THE IMPACT OF COGNITION ON TREATMENT ADHERENCE IN COMORBID BIPOLAR DISORDER AND COCAINE DEPENDENCE

APPROVED BY SUPERVISORY COMMITTEE

E. Sherwood Brown, M.D., Ph.D.

Thomas Carmody, Ph.D.

Shawn McClintock, Ph.D.

Alyson Nakamura, M.D.

Alina Suris, Ph.D.

In loving memory of my cousins

Eric Fagan and Josh Waddell

The Impact of Cognition on Treatment Adherence in Comorbid Bipolar Disorder and Cocaine Dependence

by

COLLEEN SUSAN FAGAN

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COLLEEN SUSAN FAGAN, Ph.D.

The University of Texas Southwestern Medical Center, 2012

E. SHERWOOD BROWN, M.D., Ph.D.

Although bipolar disorder and substance dependence are associated with treatment nonadherence and cognitive impairment, few studies have investigated the relationship between treatment adherence and cognitive functioning. Participants in this study were 120 outpatients with bipolar disorder and cocaine dependence enrolled in a 10 week randomized, double-blind, placebo controlled trial of lamotrigine. Baseline performance on the Stroop Color and Word Test and the Rey Auditory Verbal Learning Test were examined for their effect on retention, appointment attendance, medication adherence, and return of medication bottles. Participants with decreased scores on Word condition of the Stroop Color and Word Test were more likely and those with decreased Interference scores were as likely to attend appointments. Participants

with better Rey Auditory Verbal Learning Test Total Recall scores returned more medication bottles. Cognitive functioning did not impact medication adherence or study retention. The findings suggest a relationship between cognitive functioning and treatment attendance. Assessment and treatment of cognitive dysfunction may identify and help patients at-risk for treatment nonadherence. Future studies with a more comprehensive neuropsychological test battery and advanced medication adherence measures are warranted.

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Prior Publications

Roecklein, K. A., Schumacher, J. A., Gabriele, J. M., Fagan, C., Baran, A. S., Richert, A. C. (2010). Personalized feedback to improve CPAP adherence in obstructive sleep apnea. *Behavioral Sleep Medicine*, 8(2), 105-112.

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CHAPTER I

INTRODUCTION

Bipolar disorder is a severe and persistent mental illness. Nearly 60% of people with bipolar disorder have a lifetime comorbid substance use disorder. Comorbid bipolar disorder and substance dependence are associated with greater cognitive impairment and treatment nonadherence than the general population or either disorder alone. Treatment nonadherence can lead to symptom relapse, psychosocial dysfunction, financial debt, hospitalization, and suicide. Past research has shown a link between cognitive functioning and treatment retention and adherence in mental illnesses such as schizophrenia spectrum disorders and bipolar disorder, but few research studies have investigated the effect of cognitive functioning on treatment adherence and study retention in individuals with comorbid bipolar disorder and substance dependence.

This study is a secondary analysis of the largest clinical trial conducted, to date, of a psychopharmacologic intervention in participants with comorbid bipolar disorder and cocaine dependence. We examine the effect of baseline cognitive functioning, including verbal learning and memory, simple visual attention, inhibition, and cognitive flexibility, on study retention, appointment attendance, medication adherence, and treatment instruction adherence. Results from this study will provide information on the relationship between cognitive functioning and treatment adherence in this population and will determine whether cognitive functioning can predict adherence. If there is a relationship between cognitive functioning and treatment adherence, then cognitive assessments could be used in clinical practice to identify those who are less likely to adhere and continue in treatment. Additionally, if cognitive impairment is one of these predictors, then interventions, such as cognitive rehabilitation, appointment cards and

phone calls, medication reminders and daily pill containers, could be used to improve adherence and retention. The goal of this study is to not only advance our knowledge of cognitive functioning and treatment adherence and retention in individuals with comorbid bipolar disorder and substance dependence, but also to identify risk factors to inform future interventions and treatment of this population. By identifying risk factors and predictors of nonadherence, we can provide treatment interventions to decrease the risk of relapse, psychosocial stress, morbidity, and mortality associated with treatment nonadherence in bipolar disorder and substance dependence.

CHAPTER II

LITERATURE REVIEW

I. Diagnostic Criteria and Prevalence of Bipolar Disorder

Bipolar disorder is a complicated mental illness that can cause significant functional impairment. People unfamiliar with the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Revised (DSM-IV-TR) [American Psychiatric Association (APA) 2000)] sometimes refer to individuals as being "bipolar" if they have rapid mood lability or "mood swings," significant irritability, and/or hyperactivity, or a personality comprised of a combination of those three characteristics. Although people with bipolar disorder may experience significant anxiety and irritability, excessive energy, and labile mood, these symptoms occur during distinct time periods in conjunction with other core bipolar symptoms and tend to be egodystonic. Knowing the bipolar disorder diagnostic criteria can help prevent misdiagnosis.

Bipolar disorders in DSM-IV-TR include bipolar disorder I, bipolar disorder II, bipolar disorder not otherwise specified (NOS) and cyclothymic disorder. The disorders cannot be due to a general medication condition, substance use or side effects of a medication. The hypomania/mania episodes are the main markers of bipolar disorder.

Bipolar I disorder is defined by the presence of at least one manic episode that lasts at least one week, one manic episode of any duration that results in psychiatric hospitalization, one manic episode with psychotic features, or one mixed episode. A manic episode consists of a persistently elevated, expansive mood plus three additional symptoms of mania, or a persistently irritable mood plus four additional mania symptoms. Additional symptoms of mania include being more talkative than usual or pressure to keep talking, flight of ideas or racing thoughts,

distractibility, feeling of grandiosity or inflated self-esteem, increase in pleasurable behaviors that are risky and could have negative repercussions, psychomotor agitation or increased activity directed toward a specific goal, and a decreased need for sleep. A mixed episode involves the co-occurrence of a major depressive episode (MDE) and a manic episode that is present nearly every day for at least one week. The manic episode must cause significant impairment in functioning. Bipolar I disorder does not have to include a lifetime history of a MDE.

In contrast, bipolar II disorder is defined by the DSM-IV-TR as the lifetime presence of at least one hypomanic episode and one MDE. Although the core symptoms are identical, hypomania is differentiated from mania by symptom duration and severity. Hypomania lasts at least four days, is not severe enough to warrant hospitalization, is not accompanied by psychosis, and does not have to result in significant impairment. It does, however, need to cause a change in functioning that is clearly different from what is normal for that individual. Hypomania consists of either an irritable mood or an expansive, elevated mood followed by either three or four additional hypomanic symptoms, respectively. A MDE consists of either anhedonia or depressed mood followed by four of seven symptoms that occur most days nearly all day for at least two weeks. These seven symptoms include insomnia or hypersomnia, changes in appetite or weight, suicidal ideation, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive inappropriate guilt, and decreased attention, concentration, or ability to make decisions.

Bipolar disorder NOS is diagnosed using the DSM-IV-TR when an individual does not meet full criteria for either bipolar I or II, but shows a few symptoms of hypo(mania) and depression. It can also be diagnosed when bipolar disorder I or II seems apparent but it is unclear

if the symptoms are more related to a general medical condition, substance use, or medication-induced. An example of bipolar disorder NOS would be the development of hypomania in the presence of an antidepressant that does not fully remit after discontinuation of the medication.

Cyclothymic disorder is defined by the DSM-IV-TR as periods of depressive and hypomanic symptoms that last more than half the time over a period of two years (one year in children and adolescents) with euthymia never lasting more than two continuous months. Although one may meet criteria for a hypomanic episode, the depressive symptoms never meet criteria for MDE. One must also never meet criteria for a manic episode. Like the other disorders, the diagnosis of cyclothymia is not made if the symptoms are due to the direct physiological effects of medication or substance use or a general medical condition. The symptoms must overall cause clinically significant distress and impairment in functioning. Cyclothymia is to bipolar disorder as dysthymia is to major depressive disorder. Cyclothymia is diagnostically important because it may help identify individuals prone to developing bipolar disorder I, II, or NOS.

According to the National Comorbidity Survey replication (n = 9,282), there is a 3.9% lifetime prevalence of bipolar I and II disorders (Miklowitz & Johnson, 2006). When bipolar spectrum patients (i.e. bipolar disorder NOS and cyclothymia) are included, lifetime prevalence rates increase to 10% (Miklowitz & Johnson, 2006). Women and men are equally at risk for developing bipolar I but women are more likely than men to meet criteria for bipolar II (Miklowitz & Johnson, 2006). Among people with psychiatric illnesses, individuals with bipolar disorder have one of the highest rates of suicide (Miklowitz & Johnson, 2006). Nearly 50% of people with bipolar disorder attempt suicide (Jamison, 2000), and people with bipolar disorder

have a completed suicide rate four times higher than individuals with recurrent major depression and approximately 15 times greater than the general population (Miklowitz & Johnson, 2006).

II. Bipolar Disorder and Substance Dependence

Prevalence of comorbidity.

The prevalence of substance use disorder is much higher in persons with bipolar disorder than in the general population. In a sample of 20,291 people, researchers found a 61% lifetime prevalence rate of substance dependence in bipolar I disorder patients and a 48% prevalence rate with bipolar II disorder patients, compared to a 17% lifetime prevalence rate in the general population (Regier et al., 1990). A more recent study of 261 participants found a 42% lifetime prevalence rate of substance abuse in bipolar I and 34% in bipolar II and bipolar NOS (Suppes et al., 2001).

People with bipolar disorder may be at a greater risk for developing substance dependence, rather than less severe substance abuse. Of 43,093 people interviewed, individuals with a lifetime history of mania are 13.9 times more likely to have substance dependence relative to only 3.7 times the odds of having abuse (Grant et al., 2004). People with a history of hypomania have 4.4 times the odds of developing substance dependence compared with 1.7 times the odds of developing abuse (Grant et al., 2004). Compared to mood and anxiety disorders, bipolar I disorder is associated with the highest lifetime prevalence rate of substance abuse/dependence (Brown, Suppes, Adinoff, & Thomas, 2001).

As with the general population alcohol use disorders are the most common substance use disorders in patients with bipolar disorder (Brown, 2005). Forty-six percent of people with comorbid bipolar disorder and substance-related disorders report alcohol as their primary

substance of abuse, compared with 41% of people with bipolar disorder and substance dependence who are dependent upon all other substances combined (Brown et al., 2001). People with bipolar I disorder have a 46% lifetime prevalence rate of alcohol abuse versus the general population rate of 14% (Regier et al., 1990), and individuals with bipolar disorder are also at a greater risk of developing drug abuse or dependence (Brown et al., 2001). A 10 year follow up study with 277 participants indicated that among the drugs used by people with bipolar disorder, stimulants and cannabis are abused more than hallucinogens and sedatives (Winokur et al., 1998). Within bipolar disorder, males and those with comorbid anxiety disorders are at greater risk for substance abuse (Brown, 2005). Collectively these study statistics indicate that people with bipolar disorder have a higher risk and percentage rate of alcohol and substance abuse/dependence compared to the general population, tend to have more dependence than abuse, and have more alcohol use disorders than other substance use disorders.

This population of patients with comorbid bipolar disorder and substance abuse or dependence appears to have significantly higher morbidity and poorer psychosocial functioning. Comorbid bipolar disorder and substance abuse is associated with higher rates of suicide attempts in those who start abusing substances after the onset of bipolar disorder (Feinman & Dunner, 1996). Hospitalization rates are also higher in comorbid substance abuse and bipolar disorder (Brown, 2005). Furthermore, drug abuse during psychosis, including manic episodes, can lead to aggression and violence (Brown, 2005).

Understanding the Relationship between Bipolar and Substance Use.

Because of the high comorbidity rates between bipolar and substance use disorders, a debate has emerged regarding the relationship between the two disorders. Do the disorders develop concurrently or does one disorder lead to the other? Are people with substance

dependence misdiagnosed with bipolar disorder? Are there other unidentified factors that contribute to the development of both disorders?

When taking a patient's history, it can be difficult to discern which disorder occurred first because bipolar disorder and substance dependence both typically emerge during adolescence or early 20s (Brown, 2005). A literature review reveals a nearly equal split between reports that mood symptoms proceeded or co-occurred with substance abuse and reports that substance abuse began before the onset of mood symptoms (Brown, 2005; Kessler et al., 1996; Strakowski & DelBello, 2000). As such, a temporal relationship between the onset of bipolar versus substance abuse symptoms cannot be firmly established.

Another way to understand the relationship between bipolar disorder and substance dependence is to examine whether there is an association between mood and substance use. One study found that people were more likely to use alcohol during manic episodes and cocaine during depressed episodes (Sonne, Brady, and Morton, 1994). Another study indicated that for a subgroup of people with bipolar disorder, alcohol was associated with depression and cannabis with mania (Strakowski, DelBello, Fleck, & Arndt, 2000). There tends to be more polysubstance and amphetamine abuse during mania than with depression (Brown, 2005). However, other research shows that there are people with bipolar disorder who abuse substances no matter their mood state (Brown, 2005). Thus, while different mood states may elicit the use of particular substances, the evidence is contradictory, and any causal link between mood and drug use is unknown at this time.

Other possible causal associations between substance use and bipolar disorder are not yet firmly supported by the existing research. Increased cortisol levels during mixed states of bipolar disorder may lead to greater use of stimulants (Brown et al., 2001). Psychosocial

situations and conditions that patients with bipolar disorder experience may also lead to exposure to drugs and alcohol (Brown, 2005). For example, bipolar disorder symptoms can precipitate a loss of employment and income, which in turn can lead to homelessness; individuals who are homeless are more vulnerable to developing substance dependence (Brown, 2005).

Could it be that the high rates of bipolar disorder and substance abuse comorbidity are due to misdiagnosis of pure substance dependence disorders or substance-induced mood disorders? People with substance dependence may be misdiagnosed with bipolar disorder because psychiatric symptoms secondary to substance use and intoxication can look like mood lability and hypomania (Brown et al., 2001) and drug withdrawal can mimic depressive symptoms (Strakowski et al., 2000). Additionally, alcohol abuse can look like depression when, in fact, the depressive symptoms are really secondary to alcohol and remit after several weeks of abstinence (Brown et al., 2001). This may explain why people who abuse drugs or alcohol are sometimes diagnosed with bipolar spectrum disorders (Brown et al., 2001). Perhaps individuals with substance dependence who are actively using drugs are more likely to be misdiagnosed with bipolar disorder than those who are sober. One study found that the rate of bipolar disorder diagnoses dropped to the same level as the general population (3.4%) when participants with substance abuse became sober after three weeks in inpatient treatment (in Brown et al., 2001). In a study that accounted for misdiagnosis by excluding people with substance-induced mood disorders, a high rate of substance dependence was still found in people with bipolar disorder (Grant et al., 2004). Therefore, while it is possible that the high rate of comorbid bipolar disorder and substance dependence is due to misdiagnosis of substance-induced mood disorder, there appears to be a high comorbidity rate even after accounting for possible misdiagnosis. This finding suggests that there is validity to the comorbid diagnosis.

It is important to note that not all people who have a substance use disorder develop bipolar disorder. Only 0-11% of people who abuse substances have a history of bipolar I, while 7-25% of individuals who abuse substances have a history of bipolar II or cyclothymic disorder (Brown et al., 2001). Therefore, the diagnoses of bipolar disorder and substance abuse/dependence can and do exist separately and thus, a comorbid diagnosis is likely valid.

Other factors, such as genetics, psychosocial stress, or impulsive traits, may contribute to the development of both substance abuse and bipolar disorder. Research has indicated that there may be a genetic link then between bipolar disorder and substance dependence (Brown, 2005). For example, first degree relatives of people with bipolar disorder tend to have higher rates of alcohol-related disorders, although bipolar disorders tend to be more prevalent than substance use disorders in relatives (Brown, 2005). Psychosocial stress, which can trigger mood episodes and substance use, may contribute to the development of comorbid bipolar disorder and substance dependence (Strakowski et al., 2000). Additionally, certain traits such as impulsivity occur frequently in both substance use disorders and bipolar disorder. More research is needed to determine if these factors contribute to the development of comorbid substance use disorder and bipolar disorder. While the causal and temporal associations between bipolar disorder and substance use disorders are unclear, the high rate of comorbidity seems to be valid and not simply due to misdiagnosis.

III. Bipolar Disorder, Brain Structures, and Associated Cognitive Functioning

Although there is no one distinct cognitive profile for people with bipolar disorder, there are several cognitive domains associated with the disorder (Osuji & Cullum, 2005). Table 1 summarizes research findings on cognitive functioning in bipolar disorder. In this table, impaired

cognitive domains are notated by an "x" and cognitive domains that are normal are labeled as such. If the research literature has mixed results regarding impairment in a particular cognitive domain, then it is labeled as "mixed."

As a group, patients with bipolar disorder perform below average on several neuropsychological tests (Osuji & Cullum, 2005). Bipolar disorder is associated with deficits in working memory, executive functioning (i.e. cognitive flexibility, planning, and inhibition) and verbal learning and memory (Green, 2006). Impairments in attention, visuospatial abilities, abstract thinking and problem solving are also commonly reported in bipolar disorder (Osuji & Cullum, 2005). These cognitive deficits are present prior to the onset of bipolar disorder, present across most, if not all, mood states of the illness, and are found in first degree relatives (in Green, 2006). These cognitive impairments are present when people with bipolar disorder are compared to same-age healthy controls (Zarate, Tohen, Land, & Cavanagh, 2000).

Cognitive impairments in attention, working memory, executive function, and verbal learning and memory tend to be more severe in bipolar I compared to bipolar II disorder (Torrent et al., 2006) perhaps because greater cognitive impairment is associated with manic, rather than hypomanic, episodes (Colom, Vieta, Tacchi, Sánchez-Moreno, & Scott, 2005). Increased numbers of mood episodes have also been associated with poorer cognitive functioning (Osuji & Cullum, 2005).

These particular cognitive deficits suggest that the frontal, temporal, and subcortical brain systems are impaired in bipolar disorder (Osuji & Cullum, 2005). Within the frontal system, the anterior cingulate, basal ganglia, and temporolimbic systems have been identified as playing a role in affective disorders (Osuji & Cullum, 2005). Enlargement of the cerebral ventricles has also been reported in bipolar disorder (Osuji & Cullum, 2005), suggesting shrinkage of brain

systems (i.e. hippocampus) that may contribute to cognitive deficits. White matter abnormalities, especially hyperintensities in white matter, are more common in bipolar disorder than in other mood disorders or schizophrenia (Osuji & Cullum, 2005).

Decreased verbal learning and memory seems to be one of the most consistent impairments in bipolar disorder and thus may serve as a possible neurocognitive endophenotype (Goldberg and Burdick, 2008). Several studies have indicated a medium effect size of bipolar disorder diagnosis on verbal learning (in Jamrozinski, 2010). People with bipolar disorder, particularly those with bipolar I, show impairments in verbal learning and memory that persist even during periods of remission and euthymia (Torrent et al., 2006). One study found that people with bipolar disorder in the euthymic phase performed poorer than healthy controls on all recall trials of the California Verbal Learning Test (CVLT), a verbal memory test (Van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998).

Verbal learning and memory deficits in bipolar disorder may be cognitive trait markers for the illness, since scores on recall and recognition measures can differentiate between bipolar disorder, unipolar depression, and non-psychiatric controls (Osuji & Cullum, 2005). The degree of verbal learning and memory impairment may be affected by factors such as age, IQ, number of mood episodes, and mood symptoms (Elgamal, Sokolowska, & MacQueen, 2008). According to longitudinal studies, verbal memory tends to be poorer in people whose bipolar disorder began in childhood or adolescence (Jamrozinski, 2010). Collectively, these studies demonstrate that verbal learning and memory is impaired in people with bipolar disorder, regardless of mood state.

Working memory deficits are also observed in people with bipolar disorder. Working memory is impaired even during the euthymic phase of the illness (Torrent et al., 2006).

However, the working memory deficits associated with euthymia may be due to underlying deficits in sustained attention and vigilance (Elgamal et al., 2008), rather than a true working memory impairment. For example, when controlling for age, premorbid intelligence, and depressive symptoms, euthymic patients with bipolar disorder did not differ from healthy controls on a visual memory span backward task (in Elgamal et al., 2008), which measures working memory only. However, when controlling for these same factors, the euthymic bipolar patients did perform significantly poorer on a digit backward task, which measures working memory as well as executive functioning and attention; this suggests that deficiencies in the two latter cognitive domains account for the observed decrease in working memory (Elgamal et al., 2008). Thus, it is unclear how much working memory is impaired during euthymia in bipolar disorder.

Attention is considered a prerequisite to all higher cognitive skills (Goldberg and Burdick, 2008) and thus deficits in attention can contribute to impairment in other cognitive domains; Elgamal et al's findings above are an example of this. Sustained attention deficits appear to be characteristic of bipolar disorder, either as a trait deficit (Roiser et al., 2009) or a possible marker for bipolar disorder (Clark, Iverson, & Goodwin, 2002). Therefore, it may also be a neurocognitive endophenotype for bipolar disorder (in Goldberg and Burdick, 2008). Deficits in sustained attention have been reported in first degree relatives of people with bipolar disorder (Maalouf et al., 2010). Sustained attention is impaired during the manic phase and remission or euthymic phase of bipolar disorder (Maalouf et al., 2010) as well as during depressive episodes (Goldberg and Burdick, 2008). Similarly, selective attention is also impaired in bipolar disorder, regardless of mood state (Goldberg and Burdick, 2008). These studies

indicate that a deficit in sustained attention is a significant characteristic of bipolar disorder that is apparent across all mood states.

As noted above, executive functioning is impaired in bipolar disorder and is another one of the more consistent traits in bipolar disorder (in Goldberg and Burdick, 2008). Like verbal memory, according to longitudinal studies, executive functioning is likely to be more impaired if bipolar disorder emerges in childhood or adolescence (Jamrozinski, 2010). A few research studies indicate that executive dysfunction occurs during both unipolar depression and bipolar depression, but not during euthymic periods of bipolar disorder (Maalouf et al., 2010). This finding seems to imply that executive dysfunction may be state rather than trait dependent in bipolar disorder (Maalouf et al., 2010).

However, other studies indicate that executive functioning is impaired both during the acute, remission, and euthymic phases of bipolar disorder (Bearden, Hoffman, & Cannon, 2001; Torrent et al., 2006; Zarate et al., 2000). People with bipolar disorder whose symptoms are in remission have lower scores compared to healthy controls on tests of inhibition, such as the Stroop Color and Word Test and Go/No Go task (Jamrozinski, 2010). Similarly, when compared to healthy controls, people with bipolar disorder have increased impulsivity regardless of their current mood (Jamrozinski, 2010). While executive functioning is clearly impaired in bipolar disorder, it is unclear whether the deficit is due to mood or is a neurocognitive marker of bipolar disorder.

Deficits in attention, executive functioning, and verbal learning and memory are referred to as possible endophenotypes for bipolar disorder because they are heritable, tend to occur across all mood states, and are present in first degree relatives (Green, 2006). However, these cognitive domains may be endophenotypes for only a subgroup of people with bipolar disorder

because although many people with bipolar disorder have cognitive deficits, not all do, and not all people with bipolar disorder have similar cognitive profiles (Jamrozinski, 2010; Osuji & Cullum, 2005). As expected with most medical or psychiatric conditions, the stability and effect of the cognitive impairments in bipolar disorder vary from person to person (Jamrozinski, 2010). One reason for this variability is that individual differences in illness course and treatments impact cognitive functioning. Also, features other than the illness itself, such as age of onset and genetics can affect the level of cognitive functioning (Jamrozinski, 2010).

There are inconsistencies across research studies regarding which cognitive domains are impaired in people with bipolar disorder (Jamrozinski, 2010; Osuji & Cullum, 2005). These inconsistencies are sometimes due to methodological issues such as small sample sizes leading to poor generalizability, varying methods of defining and measuring mood states, and usage of different neurocognitive tests and diagnostic procedures for bipolar disorder (Osuji & Cullum, 2005). Variability in neurocognitive tests is problematic because a particular test can measure more than one area of cognitive functioning. Researchers also differ in their interpretation of what cognitive domains are measured by a certain test which then leads to different reporting of results (Jamrozinski, 2010).

Another possible reason for inconsistent results across studies is that confounding variables, such as psychotropic medication use, are not always taken into account. It seems that overall most psychotropic medications lead to only relatively mild cognitive impairments in people with bipolar disorder (Goldberg & Burdick, 2008). The extent to which bipolar disorder medications have a detrimental effect on cognitive functioning varies based on the type of medication (Goldberg & Burdick, 2008). There is conflicting evidence as to how much of the cognitive deficits in bipolar disorder are due to the medications versus the illness itself (Roiser et

al., 2009) and whether the medications have a detrimental or neuroprotective effect (Goldberg & Burdick, 2008).

Lithium is one such medication that has mixed results in the literature regarding its effect on cognitive functioning. A few studies have indicated that lithium has a negative impact on executive functioning and processing speed (Jamrozinski, 2010). Elderly patients with higher lithium levels tend to demonstrate more cognitive inflexibility as measured by the Wisconsin Card Sorting Test (WCST) (Forester et al., 2009). Lithium seems to impair motor speed and verbal memory (Roiser et al., 2009; Goldberg & Burdick, 2008). Lithium also may cause decreased associative fluency (Goldberg & Burdick, 2008).

Conversely, one study found that cognitive impairment only occurred in patients with bipolar disorder whose symptoms did not remit with lithium (Jamrozinski, 2010). Another study suggested that lithium does not play a role in decreasing sustained attention and working memory (Clark et al., 2002). Other recent studies also do not show evidence that lithium leads to cognitive impairment in bipolar disorder (Osuji & Cullum, 2005). Furthermore, it has been asserted that there is no clear definitive evidence of neurocognitive dysfunction associated with chronic lithium use (Goldberg & Burdick, 2008). The net effect of lithium may actually be more protective than damaging (Roiser et al., 2009). Collectively, these studies indicate that there is inconclusive evidence regarding the neurocognitive effects of lithium and more research is needed to clarify previous results.

