinical implications for treatment planning. Several different approaches for treatment of residual symptoms have been identified, and include combining treatment, sequencing treatment, crossover treatments, continuing the same treatment, augmenting treatment, or switching treatment approaches (Fava & Ruini, 2005; Segal, Vincent, & Levitt, 2002). Extant research on the treatment of residual symptoms has demonstrated support for the use of sequential treatment, particularly using a CBT approach after a response to medication (Fava et al., 1998; Fava, et al., 2002; Fava et al., 2004).

However, treatment planning for specific residual symptoms or clusters has not been systematically studied.

The findings of the current study provide some support for the use of specific treatment planning approaches based on residual symptom profiles. If the residual symptom profile includes symptoms of early insomnia, hopelessness, concentration problems, and decreased libido, then combination treatment may be an effective approach to treatment since these symptoms were reported less frequently among the Combination group than medication or psychotherapy alone. If cognitive problems (concentration, ruminations) are part of the residual symptoms profile and the patient was treated with medication, then switching to CBASP or psychotherapy in general may be an appropriate approach, since the CBASP group was less likely to report these symptoms than the Nefazodone group. Conversely, if the residual symptom profile after psychotherapy treatment included symptoms of insomnia, it may be beneficial to consider switching treatment to psychotropic medication. For those symptoms that did not differentiate treatment group, sequential treatment or combination treatment with these therapeutic approaches may no offer additional benefit. Therefore, the clinician may wish to continue with the same treatment for a longer period, add an additional medication or therapy, or discontinue the current treatment and switch to another approach (such as a different class of medications or a different psychotherapy framework). Another important finding was that the most common symptoms found among our sample after treatment with nefazodone were generally the same symptoms that have been found with previous studies of treatment with fluoxetine, reboxetine (Nelson, et al., 2005), and

tricyclics such as amitriptyline, desipramine, and imipramine (Fava, et al., 1994). Therefore, switching from one medication to another with similar residual symptom profiles may not be warranted, and instead another class of medications should be considered. Although nefazodone was taken off the market due to adverse events, it was found to be as effective as other common medications currently on the market (i.e. paroxetine, imipramine, fluoxetine, sertraline) and has demonstrated a similar profile of symptom reduction and side effects (Baldwin, Hawley, Mellors, 2001; Berlanga, Arechavalata, Heinze et al., 1997; Feiger, Kiev, Shrivastava, Wisselink, 1996; Horst & Preskorn, 1998). Therefore, these results may generalize to other drug treatments.

Further, while making treatment planning decisions, clinicians should also take into account whether the patient has fully or partially responded to treatment. The current study's findings illustrate the importance of this distinction. For example, this study's result that the Nefazodone group reported less severe insomnia symptoms than the CBASP group among partial responders only suggests that assessment of insomnia in patients receiving CBASP who have partially responded to treatment is crucial for treatment planning. Insomnia improvement may be contingent on the reduction of other depressive symptoms and thus all symptoms that remain after partial response should be identified and may be targeted for treatment.

Another implication of the current study is its contribution to understanding whether residual symptoms represent unremitted core depressive symptoms or treatment emerging symptoms (i.e. medication side effects). We found that the majority of residual symptoms reported at post treatment were also reported at baseline, suggesting that they

represent depressive symptoms that have not resolved. However, residual symptoms related to weight loss should be suspected as a side effect of nefazodone, given weight loss emerged in a substantial number of participants after treatment with nefazodone only and combination treatment, but not after CBASP treatment only.

Limitations and Future Directions

There are several limitations of the current study that must be noted. First, the use of multiple independent analyses raises the issue of a Type I error (falsely rejecting the null hypothesis). However, the primary focus was in describing the nature of symptoms across treatment groups. Therefore, these analyses are generally descriptive, and significant differences should be interpreted with this limitation in mind.

Although the use of multiple measures is a strength of this study, the HDRS and IDS-SR were not specifically designed to detect differences at the item level, as treatment efficacy studies primarily measure response using total scores. While the overall HDRS reliability estimates are mostly adequate, at the item level, internal and retest reliability coefficients are weak for many items of the HDRS. A meta analysis by Bagby et al. (2004) revealed only four items met the criteria for adequate retest reliability: depressed mood, early insomnia, psychic anxiety, and loss of libido. Item response analysis revealed that several items on the HDRS had low sensitivity to depression severity, and four items on the HDRS (psychomotor agitation, gastrointestinal symptoms, loss of insight, and weight loss) failed to differentiate depressed from healthy subjects. The items most sensitive to detect change on the HDRS were depressed mood, guilt, suicide, work/interests, and psychic anxiety. Interestingly, the current study found that these