As with lithium, there is mixed evidence regarding the cognitive impact of anticonvulsants and antipsychotic medications. Topiramate, an anticonvulsant, is sometimes associated with impairments in language, verbal and nonverbal fluency, attention, concentration, perception, working memory, and attention (Goldberg & Burdick, 2008). Valproate, another

anticonvulsant, may further exacerbate the decreased processing speed in people with bipolar disorder (Jamrozinski, 2010). Carbamazepine, which is also an anticonvulsant, has been associated with slight deficits in learning, memory, and reaction time (Goldberg & Burdick, 2008). However, one review of the literature found that the association between valproate and carbamazepine and cognitive impairment is inconclusive (in Osuji & Cullum, 2005). Additionally, the anticonvulsant lamotrigine is associated with better cognitive functioning in bipolar disorder (in Osuji & Cullum, 2005; Goldberg & Burdick, 2008). Atypical antipsychotics have sometimes been associated with deficits in executive functioning, processing speed, and verbal memory (Goldberg & Burdick, 2008). However, risperidone is associated with an increase in executive and occupational functioning in people with bipolar disorder (Osuji & Cullum, 2005). While a few research studies show that anticonvulsants and atypical antipsychotics tend to be associated with cognitive deficits, others show that specific medications (i.e. lamotrigine and risperidone) may actually help cognitive functioning. Overall, the data on anticonvulsants' and antipsychotics' cognitive effects in bipolar disorder tend to be mixed or inconclusive depending on the medication, and more research is needed to determine and clarify the effect of these bipolar medications on cognitive functioning.

There are also mixed results regarding the cognitive effects of medications used to treat bipolar depression. Patients with bipolar depression who are on psychotropic medication have greater attention deficits compared to similar patients without medications (Holmes et al., 2008); these difficulties with attention may be due to medication-related affective blunting or psychomotor slowing (Holmes et al., 2008). Other studies demonstrate that neurocognitive impairments occur more often in patients who are on psychotropic medications, even those with bipolar II disorder (in Roiser et al., 2009). Due to their anticholinergic effect, tricyclic

antidepressants tend to be associated with decreased arousal and attention, slowed processing speed, and impaired memory (Goldberg & Burdick, 2008). In contrast, non-tricyclic antidepressants [such as serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs)] appear to improve overall attention and working memory (Goldberg & Burdick, 2008). Collectively, these studies indicate that the effect of bipolar depression medications on cognitive functioning is uncertain and may vary based on the antidepressant medication type.

Although the evidence about the exact cognitive deficits in bipolar disorder remains contradictory, these cognitive impairments do appear to deleteriously and significantly affect individuals with this illness. Studies examining the impact of cognitive impairment in bipolar disorder on psychosocial functioning (i.e. employment status, social relations) show a small to medium effect size (0.35 to 0.46), for verbal learning and memory (Green, 2006). Memory deficits positively correlate with poor psychosocial functioning in bipolar disorder (Zarate et al., 2000). Memory deficits related to anhedonia and avolition best predict poor functioning in bipolar disorder (Zarate et al., 2000). Attentional shifting, verbal fluency, and auditory working memory are most often correlated with psychosocial functioning in bipolar disorder (Torres, DeFreitas, & Yatham, 2008). Improved occupational functioning is positively associated with verbal memory, fluency, and attentional shifting (Torres et al., 2008). Poor cognitive functioning, particularly memory deficits, may indirectly contribute to the social disability seen in 30 to 50% of people with bipolar disorder (Torres et al., 2008; Zarate et al., 2000). These studies indicate that cognitive functioning is associated with psychosocial outcomes in individuals with bipolar disorder and underscore the importance of studying the effect of cognitive functioning on factors that influence outcomes, such as treatment adherence.

IV. Substance Use, Brain Structures, and Associated Cognitive Functioning

Like bipolar disorder, substance dependence is associated with structural brain changes and cognitive deficits. In particular, substance dependence is related to impairment in the prefrontal cortex (PFC) (Verdejo-García, Bechara, Recknor, & Pérez-García, 2006). Neuroimaging studies have found decreased gray matter volume in the PFC of patients with substance abuse (Barry & Petry, 2008). Three main circuits of the PFC are responsible for different executive functions: the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC). Executive functions moderated by these PFC circuits underlie important functional behaviors, and the psychological sequelae of executive dysfunction in substance abusers may contribute to maladaptive behaviors such as impulsive decision making, amotivation, and denial/minimization of illness (Fals-Stewart, Shanahan, & Brown, 1995; Goldman, 1995). Poor planning and decreased inhibition in individuals who abuse cocaine may explain their difficulty in initiating and maintaining sobriety (Bolla et al., 2003). Each of these PFC cortices is associated with different brain functions and thus their impairment results in unique deficits. The following is a description of relationships between substance use and the PFC.

Individuals dependent on drugs demonstrate structural abnormalities in the DLPFC (Bechara, 2005). Additionally, the more cocaine used, the less activation in the DLPFC (Bolla et al., 2003). Dysfunction in the DLPFC can lead to cognitive inflexibility, and damage to the DLPFC is found in patients who have trouble with perseveration and attention shifting (Bechara, 2005). These cognitive inflexibilities are found in people who abuse alcohol, amphetamines, or

cocaine (Verdejo-García et al., 2006). For example, most people with substance dependence show poor performance on the Trail Making Test Part B (Reitan & Wolfson, 1985) which measures cognitive flexibility and alternating attention (Barry & Petry, 2008). Cognitive flexibility is the ability to shift between different and/or opposing tasks and to consider other problem solving techniques. Based on the above evidence, it appears that cognitive flexibility is impaired in individuals with substance abuse.

Damage to the DLPFC is also associated with poor working memory, and people who abuse alcohol, amphetamines, or cocaine demonstrate deficits in working memory as measured by neuropsychological tests such as the Cambridge Neuropsychological Automated Test Battery (CANTAB) (CeNeS Ltd. Cambridge, U.K.) (Verdejo-García et al., 2006). When compared to healthy controls, individuals dependent on substances show poorer working memory as measured by the N-back Task (Verdejo-García et al., 2006). Substance dependence is associated with a poor ability to update and filter information on working memory tasks (Verdejo-García et al., 2006). Individuals with substance dependence who have difficulties with working memory also have trouble with good decision making, suggesting a possible relationship between these two cognitive functions (Bechara, 2005). These studies indicate that substance abuse is associated with DLPFC damage resulting in poor working memory.

Individuals dependent on drugs also show damage to the OFC. Neuroimaging studies found decreased gray matter volume, particularly in the OFC, in substance abusers (Barry & Petry, 2008). People who have a pattern of chronic cocaine use have decreased structural integrity of white matter and gray matter density in the frontal regions of the brain (Porrino, Smith, Nader, & Beveridge, 2007). Animal studies indicate that longer duration of drug use is

associated with changes in OFC activity (Porrino & Lyons, 2000). Thus, there appears to be a relationship between substance abuse and OFC damage.

Impairment in the OFC is marked by emotional dysregulation, poor decision-making, and difficulty learning with stimulus reinforcement. Substance dependence is associated with OFC deficits of poor decision making and difficulty processing emotions (Verdejo-García et al., 2006). People who abuse cocaine tend to have high rates of depression, attention deficit hyperactivity disorder, and other emotional disorders (Porrino et al., 2007), and individuals who abuse multiple substances tend to have poor decision making skills (Verdejo-García et al., 2006). People with substance dependence typically show poor performance on the Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1976), which measures verbal fluency and problem solving (Barry & Petry, 2008). Impairments in problem solving can lead to making poor decisions. This difficulty with decision-making could be a result of the negative impact that substance abuse has on the nervous system and neurotransmitter functioning (Jentsch & Taylor, 1999). These studies indicate that substance abuse is associated with damage to the OFC resulting in emotional disorders, poor decision-making, and poor problem solving skills.

Lesions in the ACC are associated with low motivation and initiative and difficulty inhibiting responses, which can be indicative of impulsivity. People who abuse alcohol or amphetamines and cocaine tend to have poorer performance on tasks requiring response inhibition (Verdejo-García et al., 2006). People with substance dependence perform poorly on the Trail Making Test Part B, which measures the ability to inhibit a dominant, incorrect response (Barry & Petry, 2008). People who abuse cocaine perform poorly on a neuropsychological test of behavioral inhibition; not only does it take them longer to inhibit responses but they are also less likely to do so (Fillmore & Rush, 2002).

A significant difference was found between individuals with substance dependence and healthy controls on a self-report measure of behaviors associated with ACC and PFC dysfunctioning (The Frontal Systems Behavioral Scale; Grace & Malloy, 2001) (Verdejo-García et al., 2006). The participants who were dependent on substances endorsed more behaviors associated with apathy, disinhibition and executive dysfunction (Verdejo-García et al., 2006). Collectively these studies indicate a relationship between substance abuse and ACC damage, resulting in difficulties with inhibition.

There is mixed evidence as to whether these cognitive impairments (i.e. cognitive flexibility, working memory, decision-making, and inhibition) associated with the PFC improve during substance use remission. Several studies have demonstrated that executive functioning improves partially during abstinence (in Verdejo-García et al., 2006). Participants with substance dependence reported that their behaviors related to apathy, executive dysfunction, and disinhibition significantly decreased during abstinence (Verdejo-García et al., 2006).

However, when a battery of neuropsychological tests was used to measure executive functioning, people in remission after simultaneous abuse of several substances performed poorly compared to controls on tests that measured updating, inhibition, decision-making, and shifting (Verdejo-García & Pérez-García, 2007). Those who had formerly abused cocaine more had lower scores on tests measuring the brain's ability to update information (Verdejo-García & Pérez-García, 2007). Additionally, people who previously used heroin relative to those who once abused cocaine performed better on measures of inhibition and mental flexibility (Verdejo-García & Pérez-García, 2007). Persistent functional abnormalities in the PFC have been found in individuals dependent on cocaine, after 25 days of abstinence (Bolla et al., 2003). Studies have shown that even after six months of abstinence from substance dependence, individuals still have

signs of frontal lobe damage (Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Fein, Klein, & Finn, 2004).

Therefore, while a few research studies demonstrate that impairment in aspects of executive functioning decrease in remission, other studies show continued cognitive deficits during sobriety. These findings suggest that substance abuse may have long lasting effects on cognitive functioning and underscore the need for more research on the impact of substance abuse/dependence on cognitive functioning, especially as it relates to treatment outcomes.

Cognitive impairment in people who use cocaine.

Certain cognitive impairments are specific to cocaine abuse. An effect size analysis of neurocognitive test results from 15 empirical studies compared 481 participants with cocaine abuse or dependence with 586 healthy controls (Jovanovski, Erb, & Zakzanis, 2005). Those with cocaine abuse or dependence had significant cognitive deficits compared to healthy controls on most neuropsychological tests (Jovanovski et al., 2005). Participants who abused cocaine performed poorer on tests of working memory, visual memory and design reproduction, and attention compared to healthy controls (Jovanovski et al., 2005). Tests sensitive to attention abilities had the highest effect sizes (e.g. 0.49-0.68) demonstrating that those who abuse cocaine have definite difficulties with attention, particularly sustained and focused attention (Jovanovski et al., 2005). Participants dependent on cocaine also performed poorly on working memory tasks (Jovanovski et al., 2005). Research findings regarding the impact of cocaine use on executive dysfunction were mixed because of varying effect sizes for the results on the neuropsychological tests (Jovanovski et al., 2005). However, cocaine use was associated with greater difficulty on tests of complex, multidimensional executive functioning (i.e. Booklet Categories Test) (Jovanovski et al., 2005). Based on the above evidence, it appears that cocaine is associated with

difficulties in sustained and focused attention, working memory, visual memory and certain complex executive functioning tasks.

There is mixed evidence regarding the effects of cocaine on verbal fluency, verbal learning, and verbal memory. There are small effect sizes on tests of verbal fluency and other language functions for people with cocaine abuse or dependence (Jovanovski et al., 2005). No impairment in verbal fluency is seen, but verbal memory is decreased in those who abuse cocaine (Jovanovski et al., 2005). One study found that although participants who used cocaine performed better overall than healthy controls on tests of oral fluency, those who used cocaine in larger amounts and increased frequency prior to testing had greater deficits on tests of verbal memory and oral fluency (O'Malley, Adamse, Heaton, & Gawin, 1992). In another study, those who abused cocaine had lower scores than healthy controls on verbal memory measures but no differences were found between the groups on a test of verbal fluency (Berry et al., 1993). A study of patients who previously abused cocaine weekly and had ten days of sobriety found that they had decreased efficiency in learning verbal information, and thus were unable to store information into long term memory (Mittenberg & Motta, 1993). Collectively, these studies demonstrate that cocaine abuse is associated with poor verbal memory but it is inconclusive regarding cocaine's impact on verbal/oral fluency.

Individuals who are dependent on drugs, including cocaine, show behavior indicative of damage to the ventromedial prefrontal cortex (VPMC),which includes part of the OFC (Bechara, 2005). Because this region of the brain connects various neural networks, VPMC damage leads to changes in emotion, affect, and social behavior (Bechara, 2005). Damage in these neural networks may lead people with cocaine dependence to be more susceptible to favor short-term rewards over long term outcomes (Bechara, 2005). Additionally, individuals with substance

abuse and other people with damage to the VPMC are more likely to deny associated behavioral problems and seem to disregard any negative consequences of choosing an immediate reward (Bechara, 2005), which could lead to poor decision making. Neurocognitive tests, such as the Iowa Gambling Task, have confirmed VPMC damage in substance abusers by demonstrating deficits in decision making and other cognitive functions (Bechara, 2005). This VPMC damage may be apparent before the onset of addiction and could thus contribute to the development of cocaine addiction (Bechara, 2005). Several research studies have indicated that in addition to decision making, individuals who abuse cocaine may have difficulties with abstract reasoning and nonverbal problem solving (Porrino et al., 2007). Although the temporal association is unclear, cocaine abuse seems to be associated with damage to the VPMC, resulting in maladaptive behaviors such as denial, minimization, poor decision making, and immediate gratification.

V. Cognitive Functioning in Comorbid Substance Dependence and Bipolar Disorder

Since substance dependence and bipolar disorder are each associated with cognitive deficits, cognitive impairment may be even greater in individuals diagnosed with both disorders. However, few studies have examined neurocognition in people with this comorbidity (Levy & Weiss, 2009). Of these few studies, substance use was associated with greater cognitive deficits in participants with bipolar disorder (Levy & Weiss, 2009; van Gorp et al, 1998). Participants with comorbid bipolar disorder and alcohol dependence had significantly lower scores on the CVLT and an executive functioning test (Color-Word condition on the Stroop Color and Word Test) than healthy controls and those with bipolar disorder alone (van Gorp et al., 1998). In another study, participants with both bipolar disorder and alcohol dependence had greater

executive dysfunction and poorer verbal and nonverbal memory compared to those who only had bipolar disorder (Levy & Weiss, 2009). A history of substance abuse was associated with higher performance impulsivity in participants with bipolar disorder who had residual symptoms between mood episodes (Swann, Dougherty, Pazzaglia, Pham, & Moeller, 2004). Trait impulsivity is greater in individuals with comorbid bipolar disorder and substance dependence than people with either disorder alone (Swann et al., 2004). Table 2 compares the cognitive domains impaired in unipolar depression, bipolar disorder, and substance dependence (SUD). With the few research studies available, it appears that comorbid bipolar disorder and substance dependence are associated with executive dysfunction including impulsivity and cognitive inflexibility, and poorer verbal and nonverbal memory. More research is needed regarding the effect that bipolar disorder and substance dependence combined have on cognitive functioning.

VI. Treatment Nonadherence

Treatment nonadherence is common in people with physical illnesses. For general medical conditions, 25% of people on average are nonadherent to their medication (DiMatteo, 2004). Nonadherence to psychotropic medication varies by medication type, with a nonadherence rate of 40% to 60% for antipsychotics, 18% to 65% for mood stabilizers, and a median nonadherence rate of 63% for antidepressants (Patel & David, 2005). The percentage of people with bipolar disorder not adhering to psychotropic medication treatment ranges between 20% and 50% (Julius, Novitsky, & Dubin, 2009) and is reportedly to be as high as 60% (Lingam & Scott, 2002). Nonadherence to antipsychotic medications accounted for $1.479 billion in related hospitalization costs in 2005 in the United States (Julius et al., 2009). In addition to

higher hospitalization rates and costs, nonadherence contributes to higher rates of suicide, homelessness, substance use, physical aggression, and poor quality of life (Julius et al., 2009).

Reported rates of nonadherence to psychotropic medications vary in part because of the different methods for defining and assessing nonadherence (Colom et al., 2005). The definition of nonadherence involves more than just failing to take prescribed medication. It also includes a broader definition of not following treatment recommendations including, but not exclusively, adherence to medication. For example, there are behavioral aspects of nonadherence, such as poor appointment attendance, appointment cancellation and tardiness, and use of substances despite knowledge that it can interfere with the effectiveness of medication (Colom et al., 2005). Assessing the frequency of physician visits and monitoring retention can be used to gauge treatment adherence (Bechi et al., 2005). The World Health Organization (WHO) 2003 report defined treatment adherence as: "The extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (p. 3).

Due to the various ways that treatment nonadherence is defined, there are different ways to measure whether patients are following treatment recommendations and plans. Medication adherence measurement tools include self reports, prescription monitoring, pill counts, electronic devices, and biological measurements (such as saliva, plasma, or urine tests) (Patel & David, 2005; Fenton, Blyler, & Heinssen, 1997). With self-report measures, patients simply state if they missed any medication doses, and the proportion of doses taken versus doses prescribed is calculated. Self-report measures are easy to use but can be inaccurate due to their subjectivity and dependence upon patient memory.

Because of the potential inaccuracy of patient self-reports, more objective methods to quantify nonadherence have been developed. One such method is prescription monitoring, in which physicians and pharmacists track whether or not patients filled their prescriptions. This measure of adherence is based on the premise that people cannot take their medication if they do not fill the prescription. The usefulness of this method can be compromised by the fact that filling a prescription does not always equate to medication adherence. Pill counts can provide more information regarding medication adherence. Pill counts involve literally counting the number of pills the patient actually took in comparison to the number of pills the patient should have taken in order to calculate an adherence percentage. Limitations to pill counts include that they are time-consuming, subject to human counting errors, and patients forgetting to bring their pill bottles. Patients can also feign pill consumption by disposing of pills they should have taken (Patel & David, 2005).

Electronic devices attached to pill bottles may provide a more accurate adherence assessment than pill counts, as they record the date and time that the patient opened the pill bottle. These devices are a quicker measure of adherence and avoid the human error of miscounting pills. However, these electronic devices are very expensive. Additionally, patients could open the pill bottle but not actually take any pills, thus negating the value of the electronic device.

Another approach to assessing medication adherence is measuring the drug level in urine, blood, or saliva. However, these tests are expensive and invasive and may not accurately measure partial adherence such as missing several doses (Patel & David, 2005). Additionally, many medications do not have clinically meaningful or well established therapeutic blood levels (Patel & David, 2005).

Nonadherence can contribute to illness progression or new illnesses, increased costs, relapse in symptoms and/or substance abuse, and can contribute to early death. Although not the only way to assess adherence, medication use is a key measurement. Medication nonadherence can be determined through self-report measures, pill counts, electronic devices, and urine, blood, or saliva tests. Although there are limitations to these measurements, they can be essential for studying medication nonadherence to determine impeding factors and possible interventions.

VII. Treatment Nonadherence in Bipolar Disorder

As noted above, people with bipolar disorder have difficulty adhering to treatment regimens. In a study of 32,933 people with bipolar disorder in which 45% were taking antipsychotic medication, 48% were either partially or fully nonadherent (Sajatovic, Valenstein, Blow, Ganoczy, & Ignacio, 2006). A study with 3,681 subjects found that 40% of people with mania were either partially or fully nonadherent with their medication regimens (Sajatovic et al., 2009). In another study, nearly 56% of people with bipolar disorder were only partially adherent (i.e. missed one or more doses) with their medication in the past 10 days (Baldessarini, Perry, & Pike, 2008). Collectively, these studies suggest that a majority of patients with bipolar disorder do not consistently take their medications.

Treatment nonadherence is an important clinical factor that predicts negative short and long term outcomes for people with bipolar disorder (Gaudiano, Weinstock, & Miller, 2008). Nonadherence leads to more and longer hospitalizations which results in higher treatment costs. Clinical studies have found that of the people admitted to the hospital during a manic episode, 60-80% had discontinued their mood stabilizers in the prior month (in Colom et al., 2005). In a sample of 67 people with bipolar disorder, there was a 73% hospitalization rate within one year

for those who did not regularly take their medications (Svarstad, Shireman, & Sweeney, 2001). The hospitalization rate within one year was only 31% for those who consistently took their medications (Svarstad et al., 2001). Hospitalized patients with bipolar disorder who irregularly took their psychotropic medications spent a mean of 37 days in the hospital, costing on average about $9,701 (Svarstad et al., 2001). In contrast, those in the hospital who regularly took their medication had a mean hospital stay of four days, costing on average about $1,657 (Svarstad et al., 2001). These studies show that poor adherence is related to increased rates, time, and costs of hospitalizations.

Medication nonadherence is also associated with increased relapse and suicide risk in patients with bipolar disorder (Sajatovic et al., 2009; Miklowitz & Johnson, 2006). Medication nonadherence in bipolar disorder is related to a return of manic or depression symptoms, or an increase in preexisting symptoms (Gonzalez-Pinto et al., 2006; Sajatovic et al., 2009). As a result of symptom relapse, nonadherence to bipolar disorder treatment may lead to a decreased quality of life (Sajatovic et al., 2009) which can increase suicidal ideation. In a study of 405 patients with bipolar disorder followed over three years, those who discontinued their medications had a 16 times greater risk of suicidal behavior compared to those who stayed on a mood stabilizer (Lew, Chang, Rajagopalan, & Knoth, 2006). Another study of 72 patients with bipolar disorder indicated that suicidal behavior was increased in those who did not adhere to their lithium treatment (Gonzalez-Pinto et al., 2006). Thus, adherence to medications including mood stabilizing agents may be important to preventing suicidal behaviors.

Nonadherence in bipolar disorder appears to be multifactorial (Colom et al., 2005). Insight tends to be decreased in individuals with bipolar disorder, particularly during the manic phase (Dell'Osso et al., 2002; Williams & Collins, 2002) and may contribute to treatment

nonadherence. Patients are sometimes nonadherent because they are not educated on the nature and severity of bipolar disorder and the importance of medication (Colom et al., 2005). Thus, they are not aware of the reasons for and consequences of not adhering to treatment. Similarly, patients may also be nonadherent because they minimize, deny, or lack insight into their illness and its severity, and the necessity of long term treatment (Colom et al., 2005).

Another factor contributing to treatment nonadherence is stigma against mental illness. People with bipolar disorder sometimes experience a negative stigma regarding their illness and the fact that they have to take medication (Colom et al., 2005). They may view psychotropic medication as shameful, unhealthy, unnatural, and habit-forming (Colom et al., 2005). They may also feel that they can or should be able to control their mood on their own without the use of medication (Colom et al., 2005). Individuals with bipolar disorder who have difficulty with medication adherence tend to hold these beliefs (Colom et al., 2005). Significant people in their life may reinforce these beliefs, which then also interferes with treatment adherence (Colom et al., 2005). Additionally this negative attitude toward psychotropic medication may be reinforced by bothersome medication side effects. There are mixed results in the literature regarding the impact of side effects on medication nonadherence (Baldessarini et al., 2008; Colom et al., 2005).

Demographic variables have also been associated with treatment nonadherence in bipolar disorder. Homelessness, younger age, minority ethnicity, and comorbid substance abuse are related to nonadherence to antipsychotic medication in those with bipolar disorder (Sajatovic et al., 2006). Other factors associated with treatment nonadherence, ranked in order from most to least influential, are alcohol dependence, young age, affective comorbidity, medication side effects, comorbid obsessive compulsive disorder, and mania and hypomania (Baldessarini et al.,

2008). Similarly, another study found that the greatest risk factors for treatment nonadherence in persons with bipolar disorder are also comorbid substance abuse or dependence, younger age, comorbid personality disorders, greater severity of illness, and recent psychiatric hospitalization (Colom et al., 2000). These studies indicate that people with certain clinical and demographic characteristics, including younger age, mood symptoms and severity, minority ethnicity, and comorbid disorders, tend to be less adherent to treatment. Identification of patients with these characteristics may be helpful for understanding and preventing nonadherence.

Cognitive deficits have also been implicated as barriers to treatment adherence in bipolar disorder. Cognitive impairment is a statistically significant ($p = 0.04$) risk factor for nonadherence to bipolar disorder treatment (Baldessarini et al., 2008). Cognitive impairment may be associated with patients forgetting to follow their medication regimens or understanding the importance of adherence (Patel & David, 2005).

Treatment nonadherence is increased in people with bipolar disorder and is associated with poor outcomes. Various factors, including poor insight, stigma, clinical and demographic characteristics, medication side effects, substance use and cognitive functioning seem to impact treatment nonadherence. The identification and understanding of the factors impacting poor adherence in bipolar disorder is important for improving treatment and associated outcomes.

VIII. Treatment Nonadherence in Comorbid Bipolar Disorder and Substance Dependence

The combined aspects of substance use and bipolar disorder make treatment adherence and retention particularly difficult for individuals with this comorbidity. Substance use plays a major role in interfering with adherence to psychiatric treatment. A retrospective study of 4,312 patients with depression found that of the 333 who had substance dependence, 62% were

nonadherent with their medication compared to 48% in depressed patients without substance dependence (Akincigil et al., 2007). When comparing clinical factors most strongly related to psychiatric treatment nonadherence, substance abuse had a higher odds ratio (OR = 4.0) than personality disorder (OR = 2.6), medication side effects (OR = 2.5), and global assessment of functioning (OR = 3.6) (Herbeck et al., 2005).

Moreover, substance abuse is one of the strongest predictors of medication nonadherence in patients with bipolar disorder (Sajatovic et al., 2009). Substance abuse or dependence has been associated with poor adherence to lithium in patients with bipolar disorder (Weiss et al., 1998). Substance abuse was also related to decreased remission during hospitalization and poor medication adherence in inpatients with bipolar I disorder (Goldberg, Garno, Leon, Kocsis, & Portera, 1999). Of these inpatients who abused substances, 53% had been nonadherent to psychotropic medication treatment sometime in their life compared to 35% of patients without substance abuse (Goldberg et al., 1999). In a 12 month follow up study of 134 patients with bipolar disorder, substance dependence was the only factor related to treatment nonadherence (Keck et al., 1998). Among these 134 patients, 58% of those with substance dependence were nonadherent compared to 32% of those without substance dependence (Keck et al., 1998).

Another study of 72 participants found that those with a lifetime history of comorbid bipolar disorder and substance use were seven times more likely to not adhere to lithium (Gonzalez-Pinto et al., 2006). A study of 140 community mental health clinic patients with bipolar disorder indicated that 27 patients did not take their medication as prescribed (Sajatovic et al., 2009). Even though the other 113 patients reported past or present substance use, these 27 nonadherent patients had a higher current and lifetime use of substances than the others ($p \leq 0.01$) (Sajatovic et al., 2009). Additionally, among these 27 patients, the only significant clinical

predictor ($p = 0.05$) of treatment nonadherence was substance use (Sajatovic et al., 2009). As exemplified in these studies, the addition of substance abuse/dependence in bipolar disorder makes treatment adherence even more difficult in this population.

IX. Cognitive Functioning and Nonadherence to Psychiatric Treatment

As noted previously, various factors have been implicated in poor adherence to psychotropic medication and overall treatment. In a survey of 4,000 psychiatrists who treated over 35,000 patients, factors identified by the psychiatrists as contributing to treatment nonadherence were substance abuse, stigma, cognitive and memory dysfunction, and lack of insight (Narasimhan, Pae, Masand, & Masand, 2007). A positive relationship between cognitive functioning and treatment adherence has been reported in several studies (Donohoe et al., 2001; Clark & Goodwin, 2008; Robinson et al., 2002). In the National Institute of Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, higher neurocognitive functioning predicted longer study retention, even after accounting for symptom improvement (Keefe et al., 2007). Cognitive impairment could impact treatment adherence through poor decision making, memory deficits, and negative attitudes toward treatment. A study of 55 participants with schizophrenia spectrum disorders found that sustained attention predicted increased medication adherence and collaboration with treatment providers (Prouteau et al., 2005). These studies demonstrate that cognitive functioning does play a role in treatment adherence.

As noted above, cognitive deficits, such as confusion, psychosis, and dementia, are one of several factors that impact the way patients manage medical recommendations and respond to medications (Baldessarini, 1994). Poor cognitive functioning, particularly decreased attention and memory, could lead one to forget to take his/her medication or take the incorrect dose

(Narasimhan et al., 2007). Executive functioning, particularly the inability to learn from corrective feedback on a problem solving task, may also play a role in treatment outcome (Turner, LaRowe, Horner, Herron, & Malcolm, 2009). Increased perseveration errors on the WCST correlated negatively with treatment retention in a sample of 84 participants with cocaine dependence (Turner et al., 2009).

Cognitive deficits associated with bipolar disorder and substance dependence can contribute to treatment nonadherence in individuals with this comorbidity. Trait impulsivity seen in individuals with bipolar disorder and substance dependence can lead to treatment nonadherence (Swann et al., 2004). The poor decision making skills of people with substance dependence may contribute to their inability to make good treatment choices (Barry & Petry, 2008). Deficits in attention, organization, and planning that occur in bipolar disorder and substance dependence can also interfere with treatment adherence (Levy & Weiss, 2009). Poor planning ability was associated with decreased retention in a research study of participants with bipolar disorder and cocaine abuse (Nomamiukor & Brown, 2009). These studies emphasize the important influence of cognitive functioning on psychiatric treatment adherence and suggest that cognitive functioning may help predict adherence in individuals with comorbid bipolar disorder and substance dependence.

X. Purpose and Significance of Proposed Dissertation

As evidenced in this literature review, cognitive functioning and treatment adherence are decreased in people with bipolar disorder and/or substance dependence. There is a need to better understand the role cognitive functioning may play in treatment adherence and retention for people with comorbid bipolar disorder and substance dependence. Nonadherence to medication

and non-completion of treatment leads to symptom relapse and is associated with significant psychosocial and financial consequences. Few research studies have examined the relationship between cognitive functioning, treatment adherence, bipolar disorder, and substance dependence. The proposed dissertation will address this deficit in the literature by examining if cognitive functioning predicts treatment adherence and retention in participants with comorbid bipolar disorder and cocaine dependence.

If poor cognitive functioning does have a negative effect on treatment adherence and retention, then measures could be taken to compensate for these cognitive deficits. For example, patients may benefit from cognitive rehabilitation. Mental health professionals could assess patients for cognitive deficits, and then help patients devise strategies for medication management and appointment maintenance. Such strategies may include medication and appointments reminders, daily pill containers, involvement of family and friends to manage medication and keep up with appointments, and administering the drug via long-acting monthly injections. Understanding cognitive functioning in bipolar disorder and substance dependence and its impact on adherence can not only increase knowledge of cognitive functioning in this population but also lead to preventive and treatment strategies to increase adherence and thereby improve outcomes.

CHAPTER III

METHODS

Aims and Hypotheses

For participants with comorbid bipolar disorder I, II, or NOS and cocaine dependence:

Aim I: ***To examine the effect of cognitive functioning on treatment retention.***

Hypothesis I*: Cognitive functioning would predict treatment retention.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with time in study and predict study completion.

Aim II: ***To examine the effect of cognitive functioning on appointment attendance.***

Hypothesis II: *Cognitive functioning would predict appointment attendance.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with appointment attendance.

Aim III: ***To examine the effect of cognitive functioning on medication adherence.***

Hypothesis III: *Cognitive functioning would predict medication adherence*. Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with medication adherence.

Aim IV: ***To examine the effect of cognitive functioning on adherence to treatment instructions.***

Hypothesis IV: *Cognitive functioning would predict adherence to treatment instructions.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with the percentage of medication bottles returned.

Study Overview

This study was a secondary analysis of data from a randomized, double-blind, placebo-controlled, trial of lamotrigine add-on therapy in outpatients with bipolar disorder (depressed or mixed phase) and cocaine dependence (Brown, Sunderajan, Hu, Sowell, & Carmody, in press). The study was funded by the Stanley Medical Research Institute and approved by The University of Texas Southwestern Medical Center Institutional Review Board (IRB# 122004-024). Dr. E. Sherwood Brown served as the principle investigator on the study. All participants provided written informed consent.

Diagnoses of bipolar disorder, cocaine dependence, and other disorders were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders Clinician Version (SCID I CV) (First, Spitzer, Gibbon, & Williams, 1995) and confirmed by an evaluation by the psychiatrist. Participants attended up to 10 consecutive weekly study visits in which they met with a research assistant to complete three mood assessments including the Hamilton Rating Scale for Depression ($HRSD_{17}$) (17-item version) (Hamilton, 1960), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003), and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). Side effects were tracked using the Psychobiology of Recovery in Depression-III Somatic Symptom Scale (PRD-III) (Thase et al., 1996). The Addiction Severity Index (ASI) (McLellan et al., 1992) was administered at baseline and week 10. Cocaine craving was measured with the Cocaine Craving Questionnaire (CCQ) (Tiffany, Singleton, Haezrten, & Hennington, 1993). Using a Timeline Followback calendar (TLFB) (Sobell & Sobell, 1996), number of days and quantity of cocaine use, and other substances, was assessed at each visit. A urine drug screen was also completed at each visit to test for cocaine use. At the baseline visit, week five, and week 10, participants completed two

measures to assess cognitive functioning the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) and the Stroop Color and Word Test (Golden version) (Golden & Freshwater, 2002).

Participants were randomized to receive either lamotrigine or placebo (25mg/day). Lamotrigine and placebo were increased to 200 mg/day using a slow upward titration over five weeks to minimize side effects (e.g. rash). During the remainder of the study, additional increases in 100 mg/day increments to a maximum of 400 mg/day were made if the medication was well tolerated and at least one of three conditions was met: (1) $HRSD_{17}$ total score decreased by $\leq$ 40% from baseline, (2) CCQ total score decreased $\leq$ 25% from baseline, or (3) participants continued to use cocaine in the past week based on self-report or urine drug screen results. At each visit after baseline, participants were asked to return their pill bottles and the research assistant calculated how many pills each participant took relative to the prescribed amount. The research assistant also recorded how many total visits each participants attended and the length of time each participant was in the study. Participants were paid $30 and provided with a bus pass and $5 McDonald's coupon at each visit. During the time period that this research study was conducted, the form of payment switched from check to cash but payment method was never changed while a participant was in the study. Each participant either received check or cash but never both. Cash was provided immediately after the appointment whereas check was sent by mail two to four weeks after the appointment.

Participants

One hundred and twenty participants were enrolled in the study. Participants were recruited from outpatient psychiatry clinics and prior research studies in Dr. Brown's laboratory at The University of Texas Southwestern Medical Center and through flyers and advertisements

posted in local community papers. Participants in the treatment and placebo groups met the following inclusion criteria: (1) diagnosis of bipolar I, II or NOS disorders, (2) current depressed or mixed mood state, (3) ages 18-70 years, (4) men or women, (5) cocaine dependence with self-reported cocaine use within 14 days prior to randomization, (6) English speaking, and (7) baseline $HRSD_{17}$ score ≥ 10.

Exclusion criteria for the study included: (1) currently taking an enzyme inducing or inhibiting anticonvulsant (e.g. valproic acid, carbamazepine), (2) current severe psychotic features (e.g. daily auditory hallucinations, fixed delusions, severely disorganized thought processes) that require antipsychotic therapy *and* that *do not* appear to be secondary to cocaine use, (3) active suicidal ideation (plan and intent) or ≥ two attempts in past 12 months or any attempt in the past month, (4) highly unstable medical condition, (5) change in concomitant psychotropic medications (e.g. initiated antipsychotic) or in substance abuse treatment (e.g. began intensive outpatient treatment) within seven days prior to study entry, (6) prior history of lamotrigine therapy, and (7) vulnerable populations (e.g. pregnant or nursing women, prisoners, mentally retarded). Women of childbearing age were given a urine test to rule out pregnancy.

Substance Use and Craving Assessments

Cocaine Craving Questionnaire (CCQ)

The CCQ (Tiffany et al., 1993) was developed to replace the single-item strategy which was previously used to measure craving but had low reliability. The CCQ consists of 45 items which examine five main domains of craving: "1) desire to use cocaine, 2) anticipation of positive outcomes from cocaine use, 3) anticipation of relief from cocaine withdrawal symptoms or relief from negative mood, 4) intention and planning to use cocaine, and 5) lack of control over use" (Tiffany et al., 1993). Respondents indicate how much they agree or disagree with

each item using a seven point Likert scale in which the end points are "strongly agree" and "strongly disagree." There are two versions of the CCQ such that one version (CCQ-Now) assesses current cravings, and the second version (CCQ-General) assesses cravings during the past week. Reliability and validity of the CCQ-Now and CCQ-General were determined using 225 individuals currently abusing cocaine with no intention to quit (Tiffany et al., 1993). Factor analysis was performed on the items resulting in four main factors for the CCQ-Now (Tiffany et al., 1993). Internal consistency for these four factors ranged from 0.72 to 0.92 (Tiffany et al., 1993). For the CCQ-General, factor analysis resulted in five factors whose internal consistency ranged from 0.70 to 0.89 (Tiffany et al., 1993). Both CCQ versions demonstrated good concurrent validity with other measures of cocaine use (i.e. lower confidence in quitting cocaine and greater frequency of use over the past six months) (Tiffany et al., 1993).

Urine Drug Analysis (UDA)

The UDA for this study was conducted on-site by trained research assistants. The UDA provided immediate results and determined whether or not a substance was in the individual's body. The UDA used for this study did not measure quantity. The UDA was a panel-dip drug screen manufactured by Redwood Toxicology Laboratory in Santa Rosa, CA. The UDA assessed for the following substances at the associated cut-off levels: opioids at 2000 ng/mL, amphetamines at 1,000 ng/mL, cannabis at 50 ng/mL, cocaine at 150 ng/mL, and phencyclidine at 25 ng/mL**.**

Timeline Followback Calendar (TLFB)

The TLFB calendar (Sobell & Sobell, 1996) was initially developed to assess patterns of alcohol use on a daily basis using a calendar (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000). It has since been used to also record frequency and quantity of substance use.

The TLFB is administered as an interview by a trained professional. Substance use is calculated in terms of quantity and/or cost for each day over a specified period of time. It serves as a visual aid for interviewer and interviewee to determine pattern of substance use. The TLFB is a less invasive substance use measure than urine drug analysis (UDA) and also can measure use over a longer period of time than UDA (Fals-Stewart et al., 2000).

Test-retest reliability for the TLFB for alcohol use is over 0.85 and criterion validity is similarly as high (Fals-Stewart et al., 2000). For cocaine, the TLFB has demonstrated a high test-retest reliability with Pearson *r* values ranging from 0.74 to 0.95 (in Fals-Stewart et al., 2000). Additionally, the TLFB for cocaine was highly correlated with UDA with a Pearson *r* value of 0.81 (in Fals-Stewart et al., 2000). Test-retest reliability, using Pearson's *r*, for percentage of days of cocaine use was 0.95, 0.92, and 0.89 for 30, 90, and 365 days, respectively (Fals-Stewart et al., 2000). Concurrent validity was significant and in the moderate range when the TLFB percent days of substance use was compared with other substance use measures (i.e. ASI Drug Use Severity subscale, Drug Abuse Screening Test) (Fals-Stewart et al., 2000). Additionally, there was a significant correlation ($r = 0.74$) between urine assay results for cocaine and individuals' self-reported cocaine use on the TLFB (Fals-Stewart et al., 2000). As evidenced above, the TLFB has demonstrated high test-retest reliability and high criterion and concurrent validity.

The Addiction Severity Index (ASI), Fifth Edition

The ASI was originally published in 1980 as an interview for individuals with substance dependence to evaluate treatment outcome (McLellan et al., 1992). Since then, it has been translated into nine languages and utilized in treatment outcome studies for a variety of

substances (McLellan et al., 1992). The ASI is administered in an interview format by a trained rater.

The ASI assesses the severity of substance dependence and potential impediments to treatment by examining seven main domains: alcohol, drug, employment/financial support, psychiatric, medical, legal, and family/social relationships. Each of the seven domains is represented by a composite score which is calculated to give equal weight to all items. The composite score ranges from zero to one with higher scores indicating greater severity of substance dependence and increased treatment impediments (Zanis, McLellan, & Corse, 1997). Within each domain, questions are asked in terms of either the past 30 days and/or lifetime. The alcohol and drug domain gathers information on frequency of use, quantity of use, and route of administration (for drugs). The employment domain assesses the individual's education level, amount of income from all sources (i.e. disability, family, work, illegal), and ability to obtain employment. The legal domain inquires about criminal charges. The family/social domain collects information regarding the individual's physical and/or sexual abuse history, relationship history, safety and support of living situation, and family substance abuse and psychiatric history.

The mean time for administration of the ASI is about 50 minutes. The ASI has shown reliability and validity for individuals with substance abuse who are seeking treatment (McLellan et al., 1992). Test-retest reliability coefficients for the ASI, 5^{th} edition, are 0.83 and higher (McLellan et al., 1992). The ASI has proven valid with several different populations including those with comorbid substance dependence and mental illness (McLellan et al., 1992). The ASI is a comprehensive measurement of substance use and associated factors and has demonstrated high concurrent validity.

Mood Assessments

Hamilton Rating Scale for Depression (17-item version) $HRSD_{17}$

The $HRSD_{17}$ (Hamilton, 1960) was developed as an alternative to existing measures of depression. It was intended to remedy the limitations of previous measures that relied on self-report and thus literacy, were devised for healthy people and thus were poor at diagnostics, and were not clear in distinguishing between syndromes and symptoms (Hamilton, 1960). The $HRSD_{17}$ was developed for use in individuals already diagnosed with a mood disorder with depressive symptoms (Hamilton, 1960). The $HRSD_{17}$ is administered as an interview by a skilled, trained individual. It consists of 17 items each measured using a three point or five point scale. The $HRSD_{17}$ items address these criteria: depressed mood, guilt, suicidal ideation, work and loss of interest, insomnia, psychomotor retardation, agitation, somatic and psychic anxiety, libido, energy level, hypochondriasis, insight and weight loss. The $HRSD_{17}$ has an inter-rate reliability of 0.90 (Hamilton, 1960). Factor analysis was performed with the 17 variables and resulted in four main factors. Content validity was verified by comparing factor loading of different patients with depressive symptoms (Hamilton, 1960).

Quick Inventory of Depression Severity-Self Report (QIDS-SR)

The QIDS-SR is a 16-item abbreviated version of the Inventory of Depressive Symptomatology-Self-Report (IDS-SR) and assesses the nine criterion domains of major depressive disorder as defined in the DSM-IV-TR. Each item is rated zero to three and the total score ranges from zero to 27. The QIDS-SR was developed in 2003 by Dr. John Rush and his colleagues and was intended as an efficient and effective alternative to the IDS-SR (Trivedi et al., 2004). The QIDS-SR is very sensitive in assessing change in symptom severity and treatment (Trivedi et al., 2004). The QIDS-SR has high internal consistency (0.86) and is highly correlated

(0.83) with the IDS-SR (Trivedi et al., 2004). The QIDS-SR has high concurrent validity with the IDS-SR and these two tests also have good convergent validity (Trivedi et al., 2004). The QIDS-SR has demonstrated good criterion and construct validity (Trivedi et al., 2004).

Young Mania Rating Scale (YMRS)

The YMRS was developed in 1978 as a shorter, more sensitive, and more explicitly defined measure of the manic state than previous mania assessments (Young et al., 1978). The YMRS is composed of 11 items, each with five grades of severity, which assess the core symptoms of mania based on published descriptions (Young et al., 1978). It is rated by a trained clinician during a 15 to 30 minute interview with the patient. The YMRS has an inter-rater reliability of 0.93 for total score with significance at the 0.00 level (Young et al., 1978). Concurrent validity was established by comparing the YMRS with two previous mania assessments and there was a high correlation (0.71 to 0.89) (Young et al., 1978). The YMRS demonstrates more sensitivity to change than prior mania scales (Young et al., 1978).

Diagnostic Assessment

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

The SCID I CV (First et al., 1995) was created to introduce structured interviews in the clinical setting but is also appropriate for research. Unlike the SCID I Research Version, the SCID I CV has a separate administration and scoring booklet and is simpler for determining the diagnostic aspects of a population sample. It is not as comprehensive as the SCID I Research Version and therefore, it can be more efficient for certain purposes. For example, it does not assess specifiers for disorders. The SCID I CV is administered by a trained professional and takes approximately one hour, depending on the complexity of the psychiatric history. The test-retest reliability for the diagnosis of bipolar disorder on the SCID I CV is 0.84 (Williams et al.,

1992). The inter-rater reliability for this diagnosis is 0.79 (Skre, Onstad, Torgersen, & Kringlen, 1991). The test-retest reliability for the diagnosis of substance dependence/abuse on the SCID I CV is 0.76. The inter-rater reliability for this diagnosis ranges from 0.77 (Lobbestael, Leurgans, & Arntz, 2011) to 1.00 (Zanarini et al., 2000).

Medication Side Effects Assessment

Psychobiology of Recovery in Depression-III Somatic Symptom Scale (PRD-III)

The PRD-III was developed in 1996 for a longitudinal depression study to monitor medication side effects (Thase et al., 1996). The scale is composed of 24 items that assess a wide range of common medication side effects. It is quickly and easily administered by a trained professional.

Treatment Retention and Adherence Assessments

Study retention was measured in terms of 1) completion or noncompletion of the study, 2) the length of time in weeks the participants stayed in the study and 3) the total number of appointments attended by each participant. Treatment adherence in this study was determined using pill counts. This involved counting the number of pills the participant actually took which was compared to the number of pills prescribed to the participant. Thus, we calculated an adherence percentage. If participants forgot to bring their medication bottle, then the pill count was coded as "missing" for that week. The return percentage of medication bottles was used to measure adherence to treatment instructions.

Neuropsychological Assessments

As mentioned previously, two neuropsychological tests were administered at baseline and again at weeks five and 10. These tests were the RAVLT and the Stroop Color and Word Test. For the purposes of this secondary analysis, only scores from the baseline administrations of the

RAVLT and Stroop Color and Word Test were used. The version of the RAVLT at baseline was version two, scoring sheet 7.

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT consists of five trials of the same list of 15 unrelated words followed by one trial of an interference list of 15 words. The examiner reads each list aloud with a one second interval between each word. After each trial, participants are required to provide immediate recall of the words. There is a short delayed recall of the original list immediately following the recall of the interference list. After a 20 minute delay, participants are asked to recall all words from the original list. During the recognition phase, participants are presented with words from the two lists as well as words that are semantically and phonetically similar to the original list of words. Participants are to indicate whether or not each word was on the original list. The words in the original list are unrelated to each other and are not easily learned using categorization which makes the RAVLT a more complex verbal learning and memory test.

Raw scores for the RAVLT are calculated by adding the total number of correct words across the five trials and the total number of correct words on the short delayed and long delayed recall. A raw score on the recognition phase is calculated by subtracting the total number of false positives from the total number of true positives. *T*-scores are calculated for each of these four raw scores. *T*-scores for the RAVLT for this study were calculated using the table of metanorms provided by Schmidt (1996). The metanorms are stratified by age and divided into 10 categories. The RAVLT has alternative forms to prevent practice effects across testing sessions. The RAVLT has demonstrated good equivalent form retest reliability with coefficients in the moderate to moderately high range (Uchiyama et al., 1995). The RAVLT has also shown good validity when compared with other cognitive measures assessing similar domains. It has

"significant and strong concurrence with the Wechsler Memory Scale, the Wechsler Adult Intelligence Scale-R (WAIS-R) digit span, the Benton Visual Retention Test, the Visual Spatial Learning Test, and the CVLT" (Schutte, 2007). The RAVLT can discriminate between neurologically impaired and normal individuals (Schutte, 2007)

The RAVLT is a measure of verbal declarative learning and memory. It measures the ability to learn and retain new information. Declarative memory is associated with the PFC, medial temporal lobe, hippocampus, and anterior thalamic nuclei (Robbins, Ersche, & Everitt, 2008). The RAVLT may predict treatment adherence and retention because attending appointments and taking medications on time and as prescribed requires an ability to learn and remember information. Treatment adherence also requires an ability to accurately recall what the physician said regarding medication regimen. Thus, the verbal learning and memory component of the RAVLT may predict treatment adherence and retention.

Stroop Color and Word Test (Golden Version)

The Stroop Color and Word Test consists of three conditions in which participants have 45 seconds to read aloud as many words or colors as possible, equally divided into five columns, per condition (Golden & Freshwater, 2002). The first condition ("word") has the words "red, green, blue" printed in black letters. The second condition ("color") consists of five columns with 20 series of four "x's" in each column. Each set of four "x's" is printed in either red, green, or blue ink and participants are required to the name the color. The third condition ("color-word") combines the concepts of the previous two conditions. The words "red, green, blue" are printed in either red, green, or blue ink but never the same color as the word itself. Participants are required to say aloud the color of the ink rather than the word. During each condition, the

examiner records self-corrected responses and responses in which the examiner corrected the participant.

Raw scores for each condition are determined by adding the number of items the participant said in 45 seconds (Golden & Freshwater, 2002). This raw score is compared to an estimated raw score based on the participant's age and education. The difference value between the raw and estimated scores is used to determine a *T*-score. The Interference *T*-score is based on the result of the following equation: Color Word raw score – [(Word raw score x Color raw score) / (Word raw score + Color raw score)]. The Interference *T*-score is a measure of the level of inhibition. The Stroop Color and Word Test has demonstrated high test-retest reliability scores of 0.88, 0.79, and 0.71 for the three raw scores, respectively (Jensen, 1965) and 0.70 for the raw interference score across various cohorts (Golden, 1975b).

The Stroop Color and Word Test is a measure of attention and executive functioning, including inhibition (impulse control), and cognitive flexibility (Golden & Freshwater, 2002). These cognitive domains are mainly related to the ACC (Clark & Goodwin, 2008). Results from the Stroop Color and Word Test may be predictive of treatment adherence and retention because of the mechanisms of these three cognitive domains. Impulse control is important to treatment adherence because taking psychotropic medications can involve forgoing short-term negative side effects for long-term gains that are not immediately apparent. Cognitive flexibility is important to treatment adherence and retention because patients need the ability to problem solve in different ways to manage their medication and appointments. Attention is important to treatment adherence because it facilitates being mindful of when and how much medication to take and keeping up with appointments.