symptoms failed to differentiate treatment groups on the frequency and severity of residual symptoms. Additionally, the HDRS has been criticized for demonstrating poor factor structure and measuring multiple symptoms in one item (Bagby et al., 2004). For example, the somatic anxiety item includes gastrointestinal, cardiovascular, respiratory, and urinary symptoms. Symptom differences between treatment groups may be masked by the inclusion of multiple symptoms per item. Also, the breadth of symptoms represented and the range of item scores may be too narrow to detect subtle differences between groups in responders. The HDRS is weighted heavily toward somatic symptoms and less on interpersonal or cognitive symptoms. Since CBASP targets cognitive and interpersonal functioning, true differences between treatment groups in these domains may have gone undetected due the limited scope of content areas represented with these measures.

Another limitation is the lack of a placebo group. It would be interesting to compare residual symptoms in placebo responders compared to nefazodone and CBASP responders in order to provide further evidence that residual symptoms are affected by treatment. A related issue is that the participants were not blind to the treatment group to which they were randomized; therefore, the results may reflect an element of response bias. However, to counteract this limitation, the clinicians who administered the HDRS interviews were unaware of the participants' treatment group assignment. Also, the restrictive exclusion criteria (i.e. exclusion of co-morbid psychiatric diagnoses, unstable medical conditions, failed response to previous medication trials) and use of a medication that is no longer on the market may attenuate the generalizability of our findings.

Future research could expand on this study in several ways. First, identifying predictors of specific residual symptoms could facilitate tailored treatment planning and reduce the frequency of residual symptoms after treatment. Further, follow-up studies should examine the effect of specific residual symptoms on depression course and psychosocial functioning. This study should be replicated with other treatments, such as a variety of classes of medications and with other psychotherapy approaches, since there is a dearth of research on specific residual symptoms after response to psychotherapy. The development and use of measures that offer greater scope of content and range per item in order to detect subtle differences among responders would also be a significant contribution to residual symptom research. Also, to facilitate comparison across studies, future research to strive to use operational definitions of outcome criteria that are consistent with other research, and in particular follow the guidelines that have been developed (i.e. the McArthur Task Force guidelines). Finally, given that chronically depressed patients have unique developmental and interpersonal characteristics, and, compared to episodically depressed patients are more likely to experience residual symptoms, research should distinguish between episodic and chronic depression courses. Studies that directly compare residual symptom profiles between episodic and chronic depression samples would contribute substantially to depression research and clinical practice.

References

Akiskal, H.S. (1997). Overview of chronic depressions and their clinical management. In: Akiskal, H.S., Cassano, G.B. (Eds.). *Dysthymia and the spectrum of chronic depressions.* New York, NY: Guildford Press.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Arnow, B.A. & Constantino, M.J. (2003). Effectiveness of psychotherapy and combination treatment for chronic depression. *Journal of Clinical Psychology, 59,* 893-905.

Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B. (2004). The Hamilton Depression Rating Scale: Has the gold standard become a lead weight? *American Journal of Psychiatry, 161,* 2163-2177.

Baldwin, D.S., Hawley, C.J., Mellors, K. (2001). A randomized double-blind controlled comparison of nefazodone and paroxetine in the treatment of depression: Safety, tolerability, and efficacy in continuation phase treatment. *Journal of Psychopharmacology, 15,* 161-165.

Bandura, A. (1977). *Social learning theory.* Englewood Cliffs, NJ: Prentice-Hall.

Beck, A. (1996). *Beck Depression Inventory-Second Edition.* San Antonio, TX: The Psychological Corporation.

Beck, A.T., Rush, A.J., Shaw, B.F., Emery, G. (1979). *Cognitive Therapy of Depression.* New York, NY: The Guilford Press.

Belsher, G., Costello, C. G. (1988). Relapse after recovery from unipolar depression: A critical review. *Psychological Bulletin, 104,* 84-96.

Berlanga, C., Arechavalata, B., Heinze, G., Campillo, C., Torres, M., Caballero, A. et al. (1997). A double blind comparison of nefazodone and fluoxetine in the treatment of depressed patients. *Salud Mental, 20,* 1-8.

Blehar, M.D. & Oren, D.A. (1997). Gender differences in depression. *Medscape Women's Health, 2,* 3.

Bland, R.C. (1997). Epidemiology of affective disorders: A review. *Canadian Journal of Psychiatry, 42,* 367-377.

Boulenger, J.P. (2004). Residual symptoms of depression: Clinical and theoretical implications. *European Psychiatry, 19,* 209-213.