Overview of Data Collection and Statistical Analyses

For the primary analysis, data were collected weekly and kept in a binder by the study research coordinator. All assessments were rescored for accuracy by another research assistant and corrections were made as needed. The data were then entered into two SPSS databases by separate research interns trained in SPSS data entry. The two databases were compared for any discrepancies and changes were made based on a review of the original data. A copy of the primary database was used for this secondary analysis. To this database, additional data were entered by this author in order to have the independent and dependent variables needed to test the hypotheses. The additional dependent variables created and used by this author included the following: total number of weeks attended in the study after baseline, adherence based on weeks attended after baseline, percentage of pills taken for each week in the study, mean percentage of pills taken across the study, adherence based on mean percentage of pills taken, percentage of pill bottles returned for each week in the study, mean percentage of pill bottles returned across the study and adherence based on mean percentage of pill bottles returned. Adherence variables for weeks attended after baseline, mean percentage of pills taken, and bottle return rate were dichotomized as nonadherent (<90%) and adherent (≥90%). Ninety percent was chosen based on prior research on adherence (Hinkin et al., 2002; Osterberg & Blaschke, 2005) and on this sample's means for percentage of pills taken and percentage of pill bottles returned. There is no universal standard for what determines adequate adherence, with studies defining "good" adherence as ranging from 80% to 95% (Osterberg & Blaschke, 2005). In a study of the impact of cognitive dysfunction on medication adherence in adults with Human Immunodeficiency Virus (HIV), participants who took 95% of their required doses were considered "good adherers" and those who took 90% were considered "adequate adherers" (Hinkin et al., 2002). Another study on cognitive functioning and medication adherence used 85% as a demarcation line for

describing medication adherence in their study sample (Insel, Morrow, Brewer, & Figueredo, 2006). Given the high percentage of pill bottles returned (*M* = 86.00%) and high percentage of pills taken (*M* = 92.64%) in this dissertation, it was believed that 90% would be a fair compromise based on the prior studies.

For weeks attended, adherence was also defined as attending 90% (9 or more) of post baseline appointments. There is no clear definition of high versus low appointment adherence in the literature on bipolar disorder (Gaudiano et al., 2008). Ninety percent was chosen in this study because it has been considered high adherence in other studies on retention in cocaine dependence and/or bipolar disorder (Siqueland et al., 2002; Colom et al., 2003). It was also felt that this more stringent measure of retention would be more clinically meaningful.

Calculations were completed using Excel formulas to compute results for certain variables. To calculate the percentage of pills taken for each week for each participant, the chart for each participant was examined and the following formula was used to determine the percentage of pills taken for that week: (pills taken/pills should have taken for that week) x 100. If pill bottles were not returned for a particular week, it was coded as missing (-98). If the participant did not attend their appointment, it was coded as missing (-99). In several instances, the research assistant did not record pill counts, so this was also coded as missing (-97). Pill counts were not recorded for those who only attended the baseline visit. The mean of all the pill count percentages for the participant's time in the study, excluding any weeks coded as missing, was used to calculate each participant's mean percentage of medication taken during the study.

To calculate the percentage of pill bottles returned, this author used the formula: (pill bottles returned/number of pill bottles that should have been returned) x 100. The percentage of pill bottles returned was coded as missing if the participant only attended the baseline visit (-99)

or if the research assistant did not record the pill count, which made the return of the pill bottle inconclusive (-97). Other dependent variables used in these analyses included dichotomized completer and noncompleter and last week in study.

Independent variables added for the purpose of this dissertation included dichotomized baseline cognitive scores for the Word, Color, Color-Word, and Interference *T*-scores on the Stroop Color and Word Test and for the RAVLT Immediate Recall Total *T*-score and Delayed Recall t-score. These *T*-scores were dichotomized as ≤ 42 (low average and below) and ≥ 43 (average and above). The covariate of bipolar type was also dichotomized as bipolar I disorder versus bipolar II disorder or bipolar disorder NOS. The other covariates used in these analyses included payment method defined as cash or check, baseline ASI employment score, amount spent on cocaine at baseline, and treatment group. These four covariates, excluding treatment group, had the highest correlations with the dependent variables compared to the other potential covariates (i.e. baseline $HRSD_{17}$ and YMRS scores). Treatment group did not have a strong correlation with the dependent variables but was considered important to include given that it was the independent variable for the original study. Since initial analyses found that the only effect of the study medication (lamotrigine) on participants was in regard to the amount spent on cocaine, both the placebo and treatment groups were used in the analyses for this dissertation.

Descriptive statistics were reported on all 120 participants, including gender, age, ethnicity, diagnosis, household income, and education level. Any participant who did not return after the baseline visit was excluded in the analysis of the outcome variables regarding medication. The Statistical Package for Social Sciences (SPSS) Versions 12.0 and 17.0 for PC were used to analyze the data. Values were considered significant at $p \leq 0.05$. *T*-scores for Stroop Color and Word Test Condition 1 (word naming) and Condition 2 (color naming) were

used to assess simple visual attention. *T*-scores for Stroop Color and Word Test Condition 3 (color word naming) and for Interference were used to assess inhibition and cognitive flexibility. *T*-scores for immediate recall and delayed recall trials on the RAVLT were used to assess verbal learning and memory.

Statistical Analyses for Aims and Hypotheses

For participants with comorbid bipolar disorder I, II, or NOS and cocaine dependence:

Aim I: ***To examine the effect of cognitive functioning on treatment retention.***

Hypothesis I: *Cognitive functioning would predict treatment retention.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with time in study and predict study completion.

Statistical Analysis: A survival analysis (Cox Proportional Hazards) was performed to measure the dependent variable of time in study (last week in study) with the covariates (bipolar type dichotomized, ASI employment baseline score, treatment group, amount spent on cocaine at baseline, payment method during study) and cognitive variables (dichotomized) placed in the same analysis. A binary logistic regression of completer vs. noncompleter was also performed to measure study retention. As with the survival analysis, all cognitive variables (dichotomized) and covariates were included in the logistic regression analysis.

Aim II: ***To examine the effect of cognitive functioning on appointment attendance.***

Hypothesis II: *Cognitive functioning would predict appointment attendance.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with appointment attendance.

Statistical Analysis: An ANCOVA was performed to measure the dependent variable, number of appointments attended in the study. All of the covariates (bipolar type dichotomized, ASI employment baseline score, treatment group, amount spent on cocaine at baseline, payment method during study) and cognitive variables (dichotomized) were placed in the same analysis. A binary logistic regression was also performed with number of weeks in study dichotomized as adherent (≥ 9) and nonadherent (< 9). All of the covariates (bipolar type dichotomized, ASI employment baseline score, treatment group, amount spent on cocaine at baseline, payment method during study) and cognitive variables (dichotomized) were placed in the same analysis.

Aim III: ***To examine the effect of cognitive functioning on medication adherence.***

Hypothesis III: *Cognitive functioning would predict medication adherence.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with medication adherence.

Statistical Analysis: An ANCOVA was performed to measure the dependent variable, mean percentage of pills taken during participants' time in the study. The covariates (bipolar type dichotomized, ASI employment baseline score, treatment group, amount spent on cocaine at baseline, payment method during study) and cognitive variables (dichotomized) were placed together in the same analysis. In instances in which pill bottles were not returned, pill count for that week was not included in the calculation of mean percentage of pills taken. A binary logistic regression was also performed with mean percentage of pills taken dichotomized as adherent (≥ 90%) and nonadherent (< 90%). The same rules applied as for the ANCOVA.

Aim IV: ***To examine the effect of cognitive functioning on adherence to treatment instructions.***

Hypothesis IV: *Cognitive functioning would predict adherence to treatment instructions.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention will be positively associated with the percentage of pill bottles returned.

Statistical Analysis: An ANCOVA was performed to measure the dependent variable, the percentage of pill bottles returned of the pill bottles that should have been returned. The covariates (bipolar type dichotomized, ASI employment baseline score, treatment group, amount spent on cocaine at baseline, payment method during study) and cognitive variables (dichotomized) were placed in the same analysis. A binary logistic regression was also performed to measure the percentage of pill bottles returned with the variable dichotomized as adherent (≥ 90%) and nonadherent (< 90%). The same rules applied as for the ANCOVA.

CHAPTER IV

RESULTS

Descriptive Statistics for the Total Sample

A total of 120 participants were enrolled in this study. The lamotrigine and placebo groups were each were composed of 60 participants. The sample size was decreased to 106 for most statistical tests due to missing data on baseline measures (i.e. Stroop Color and Word Test, RAVLT, and ASI employment index) and/or the exclusion of eight participants who came to the baseline appointment only. Demographic information for the total sample of 120 participants is provided in Table 3. The mean age for the sample was 44.05 (*SD* = 8.81) and the mean years of education was 13.55 (*SD* = 2.24). Most participants were men (60.80%). African-Americans comprised most of the sample (61.70%) with Caucasians accounting for 30.80%, and Hispanics accounting for 5.00%. Fifty-eight percent of the sample had an annual income less than $15,000 and 13.00% of the sample made over $40,000 a year.

Baseline clinical information for the total sample is provided in Table 4. More than half (54.80%) of the sample were diagnosed with bipolar I disorder and 35% of the sample were diagnosed with bipolar II disorder. Approximately eleven percent (10.80%) of the sample had bipolar disorder NOS. At the baseline visit, most participants (89.20%) had a current depressed mood state. The remainder (10.80%) of the sample had a mixed mood state. The baseline mean score on the $HRSD_{17}$ was 21.35 (*SD* = 6.23) which was indicative of severe depression (Rush et al., 2003). The baseline mean QIDS-SR score was 14.46 (*SD* = 4.99) which was in the moderate depression severity range (Rush et al., 2003). The mean YMRS score at baseline was 15.18 (*SD* = 8.92). Few participants were taking psychotropic medication in the two weeks prior to the start of the study. The percent of participants taking lithium was 6.70%. The percent of participants

taking antipsychotics was 4.20%. The percent of participants taking antidepressants was 17.50%. The percent of participants taking sedatives was 9.10%. No participants were taking anticonvulsants.

Baseline substance use information for the total sample is provided in Table 5. All participants met criteria for cocaine dependence. Of the total sample, 80.90% had another current or past substance use disorder. Sixty-four percent met criteria for alcohol abuse or dependence at baseline. Most (78.30%) had a positive urine drug screen for cocaine at baseline. The mean amount of money spent on cocaine during the two weeks prior to baseline was $299.75 (*SD* = $473.60). The mean quantity of cocaine used during this same time period was 10.47 grams (*SD* = 37.96g).

Baseline cognitive characteristics of the total sample are provided in Table 6. Due to missing data, the sample size for the baseline cognitive measures ranged from 117 to 119. The percentages presented in the table are based on all 120 participants and the percentages do not add up to 100% for cognitive measures that had missing data. The mean and standard deviation raw score and *T*-score are reported for each cognitive independent variable. The mean *T*-scores for all the cognitive variables fell in the upper end of the low average range, or were in the average range. The frequencies and percentages for the dichotomized *T*-score descriptive categories (low average range or less and average range or greater) are also reported for each cognitive variable. For the RAVLT Total Recall, more participants (51.70% versus 47.50%) scored in the low average range or less. For the RAVLT Delayed Recall and for the Stroop Color and Word Test conditions Word and Color, more participants scored in the average range or greater than in the low average range or less. For the Stroop Color and Word Test conditions

Color-Word and Interference, significantly more participants (69.20% and 82.00%, respectively) scored in the average range or greater than in the low average range or less.

Descriptive statistics for the dependent variables are listed in Table 7. The results reported for treatment retention and attendance are based on the total sample. The results reported for treatment adherence are based only on those participants who returned after the baseline visit because no adherence data were available on those without a post-baseline assessment. Due to missing data on measures or inability to calculate percentages of pills taken, a few participants were not included in these analyses. The mean last week in the study was 7.48 (*SD* = 3.39). The percent of participants who completed the study was 53.30%. Forty percent of participants attended nine or more appointments and the mean appointment attendance was 6.68 weeks (*SD* = 3.28) for the total sample. Over half (57.50%) of participants took 90% or more of their pills and the mean percentage of pills taken was 92.64% (*SD* = 8.77%) for the total sample. Over half (55.00%) of participants returned their pill bottle 90% or more of the time and the mean percentage of pill bottles returned was 86.00% (*SD* = 21.28%) for the total sample.

In addition to descriptive statistics for the total sample of 120 participants, descriptive statistics are reported for each of the smaller samples included in each analysis. See Tables 8-12 for demographic, clinical, substance use, cognitive, and treatment adherence statistics for the sample included in the treatment retention and attendance statistical analyses. See Tables 13-17 for this information for the sample included in the medication adherence statistical analyses. See Tables 18-22 for demographic, clinical, substance use, cognitive, and treatment adherence statistics for the sample included in the treatment instruction adherence statistical analyses.

Correlation Analyses to Assess for Multicollinearity and Covariates

Correlation analyses were performed to determine the relationship between the independent and dependent variables and to assess for multicollinearity among the independent variables. Multicollinearity was defined as $r = 0.90$ or greater (Pallant, 2001). See Table 23 for correlations between the independent and dependent variables and see Table 24 for correlations between the independent variables. The correlation coefficients between the independent variables tended to be low to moderate ($r = -0.01$ to 0.53) and thus there was not any multicollinearity between them.

Covariates were chosen through a strategic process. Based on the sample size of this study, five covariates could be used in the analyses. Since it was the independent variable in the primary study and thus considered an important factor in our study, treatment group was selected as a covariate. Based on research, relevant baseline variables, including age, gender, education, income, baseline $HRSD_{17}$ score, and baseline YMRS score, bipolar type (I, II, or NOS), baseline ASI Employment composite score, amount in dollars spent on cocaine in the two weeks prior to baseline, and study payment method (cash or check), were chosen and correlated with the dependent variables. Based on these resulting correlation coefficients, those variables that were not significantly ($p > 0.05$) correlated with any dependent variables were excluded as potential covariates. Of the remaining potential covariates, those four variables that had the most correlations with the dependent variables were chosen. As a result, bipolar type, amount spent in dollars on cocaine at baseline, study payment method, and baseline ASI Employment composite score were selected as covariates for this study. See Table 25 for correlations among the dependent variables and potential covariates. See Table 26 for correlations among the dependent

variables and the selected covariates. The same five covariates were used in all statistical analyses.

Outliers

Box plots for each cognitive independent variable were created to determine if there were any outliers. Outliers were defined as the sample minimum and sample maximum if they deviated more than 45 *T*-score points from each other and/or *T*-score(s) that were outside the normal curve of *T*-scores for that cognitive measure (Pallant, 2001). There were two outliers for Stroop Color and Word Test condition Word, two outliers for Stroop Color and Word Test condition Color, three outliers for Stroop Color and Word Test condition Color-Word, two outliers for RAVLT Total Recall, and none for Stroop Color and Word Test condition Interference or RAVLT Delayed Recall. All statistical analyses were performed with the outliers included and then again with the outliers excluded. There was no significant difference in results when outliers were included or excluded in the analyses. Confidence intervals for odds ratios were also not reduced significantly by the exclusion of outliers. Therefore, the results described in the findings below are from the statistical analyses that included outliers.

Results for the Aims and Hypotheses

For participants with comorbid bipolar disorder I, II, or NOS and cocaine dependence:

Aim I: ***To examine the effect of cognitive functioning on treatment retention.***

Hypothesis I: *Cognitive functioning would predict treatment retention.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention would be positively associated with time in study and predict study

completion.

Statistical Analysis: A Cox Proportional Hazards survival analysis was performed with the six dichotomized cognitive variables as the independent variables and the last week in the study as the dependent variable. The covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also used in the analysis. The sample size was reduced by 14 to 106 due to missing data for baseline measures. Nine participants were excluded due to missing baseline ASI employment index scores. Two participants were excluded due to missing baseline RAVLT data. Three participants were excluded due to missing baseline Stroop Color and Word Test data. As shown in Table 27, there were no significant results for the cognitive measures.

None of the cognitive variables or covariates had a significant effect on treatment retention. Figures 1-6 show the survival curve for time in study as specified for each cognitive variable. Table 42 shows the mean last week in the study for the two dichotomized *T*-score categories (average or greater and low average or less) for each of the cognitive measures.

A binary logistic regression was also performed with the six dichotomized cognitive variables as the independent variables and completer/noncompleter as the dependent variable. The covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included. The sample size was reduced by 14 to 106 due to missing data on baseline measures. Nine participants were excluded due to missing baseline ASI employment

index scores. Two participants were excluded due to missing RAVLT data. Three participants were excluded due to missing baseline Stroop Color and Word Test data.

As show in Table 28, none of the cognitive measures were significantly associated with study completion. None of the covariates were significantly associated with study completion. See Tables 36-41 for information on the mean *T*-scores of each cognitive measure for completers and noncompleters.

Aim II: ***To examine the effect of cognitive functioning on appointment attendance.***

Hypothesis II: *Cognitive functioning would predict appointment attendance.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention would be positively associated with appointment attendance.

Statistical Analysis: An ANCOVA was performed with the six dichotomized cognitive variables as independent variables and total number of weeks attended after baseline as the dependent variable. All covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included in the analysis. The sample size was reduced by 14 to 106 due to missing data on baseline measures. Nine participants were excluded due to missing baseline ASI employment index score. Two participants were excluded due to missing RAVLT data. Three participants were excluded due to missing baseline Stroop Color and Word Test data.

The Levene's test of equality was not significant ($p = 0.21$) and, thus, the assumption of homogeneity of variance was met. As show in Table 29, none of the cognitive measures were significant for appointment attendance. Stroop Color and Word Test Interference *T*-score (F (1, 94) = 2.78, $\eta = 0.03$) showed a trend ($p = 0.10$) for

appointment attendance with participants who scored in the average range or higher on Stroop Color and Word Test interference at baseline attending more of their study appointments (M = 7.47, SD = 0.38) than participants who scored in the low average range or less (M = 5.92, SD = 0.77). Table 43 shows the mean number of attended appointments for the two dichotomized T-score categories for each of the cognitive measures. The covariate bipolar type (F (1, 94) = 4.26, η = 0.04) had a significant (p = 0.04) effect on appointment attendance such that participants with bipolar II or NOS attended more study appointments (M = 7.28, SD = 0.48) than participants with bipolar I (M = 6.12, SD = 0.49). The covariate payment method (F (1, 94) = 14.43, η = 0.13) also had a significant (p <0.0001) effect on appointment attendance with participants who received cash attending more appointments (M = 7.86, SD = 0.52) than those participants who received checks (M = 5.54, SD = 0.48). No other covariates had a significant effect on appointment attendance.

A binary logistic regression was also performed with the six dichotomized cognitive variables as independent variables and the number of weeks attended after baseline dichotomized as adherent/nonadherent to appointment attendance as the dependent variable. The covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included. The sample size was reduced by 14 to 106 due to missing data on baseline measures. Nine participants were excluded due to missing baseline ASI employment index score. Two participants were excluded due to missing RAVLT data. Three participants were excluded due to missing baseline Stroop Color and Word Test data.

See Table 30 for results from this binary logistic regression. Stroop Color and Word Test condition Word was significant ($p = 0.03$) such that participants who scored in the low average range or less were 3.19 times more likely to attend their appointments than participants who scored in the average range or higher. Stroop Color and Word Test Interference was significant ($p = 0.04$) such that participants who scored in the low average range or less were 0.19 times as likely to attend their appointments as participants who scored in the average range or higher. See Tables 36 – 41 for information on the mean *T*-scores of each cognitive measure for those who were adherent or nonadherent to appointment attendance. Payment method was the only significant ($p < 0.0001$) covariate in the analysis such that participants who received checks were 0.12 times as likely to attend appointments as those who received cash.

Aim III: ***To examine the effect of cognitive functioning on medication adherence.***

Hypothesis III: *Cognitive functioning would predict medication adherence.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention would be positively associated with medication adherence.

Statistical Analysis: An ANCOVA was performed with the six dichotomized cognitive variables as independent variables and mean percentage of pills taken as the dependent variable. All covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included in the analysis. The sample size was 91 since 29 participants were excluded from the analysis due to missing data on baseline measures, inability to calculate pill counts, and the exclusion of eight participants who did not return after baseline.

The Levene's test was significant (p <0.0001). Since this indicates that a test does not meet the assumption of homogeneity of variance, the dependent variable mean percentage of pills taken was transformed using a reflect square root transformation. However, this did not improve the skewness and kurtosis. The use of a nonparametric test was considered but few exist for the ANCOVA. One nonparametric test that was considered (i.e. Brown-Forsythe) relies on transformed variables. Given that our transformed variable did not improve skewness and kurtosis, such a nonparametric test was considered unhelpful for our purposes.

We reported the results of our ANCOVA despite the significant Levene's test. As shown in Table 32, there were no significant results for the cognitive measures. Table 44 shows the mean percent of pills taken for the two dichotomized *T*-score categories for each of the cognitive measures. Payment method (F (1, 91) = 4.41, η = 0.05) was the only significant (p = 0.04) covariate with those participants who received cash having a higher percentage of pills taken (M = 94.70, SD = 1.40) than those who received check (M = 91.13, SD = 1.42).

A binary logistic regression was also performed with the six dichotomized cognitive variables as independent variables and mean percentage of pills taken dichotomized as adherent/nonadherent as the dependent variable. The covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included. The sample size was 91 because 29 participants were excluded from the analysis due to missing data on baseline measures, inability to calculate pill counts, and the exclusion of eight participants who did not return after baseline.

As shown in Table 33, there were no significant results for the cognitive measures. See Tables 36 – 41 for information on the mean *T*-scores of each cognitive measure for those who were adherent or nonadherent to medication. Payment method was the only significant ($p = 0.04$) covariate such that those participants who received checks during the study were 0.30 times as likely to be adherent to medication as those who received cash payment.

Aim IV: ***To examine the effect of cognitive functioning on adherence to treatment instructions.***

Hypothesis IV: *Cognitive functioning would predict adherence to treatment instructions.* Scores on measures of verbal learning and memory, inhibition and cognitive flexibility, and simple visual attention would be positively associated with the percentage of pill bottles returned.

Statistical Analysis: An ANCOVA was performed with the six dichotomized cognitive variables as independent variables and percentage of pill bottles returned as the dependent variable. All covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included. The sample size was 106 due to missing data on baseline measures and the exclusion of eight participants who did not return after baseline.

The Levene's test of equality was not significant ($p = 0.88$) and thus the assumption of homogeneity of variance was met. As shown in Table 34, RAVLT Total Recall *T*-score (F (1, 94) = 4.86, $\eta = 0.05$) had a significant effect ($p = 0.03$) on the percentage of returned pill bottles. Participants who scored in the average range or higher returned more of their pill bottles ($M = 90.06$, $SD = 10.00$) than participants who scored in

the low average range or less (M = 62.90, SD = 9.25). Table 45 shows the percentage of pill bottles returned for the two dichotomized T-score categories for each of the cognitive measures. Payment method (F (1, 94) = 4.50, η = 0.05) was the only significant (p = 0.04) covariate with those participants who received cash having a higher percentage rate of returned pill bottles (M = 88.54, SD =9.72) than those who received check (M = 64.42, SD = 8.93).

A binary logistic regression was also performed with the six dichotomized cognitive variables as independent variables and percentage of pill bottles returned dichotomized as adherent/nonadherent as the dependent variable. The covariates (treatment group, baseline amount spent on cocaine, payment method, bipolar type, and ASI Employment composite score) were also included. The sample size was 98 since 22 cases were dropped from the analysis due to the exclusion of eight participants who did not return after the baseline visit, missing data on baseline measures, and five cases in which it was unknown whether or not a pill bottle was returned.

As shown in Table 35, there were no significant results for the cognitive measures. None of the covariates were significant. See Tables 36-41 for information on the mean T-scores of each cognitive measure for those participants who were adherent or nonadherent to the percentage of pill bottles returned.

Exploratory Analyses

To better understand the results from Aim II, additional analyses were performed to determine what factors may have contributed to the unexpected negative relationship between Stroop Color and Word Test condition Word performance and appointment attendance. Possible

relevant variables were correlated with Stroop Color and Word Test condition Word and appointment attendance to determine the factors with the strongest associations. These variables included demographics (i.e. age, gender, education, income, etc.), baseline mood scores, baseline cocaine use, ASI composite scores, type of psychotropic medications at baseline, bipolar type, payment method, and change in mood and cocaine use from baseline to exit. Age, number of antidepressants taken at baseline, and ASI Employment composite score were significantly correlated ($p \leq 0.05$) with both baseline Stroop Color and Word Test condition Word *T*-score or *T*-score category (i.e. low average or less and average or greater) and number of attended appointments. These correlations are presented in Table 31.

CHAPTER V

DISCUSSION

This study addressed the effect of cognitive functioning on psychiatric treatment adherence and retention in participants with comorbid bipolar disorder and cocaine dependence. This study sought to address the paucity of research literature on treatment adherence and cognitive functioning in comorbid bipolar disorder and cocaine dependence. The primary goals of the current study were to explore the level of cognitive impairment in bipolar disorder and cocaine dependence and the ability of cognitive functioning to predict treatment adherence and retention. The results from this study indicated that cognitive functioning had little effect on measures of treatment adherence and retention in this population. However, verbal learning and memory affected the return of treatment-related items to appointments, while poor simple attention, but average cognitive flexibility were associated with attending more appointments.

I. Analysis of Descriptive Statistics and Substance Use Statistics

The demographics of this sample varied from other studies of people with bipolar disorder (Hirschfeld, Lewis, & Vornik, 2003; Kupfer et al., 2003). Most participants in this dissertation were male (60.80%) and most were African-American (61.70%). The median age of participants was 44.05 years and the mean years of education were 13.55. More than half (58.30%) of the sample reported a yearly household income under $15,000 and 27.40% made between $15,001 and $50,000 a year. Seventy-four percent of participants were not taking any psychotropic medications.

These demographic statistics of this study were compared to those from a survey conducted by The Stanley Center Bipolar Disorder Registry of 2,839 participants with self-reported bipolar disorder (Kupfer et al., 2003). Sixty-four percent of the 2,839 participants were women and 90% were Caucasian. The median age of participants was 40.10 years and over 60% had completed at least one to two years of college (Kupfer et al., 2003). The Stanley Center Bipolar Disorder Registry study did not report mean household income, but did indicate that 64% percent of the participants were unemployed. In a study of 600 participants diagnosed with bipolar disorder, the mean household income was $37, 450, with 30% of participants making less than $15,000 and 44% of participants making between $15,001 and $50,000 a year (Hirschfeld et al., 2003). In The Stanley Center Bipolar Disorder Registry, 33% of participants were taking at least three different types of psychotropic medications (Kupfer at al., 2003), and 97% of the 600 participants in another study were taking at least one psychotropic medication (Hirschfeld et al., 2003). The demographics of our sample differed in that more participants were male and African-American and less were educated, prosperous, or medicated. Thus, due to the comorbid cocaine use, region of the country where the study was conducted, or clinical research setting the participants differed somewhat in demographic characteristics from other bipolar disorder studies. This difference may impact the external validity or generalizability of the findings.