Brown, C., Schulberg, H.C., & Modonia, M.J. (1995). Assessing depression in primary care practice with the Beck Depression Inventory and the Hamilton Rating Scale for Depression. *Journal of Psychological Assessment, 7,* 59-65.

Browne, G., Steiner, M., Roberts, J., Gafni, A., Byrne, C., Dunn, E., et al. (2002). Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and cost. *Journal of Affective Disorders, 68,* 317-330.

Casacalenda, N., Perry, J.C., Looper, K. (2002). Remission in major depressive disorder: A comparison of pharmacotherapy, psychotherapy, and control conditions. *American Journal of Psychiatry, 159,* 1354-1360.

Cohen, J. & Cohen, P. (1983). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences-Second Edition.* New Jersey: Lawrence Erlbaum Associates, Inc.

Cole, J.C., Motivala, S.R., Dang, J., Lucko, A., Lang, N., Levin, M.J., Oxman, M.N., Irwin, M.R. (2004). Structural validation of the Hamilton Depression Rating Scale. *Journal of Psychopathology and Behavioral Assessment, 26,* 241-254.

Cornwall, P.L., Scott, J. (1997). Partial remission in depressive disorders. *Acta Psychiatric Scandinavia, 95,* 265-271.

Corruble, E., Legrand, J.M., Duret, C., Charles, G., & Guelfi, J.D. (1999). IDS-C and IDS-SR: Psychometric properties in depressed in-patients. *Journal of Affective Disorders, 56,* 95-101.

Coryell W. & Winokur, G. (1992). Course and outcome. In Paykel, E.S. (Ed.): *Handbook of Affective Disorders, 2nd edition.* New York: Guilford Press.

Covert, M.V., Tangney, J.P., Maddux, J.E., Heleno, N.M. (2003). Shame-proneness, guilt-proneness, and interpersonal problem solving: A social cognitive analysis. *Journal of Social and Clinical Psychology, 22,* 1-12.

Cuffel, B.J., Azocar, F., Tomlin, M., Greenfield, S.F., Busch, A.B., & Croghan, T.W. (2003). Remission, residual symptoms, and non-response in the usual treatment of major depression in managed clinical practice. *Journal of Clinical Psychiatry, 64,* 397-402.

de Jong, R., Treiber, R., Henrich, G. (1986). Effectiveness of two psychological treatments for inpatients with severe and chronic depressions. *Cognitive Therapy Research, 10,* 645-663.

DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., et al. (2005). Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Archives of General Psychiatry, 62,* 409-416.

Durand, V.M. & Barlow, D.H. (2000). *Abnormal Psychology: 2nd Edition.* Belmont, CA: Wadsworth/Thomson Learning.

Einerson, T.R., Addis, A., Mittmann, N., Iskedjian, M. (1999). Meta-analysis of Venlafaxine, SSRIs, and TCAs in the treatment of Major Depressive Disorder. *Canadian Journal of Clinical Pharmacology, 5,* 205-216.

Elkin, I., Shea, M.T., Watkins, J.T., Imber, S.D., Sotsky, S.M., Collins, J.F., et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. *Archives of General Psychiatry, 46,* 971-982.

Fava, G.A., Fabbri, S., Sonino, N. (2002). Residual symptoms in depression: An emerging therapeutic target. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 26,* 1019-1027.

Fava, G.A., Grandi, S., Zielezny, M., Canestrari, R., Morphy, M.A. (1994). Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *American Journal of Psychiatry, 151,* 1295-1299.

Fava, G.A., Kellner, R., Lisansky, J., Park, S., Perini, G.I., Zielezny, M. (1986). Rating depression in normals and depressives. *Journal of Affective Disorders, 11,* 29-33.

Fava, G.A., Rafanelli, C., Grandi, S., Conti, S., Belluardo, P. (1998a). Prevention of recurrent depression with cognitive behavioral therapy. *Archives of General Psychiatry, 55,* 816-820.

Fava, G.A., Rafanelli, C., Grandi, S., Canestrari, R., Morphy, M.A. (1998b). Six year outcome for cognitive behavioral treatment of residual symptoms in major depression. *American Journal of Psychiatry, 155,* 1443-1445.

Fava, G.A. & Ruini, C. (2005). What is the optimal treatment of mood and anxiety disorders? *Clinical Psychology: Science and Practice, 12,* 92-96.

Fava, G.A., Ruini, C., Rafanelli, C., Finos, L., Conti, S., Grandi, S. (2004). Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *American Journal of Psychiatry, 161,* 1872-1876.

Fava, M. Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Alpert, J.E., McGrath, P.J., et al. (2006). A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: A Star*D report. *American Journal of Psychiatry, 163,* 1161-1172.

Fawcett, J. (1994). Antidepressants: Partial response in chronic depression. *British Journal of Psychiatry, 165 (suppl. 26),* 37-41.

Feiger, A. Kiev, A, Shrivastava, R.K., Wisselink, P.G. (1996). Nefazodone versus sertraline in outpatients with major depression: Focus on efficacy, tolerability, and effects on sexual function and satisfaction. *Journal of Clinical Psychiatry, 57 (Suppl 2),* 53-62.

Fennell, M.J.V. & Teasdale, J.D. (1986). Cognitive therapy with chronic, drug-refractory depressed outpatients: A note of caution. *Cognitive Therapy Research, 6,* 455-460.

First, M.B., Spitzer, R.L., Gibbon, M., Williams (1995). *Structured Clinical Interview for Axis I DSM-IV Disorders.* New York, NY: New York State Psychiatric Institute of Biometrics Research Development.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, & Benjamin. (1994). Structured clinical interview for Axis I DSM-IV disorders: patient edition (SCID-II, version 2.0). New York, NY: New York State Psychiatric Institute Biometrics Research Department.

Frank, E., Prien, R.E., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W. et al. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse and recurrence. *Archives of General Psychiatry, 48,* 851-855.

Gibbons, R.D., Clark, D.C., Kupfer, D.J. (1993). Exactly what does the Hamilton Depression Rating Scale measure? *Journal of Psychiatric Research, 27,* 259-273.

Gonzales, L., Lewinson, P., Clarke, G. (1985). Longitudinal follow-up of unipolar depressives: An investigation of predictors of relapse. *Journal of Consulting and Clinical Psychology, 53,* 461-469.

Greenberg, P.E., Stiglin, L.E., Finkelstein, S.N., & Berndt, E.R. (1993). The economic burden of depression in 1990. *Journal of Clinical Psychiatry, 54,* 405-418.

Grunebaum, M.F., Keilp, J., Li., S., Ellis, S.P., Burke, A.K., Oquendo, M.A., Mann, J.J. (2005). Symptom components of standard depression scales and past suicidal behavior. *Journal of Affective Disorders, 87,* 73-82.

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social Clinical Psychology, 6,* 278-296.

Harpin, R.E., Liberman, R.P., Marks, I., Stern, R., Bohannon, W.E. (1982). Cognitive behavior therapy for chronically depressed patients: A controlled pilot study. *Journal of Nervous mental Disorders, 170,* 295-301.

Hellerstein, D.J., Yanowitch, P., Rosenthal, J., Wallner Samstag, L., Maurer, M., Kasch, K., et al. (1993). A randomized double blind study of fluoxetine versus placebo in the treatment of dysthymia. *American Journal of Psychiatry, 150,* 1169-1175.

Hirschfeld, R.M.A. (1999). Efficacy of SSRIS and newer antidepressants in severe depression: Comparison with TCAs. *Journal of Clinical Psychiatry, 60,* 326-335.

Hollon, S.D., DeRubeis, R.J., Evans, M.D., Wiemer, M.J., Garvey, M.J., Grove, W.M., et al. (1992). Cognitive therapy and pharmacotherapy for depression, singly or in combination. *Archives of General Psychiatry, 49,* 774-781.

Horst, W.D. & Preskorn, S.H. (1998). Mechanisms of action and clinical characteristics of three atypical antidepressants: Venlafaxine, nefazodone, and bupropion. *Journal of Affective Disorders, 51,* 237-254.

Howland, R.H. (1993). General health, health care utilization, and medical comorbidity in dysthymia. *International Journal of Psychiatry in Medicine, 23,* 211-238.

Judd, L.L., Akiskal, H.S. (2000). Delineating the longitudinal structure of depressive illness: beyond clinical subtypes and duration thresholds. *Pharmacopsychiatry, 33,* 3-7.

Judd, L.L., Akiskal, H.S, Paulus, M.P. (1997). The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *Journal of Affective Disorders, 45,* 5-18.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell,W., et al. (1998a). A prospective 12 year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry, 55,* 694-700.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., et al. (1998b). Major depressive disorder: A prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *Journal of Affective Disorders, 50,* 97-108.

Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., et al. (2000). Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *American Journal of Psychiatry, 157,* 1501-1504

Julien, R.M. (2001). *A Primer of Drug Action.* New York, NY: Henry Holt and Company, LLC.