Substance Use Statistics.

Substance use may be a contributing factor to the low number of psychotropic medications taken in our study compared to the abovementioned studies. Substance abuse is associated with decreased medication adherence (Akincigil et al., 2007) and is one of the strongest predictors of medication nonadherence in bipolar disorder (Sajatovic et al., 2009).

Participants in our study may have been less likely to be on psychotropic medications as a result of their dependence on cocaine.

The demographics of our participants are mixed in their representation of people who use cocaine. The gender distribution of our sample was similar to the distribution on other reports of people with cocaine dependence. The male to female ratio of cocaine use is 1.5-2.0:1 (APA, 2000) which is similar to the ratio in our study of 1.4:1. Likewise, males are twice as likely as women to have met criteria for cocaine abuse or dependence in the past year (Office of Applied Studies, 2004). However, our sample is slightly older than might be expected in a cocaine dependence study. The age group with the highest use of cocaine is 18 to 25 year olds which differs from the mean age of 44 years in our study (APA, 2000; Office of Applied Studies, 2004), but the age group of 40-44 has the second highest rate (29.9%) of lifetime cocaine use (Office of Applied Studies, 2004). Those with a few years of college education tend to have the highest rate (18.8%) of lifetime cocaine use compared to those with other levels of education (Office of Applied Studies, 2004).

The ethnicity of our sample is mixed in its representation of people who use cocaine but is similar to those who have cocaine abuse or dependence. Lifetime cocaine use tends to be higher in Caucasians (17.5% lifetime rate) than in African-Americans (12.8% lifetime rate), (Office of Applied Studies, 2004). However, past year cocaine use is nearly equal among African-Americans (2.6%) and Caucasians (2.5%) (Office of Applied Studies, 2004), and rates of current cocaine abuse or dependence is slightly higher in African-Americans (1.1%) than in Caucasians (0.5%) (Office of Applied Studies, 2004). African-Americans have the highest lifetime rates of crack cocaine use (5.5%) and highest past year use (1.7%) (Office of Applied

Studies, 2004). This suggests that our participants, in terms of ethnicity, are representative of individuals who abuse or are dependent on cocaine.

II. Analysis of Baseline Cognitive Functioning Characteristics

Rey Auditory Verbal Learning Test.

Participants in this study generally had lower than average RAVLT *T*-scores. These RAVLT scores were similar to what would be expected in patients with bipolar disorder (Goldberg & Burdick, 2008; Osuji & Cullum, 2005; Torrent et al., 2006). The RAVLT is a measure of verbal learning and memory. The Total Recall score measures the ability to learn a word list across five learning trials. The Delayed Recall score measures long term verbal memory of those words. Individuals with bipolar disorder in the depressed phase tend to have poor learning ability and verbal short-term memory (Torrent et al., 2006; Goldberg & Burdick, 2008). Verbal learning and memory difficulties occur across all mood states of bipolar disorder, and thus have been considered a possible cognitive endophenotype for this disorder (Torrent et al., 2006; Osuji & Cullum, 2005). Our results appear to confirm that supposition.

The mean *T*-scores on the RAVLT for participants in this study were in the low average range which was similar to the results in other bipolar disorder studies using the RAVLT. In a study of 60 participants, those with bipolar depression learned and recalled significantly less words on the RAVLT than healthy controls and participants with unipolar depression (Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987). In a study of 40 participants with bipolar disorder and a history of depression, they showed significant impairment in learning and recall on the RAVLT compared to healthy controls (Ferrier, Stanton, Kelly, & Scott, 1999). A meta-analysis of eleven studies which utilized either the RAVLT or the CVLT found that participants with bipolar disorder had significantly lower scores than healthy controls, particularly on Total

Recall of learned words (Robinson et al., 2006). Collectively these studies indicate that the verbal learning and memory performance of our sample was similar to that of others with bipolar disorder.

The participants' mean low average *T*-scores on the RAVLT are similar to the results in other neurocognitive studies of people with cocaine dependence. Overall, individuals with cocaine dependence have poor verbal learning and memory. One study found that those who used cocaine in larger amounts and more frequently prior to testing had greater deficits on measures of verbal memory (O'Malley, Adamse, Heaton, & Gawin, 1992). Another study found that those who abused cocaine had lower scores than controls on verbal memory tests (Berry et al., 1993). Individuals who had ten days of sobriety after previous weekly cocaine use had decreased efficiency in learning verbal information and maintaining it in long-term memory (Mittenberg and Motta, 1993). Our sample was representative of people with cocaine dependence who have poor functioning on verbal learning and memory measures.

Stroop Color and Word Test.

The mean *T*-scores on the Stroop Color and Word Test were higher than reported in participants with bipolar disorder in some other studies. The Stroop Color and Word Test is a measure of simple attention and executive functioning, including inhibition (impulse control) and cognitive flexibility (Golden & Freshwater, 2002). It also assesses working memory and processing speed (Strauss, Sherman, and Spreen, 2006). Studies have shown that participants with bipolar disorder have deficits in these cognitive domains (Green, 2006; Osuji and Cullum, 2005). However, on each of the four Stroop Color and Word Test scores, more than half of the participants in this study performed in the average range or higher. This result seemed to indicate that most participants in this study did not have impaired working memory, inhibition,

processing speed, or attention that is typically observed in people with bipolar disorder. However, since only the Stroop Color and Word Test was used to assess these domains, it is premature to suggest such a conclusion. Participants with depression, especially bipolar as opposed to unipolar, have typically demonstrated lower performance on the Stroop Color and Word Test than healthy controls (Borkowska & Rybakowski, 2001). In a meta-analysis of 11 studies that utilized the Stroop Color and Word Test, patients with bipolar disorder performed significantly lower than healthy controls (Robinson et al., 2006). Collectively, these studies indicate that our participants overall performed better on the Stroop Color and Word Test compared to participants with bipolar disorder in previous studies.

The participants' mean *T*-scores on the Stroop Color and Word Test conditions Color-Word and Interference were higher than in other neurocognitive studies of participants with cocaine dependence (Jovanovski et al., 2005; Verdejo-García & Pérez-García, 2007). Individuals with cocaine dependence tend to have poor inhibition, working memory, and attention (Jovanovski et al., 2005). However, one study found that working memory was not impaired during cocaine use compared to age and gender matched healthy controls, and that attention was actually poorer during the initial weeks of abstinence (Pace-Schott et al., 2008). Our sample's performance on measures of inhibition and simple attention is mixed in terms of their representation of people with cocaine dependence.

III. Analysis of Treatment Adherence and Retention Characteristics

The treatment adherence and retention rates of participants in this study were comparable to rates reported in the research literature. In this study, 42.50% of participants took less than 90% of their study medication as prescribed, which was similar to larger studies that found 48.10% and 56.50% partial or full medication nonadherence rates among people with bipolar

disorder (Sajatovic et al., 2006; Baldessarini et al., 2008). Likewise, studies of people with comorbid substance dependence and bipolar disorder have reported psychiatric treatment nonadherence rates ranging from 53% to 58% (Goldberg et al., 1999; Keck et al., 1998).

Participants in this study also had treatment retention and completion rates typically seen in individuals with bipolar disorder and/or cocaine dependence. Only 40% of participants attended 90% or more of their appointments and approximately half (53.30%) completed the study. This attendance rate was similar to other cocaine clinical trials in which completion rates were less than 50% (in Stotts et al., 2007). Conversely, the drop-out rate in this study was 47.50%, which was similar to other medication trials in comorbid bipolar disorder and substance dependence (Prisciandaro, Rembold, Brown, Brady, & Tolliver, 2011). The treatment adherence and retention rates of our study's participants were similar to the findings in prior research with people who have bipolar disorder and/or cocaine dependence.

IV. Analysis of Study Results

Cognitive Functioning and Treatment Retention.

Our hypothesis regarding the impact of cognitive functioning on treatment retention in comorbid bipolar disorder and cocaine dependence was not supported by our data. The level of cognitive functioning at baseline was not associated with length of time participants remained in the study or whether participants completed the study. The cognitive tests used in this study assessed the ability to inhibit automatic responses, to shift cognitive set, to learn and recall new information, and to attend to simple visual stimuli. The study results suggest that these cognitive abilities are not associated with treatment completion for bipolar disorder and cocaine dependence.

This result differed from previously reported research on this population. In a placebo-controlled trial of 56 participants with cocaine dependence who received cognitive behavioral relapse prevention therapy (CBT-RP) plus venlafaxine or gabapentin, those with poorer cognitive functioning dropped out early from the study (Aharonovich, Nunes, & Hasin, 2003). Unlike our study results, the participants who did not complete that study had lower scores on measures of attention, memory, spatial ability, speed, and accuracy as measured by the computerized MicroCog test battery (Powell, Kaplan, Whitla, Catlin, & Funkenstein, 1993) (Aharonovich et al., 2003). However, similar to this study, inhibition and cognitive flexibility did not seem to impact retention since those participants who completed and dropped out did not differ in their performance on the WCST (Aharonovich et al., 2003).

Cognitive Functioning and Appointment Attendance.

The results of our study were mixed in their support of hypothesis II which stated that cognitive functioning would be associated with appointment attendance. Poor inhibition and cognitive flexibility, as measured by the Stroop Color and Word Test Interference *T*-score, were associated with decreased likelihood of attending appointments. This result was similar to the findings in another study in which increased baseline impulsivity, as measured by the Barratt Impulsivity Scale (BIS-11), predicted drop-out in a placebo-controlled clinical trial of buspirone for cocaine dependence (Moeller et al., 2001). Similarly, in a clinical trial of lamotrigine for participants with comorbid bipolar disorder and cocaine or amphetamine dependence, greater non-planning impulsivity was associated with poorer retention (Akingbala, Dhanani, Brown, 2006). Poor Stroop Color and Word Test Interference *T*-scores have been associated with lower attendance to treatment appointments (Carpenter, Schreiber, Church, and McDowell, 2006). The results from these studies support our finding that inhibition and cognitive flexibility are positively related to treatment attendance.

This dissertation also found that poorer simple visual attention, as measured by the Stroop Color and Word Test condition Word, was associated with better attendance to treatment appointments. The mean performance of our sample on the Stroop Color and Word Test condition Word is similar to other research results that found an association between bipolar disorder and/or cocaine use and poor attention (Jovanovski et al., 2005; Osuji and Cullum, 2005) and processing speed (Carpenter et al., 2006). Similar to our study, a trend was found between longer reaction time on the Word condition of the Stroop Color and Word Test and higher completion rates for participants with cocaine dependence seeking treatment (Streeter et al., 2008). However, prior research has shown that better performance on the Word condition of the Stroop Color and Word Test and other measures of attention lead to increased appointment attendance (Aharonvich et al., 2003; Streeter et al., 2008). Similarly, higher scores on the MicroCog measure of attention were significantly correlated with increased weeks in treatment (Aharonvich et al., 2003). Collectively, these studies indicated that there is mixed evidence supporting our finding.

Our study found several factors that were associated with performance on the Word condition of the Stroop Color and Word Test and appointment attendance and that may help explain the results in this study. These factors included age, ASI Employment composite score, and antidepressant use. Perhaps our study does not imply that poor visual attention improves adherence, but rather that the factors associated with poor attention contribute to better appointment attendance. Thus, examining these factors may be more important for understanding and improving treatment adherence.

Age

Older age was one of the factors associated with lower simple attention and processing speed and higher attendance. Those who were older had lower scores on the Word condition of the Stroop Color and Word Test, but attended more appointments. Performance on the Word condition of the Stroop Color and Word Test decreases as people age due to slower processing speed (Golden & Freshwater, 2002). The literature generally supports the supposition that age impacts treatment attendance. In a 12 week clinical trial of risperidone and cognitive behavioral therapy (CBT) for 80 participants with cocaine dependence, older age was found to be predictive of study completion (Stotts et al., 2007). In a study of 599 men in treatment for alcohol or substance abuse or dependence, an age over 40 years was related to longer length of stay in treatment (Mertens & Weisner, 2000).

One of the greatest risk factors for treatment nonadherence in people with bipolar disorder is younger age (Colom et al., 2000). In a study of psychosocial treatment for cocaine dependence, younger age was significantly associated with drop out and decreased appointment attendance (Siqueland et al., 1998). Homelessness and younger age were related to nonadherence to antipsychotic medication in those with bipolar disorder (Sajatovic et al., 2006).

Not all studies concurred with these findings. In a clinical trial of naltrexone and CBT for 80 participants with cocaine dependence and five days of abstinence, older age was associated with earlier drop out (Stotts et al., 2007), and in an eight-week placebo-controlled trial of acamposate in participants with comorbid bipolar disorder and alcohol dependence, age was not a predictor of treatment attendance (Prisciandaro et al., 2011).While these few studies did not find a relationship between older age and higher appointment attendance, most studies concurred with our finding that older participants tended to stay in treatment longer.

Baseline ASI Employment

Higher (poorer) baseline ASI employment composite score was also associated with low simple attention and processing speed and higher attendance. Low cognitive functioning is associated with decreased psychosocial and occupational functioning (Torres et al., 2008; Zarate et al., 2000), which might contribute to higher ASI employment scores. The association between ASI employment score and treatment attendance is mixed in other studies. The ASI employment composite score, particularly greater need for employment counseling, is a significant predictor of outpatient substance abuse treatment retention (McCaul, Svikis, & Moore, 2001). In a study of 599 men who were treated for alcohol or substance abuse or dependence, employers' threats of possible unemployment were associated with longer treatment stays (Mertens & Weisner, 2000). Collectively these studies support our supposition that baseline ASI employment index scores are associated with both poorer simple visual attention and higher appointment attendance.

However, for the 317 women in the abovementioned study, higher family income was significantly associated with longer stay in treatment, and there was a trend towards lower (better) ASI employment composite scores associated with longer stay in treatment (Mertens & Weisner, 2000). In an eight-week placebo-controlled clinical trial of acamprosate in participants with comorbid bipolar disorder and alcohol dependence, employment status was not a predictor of treatment attendance (Prisciandaro et al., 2011). While our study found a relationship between higher (poorer) ASI employment composite score, indicative of unemployment or financial problems, and higher appointment attendance, these other studies found either no relationship or that increased income and lower (better) ASI employment index scores are associated with

higher attendance. This difference between findings may be due to the fact that we paid participants for appointment attendance and participation in the study was free.

Antidepressant Use

Use of antidepressants at baseline was another factor associated with both poorer performance on the Word condition of the Stroop Color and Word Test and appointment attendance in our study. Of note, use of a psychotropic medication, regardless of type, at baseline was not associated with both performance on the Word condition of the Stroop Color and Word Test and appointment attendance. Thus, it appeared that this effect was specific to antidepressants. One would anticipate that good adherence to one medication would be associated with good adherence to an additional medication. A study of veterans with bipolar disorder with and without comorbid substance dependence found that those who took a greater number of different medications were more adherent (Sajatovic, Bauer, Kilbourne, Vertrees, & Williford, 2006).

Antidepressants have been shown to help improve adherence to concomitant medications by decreasing depressive symptoms such as suicidal ideation, anhedonia, decreased energy, and distractibility, which may contribute to nonadherence (Yun, Maravi, Kobayashi, Barton, & Davidson, 2005). In our study, the participants on antidepressants did not have higher $HRSD_{17}$ or QIDS-SR scores at baseline, so the effect does not appear to be from depression severity.

It is unclear why antidepressant use would be associated with poorer performance on the Word condition of the Stroop Color and Word Test. There is limited data on the effect of antidepressants on cognitive functioning, but most studies show an overall neurocognitive protective effect (Goldberg & Burdick, 2008). Anticholinergic medications, such as the less commonly prescribed tricyclic antidepressants, may have a negative effect on verbal learning

and memory, and tend to be associated with decreased arousal and attention, and slowed processing speed (Goldberg & Burdick, 2008). In general while other studies support our finding of a relationship between antidepressant use and greater attendance, prior research is mixed regarding the relationship between antidepressant use and poorer cognitive functioning such as simple visual attention.

Cognitive Functioning and Medication Adherence.

This study did not find a relationship between cognitive functioning and medication adherence in participants with comorbid bipolar disorder and cocaine dependence. Performance on verbal learning and memory, simple visual attention, inhibition, and cognitive flexibility measures was not associated with adherence to medication regimens. There are mixed results in the literature regarding the relationship between cognitive functioning and medication adherence. Similar to our results, one study found that memory, as measured by the CVLT and WMS III Logical Memory, was not a predictor of medication adherence in older adults (Insel et al., 2006).

It has been suggested that taking medication requires good encoding and storage of information about the importance of taking the medicine (Insel et al., 2006). In a study of adults with HIV, participants with impaired higher-order attention had low medication adherence rates (Hinkin et al., 2002). A main effect for memory impairment, as measured by the CVLT, was associated with poorer medication adherence and a logistic regression showed that those with memory dysfunction were two times more likely to have taken less than 90% of their medication dosages than those with higher CVLT scores (Hinkin et al., 2002). Unlike our study, most prior research has found a positive relationship between cognitive functioning and medication adherence.

Our study did not find a relationship between executive functioning and medication adherence. Research results vary on the relationship between this cognitive domain and medication adherence. Executive dysfunction was associated with lower medication adherence rates in a population of adults with HIV (Hinkin et al., 2002). Executive functioning, as measured by the WCST, and working memory, as measured by the WMS III Letter Number Sequencing and Digit Span Backward, were significant predictors of medication adherence (Insel et al., 2006). However, in a study of adherence to cholesterol medication, mental flexibility (an executive function domain), as measured by the Digit Vigilance Test and Trail Making Test Part B, did not significantly predict medication adherence (Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004). Results in the literature are mixed regarding our finding that there is no relationship between executive functioning and medication adherence.

Cognitive Functioning and Treatment Instruction Adherence.

This study found a relationship between cognitive functioning and adherence to treatment instructions in participants with comorbid bipolar disorder and cocaine dependence. Better verbal learning and immediate recall had a positive effect on the percentage of pill bottles returned at study visits. Although a much simpler task than activities of daily living or job related duties, the return of pill bottles may be related to learning psychosocial and occupational functioning tasks or skills acquisition because of the learning and memory component. The Global Assessment of Functioning (GAF) is a measure of psychosocial and occupational impairment as well as symptom severity associated with a psychiatric illness. Perhaps adherence to treatment instructions is similar to the psychosocial/occupational functioning measured by the GAF because of the need to remember and execute a task. In a study of 40 participants with bipolar disorder, poorer performance on all subtests of the CVLT was associated with poorer

psychosocial and occupational functioning as measured by the GAF (Martínez-Arán et al., 2004). The research literature shows a positive relationship between verbal learning and short-term memory and psychosocial and occupational functioning (Deckersbach et al., 2010). Cognitive impairment, especially in the domains of verbal learning and memory, has a significant negative impact (medium effect sizes ranging from 0.35 to 0.46) on psychosocial functioning in bipolar disorder (Green, 2006). If the return of a treatment related item (i.e. pill bottle) is similar to the skills acquisition needed for psychosocial or occupational functioning, then prior research supports our finding.

There was no relationship between adherence to treatment instructions and verbal delayed recall, simple visual attention, inhibition, or cognitive flexibility. This result differed from other studies that examined the effect of cognitive functioning on outcome behaviors. As mentioned in the study above, poorer performance on the CVLT delayed recall was associated with lower GAF scores (Martínez-Arán et al., 2004). The Interference score on the Stroop Color and Word Test was positively correlated with GAF scores (Martínez-Arán et al., 2004). While verbal learning and immediate recall had an effect in our study on the percentage of pill bottles returned, no relationship was found with the other cognitive domains. Of note, participants in our study were given a verbal reminder to return the pill bottle both when given the bottle and during a reminder call the day before the next visit. It is possible that these reminders, instead of cognitive functioning ability, accounted for the increased percentage of returned pill bottles.

Covariates Significantly Related to Adherence and Retention.

Payment Method

One of the concerns of this study was if payment method influenced treatment retention and adherence or negated poor performance on cognitive measures. For these reasons, payment method was used as a covariate in all analyses. This study found relationships between payment

method and appointment attendance, medication adherence, and instruction adherence in participants with bipolar disorder and cocaine dependence. Previous studies also found correlations between payment method and adherence. In a study of patients with tuberculosis, those who received a $5 grocery coupon versus no coupon for attending treatment visits were more likely to complete treatment within 32 weeks and 52 weeks (Bock, Sales, Roger, & DeVoe, 2001). Incentives of $3 coupons also led to increased attendance in research participants with comorbid psychiatric illness and substance abuse (Carey & Carey, 1990). A review of 11 studies published from 1976 to 1996 which used monetary incentives to improve medication or appointment adherence found that participants who received financial incentives were more likely to adhere to treatment (Giuffrida & Torgerson, 1997). Although there is concern regarding the ethics of using financial incentives to increase treatment adherence (Claasen et al., 2007), such methods have shown efficacy for improving treatment adherence and outcomes. The results from this study may lend support for the use of contingency management in substance dependence treatment.

In this study, the receipt of cash as an immediate reward versus check as a delayed (up to four weeks) reward had a significant impact on several aspects of adherence. A possible explanation for this result is that an immediate reward works better for a population who has difficulty with impulsivity and delayed gratification. This study sample also had a mean low income and so may have had more need and motivation for immediate money. Because our sample was still using cocaine, cash may have also been more desired as a way to pay for their drug use. Cash is more convenient and less cumbersome than check for transference to buy needed/desired items.

Bipolar Type

This study found a relationship between bipolar type and appointment attendance for people with bipolar disorder and cocaine dependence. Those with bipolar I were less likely to attend appointments than those with bipolar II. There is limited research regarding the relationship between bipolar type (I, II, or NOS) and treatment adherence. In two clinical research studies, participants with bipolar I and alcohol or cocaine dependence had a lower retention rate than those with bipolar II and substance dependence (Nomamiukor & Brown, 2009).

Our study found no relationship between bipolar type and medication adherence. This is similar to the findings of Baldessarini et al., who also found no relationship between bipolar type and medication adherence in a study of 429 patients with bipolar disorder (Baldessarini & et al., 2008). More research is needed regarding the relationship between bipolar type and treatment adherence to determine the validity of our finding.

V. Clinical Implications

The results of this study may provide support for the use of contingency management to increase treatment adherence and retention. Participants who received cash were more likely to attend appointments, take their medication, and return their pill bottles. The use of an immediate reward such as cash, rather than a delayed reward, such as check, was associated with greater adherence. One method for encouraging sobriety and treatment adherence is contingency management, in which individuals receive incentives for a desired behavior, such as decreased quantity and days of substance use, removal of drug paraphernalia, or treatment attendance. It operates on the principle of positive reinforcement. The use of these incentives (i.e. coupons, cash, etc.) has proven successful in several studies (Bock et al., 2001; Carey & Carey, 1990; Giuffrida & Torgerson, 1997). This dissertation did not have a control group of participants who

received no payment for attending appointments, so it is not possible to know if the observed effect was from the payment itself or another factor. That cash had more of an impact than a delayed check suggests that the use of similar immediate rewards, such as coupons, desirable prizes, or transportation passes, may help increase attendance and medication adherence. Whether the receipt of cash is similar to the receipt of other immediate but noncash incentives (i.e. coupons or bus passes) is debatable; regardless both are associated with improving treatment adherence.

Although participants in our study did not receive CBT, the nature of weekly visits that inquire about participants' mood and functioning is inherently supportive and the relationship between research assistant and participant can have components similar to a therapeutic alliance. Even though our study found a minimal effect of cognitive functioning on treatment adherence and retention, the aims of our study raise the question of whether cognitively-oriented therapies are appropriate for individuals with cocaine dependence and bipolar disorder who have cognitive impairments. Cognitive behavioral approaches and psychoeducation have proven effective in increasing treatment adherence (in Claasen et al., 2007). CBT-RP has been seen as one of the more beneficial and effective treatments for cocaine dependence (Carroll et al., 1994). However, given the cognitive component of CBT-RP, individuals with cognitive impairments may find the treatment too difficult or stressful, and thus be less inclined to continue with CBT-RP. In a study of eighteen non-depressed cocaine dependent participants who received CBT-RP, more than half of those who dropped out early in treatment had lower neuropsychological test scores at baseline (Aharonovich et al., 2003). In a study of 56 depressed and non-depressed participants with cocaine dependence, those with poor attention were less likely to remain in CBT-RP and medication treatment (Aharonvich et al., 2003). These results emphasize the importance of

cognitive functioning to treatment retention and adherence and that treatment providers should be aware of clients' cognitive abilities when tailoring treatment to them and helping them attend to treatment (Aharonvich et al., 2003). Methods to cope with this decreased cognitive functioning may include written information and instructions clients can take with them, reminder calls, and appointment cards.

While CBT-RP has shown efficacy for improving treatment adherence and decreasing cocaine dependence, similar cognitive behavioral treatments that address the impaired psychosocial functioning in bipolar disorder have not always provided improvements above and beyond collaborative care control groups or substantially impacted psychosocial functioning (Deckersback et al., 2010). Compromised cognitive abilities may account for the ineffectiveness of these cognitively based treatments. Cognitive rehabilitation for bipolar disorder is a relatively new concept, and few studies have investigated this treatment (Deckersbach et al., 2010). However, it is a promising development in ameliorating the functional difficulties secondary to bipolar disorder. Cognitive remediation (CR) treatment includes not only traditional CBT components, but also techniques to improve executive function, attention, and memory (Deckersbach et al., 2010). CR targets depressive symptoms and cognitive impairments that decrease functioning; it consists of fourteen, 50 minute individual sessions over four months that focus on (1) monitoring and treatment of mood symptoms, (2) organization, planning, and time management, and (3) attention and memory (Deckersbach et al., 2010). In a study of 18 participants with bipolar disorder who had poor executive function, attention, and memory, CR significantly decreased depressive symptoms, total lost work performance, and executive dysfunction at the end of treatment (Deckersbach et al., 2010).