Karp, J.F., Buysse, D.J., Houck, P.R., Cherry, C., Kupfer, D.J., Frank, E. (2004). Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. *American Journal of Psychiatry, 161,* 1877-1884.

Kiesler, D. J. (1996). *Contemporary interpersonal theory and research: Personality, psychopathology, and psychotherapy*. New York: Wiley.

Keller, M.B. (1990). Diagnostic and course of illness variable pertinent to refractory depression. In A. Tasman, S.M. Goldfinger, & C.A. Kaufman, (Eds.), *Review of Psychiatry* (Vol. 9, PP. 10-32). Washington, DC: American Psychiatric Press.

Keller, M.B. (2003). Past, present, and future directions for defining optimal treatment outcomes in depression: Remission and beyond. *Journal of the American Medical Association, 289,* 3152-3160.

Keller, M.B., Gelenberg, A.J., Hirschfeld, R.M.A., Rush, A.J., Thase, M.E., Kocsis, J.H., et al. (1998). The treatment of chronic depression. Part 2: A double-blind, randomized trial of sertraline and imipramine. *Journal of Clinical Psychiatry, 59,* 598-607.

Keller, M.B., Hanks, D.L., Klein, D.N. (1996). Summary of the DSM-IV mood disorders field trial and issue overview. *Psychiatric Clinics of North America, 19,* 1-28.

Keller, M.B., Lavori, P.W., Endicott, J., Coryell, W., & Klerman, G.L. (1983). "Double depression": Two-year follow-up. *American Journal of Psychiatry, 140,* 689-694.

Keller, M.B., Lavori, P.W., Lewis, C.E., Klerman, G.L. (1983). Predictors of relapse in major depressive disorder. *Journal of the American Medical Association, 250,* 3299-3304.

Keller, M.B., Lavori, P.W., Mueller, T.I., Endicott, J., Coryell, W., & Hirschfeld, R.M.A. (1986). The persistent risk of chronicity in recurrent episodes of non-bipolar major depressive disorders: A prospective follow-up. *American Journal of Psychiatry, 143,* 24-28.

Keller, M.B., Lavori, P.W., Mueller, T.I., Endicott, J., Coryell, W., Hirschfeld, R.M.A., & Shea, T. (1992). Time to recovery, chronicity, and levels or psychopathology in major depression: A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry, 49,* 809-816.

Keller, M.B., McCullough, J.P., Klein, D.N., Arnow, B., Dunner, D., Gelenberg, A.J., et al. (2000). A comparison of nefazodone, the Cognitive Behavioral Analysis System of Psychotherapy, and their combination for the treatment of chronic depression. *The New England Journal of Medicine, 342,* 1462-1470.

Kennedy, N. & Paykel, E.S. (2004). Residual symptoms at remission from depression: Impact on long-term outcome. *Journal of Affective Disorders, 80,* 135-144.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12 month prevalence of DSM-III-R psychiatric disorders in the United States. *Archives of General Psychiatry, 51,* 8-19.

Klein, D.N., Norden, K., Ferro, T., Leader, J.B., Casch, K.L., Klein, L.M., et al. (1998). Thirty-month naturalistic follow-up study of early-onset dysthymic disorder: Course, diagnostic stability, and prediction of outcome. *Journal of Abnormal Psychology, 107,* 338-348.

Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H. et al. (1999). Age of onset in chronic major depression: Relation to demographic and clinical variables, family history, and treatment response. *Journal of Affective Disorders, 55,* 149-157.

Klein, D.N., Schwartz, J.E., Rose, S., & Leader, J.B. (2000). Five-year course outcome of dysthymic disorder: A prospective, naturalistic follow-up study. *American Journal of Psychiatry, 157,* 931-939.

Klerman, G.L., Weissman, M.M., Rounsaville, B.J., Chevron, E.S. (1984). *Interpersonal Psychotherapy of Depression.* Basic Books.

Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Younkers, K.A., McCullough, J.P., Keitner, G.I., et al. (1998). Gender differences in treatment response to sertraline versus imipramine in chronic depression. *American Journal of Psychiatry, 157,* 1445-1452.

Lesperance, F., Frasure-Smith, N., Juneau, M., Theroux, P. (2000). Depression and 1-year prognosis in unstable angina. *Archives of Internal Medicine, 160,* 1354-1360.

McCullough, J.P. (1984). Cognitive-behavioral analysis system of psychotherapy: An interactional treatment approach for dysthymic disorder. *Psychiatry, 47,* 234-250.

McCullough, J.P. (1991). Psychotherapy for dysthymia: Naturalistic study of ten patients. *Journal of Nervous and Mental Disease, 179,* 734-740.

McCullough, J.P. (2000). *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy.* New York: Guilford.

McCullough, J.P. (2006). *Treating Chronic Depression with Disciplined Personal Involvement: Cognitive Behavioral Analysis System of Psychotherapy (CBASP).* New York: Springer.

McCullough, J.P., Klein, D.N., Borian, F.E., Howland, R.H., Riso, L.P., Keller, M.B., & Banks, P.L. (2003). Group comparisons of DSM-IV subtypes of chronic depression: Validity of the distinctions, Part 2. *Journal of Abnormal Psychology, 112,* 614-622.

McCullough, J.P., Klein, D.N., Keller, M.B., Holzer, C.E., Davis, S.M., Kornstein, S.G., et al. (2000). Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymia (double depression): Validity of the distinction. *Journal of Abnormal Psychology, 109,* 419-427.

McCullough, J.P., Kornstein, S.G., McCullough, J.P., Belyea-Caldwell, S., Kaye, A.L., Roberts, C., et al. (1996). Differential diagnosis of chronic depressive disorders. *The Psychiatric Clinics of North America, 19,* 55-71.

Menza, M., Marin, H., Sokol-Opper, R. (2003). Residual symptoms in depression: Can treatment be symptom-specific? *Journal of Clinical Psychiatry, 64,* 516-523.

Mercier, M., Stewart, J., & Quitkin, J. (1992). A pilot sequential study of cognitive therapy and pharmacotherapy of atypical depression. *Journal of Clinical Psychiatry, 53,* 166-170.

Mintz, J., Mintz, L.I., Arruda, M.J., Hwang, S.S. (1992). Treatments of depression and the functional capacity to work. *Archives of General Psychiatry, 49,* 761-768.

Montgomery, S.A. & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134,* 382-389.

Mueller, T.I., Keller, M.B., Leon, A.C., Solomon, D.A., Shea, M.T., Coryell, W., Endicott, J. (1996). Recovery after 5 years of unremitting major depressive disorder. *Archives of General Psychiatry, 53,* 794-799.

Murphey, G.E., Simons, A.D., Wetzel, R.D., Lustman, PJ. (1984). Cognitive therapy and pharmacotherapy: Singly and together in the treatment of depression. *Archives of General Psychiatry, 41,* 33-41.

National Institute of Mental Health (NIMH). (1999). *The Numbers Count* (NIH Publication No. NIH 994584) [Online]. Available: http://www.NIMH.NIH.gov/publicat/numbers.CFM

Nierenberg, A.A., Keefe, B.R., Leslie, V.C., Alpert, J.E., Pava, J.A., Worthington, J.J., et al. (1999). Residual symptoms in depressed patients who respond acutely to fluoxetine. *Journal of Clinical Psychiatry, 60,* 221-225.

Ogrodniczuk, J.S., Piper, W.E., Joyce, A.S. (2004). Residual symptoms in depressed patients who successfully respond to short-term psychotherapy. *Journal of Affective Disorders, 82,* 469-473.

Pancheri, P., Picardi, A., Pasquini, M., Gaetano, P., Biondi, M. (2002). Psychopathological dimensions of depression: A factor study of the 17 item Hamilton depression rating scale in unipolar depressed outpatients. *Journal of Affective Disorders, 68,* 41-47.

Papakostas, G., Petersen, T., Denninger, J.W., Tossani, E., Pava, J.A., Alpert, J.E., et al. (2004). Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. *Journal of Clinical Psychopharmacology, 24,* 507-511.

Paykel, E.S. (1985). The Clinical Interview of Depression. *Journal of Affective Disorders, 9,* 85-96.

Paykel, E.S. (1994). Historical overview of outcome of depression. *British Journal of Psychiatry Supplement, 26,* 6-8.

Paykel, E.S. (1998). Remission and residual symptomatology in major depression. *Psychopathology, 31,* 5-14.

Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine,25,* 1171-1180.

Piaget, J. (1954). *The constructions of reality in the child.* New York: Basic Books. (Original work published 1937).

Piaget, J. (1981). *Intelligence and affectivity: Their relationship during child development.* Palo Alto, CA: Annual Review Monographs. (Original work published 1954).

Riso, L.P., Miyatake, R.K., Thase, M.E. (2002). The search for determinants of chronic depression: A review of six factors. *Journal of Affective Disorders, 70,* 103-115.

Robins, L.N. & Regier, D.A. (1990). *Psychiatric Disorders in America, The Epidemiologic Catchment Area Study.* New York, NY: The Free press.