Given the small sample size of that study, lack of a control group, and drop out, more research is needed to determine the effectiveness of CR for people with bipolar disorder who have cognitive functioning deficits. While our study did not address CR and there was a minimal effect from cognitive functioning on treatment adherence, participants generally were representative of people with bipolar disorder and cocaine dependence in terms of low cognitive functioning. CR may be a promising new treatment for this population in cases where cognitive functioning has a larger effect on adherence.

Likewise, although the results from this study showed only a partial effect of cognitive functioning on treatment adherence, it draws attention to the possibility of using cognitive measures to predict adherence. Poor performance on measures of interference and inhibition to automatic responses has been associated with poor adherence to cognitive-behavioral coping skills treatment and pharmacotherapy for drug dependence (Carpenter et al., 2006). As a measure of cognitive control and prepotent response, the Stroop Color and Word Test may help identify individuals with cocaine dependence who have difficulty inhibiting a habitual response of cocaine use and treatment nonadherence (Streeter et al., 2008). Treatment providers may find it helpful to assess and understand the cognitive difficulties of their patients and address them so they do not impede treatment adherence and outcomes. Neuropsychological measures, such as the Stroop Color and Word Test and RAVLT, could possibly be used to identify individuals at risk for treatment drop-out, and these at-risk individuals could then receive adherence interventions (i.e. reminder cards and calls, incentives, improved relationship with research assistant) (Streeter et al., 2008).

VI. Strengths

Few studies have investigated populations who have both bipolar disorder and substance dependence. One of the primary strengths of this study is the inclusion of a comorbid sample. It is important to study this comorbidity because 61% of individuals with bipolar I disorder and 48% of individuals with bipolar II disorder have a lifetime history of substance dependence (Regier et al., 1990). Treatment nonadherence is greater in individuals who have both bipolar disorder and substance abuse/dependence versus those who have just one of these disorders (Akincigil et al., 2007). Due to the high prevalence of substance dependence in bipolar disorder, this study adds meaningful information regarding comorbid bipolar disorder and cocaine dependence. Furthermore, to date, this study is the largest trial of participants with bipolar disorder and cocaine dependence.

The analysis of *T*-scores, rather than raw scores, for cognitive measures increases statistical power as well as clinical meaningfulness because *T*-scores account for normative values such as age and education. Further categorizing *T*-scores into two groups (i.e. average range or higher and low average range and less) also provided for more clinically relevant results. The measurement of adherence with various techniques (i.e. study retention, appointment attendance, pill counts, and pill bottle return) allowed us to expand the definition of adherence and also examine specific components of adherence.

Although study participants were defined as having comorbid bipolar disorder and cocaine dependence, many had a current or past history of other substance abuse and/or dependence. Nearly 80% of the participants met criteria for current and/or lifetime abuse or dependence on another substance and 64% of participants met criteria for current and/or lifetime alcohol abuse or dependence. It may be more accurate, then, to define our population as having comorbid bipolar disorder and alcohol and/or substance dependence with a focus on cocaine use.

This heterogeneity in substance use may actually increase the external validity of this study, as it likely reflects real-life clinical populations who have more than one substance of choice. Individuals who abuse one substance often have a lifetime history of abuse or dependence on a second substance.

VII. Limitations

There are several limitations of this study. Because it was a secondary analysis of a pre-existing data set, the measures examined were limited to those used in the prior study. Therefore, although additional neuropsychological tests may have measured other known impaired cognitive domains in bipolar disorder and substance dependence, the only cognitive measures available for this analysis were the Stroop Color and Word Test and the RAVLT. This subsequently limited what types of cognitive functions were investigated and inadvertently excluded other important, relevant cognitive domains that may play a role in treatment adherence such as organization and planning, working memory, and sustained attention.

While most participants in this study did not show poor performance on the Stroop Color and Word Test, this does not necessarily mean that they did not have difficulties with inhibition, cognitive flexibility, simple attention, and other domains assessed by the Stroop Color and Word Test. Additional, more comprehensive testing of these domains may have been more sensitive to impairments in this population. For example, measures such as the Trails Making Test, Parts A and B may have been better measures of visual attention and cognitive flexibility than the Stroop Color and Word Test. Although the Stroop Color and Word Test Interference score is a valid, reliable measure of inhibition, the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) provides a fourth condition on the Stroop Color and Word Test that requires one to switch back and forth between naming the dissonant ink colors and reading the conflicting

words. This task assesses more complex inhibition, initiation, and cognitive flexibility. Thus, this D-KEFS Color-Word Interference Test may provide more cognitive information.

Although the RAVLT is a valid and reliable measure of verbal learning and memory, the CVLT-II would have provided information regarding abilities to use strategies to remember information. Other measures such as the Wechsler Memory Scale Logical Memory tests could have provided information about verbal learning and memory in the context of a story. The measurement of memory strategies and the effect of verbal learning on memory could be more clinically meaningful for the purposes of assessing cognitive functioning on medication and treatment instruction adherence.

The use of a short cognitive battery limited this study. A more comprehensive battery could have allowed for more informative results regarding the effect of cognitive functioning on treatment adherence and retention in individuals with comorbid bipolar disorder and cocaine dependence. A more comprehensive battery could have measured the domains known to be affected in bipolar disorder and substance dependence, and it may have picked up on more subtle deficiencies or determined the reliability/consistency of results. Further, it could have allowed for measurement of lateralization and cortical versus subcortical impairment to better understand the brain areas associated with bipolar disorder and substance dependence.

Just as there were limitations in cognitive measures due to a pre-existing data set, there were also restrictions in treatment adherence measurements. Pill counts may not be the most valid measure of medication adherence. Such counts can be subject to calculation error and they only measure the number of pills left in the bottle compared to the number of pills that should be left in the bottle. It presumes that the individual ingested all of the medication not present in the bottle but it is also possible that the pills were disposed of, lost, or stolen. Also, pill counts

cannot measure the degree of adherence in the same way as blood or urine assays can measure the medication levels in a person's body; a therapeutic or higher assay level implies a greater degree of adherence. Furthermore, pill counts rely on the participant remembering to return their pill bottle. In this study, participants would forget to bring their bottles, effectively eliminating the pill counts for that visit.

As with many research experiments conducted in a laboratory, it is uncertain how much and in what ways this particular study is generalizable to real world applications. There are several factors that may diminish the external validity of this study. Randomization to placebo or an active medication does not occur in clinical settings, so the impact that this randomization procedure had on our results is unknown. However, treatment group was used as a covariate in all analyses and never had a significant impact on treatment adherence and retention. In the primary study, treatment group also did not have an impact on mood and cocaine use (Brown et al., in press). Regardless, the use of randomization to a treatment group is a possible limitation given that it does not occur in non-research settings.

Research ethics require that participants receive a fair, but not coercive, reimbursement for their participation in a study. The participants in this study received money, either in cash or check, to attend appointments. Although the amount ($30 per appointment) was relatively small by certain standards, it may have been significant for this population since 58.00% of participants made below $15,000 a year. The type of payment (cash or check) had a significant effect on appointment attendance and medication adherence; those who received cash were more likely to attend appointments and take their medication. The use of payment in our study is another limitation to external validity, given the significance of payment on adherence and that people do not receive payment in clinical settings when they attend appointments.

Another factor that may impact the external validity of this study is the low percentage (26.30%) of participants who received psychotropic medications at baseline. We only measured adherence to the study medication, not to other psychotropic medications. It is unknown how many of the 26.30% were actually taking their other psychotropic medications. Given these limitations, this study does not allow for much examination of the effect of psychotropic medications on cognitive functioning and/or on treatment adherence and retention.

This study was the largest trial ever reported of bipolar disorder and cocaine dependence. However, the sample size of 120 participants was reduced to 106, 98, and 91 in this study's analyses due to drop-out and missing pill count and baseline data. These modest sample sizes may have accounted for the wide range in confidence intervals. Thus, it lowered the confidence in the results. Although there were statistically significant findings, the large confidence intervals and small effect sizes for the cognitive variables limited the clinical relevance of the significant results. Additionally, multiple outcomes were used without adjustment for multiple comparisons which increased the chance of a Type I error. However, a Bonferroni correction or other adjustment may have increased the chance of a Type II error.

VIII. Future Directions

Because there is a paucity of research examining the effect of cognitive functioning on treatment adherence and retention in comorbid bipolar disorder and substance dependence, more studies are needed to either confirm or refute the results from this current study. Such studies should include a larger sample size, improved pill count data, and a comprehensive neurocognitive battery to maximize the statistical power of the analyses and increase confidence in the results. Since this study was a secondary analysis of a data set, it was limited to the

cognitive measures included in the initial study. In addition to the cognitive domains examined in this study, other cognitive domains such as executive function (i.e. planning, problem solving), memory (i.e. working, short-term, and visual), verbal fluency, and attention (i.e. sustained, selective) should be included in future studies of comorbid bipolar disorder and substance dependence.

Future studies should also include healthy controls to more clearly determine what effects are due to bipolar disorder and substance dependence. The inclusion of participants without bipolar disorder and substance dependence would provide a comparison group and thus allow one to better understand the effect of this comorbidity on cognitive functioning. It would also be helpful to study cognitive functioning in participants with bipolar disorder with and without substance dependence. Such a study would help clarify what cognitive factors are associated with bipolar disorder alone and any additional impact of substance dependence. Since this study aimed to focus solely on cocaine dependence, but a majority of participants (80%) had another current or lifetime substance dependence, it may be useful to obtain a "purer" sample of individuals with only cocaine dependence. However, obtaining such a sample may be difficult and reduce the external validity of the results since most individuals do not meet lifetime dependence or abuse for just one substance. Thus, it may be more useful to acknowledge the overlap in substance abuse/dependence disorders.

External validity may also be improved by conducting this same study in the community, such as in mental health clinics, rather than in a research laboratory. This would increase external validity by excluding the use of placebo medication and including the use of various psychotropic medications. Examining participants on various psychotropic medications could help determine whether medications have a deleterious, neuroprotective, or minimal impact on

cognitive functioning and treatment adherence in bipolar disorder. Conducting this study in various non-research settings, such as community mental health clinics and psychiatry/psychology offices, may also help increase the diversity (i.e. education level, income level, and ethnicity) of the population sample. However, given the likely increased variability in participant factors in mental health clinics and hence potential study covariates, conducting this study in the community may decrease the internal validity, making it more difficult to determine and interpret results. Furthermore, clinical trials of medications are needed before they can be approved for use outside of a research setting. Few clinical trials investigate medications to treat comorbid bipolar disorder and substance dependence. Thus, more clinical trials are needed to find treatment for this under-researched population.

Future studies may also benefit by examining the differences between bipolar types regarding cognitive functioning and its effect on treatment adherence and retention since bipolar disorders I and II tend to differ in cognitive dysfunction severities (Torrent et al., 2006; Colom et al., 2005). Also, since the number of lifetime mood episodes and age of first episode have been shown to affect cognitive functioning in bipolar disorder (Osuji & Cullum, 2005), it would be useful to examine these factors as potential covariates in future studies. This current study did not measure these variables, and thus could not include them as covariates in the analyses.

Finally, future studies on cognitive functioning and treatment adherence and retention in bipolar disorder and substance dependence may benefit from other methods of measuring medication adherence. Pill counts are not always the most effective, accurate way to determine whether or not individuals took their medication. Greater accuracy of pill adherence may be obtained through electronic measurements [i.e. Medication Event Marketing System (MEMS)

caps] or blood levels. The addition of an inert tracer, like riboflavin, to pills has also been used in studies to measure medication adherence (Johnson et al., 2000).

IX. Conclusion

Bipolar disorder is a severe and persistent mental illness. Nearly 60% of people with bipolar disorder have a comorbid substance use disorder. Both bipolar disorder and substance dependence are associated with cognitive impairment and treatment nonadherence. Past research has shown a link between cognitive functioning and treatment retention and adherence in other disorders. Few research studies have investigated the effect of cognitive functioning on treatment adherence and retention in participants with comorbid bipolar disorder and substance dependence. This study was a secondary analysis of the largest clinical trial ever reported of comorbid bipolar disorder and cocaine dependence. This secondary analysis examined the effect of baseline cognitive functioning, including verbal learning and memory, simple visual attention, inhibition, and cognitive flexibility, on study retention, appointment attendance, medication adherence, and adherence to treatment instructions. The results indicated that cognitive functioning had a minimal impact on treatment adherence and retention in this population. Poor simple visual attention was associated with better attendance, poor inhibition and cognitive flexibility was associated with less attendance, and average verbal learning and immediate recall was associated with returning a treatment-related item (pill bottle) to appointments. The significance of these results was limited by the large confidence intervals and small effect sizes. Future studies that include a larger sample size, a more comprehensive neuropsychological test battery, and advanced medication adherence measures are needed to assess the effect cognitive

functioning has on treatment adherence and retention in bipolar disorder and cocaine dependence.

CHAPTER VI

TABLES

Table 1

Cognitive Functioning in Bipolar Disorder by Mood State

Cognitive Domain	Euthymia	Depression	Mania
Executive Functioning			
Reasoning and Problem Solving	normal	x	x
Planning	normal	normal	x
Set Shifting	x	normal	x
Cognitive Control	x	x	x
Inhibition/Impulse Control	x	mixed	x
Memory			
Working Memory	mixed	x	x
Implicit Memory	normal	normal	normal
Short Term Memory	x	x	x
Visual Memory	mixed	x	x
Verbal Learning and Memory			
Immediate and Delayed Recall	x	x	x
Recognition	mixed	x	x
Verbal Fluency	x	x	x
Attention			
Selective Attention	x	x	x
Sustained Attention	x	x	x

Note: x = impaired; mixed = mixed results in research; normal = no impairment

Table 2

Cognitive Functioning in Bipolar Disorder, Unipolar Depression, and Substance Dependence

Cognitive Domain	Unipolar Depression	Bipolar	SUD
Executive functioning	x	x	x
Cognitive flexibility	x	x	x
Verbal fluency	normal	x	normal
Visuospatial memory	x	x	x
Working memory	x	x	x
Short term memory	x	x	x
Verbal learning	x	x	x
Attention/concentration	x	x	x

Note: x = impaired; normal = no impairment

Characteristics of the Total Sample

Table 3

Socio-demographic Characteristics of the Total Sample

Characteristic	Total Sample (N = 120)
Age, Mean (*SD*)	44.05 (8.81)
Years of Education, Mean (SD)	13.55 (2.24)
Gender, *N* (%)	
Male	73 (60.80%)
Female	47 (39.20%)
Ethnicity, *N* (%)	
African-American	74 (61.70%)
Caucasian	37 (30.80%)
Hispanic	6 (5.00%)
Other	3 (2.50%)
Annual Income, *N* (%)	
Less than $15,000	70 (58.30%)
$15, 000 - $40,000	29 (24.10%)
More than $40,000	15 (13.00%)

Table 4

Clinical Characteristics of the Total Sample at Baseline

Characteristic	Total Sample (N = 120)
Bipolar Type, *N* (%)	
I	65 (54.20%)
II	42 (35.00%)
NOS	13 (10.80%)
Mood State, *N* (%)	
Depressed	107 (89.20%)
Mixed	13 (10.80%)
Psychotropic Medications, *N* (%)	
None	87 (73.7%)
Lithium	8 (6.70%)
Anticonvulsants	0 (0.00%)
Antipsychotics	5 (4.20%)
Antidepressants	21 (17.50%)
Sedatives, Hypnotics, Anxiolytics	11 (9.10%)
Treatment Group (Lamotrigine), *N* (%)	60 (50.00)
Payment Type (Cash), N (%)	42 (35.00)
$HRSD_{17}$ Score, Mean (*SD*)	21.35 (6.23)
YMRS Score, Mean (*SD*)	15.18 (8.92)
QIDS-SR Score, Mean (*SD*)	14.46 (4.99)
ASI Employment Score, Mean (*SD*)	0.70 (0.25)

Note: $HRSD_{17}$ = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology; ASI = Addiction Severity Index

Table 5

Substance Use Characteristics of the Total Sample at Baseline

Characteristic	Total Sample (*N* = 120)
Cocaine Dependence, *N* (%)	120 (100%)
Other Substance Abuse or Dependence, *N* (%)	97 (80.90%)
Alcohol Abuse or Dependence, *N* (%)	77 (64.10%)
UDS Positive for Cocaine, *N* (%)	94 (78.30%)
Amount Spent on Cocaine in two weeks ($), Mean (*SD*)	299.75 (473.60)
Amount Cocaine Used in Grams in two weeks, Mean (*SD*)	10.47 (37.96)

Note: UDS = Urine Drug Screen

Table 6

Cognitive Functioning Characteristics of the Total Sample at Baseline

Characteristic	Total Sample (N = 120)
RAVLT	
Total Recall *T*-Score, Mean (*SD*)	41.75 (10.38)
Low Average Range or Less, *N* (%)	62 (51.70)
Average Range or Greater, *N* (%)	57 (47.50)
Delayed Recall *T*-Score, Mean (*SD*)	44.38 (8.81)
Low Average Range or Less, *N* (%)	55 (45.80)
Average Range or Greater, *N* (%)	63 (52.50)
Stroop Color and Word Test	
Word *T*-Score, Mean (*SD*)	42.43 (11.10)
Low Average Range or Less, *N* (%)	56 (46.70)
Average Range or Greater, *N* (%)	61 (50.80)
Color *T*-Score, Mean (*SD*)	41.45 (10.74)
Low Average Range or Less, *N* (%)	53 (44.20)
Average Range or Greater, *N* (%)	64 (53.30)
Color-Word *T*-Score, Mean (*SD*)	47.32 (8.69)
Low Average Range or Less, *N* (%)	34 (28.30)
Average Range or Greater, *N* (%)	83 (69.20)
Interference *T*-Score, Mean (*SD*)	49.73 (7.48)
Low Average Range or Less, *N* (%)	18 (15.00)
Average Range or Greater, *N* (%)	99 (82.00)

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 7

Treatment Retention and Adherence Characteristics of the Total Sample

Characteristic	Total Sample (N = 120)
Treatment Retention	
Last Week in Study, Mean (*SD*)	7.48 (3.39)
Completer, *N* (%)	64 (53.30)
Noncompleter, *N* (%)	56 (46.70)
Treatment Adherence	
Appointments Attended, Mean (*SD*)	6.68 (3.28)
Appointment Adherence ≥ 9, *N* (%)	48 (40.00)
Percentage of Pills Taken, Mean (*SD*)	92.64 (8.77)*
Pill Count Adherence ≥ 90%, *N* (%)	69 (57.50)*
Percentage of Pill Bottles Returned, Mean (*SD*)	86.00 (21.28)**
Pill Bottle Return Adherence ≥ 90%, *N* (%)	66 (55.00)**

**Sample size is 95 due to participant drop out after baseline and missing data.*
*** Sample size is 106 due to participant drop out after baseline and missing data.*

Characteristics of the Sample for Treatment Retention and Attendance Analyses

Table 8

Socio-demographic Characteristics of the Sample for Treatment Retention and Adherence Analyses

Characteristic	Treatment Retention and Attendance Sample (n = 106)
Age, Mean (*SD*)	43.98 (8.52)
Years of Education, Mean (*SD*)	13.51 (2.30)
Gender, *n* (%)	
Male	64 (60.40)
Female	42 (39.60)
Ethnicity, *n* (%)	
African-American	67 (63.20)
Caucasian	32 (30.20)
Hispanic	5 (4.70)
Other	2 (1.80)
Annual Income, *n* (%)	
Less than $15,000	60 (56.60)
$15, 000 - $40,000	27 (25.50)
More than $40,000	14 (13.20)

Table 9

Baseline Clinical Characteristics of the Sample for Treatment Retention and Attendance Analyses

Characteristic	Treatment Retention and Attendance Sample (n = 106)
Bipolar Type, *n* (%)	
I	58 (54.70)
II	40 (37.70)
NOS	8 (7.50)
Mood State, *n* (%)	
Depressed	95 (89.60)
Mixed	11 (10.40)
Psychotropic Medications, *n* (%)	
None	78 (73.60)
Lithium	7 (6.60)
Anticonvulsants	0 (0.00)
Antipsychotics	4 (3.80)
Antidepressants	19 (17.90)
Sedatives, Hypnotics, Anxiolytics	9 (8.40)
Treatment Group (Lamotrigine), *n* (%)	51 (48.10)
Payment Type (cash), *n* (%)	40 (37.70)
$HRSD_{17}$ Score, Mean (*SD*)	21.29 (6.39)
YMRS Score, Mean (*SD*)	14.78 (8.79)
QIDS-SR Score, Mean (*SD*)	14.14 (5.01)
ASI Employment Score, Mean (*SD*)	0.70 (0.25)

Note: $HRSD_{17}$ = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology; ASI = Addiction Severity Index

Table 10

Baseline Substance Use Characteristics of Sample for Treatment Retention and Attendance Analyses

Characteristic	Treatment Retention and Attendance Sample (*n* = 106)
Cocaine Dependence, *n* (%)	106 (100.00)
Other Substance Abuse or Dependence, *n* (%)	56 (52.83)
Alcohol Abuse or Dependence, *n* (%)	63 (59.40)
UDS Positive for Cocaine, *n* (%)	80 (75.50)
Amount Spent on Cocaine in two weeks ($), Mean (*SD*)	310.71 (500/09)
Amount Cocaine Used in Grams in two weeks, Mean (*SD*)	11.19 (40.33)

Note: UDS = Urine Drug Screen

Table 11

Baseline Cognitive Functioning Characteristics of the Sample for Treatment Retention and Attendance Analyses

Characteristic	Treatment Retention and Attendance Sample (n = 106)
RAVLT	
Total Recall *T*-Score, Mean (*SD*)	42.27 (10.22)
Low Average Range or Less, *n* (%)	53 (50.00)
Average Range or Greater, *n* (%)	53 (50.00)
Delayed Recall *T*-Score, Mean (*SD*)	44.58 (8.97)
Low Average Range or Less, *n* (%)	49 (46.20)
Average Range or Greater, *n* (%)	57 (53.80)
Stroop Color and Word Test	
Word *T*-Score, Mean (*SD*)	41.94 (11.18)
Low Average Range or Less, *n* (%)	51 (48.10)
Average Range or Greater, *n* (%)	55 (51.90)
Color *T*-Score, Mean (*SD*)	41.60 (10.65)
Low Average Range or Less, *n* (%)	46 (43.40)
Average Range or Greater, *n* (%)	60 (56.60)
Color-Word *T*-Score, Mean (*SD*)	47.39 (8.65)
Low Average Range or Less, *n* (%)	30 (28.30)
Average Range or Greater, *n* (%)	76 (71.70)
Interference *T*-Score, Mean (*SD*)	49.84 (7.32)
Low Average Range or Less, *n* (%)	16 (15.1)
Average Range or Greater, *n* (%)	90 (84.90)

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 12

Retention and Adherence Characteristics of the Sample for Treatment Retention and Attendance Analyses

Characteristic	Treatment Retention and Attendance Sample (n = 106)
Treatment Retention	
Last Week in Study, Mean (*SD*)	7.95 (3.40)
Completer, *n* (%)	56 (52.80)
Noncompleter, *n* (%)	50 (47.20)
Treatment Adherence	
Appointments Attended, Mean (*SD*)	6.94 (3.05)
Appointment Adherence ≥ 9, *n* (%)	43 (40.60)
Percentage of Pills Taken, Mean (*SD*)	92.94 (7.31)
Pill Count Adherence ≥ 90%, *n* (%)	66 (62.30)
Percentage of Pill Bottles Returned, Mean (*SD*)	72.97 (52.64)
Pill Bottle Return Adherence ≥ 90%, *n* (%)	62 (58.50)

Characteristics of the Sample for Medication Adherence Analyses

Table 13

Socio-demographic Characteristics of the Sample for Medication Adherence Analyses

Characteristic	Medication Adherence Sample (n = 91)
Age, Mean (*SD*)	43.73 (8.71)
Years of Education, Mean (*SD*)	13.63 (2.36)
Gender, *n* (%)	
Male	50 (54.90)
Female	41 (45.10)
Ethnicity, *n* (%)	
African-American	58 (63.70)
Caucasian	27 (29.70)
Hispanic	4 (4.40)
Other	2 (2.20)
Annual Income, *n* (%)	
Less than $15,000	53 (58.20)
$15, 000 - $40,000	21 (23.10)
More than $40,000	13 (14.30)

Table 14

Baseline Clinical Characteristics of the Sample for Medication Adherence Analyses

Characteristic	Medication Adherence Sample (n = 91)
Bipolar Type, n (%)	
I	49 (53.80)
II	36 (39.60)
NOS	6 (6.60)
Mood State, *n* (%)	
Depressed	82 (90.10)
Mixed	9 (9.90)
Psychotropic Medications, *n* (%)	
None	64 (70.30)
Lithium	7 (7.70)
Anticonvulsants	0 (100.00)
Antipsychotics	4 (4.40)
Antidepressants	18 (19.80)
Sedatives, Hypnotics, Anxiolytics	9 (9.90)
Treatment Group (Lamotrigine), *n* (%)	46 (50.50)
Payment Type (Cash), *n* (%)	40 (44.00)
$HRSD_{17}$ Score, Mean (*SD*)	21.12 (6.25)
YMRS Score, Mean (*SD*)	14.42 (8.86)
QIDS-SR Score, Mean (*SD*)	14.00 (5.16)
ASI Employment Score, Mean (*SD*)	0.69 (0.25)