Rush, A.J. (1996). Assessing outcome in practice: A paradigm shift? *Current Opinion on Psychiatry, 9, 1-2.*

Rush, A.J., Beck, A.T., Kovacs, M., & Hollon, S. (1977). Comparative efficacy of cognitive therapy and imipramine in the treatment of depressed outpatients. *Cognitive Therapy and Research, 1,* 17-37.

Rush, A.J., Giles, D.E., Schlesser, M.A., Fulton, C.L., Weissenberger, J.E., Burns, CT. (1986). The Inventory for Depressive Symptomatology (IDS): Preliminary findings. *Psychiatry Research, 18,* 65-87.

Rush, A.J., Guillion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H. (1996). The Inventory of Depressive Symptomotology (IDS): Psychometric properties. *Psychological Medicine, 26,* 477-486.

Rush, A.J. & Trivedi, M.H. (1995). Treating depression to remission. *Psychiatric Annals, 25,* 704-705.

Rush, A.J., Trivedi, M.H., Carmody, T.J., Ibrahim, H.M., Markowitz, J.C., Keitner, G.I. (2005). Self-reported depressive symptom measures: Sensitivity to detecting change in a randomized, controlled trial of chronically depressed, nonpsychotic outpatients. *Neuropsychopharmacology, 30,* 405-416.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Stewart, J., Nierenberg, A.A., Thase, M.E., et al. (2006). Bupropion-SR, sertraline, or venlafaxine –XR, after failure of SSRIs for depression. *New England Journal of Medicine, 254,* 1231-1242.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J., Warden, D., et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry, 163,* 1905-1917.

Schaefer, K.L., Vrana, S.R., McCullough, J.P., Williams, L. (2004). *Adult attachment as a developmental mediator for chronic depression.* Manuscript to be submitted for publication.

Scott, J. (2001). Cognitive therapy for depression. *British Medical Bulletin, 57,* 101-113.

Scott, C., Tacchi, M.J., Jones, R., Scott, J. (1997). Acute and one-year outcome of a randomized controlled trial of brief cognitive therapy for major depressive disorder in primary care. *British Journal of Psychiatry, 171,* 131-134.

Segal, Z., Vincent, P., Levitt, A. (2002). Efficacy of combined, sequential and crossover psychotherapy and pharmacotherapy in improving outcomes in depression. *Journal of Psychiatry Neuroscience, 27,* 281-290.

Shea, M.T., Elkin, I., Imber, S.D., Sotsky, S.M., Watkins, J.T., Collins, J.F., et al. (1992). Course of depressive symptoms over follow-up. *Archives of General Psychiatry, 49,* 782-787.

Simon, G.E. (2000). Long-term prognosis of depression in primary care. *Bulletin of the World Health Organization, 78,* 439-445.

Skinner, B. F. (1953). *Science and Human Behavior.* New York: Macmillan.

Spitzer, R.L., Endicott, J., Robins, E. (1978). Research diagnostic criteria: Rationale and reliability. *Archives of General Psychiatry, 35,* 773-782.

Stravynski, A., Shahar, A., Verreault, R. (1991). A pilot study of the cognitive treatment of dysthymic disorder. *Behavioral Psychotherapy, 19,* 369-372.

Tangney, J.P. (1991). Moral affect: The good, the bad, and the ugly. *Journal of Personality and Social Psychology, 61,* 598-607.

Thase, M.E., Fasiczka, A.L., Berman, S.R., Simons, A.D., Reynolds, C.F. (1998). Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. *Archives of General Psychiatry, 55,* 138-144.

Thase, M.E., Greenhouse, J.B., Frank, E., Reynolds, C.F., Pilkonis, P.A., Hurley, K., et al. (1997). Treatment with major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Archives of General Psychiatry, 54,* 1009-1015.

Thase, M.E., Reynolds, C.F., Frank, E., Jennings, J.R., Nofzinger, E., Fasiczka, A.L., et al. (1994). Polysomnographic studies of unmedicated depressed men bore and after treatment with cognitive behavior therapy. *American Journal of Psychiatry, 151,* 1615-1622.

Thase, M.E., Rush, A.J., Manber, R., Kornstein, S.G., Klein, D.N., Markowitz, J.C., et al. (2002). Differential effects of nefazodone and cognitive behavioral analysis system of psychotherapy on insomnia associated with chronic forms of major depression. *Journal of Clinical Psychiatry, 63,* 493-500.

Thase, M.E., Simons, A.D., McGeary, J., Cahalane, J.F., Hughes, C., Harden, T., et al. (1992). Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. *American Journal of Psychiatry, 149,* 1046-1052.