Note: $HRSD_{17}$ = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology; ASI = Addiction Severity Index

Table 15

Baseline Substance Use Characteristics of the Sample for Medication Adherence Analyses

Characteristic	Medication Adherence Sample (n = 91)
Cocaine Dependence, *n* (%)	91 (100.00)
Other Substance Abuse or Dependence, *n* (%)	49 (53.85)
Alcohol Abuse or Dependence, *n* (%)	55 (60.40)
UDS Positive for Cocaine, *n* (%)	68 (74.70)
Amount Spent on Cocaine in two weeks ($), Mean (*SD*)	312.69 (530.62)
Amount Cocaine Used in Grams in two weeks, Mean (*SD*)	11.44 (43.09)

Note: UDS = Urine Drug Screen

Table 16

Baseline Cognitive Functioning Characteristics of the Sample for Medication Adherence Analyses

Characteristic	Medication Adherence Sample (n = 91)
RAVLT	
Total Recall *T*-Score, Mean (*SD*)	43.20 (9.88)
Low Average Range or Less, *n* (%)	43 (47.30)
Average Range or Greater, *n* (%)	48 (52.70)
Delayed Recall *T*-Score, Mean (*SD*)	44.84 (9.16)
Low Average Range or Less, *n* (%)	41 (45.10)
Average Range or Greater, *n* (%)	50 (54.90)
Stroop Color and Word Test	
Word *T*-Score, Mean (*SD*)	41.38 (11.26)
Low Average Range or Less, *n* (%)	45 (49.50)
Average Range or Greater, *n* (%)	46 (50.50)
Color *T*-Score, Mean (*SD*)	41.16 (11.32)
Low Average Range or Less, *n* (%)	43 (47.30)
Average Range or Greater, *n* (%)	48 (52.70)
Color-Word *T*-Score, Mean (*SD*)	47.48 (9.01)
Low Average Range or Less, *n* (%)	25 (27.5)
Average Range or Greater, *n* (%)	66 (72.50)
Interference *T*-Score, Mean (*SD*)	50.42 (7.50)
Low Average Range or Less, *n* (%)	13 (14.30)
Average Range or Greater, *n* (%)	78 (85.70)

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 17

Retention and Adherence Characteristics of the Sample for Medication Adherence Analyses

Characteristic	Medication Adherence Sample (n = 91)
Treatment Retention	
Last Week in Study, Mean (*SD*)	7.91 (3.20)
Completer, *n* (%)	46 (50.50)
Noncompleter, *n* (%)	45 (49.60)
Treatment Adherence	
Appointments Attended, Mean (*SD*)	6.70 (2.94)
Appointment Adherence ≥ 9, *n* (%)	37 (40.70)
Percentage of Pills Taken, Mean (*SD*)	92.94 (7.31)
Pill Count Adherence ≥ 90%, *n* (%)	66 (72.50)
Percentage of Pill Bottles Returned, Mean (*SD*)	86.01 (20.45)
Pill Bottle Return Adherence ≥ 90%, *n* (%)	55 (60.40)

Characteristics of the Sample for Pill Bottle Adherence Analyses

Table 18

Socio-demographic Characteristics of the Sample for Pill Bottle Adherence Analyses

Characteristic	Pill Bottle Adherence Sample (n = 98)
Age, Mean (*SD*)	43.92 (8.61)
Years of Education, Mean (*SD*)	13.56 (2.35)
Gender, *n* (%)	
Male	56 (57.10)
Female	42 (42.90)
Ethnicity, *n* (%)	
African-American	63 (64.30)
Caucasian	29 (29.60)
Hispanic	4 (4.10)
Other	2 (2.00)
Annual Income, *n* (%)	
Less than $15,000	55 (56.10)
$15, 000 - $40,000	24 (24.40)
More than $40,000	14 (14.30)

Table 19

Baseline Clinical Characteristics of the Sample for Pill Bottle Adherence Analyses

Characteristic	Pill Bottle Adherence Sample (n = 98)
Bipolar Type, *n* (%)	
I	52 (53.10)
II	38 (38.80)
NOS	8 (8.20)
Mood State, *n* (%)	
Depressed	89 (90.80)
Mixed	9 (.20)
Psychotropic Medications, *n* (%)	
None	71 (72.40)
Lithium	7 (7.10)
Anticonvulsants	0 (0.00)
Antipsychotics	4 (4.10)
Antidepressants	18 (18.40)
Sedatives, Hypnotics, Anxiolytics	9 (9.20)
Treatment Group (Lamotrigine), *n* (%)	47 (48.00)
Payment Type (cash), *n* (%)	40 (40.80)
$HRSD_{17}$ Score, Mean (*SD*)	21.38 (6.35)
YMRS Score, Mean (*SD*)	14.86 (8.84)
QIDS-SR Score, Mean (*SD*)	14.01 (5.08)
ASI Employment Score, Mean (*SD*)	0.70 (0.25)

Note: $HRSD_{17}$ = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology; ASI = Addiction Severity Index

Table 20

Baseline Substance Use Characteristics of the Sample for Pill Bottle Analyses

Characteristic	Pill Bottle Adherence Sample (n = 98)
Cocaine Dependence, *n* (%)	98 (100.00)
Other Substance Abuse or Dependence, *n* (%)	51 (52.04)
Alcohol Abuse or Dependence, *n* (%)	59 (60.20)
UDS Positive for Cocaine, *n* (%)	74 (75.50)
Amount Spent on Cocaine in two weeks ($), Mean (*SD*)	315.01 (515.97)
Amount Cocaine Used in Grams in two weeks, Mean (*SD*)	11.13 (41.55)

Note: UDS = Urine Drug Screen

Table 21

Baseline Cognitive Functioning Characteristics of the Sample for Pill Bottle Adherence Analyses

Characteristic	Pill Bottle Adherence Sample (n = 98)
RAVLT	
Total Recall *T*-Score, Mean (*SD*)	42.90 (10.03)
Low Average Range or Less, *n* (%)	46 (46.90)
Average Range or Greater, *n* (%)	52 (53.10)
Delayed Recall *T*-Score, Mean (*SD*)	44.79 (9.07)
Low Average Range or Less, *n* (%)	45 (45.90)
Average Range or Greater, *n* (%)	53 (54.10)
Stroop Color and Word Test	
Word *T*-Score, Mean (*SD*)	41.65 (11.15)
Low Average Range or Less, *n* (%)	47 (48.00)
Average Range or Greater, *n* (%)	51 (52.00)
Color *T*-Score, Mean (*SD*)	41.40 (11.02)
Low Average Range or Less, *n* (%)	44 (44.90)
Average Range or Greater, *n* (%)	54 (55.10)
Color-Word *T*-Score, Mean (*SD*)	47.40 (8.88)
Low Average Range or Less, *n* (%)	28 (28.60)
Average Range or Greater, *n* (%)	70 (71.40)
Interference *T*-Score, Mean (*SD*)	50.05 (7.43)
Low Average Range or Less, *n* (%)	15 (15.30)
Average Range or Greater, *n* (%)	83 (84.70)

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 22

Treatment Retention and Adherence Characteristics of the Pill Bottle Adherence Analyses Sample

Characteristic	Pill Bottle Adherence Sample (n = 98)
Treatment Retention	
Last Week in Study, Mean (*SD*)	8.13 (3.21)
Completer, *n* (%)	52 (53.10)
Noncompleter, *n* (%)	46 (46.90)
Treatment Adherence	
Appointments Attended, Mean (*SD*)	7.09 (2.88)
Appointment Adherence ≥ 9, *n* (%)	40 (40.80)
Percentage of Pills Taken, Mean (*SD*)	92.94 (7.31)
Pill Count Adherence ≥ 90%, *n* (%)	66 (67.30)
Percentage of Pill Bottles Returned, Mean (*SD*)	86.91 (19.99)
Pill Bottle Return Adherence ≥ 90%, *n* (%)	62 (63.30)

Correlation Analyses

Table 23

Pearson Correlations (r) Among Independent and Dependent Variables (N = 120)

	Stroop Color and Word Test Word	Stroop Color and Word Test Color	Stroop Color and Word Test Color-Word	Stroop Color and Word Test Interference	RAVLT Total Recall	RAVLT Delayed Recall
Completer/ Noncompleter	0.11	-0.00	0.08	0.02	0.04	-0.05
Last Week in Study	-0.07	0.00	0.00	0.04	-0.01	0.01
Number of Weeks in Study	-0.13	-0.04	0.05	0.08	-0.02	-0.04
Adherence ≥ 9 weeks	-0.18	-0.04	0.05	0.10	-0.09	-0.11
Percentage of Pills Taken	-0.10	-0.02	0.18	0.11	-0.05	-0.16
Pill Count Adherence ≥ 90%	-0.10	-0.02	0.10	0.08	-0.12	-0.13
Percentage of Pill Bottles Returned	-0.02	-0.01	-0.04	-0.06	0.23*	0.06
Pill Bottle Return Adherence ≥ 90%	-0.05	0.06	-0.04	-0.03	0.01	0.08

*Note: *p = .01; **p = .05; RAVLT = Rey Auditory Verbal Learning Test*

Table 24

Pearson Correlations (r) Among Independent Variables Classified by T-Score Category (N = 120)

	Stroop Color and Word Test Word	Stroop Color and Word Test Color	Stroop Color and Word Test Color-Word	Stroop Color and Word Test Interference	RAVLT Total Recall	RAVLT Delayed Recall
Stroop Color and Word Test Word	1	0.40**	0.29**	-0.07	0.07	0.06
Stroop Color and Word Test Color	0.40**	1	0.21*	-0.25**	-0.01	0.04
Stroop Color and Word Test Color-Word	0.29**	0.21*	1	0.41**	0.05	0.07
Stroop Color and Word Test Interference	-0.08	-0.25**	0.41**	1	0.11	0.06
RAVLT Total Recall	0.07	-0.01	0.06	0.11	1	0.53**
RAVLT Delayed Recall	0.06	0.04	0.07	0.06	0.53**	1

*Note: *p = .01; ** p = .05; RAVLT = Rey Auditory Verbal Learning Test*

Table 25

Pearson Correlations (r) Among Dependent Variables and Potential Covariates (N = 120)

	Gender	Age	Education	Income	YMRS Score	$HRSD_{17}$ Score
Completer/ Noncompleter	-0.03	-0.10	0.10	-0.03	0.02	-0.02
Last Week in Study	-0.05	0.11	-0.04	0.03	0.03	0.02
Number of Weeks in Study	-0.06	0.15	-0.03	0.10	-0.03	-0.04
Adherence ≥ 9 weeks	-0.10	0.11	-0.05	0.15	-0.03	-0.08
Percentage of Pills Taken	-0.06	0.00	-0.12	-0.06	-0.08	-0.07
Pill Count Adherence ≥ 90%	-0.11	-0.08	-0.12	-0.14	-0.02	-0.04
Percentage of Pill Bottles Returned	0.18	0.05	0.00	-0.03	0.07	0.08
Pill Bottle Return Adherence ≥ 90%	0.13	0.07	-0.04	0.11	-0.11	-0.11

*Note: *p = .01; **p = .05; YMRS = Young Mania Rating Scale; $HRSD_{17}$ = Hamilton Rating Scale for Depression*

Table 26

Pearson Correlations (r) Among Dependent Variables and Covariates (N = 120)

	Treatment Group	Payment Method	Bipolar Type	BL ASI Employment	BL Amount Spent on Cocaine
Completer/ Noncompleter	0.07	-0.13	-0.16	-0.23*	0.19*
Last Week in Study	-0.07	0.16	0.22*	0.23*	-0.17
Number of Weeks in Study	-0.03	0.29**	0.19*	0.19	-0.14
Adherence ≥ 9 weeks	0.00	0.33**	0.10	0.17	-0.17
Percentage of Pills Taken	-0.01	0.18	-0.02	-0.13	0.00
Pill Count Adherence ≥ 90%	0.02	0.19	0.02	-0.04	-0.08
Percentage of Pill Bottles Returned	-0.11	0.13	0.06	0.03	-0.05
Pill Bottle Return Adherence ≥ 90%	-0.12	-0.11	-0.06	0.03	-0.10

Note: p = .01; **p = .05; BL = Baseline; ASI = Addiction Severity Index*

Table 27

Survival Analysis of Effect of Cognitive Functioning on Last Week in Study

Cognitive Measure	All Participants OR (95% CI)	*p* value
Stroop Word *T*-Score Category	0.87 (0.56-1.34)	0.53
Stroop Color *T*-Score Category	1.32 (0.82-2.11)	0.25
Stroop Color-Word *T*-Score Category	0.93 (0.56-1.56)	0.78
Stroop Interference *T*-Score Category	1.30 (0.67-2.54)	0.44
RAVLT Total Recall *T*-Score Category	0.82 (0.52-1.30)	0.40
RAVLT Delayed Recall *T*-Score Category	1.11 (0.71-1.73)	0.65

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 28

Binary Logistic Regression Model of Effect of Cognitive Functioning on Study Completion

Cognitive Measure	All Participants OR (95% CI)	*p* value
Stroop Word *T*-Score Category	0.54 (0.21-1.42)	0.21
Stroop Color *T*-Score Category	2.24 (0.81-6.21)	0.12
Stroop Color-Word *T*-Score Category	0.78 (0.25-2.42)	0.67
Stroop Interference *T*-Score Category	1.78 (0.45-7.00)	0.41
RAVLT Total Recall *T*-Score Category	0.73 (0.26-2.00)	0.54
RAVLT Delayed Recall *T*-Score Category	1.34 (0.48-3.71)	0.58

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 29

Analysis of Covariance for the Effect of Cognitive Functioning on Total Weeks Attended After Baseline

Cognitive Measure	*df*	*F*	η	*p*
Stroop Word *T*-Score Category	1	1.52	0.02	0.22
Stroop Color *T*-Score Category	1	0.91	0.01	0.34
Stroop Color-Word *T*-Score Category	1	0.01	0.00	0.90
Stroop Interference *T*-Score Category	1	2.80	0.03	0.10
RAVLT Total Recall *T*-Score Category	1	0.45	0.01	0.50
RAVLT Delayed Recall *T*-Score Category	1	0.05	0.00	0.83

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 30

Binary Logistic Regression Model of Effect of Cognitive Functioning on Post-Baseline Attendance Adherence

Cognitive Measure	All Participants OR (95% CI)	*p* value
Stroop Word *T*-Score Category	3.19 (1.09-9.28)*	0.03
Stroop Color *T*-Score Category	0.43 (0.14-1.30)	0.14
Stroop Color-Word *T*-Score Category	1.15 (0.33-3.93)	0.83
Stroop Interference *T*-Score Category	0.19 (0.04-0.96)*	0.04
RAVLT Total Recall *T*-Score Category	1.14 (0.38-3.39)	0.82
RAVLT Delayed Recall *T*-Score Category	1.49 (0.49-4.53)	0.48

*Note: *p* < .05; c*ovariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test*

Table 31

Pearson Correlations Between Stroop Word T-Score, Appointment Attendance, and Their Associated Factors

	BL Stroop Word *T*-score	BL Stroop Word *T*-score Category	# of Attended Appointments	Appointment Adherence
Age	-0.24***	-0.27***	0.15*	0.11
BL ASI Employment Score	-0.20**	-0.14	0.19**	0.17*
BL # of Antidepressants	-0.20**	-0.11	0.18**	0.16*

*Note: ***p < 0.01; **p <0.05; *p < 0.10; BL = Baseline; ASI = Addiction Severity Index*

Table 32

Analysis of Covariance for the Effect of Cognitive Functioning on Pill Count

Cognitive Measure	*df*	*F*	η	*p*
Stroop Word *T*-Score Category	1	1.40	0.02	0.24
Stroop Color *T*-Score Category	1	0.13	0.00	0.72
Stroop Color-Word *T*-Score Category	1	1.47	0.02	0.23
Stroop Interference *T*-Score Category	1	0.08	0.00	0.78
RAVLT Total Recall *T*-Score Category	1	0.25	0.00	0.62
RAVLT Delayed Recall *T*-Score Category	1	0.03	0.00	0.86

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 33

Binary Logistic Regression Model of the Effect of Cognitive Functioning on Medication Adherence

Cognitive Measure	All Participants OR (95% CI)	*p* value
Stroop Word *T*-Score Category	2.26 (0.70-7.37)	0.17
Stroop Color *T*-Score Category	0.81 (0.25-2.64)	0.73
Stroop Color-Word *T*-Score Category	0.55 (0.14-2.16)	0.39
Stroop Interference *T*-Score Category	0.65 (0.13-3.30)	0.60
RAVLT Total Recall *T*-Score Category	1.76 (0.52-5.97)	0.36
RAVLT Delayed Recall *T*-Score Category	1.05 (0.30-3.72)	0.94

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 34

Analysis of Covariance for the Effect of Cognitive Functioning on Pill Bottle Return Rate

Cognitive Measure	*df*	*F*	η	*p*
Stroop Word *T*-Score Category	1	0.00	0.00	0.97
Stroop Color *T*-Score Category	1	0.23	0.00	0.64
Stroop Color-Word *T*-Score Category	1	0.17	0.00	0.68
Stroop Interference *T*-Score Category	1	0.04	0.00	0.84
RAVLT Total Recall *T*-Score Category	1	4.86*	0.05	0.03
RAVLT Delayed Recall *T*-Score Category	1	0.16	0.00	0.69

*Note: *p* < .05; *covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test*

Table 35

Binary Logistic Regression Model of the Effect of Cognitive Functioning on Pill Bottle Return Adherence

Cognitive Measure	All Participants OR (95% CI)	*p* value
Stroop Word *T*-Score Category	1.30 (0.47-3.55)	0.61
Stroop Color *T*-Score Category	0.71 (0.25-2.00)	0.51
Stroop Color-Word *T*-Score Category	1.86 (0.54-6.35)	0.32
Stroop Interference *T*-Score Category	0.81 (0.19-3.44)	0.77
RAVLT Total Recall *T*-Score Category	1.06 (0.37-3.06)	0.91
RAVLT Delayed Recall *T*-Score Category	0.62 (0.21-1.80)	0.38

Note: covariates: bipolar type, baseline ASI Employment index score, payment type, amount spent on cocaine at baseline, and treatment group; RAVLT = Rey Auditory Verbal Learning Test

Table 36

Comparison of Baseline RAVLT Total Recall T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	40.73	1.68		
Noncompleter (N)	46.43	2.21	-5.70**	0.06
Number of Wks Attended				
Adherent ≥9 wks (A)	45.08	2.42		
Nonadherent <9wks (N)	42.08	1.61	3.00	0.36
Percentage of Pills Taken				
Adherent ≥90% (A)	42.72	1.23		
Nonadherent <90% (N)	44.44	2.21	-1.72	0.49
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	43.98	1.53		
Nonadherent <90% (N)	43.18	1.75	0.80	0.70

*Note: **p = <0.10; RAVLT = Rey Auditory Verbal Learning Test*

Table 37

Comparison of Baseline RAVLT Delayed Recall T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	44.60	1.54		
Noncompleter (N)	45.10	2.02	-0.50	0.86
Number of Wks Attended				
Adherent ≥9 wks (A)	43.63	2.21		
Nonadherent <9wks (N)	46.07	1.47	-2.44	0.41
Percentage of Pills Taken				
Adherent ≥90% (A)	43.79	1.12		
Nonadherent <90% (N)	45.90	2.01	-2.11	0.36
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	45.29	1.40		
Nonadherent <90% (N)	44.41	1.60	0.88	0.65

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 38

Comparison of Baseline Stroop Word T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	39.91	1.89		
Noncompleter (N)	43.70	2.49	3.37	0.26
Number of Wks Attended				
Adherent ≥9 wks (A)	41.77	2.74		
Nonadherent <9wks (N)	41.84	1.81	-0.07	0.98
Percentage of Pills Taken				
Adherent ≥90% (A)	41.69	1.38		
Nonadherent <90% (N)	41.93	2.48	-0.24	0.93
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	40.94	1.73		
Nonadherent <90% (N)	42.68	1.97	-1.74	0.46

Table 39

Comparison of Baseline Stroop Color T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	42.14	1.95		
Noncompleter (N)	38.93	2.56	3.21	0.36
Number of Wks Attended				
Adherent ≥9 wks (A)	38.75	2.81		
Nonadherent <9wks (N)	42.33	1.86	-3.58	0.34
Percentage of Pills Taken				
Adherent ≥90% (A)	41.05	1.42		
Nonadherent <90% (N)	40.02	2.55	1.03	0.72
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	40.08	1.78		
Nonadherent <90% (N)	40.99	2.03	-0.91	0.71

Table 40

Comparison of Baseline Stroop Color-Word T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	45.99	1.52		
Noncompleter (N)	49.84	2.00	-3.85	0.16
Number of Wks Attended				
Adherent ≥9 wks (A)	50.12	2.20		
Nonadherent <9wks (N)	45.70	1.45	4.42	0.14
Percentage of Pills Taken				
Adherent ≥90% (A)	47.70	1.11		
Nonadherent <90% (N)	48.12	1.99	-0.42	0.85
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	48.14	1.39		
Nonadherent <90% (N)	47.68	1.58	0.46	0.81

Table 41

Comparison of Baseline Stroop Interference T-Scores for Each Dependent Variable

	Mean	Std Error	Mean Difference (A - N)	Significance
Study Completion				
Completer (A)	48.87	1.26		
Noncompleter (N)	53.33	1.66	-4.46	0.05
Number of Wks Attended				
Adherent ≥9 wks (A)	48.26	1.21		
Nonadherent <9wks (N)	53.94	1.82	5.67*	0.02
Percentage of Pills Taken				
Adherent ≥90% (A)	50.51	0.92		
Nonadherent <90% (N)	51.69	1.65	-1.19	0.53
Percentage of Pill Bottles Returned				
Adherent ≥90% (A)	51.48	1.16		
Nonadherent <90% (N)	50.72	1.31	0.76	0.63

**p = <0.05*

Table 42

Comparison of Last Week in Study for Each Cognitive Measure

	Mean	Std Error	Mean Difference (L - A)	Significance
RAVLT Total Recall *T*-Score				
Low Average and below (L)	7.45	0.57		
Average and above (A)	7.29	0.64	0.16	0.83
RAVLT Delayed Recall *T*-Score				
Low Average and below (L)	7.30	0.62		
Average and above (A)	7.44	0.58	-0.14	0.77
Stroop Word *T*-Score				
Low Average and below (L)	7.60	0.59		
Average and above (A)	7.15	0.59	0.44	0.71
Stroop Color *T*-Score				
Low Average and below (L)	7.29	0.65		
Average and above (A)	7.45	0.52	-0.17	0.82
Stroop Color-Word *T*-Score				
Low Average and below (L)	7.70	0.61		
Average and above (A)	7.05	0.65	0.64	0.46
Stroop Interference *T*-Score				
Low Average and below (L)	6.97	0.91		
Average and above (A)	7.77	0.43	-0.80	0.46

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 43

Comparison of Post-Baseline Appointments Attended for Each Cognitive Measure

	Mean	Std Error	Mean Difference (L - A)	Significance
RAVLT Total Recall *T*-Score				
Low Average and below (L)	6.92	0.50		
Average and above (A)	6.47	0.54	0.45	0.50
RAVLT Delayed Recall *T*-Score				
Low Average and below (L)	6.77	0.53		
Average and above (A)	6.62	0.51	0.15	0.67
Stroop Word *T*-Score				
Low Average and below (L)	7.08	0.50		
Average and above (A)	6.31	0.51	0.77	0.22
Stroop Color *T*-Score				
Low Average and below (L)	6.40	0.56		
Average and above (A)	7.01	0.46	-0.62	0.34
Stroop Color-Word *T*-Score				
Low Average and below (L)	6.65	0.54		
Average and above (A)	6.74	0.55	-0.09	0.90
Stroop Interference *T*-Score				
Low Average and below (L)	5.92	0.77		
Average and above (A)	7.47	0.38	-1.55	0.10

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 44

Comparison of Percentage of Pills Taken for Each Cognitive Measure

	Mean	Std Error	Mean Difference (L - A)	Significance
RAVLT Total Recall *T*-Score				
Low Average and below (L)	93.38	1.40		
Average and above (A)	92.44	1.53	0.94	0.62
RAVLT Delayed Recall *T*-Score				
Low Average and below (L)	93.08	1.55		
Average and above (A)	92.74	1.42	0.34	0.86
Stroop Word *T*-Score				
Low Average and below (L)	93.97	1.39		
Average and above (A)	91.86	1.48	2.11	0.24
Stroop Color *T*-Score				
Low Average and below (L)	92.58	1.55		
Average and above (A)	93.25	1.35	-0.66	0.72
Stroop Color-Word *T*-Score				
Low Average and below (L)	91.64	1.57		
Average and above (A)	94.19	1.51	-2.55	0.23
Stroop Interference *T*-Score				
Low Average and below (L)	93.27	2.18		
Average and above (A)	92.56	1.05	0.71	0.78

Note: RAVLT = Rey Auditory Verbal Learning Test

Table 45

Comparison of Percentage of Pill Bottles Returned for Each Cognitive Measure

	Mean	Std Error	Mean Difference (L - A)	Significance
RAVLT Total Recall *T*-Scores				
Low Average and below (L)	62.90	9.25		
Average and above (A)	90.06	10.00	-27.15	0.03
RAVLT Delayed Recall *T*-Scores				
Low Average and below (L)	78.98	9.84		
Average and above (A)	73.98	9.55	5.01	0.69
Stroop Word *T*-Scores				
Low Average and below (L)	76.71	9.34		
Average and above (A)	76.26	9.52	0.45	0.97
Stroop Color *T*-Scores				
Low Average and below (L)	79.34	10.45		
Average and above (A)	73.62	8.53	5.71	0.64
Stroop Color-Word *T*-Scores				
Low Average and below (L)	79.36	10.10		
Average and above (A)	73.60	10.33	5.77	0.68
Stroop Interference *T*-Scores				
Low Average and below (L)	74.71	14.39		
Average and above (A)	78.25	7.14	-3.55	0.84