Tranter, R., O'Donovan, C., Chandarana, P., Kennedy, S. (2002). Prevalence and outcome of partial remission in depression. *Journal of Psychiatry Neuroscience, 27,* 241-247.

Trivedi, M.H., Fava, M., Wisniewski, S.R., Thase, M.E., Quitkin, F., Warden, D. et al. (2006). Medication augmentation after the failure of SSRIs for depression. *New England Journal of Medicine, 354,* 1243-1252.

Van Londen, L., Molenaar, R.P.G., Goekoop, J.G., Zwinderman, A.H., Rooijmans, H.G.M. (1998). Three to 5 year prospective follow-up of outcome in major depression. *Psychological Medicine, 28,* 731-735.

Vincent, N., Penner, S., Lewycky, S. (2006). What predicts patients' perceptions of improvement in insomnia? *Journal of Sleep Research, 15,* 301-308.

Weissman, M.M., Bland, R.C., Canino, G.J., Favarelli, C. Greenwald, S., Hwu, H.G., et al. (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association, 276,* 293-299.

Weisman, M.M. & Klerman, G.L. (1977). The chronic depressive in the community: Unrecognized and poorly treated. *Comprehensive Psychiatry, 18,* 523-532.

Young, J.E., Weinberger, A.D., Beck, A.T. (2001). Cognitive therapy for depression. In D.H. Barlow (Ed.), *Clinical Handbook of Psychological Disorders* (pp.264-308). New York, NY: The Guilford Press.

Zajecka, J.M. (1996). The effect of nefazodone on co-morbid anxiety symptoms associated with depression: Experience in family practice and psychiatric outpatient settings. *Journal of Clinical Psychiatry, 57 (suppl 2),* 10-14.

Zajecka, J.M. (2003). Treating depression to remission. *Journal of Clinical Psychiatry, 64 (suppl 15),* 7-12.

Appendix A.

Factor Structure of the HDRS

	FACTOR				
HDRS ITEM	Psychic Depression	Anxiety	Sleep Disturbance	Loss of Motivated Behavior	Disturbed Thinking
1. Depressed mood	X				
2. Guilt	X				
3. Suicide	X				
4. Early Insomnia			X		
5. Middle Insomnia			X		
6. Late Insomnia			X		
7. Work/activities				X	
8. Psychomotor Retardation	X				
9. Psychomotor Agitation		X			
10. Psychic Anxiety		X			
11. Somatic Anxiety		X			
12. Appetite				X	
13. Energy					
14. Genital				X	
15. Hypochondriasis		X			
16. Weight loss				X	
17. Insight					X
18. Diurnal variation					
19. Depersonalization					X
20. Paranoid Symptoms					X
21. OCD Symptoms					X
22. Helplessness	X				
23. Hopelessness	X				
24. Worthlessness	X				

Appendix B

Factor Structure of the IDS-SR

	FACTORS		
IDS-SR ITEMS	Cognitive/Mood	Anxiety/Arousal	Sleep Disturbance
1. Initial Insomnia			X
2. Middle Insomnia			X
3. Early Awakening			X
4. Hypersomnia			X
5. Sad Mood	X		
6. Irritability		X	
7. Anxious/tense		X	
8. Mood reactivity	X		
9. Mood variation			
10. Mood quality	X		
11. Appetite decrease	X		
12. Appetite increase	X		
13. Weight decrease	X		
14. Weight increase	X		
15. Concentration	X	X	
16. Self-criticism/blame	X		
17. Future pessimism	X		
18. Suicidal thoughts	X		
19. Interest in activities	X		
20. Energy/fatigability	X	X	
21. Pleasure/enjoyment	X		
22. Decreased libido	X		
23. Psychomotor retardation		X	
24. Agitation		X	X
25. Somatic complaints		X	
26. Sympathetic arousal		X	
27. Panic/phobic symptoms		X	
28. Constipation/diarrhea		X	
29. Rejection Sensitivity	X	X	
30. Leaden Paralysis		X	

Vita

Katherine Louise Schaefer was born on November 19, 1977 in St. Charles, Illinois. She graduated from Geneva High School in 1995 and went on to pursue a college education at Northern Illinois University in DeKalb, IL, where she achieved her Bachelors of Arts degree in psychology in 1999. In 2004, she received her Masters of Science degree in clinical psychology at Virginia Commonwealth University in Richmond, Virginia. Throughout her graduate education, her research and clinical emphasis has been in the area of chronic depression and treatment outcomes. She is currently completing her clinical internship at Northwestern University Feinberg School of Medicine in Chicago, Illinois, where she will also be completing her postdoctoral fellowship.