*Note: RAVLT = Rey Auditory Verbal Learning Test *p = <0.05*

CHAPTER VII

FIGURES

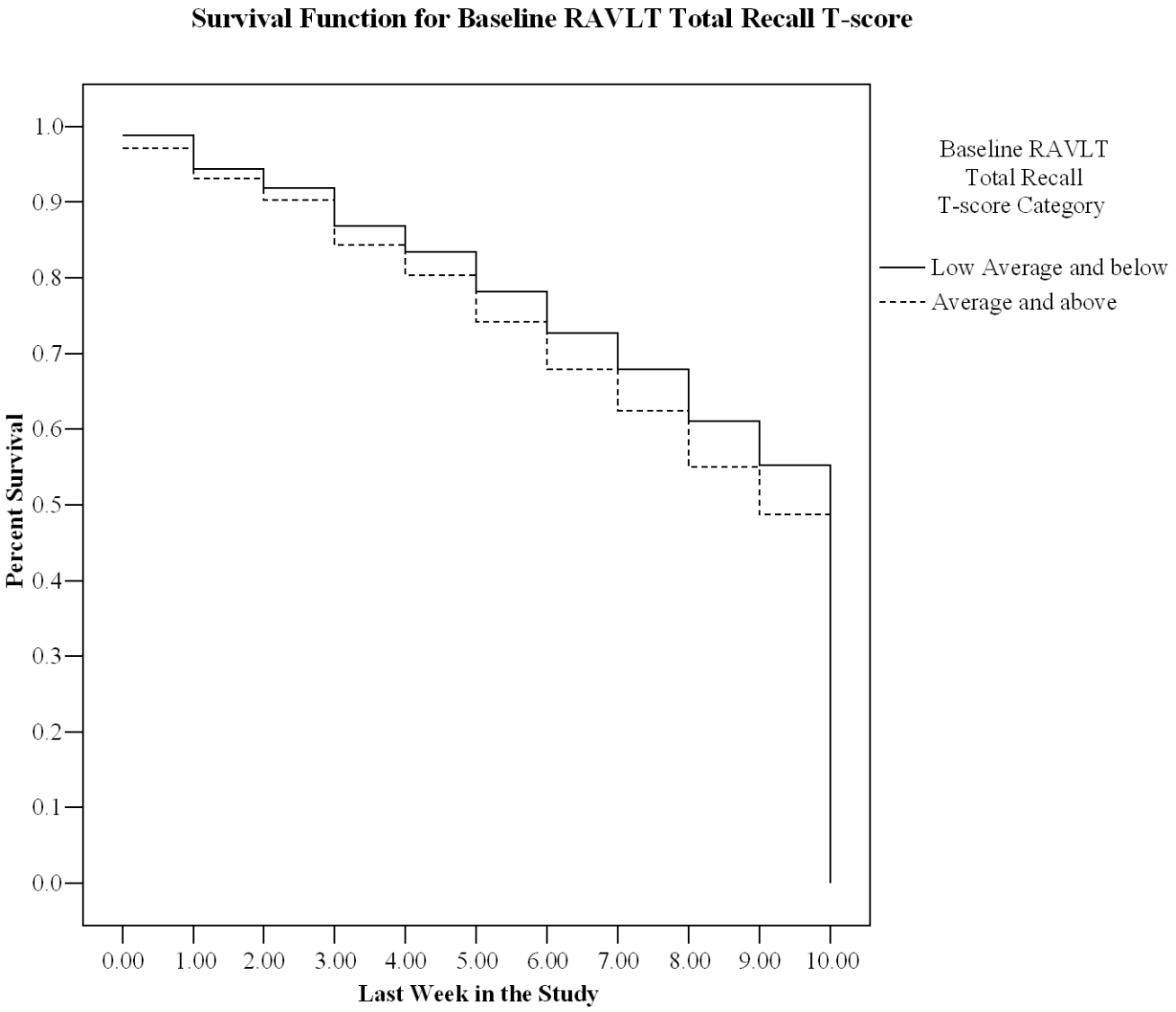

Figure 1. Survival Curve for Last Week in Study, Specified for RAVLT Total Recall T-Score

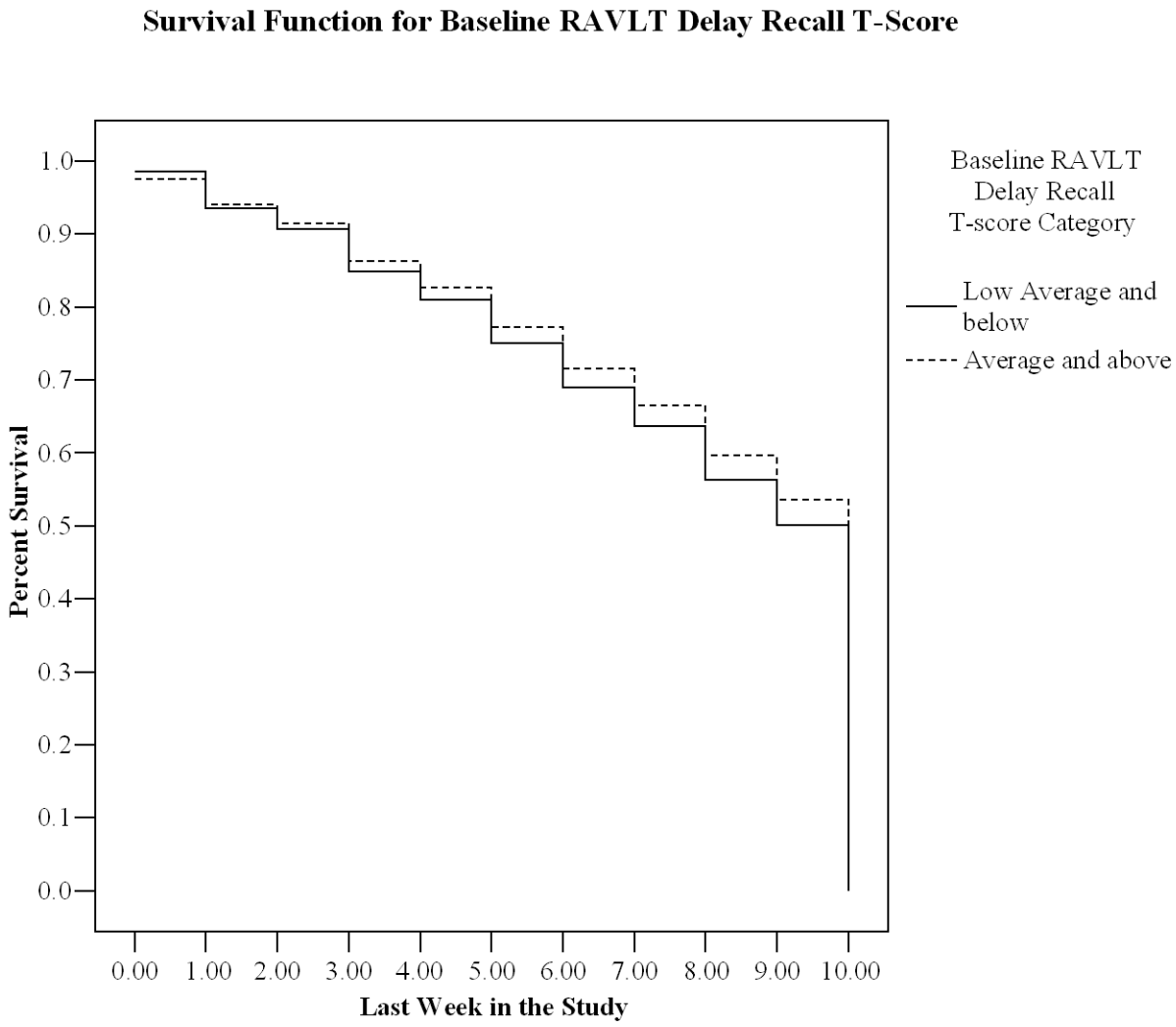

Figure 2. Survival Curve for Last Week in Study, Specified for RAVLT Delayed Recall T-Score

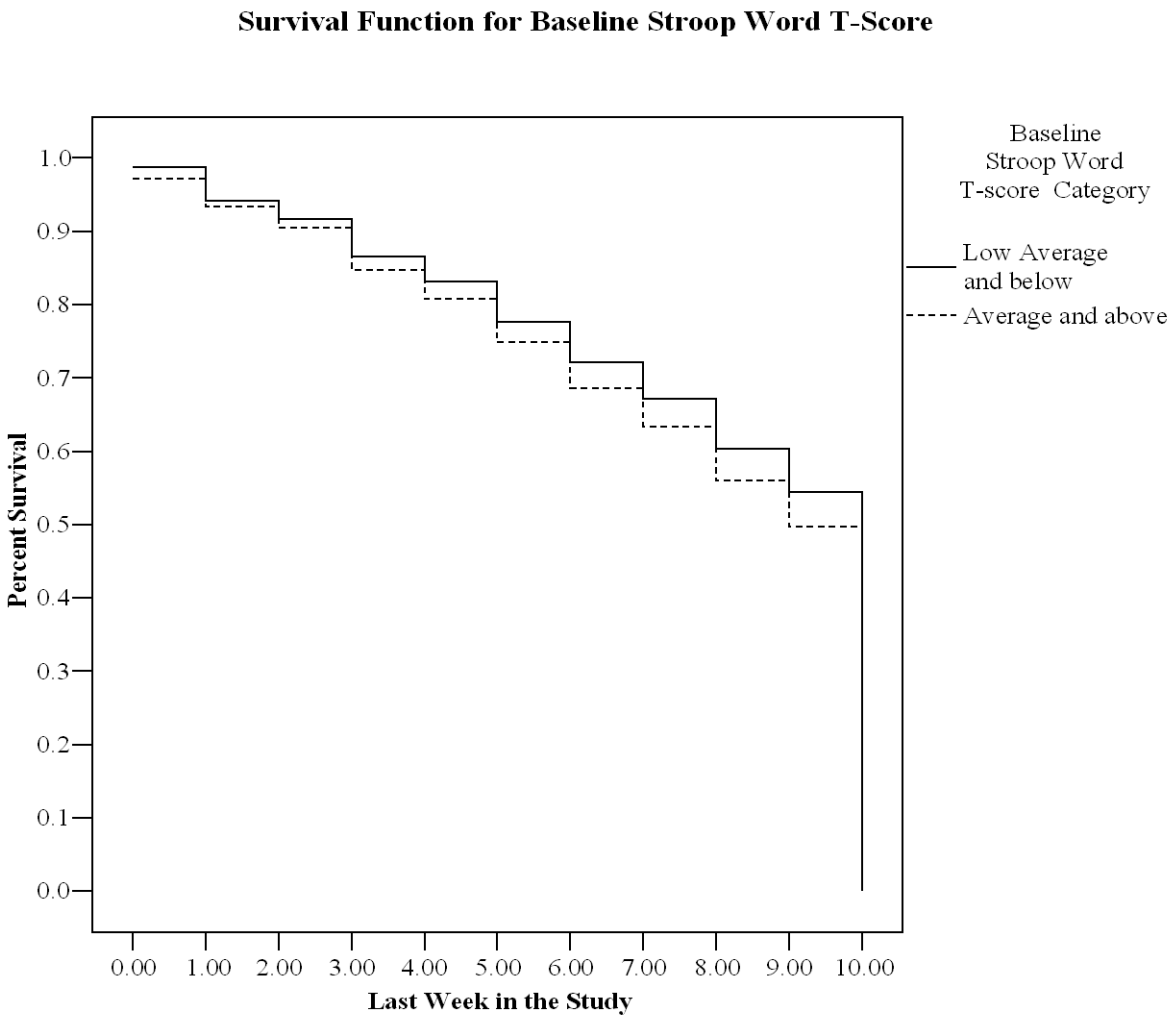

Figure 3. Survival Curve for Last Week in Study, Specified for Stroop Word T-Score

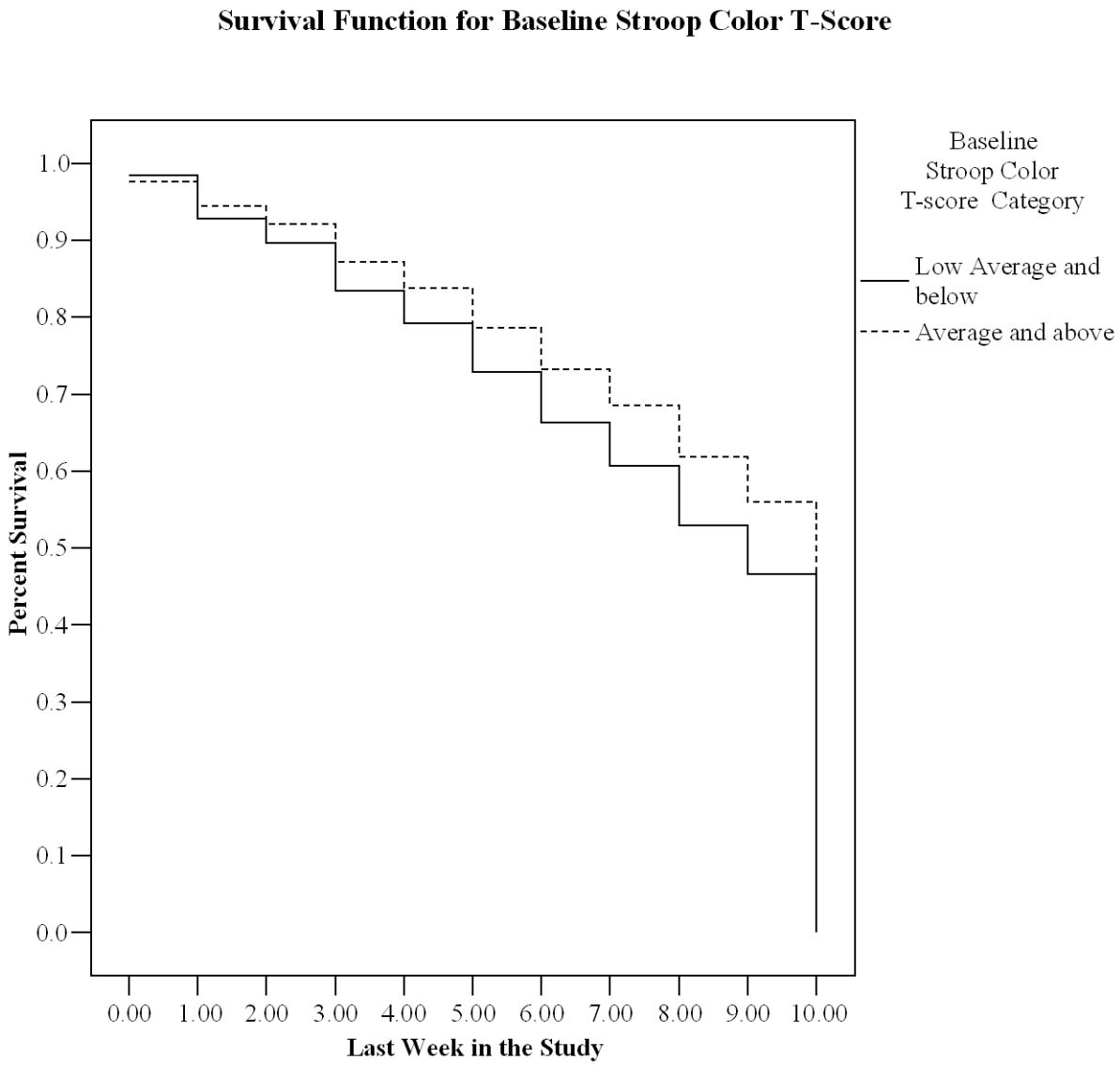

Figure 4. Survival Curve for Last Week in Study, Specified for Stroop Color T-Score

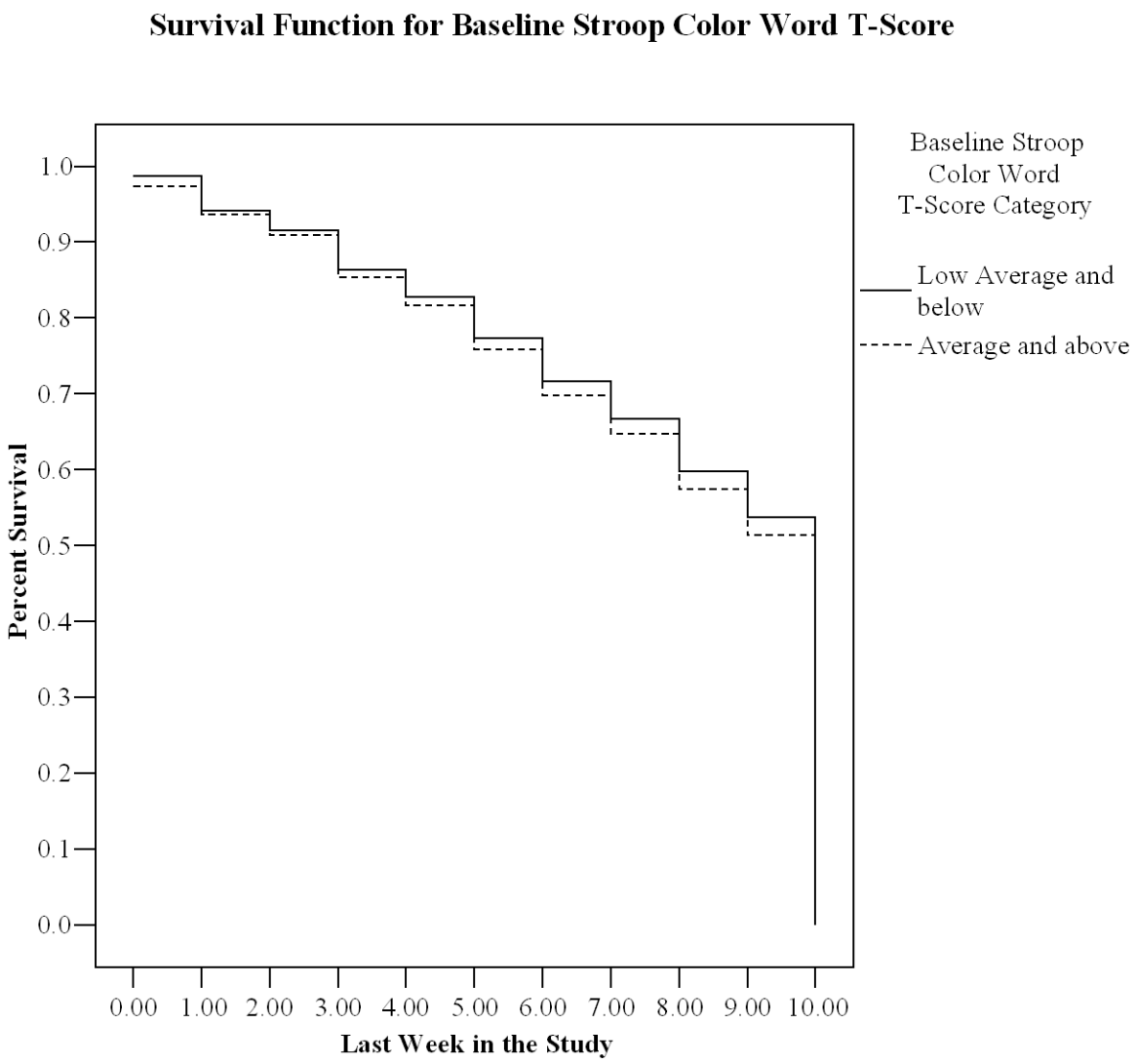

Figure 5. Survival Curve for Last Week in Study, Specified for Stroop Color Word T-Score

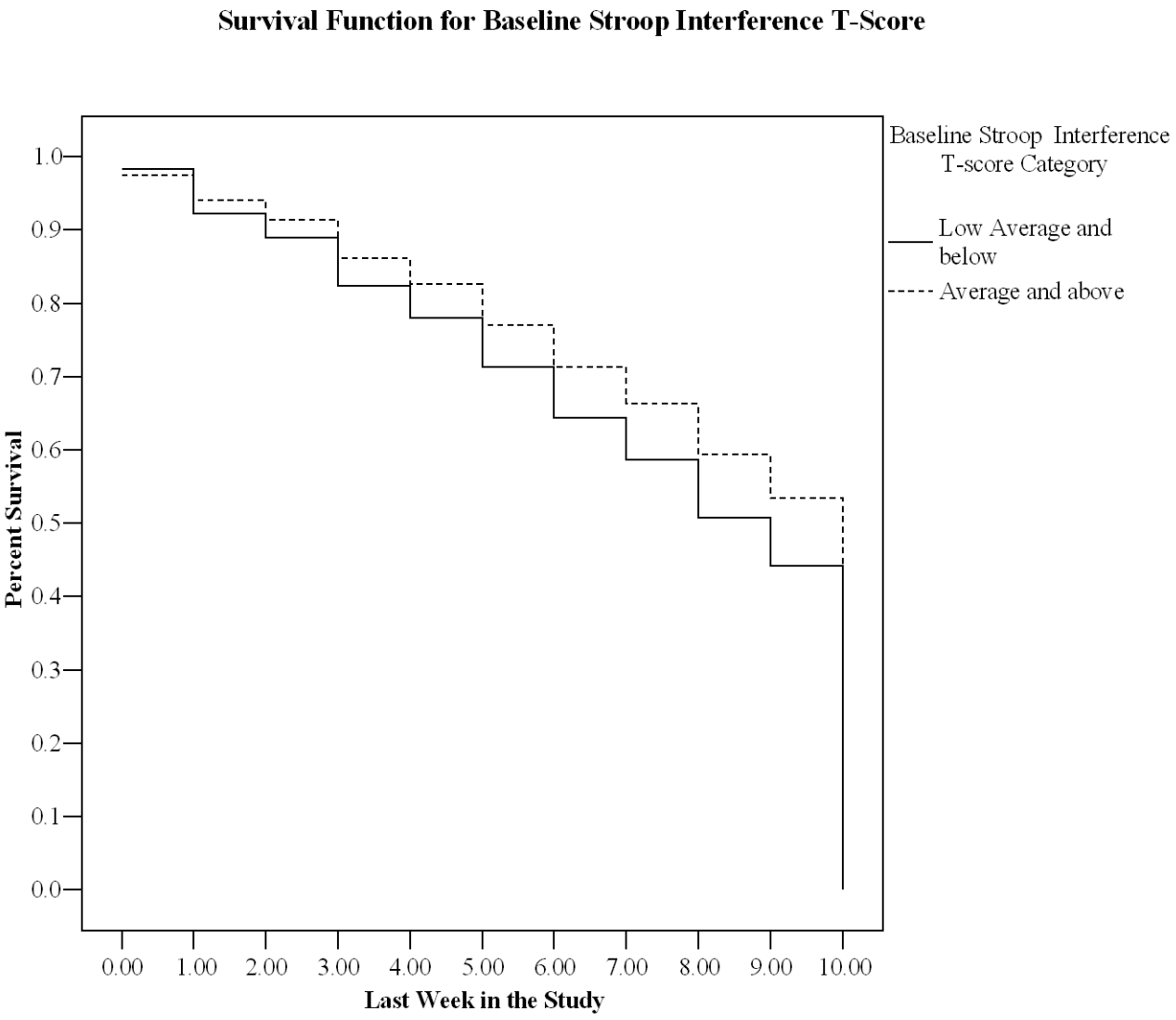

Figure 6. Survival Curve for Last Week in Study, Specified for Stroop Interference T-Score

CHAPTER VIII

REFERENCES

Akincigil, A., Bowles, J. R., Levin, C., Walkup, J. T., Jan, S., & Crystal, S. (2007). Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Medical Care, 45*(4), 363-369.

Akingbala, F., Dhanani, N., & Brown, E. S. (2006). Impulsivity in patients with BPD and cocaine or amphetamine dependence given lamotrigine. *Journal of Dual Diagnosis, 2*, 73–83.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th edition). Washington, DC: Author.

Aharonovich, E., Nunes, E., & Hasin, D. (2003). Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug and Alcohol Dependence, 71*, 207-211.

Baldessarini, R. J. (1994). Enhancing treatment with psychotropic medicines. *Bulletin of the Menninger Clinic, 54*(2), 224-242.

Baldessarini, R. J., Perry, R., & Pike, J. (2008). Factors associated with treatment nonadherence among U.S. bipolar disorder patients. *Human Psychopharmacology: Clinical and Experimental, 23*, 95-105.

Barry, D., & Petry, N. M. (2008). Predictors of decision-making on the Iowa gambling task: Independent effects of lifetime history of substance use disorders and performance on the trail making test. *Brain Cognition, 66*(3), 243-252.

Bearden, C. E., Hoffman, K. M., & Cannon, T. D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: A critical review. *Bipolar Disorder, 3*(3), 106-150.

Bechi, M., Papini, B., Cocchi, F., Anselmetti, S., Ermoli, E., Smeraldi, E., & Cavallaro, R. (2005). Attitude toward treatment in schizophrenia: Influences of cognitive dimensions. *Clinical Neuropsychiatry*, *2*(4), 237-242.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience, 8*(11), 1458-1463.

Benton, A.L., & Hamsher, K. (1976). *Multilingual aphasia examination manual*. Iowa City: University of Iowa.

Berry, J., van Gorp, W. G., Herzberg, D. S., Hinkin, C., Boone, K., Steinman, L., & Wilkins, J. N. (1993). Neuropsychological deficits in abstinent cocaine abusers: Preliminary findings after two weeks of abstinence. *Drug and Alcohol Dependence, 32*(3), 231-237.

Bock, N. N., Sales, R. M., Rogers, T., & DeVoe, B. (2001). A spoonful of sugar…: Improving adherence to tuberculosis treatment using financial incentives. *International Journal of Tuberculosis and Lung Diseases, 5*(1), 96-98.

Bolla, K. I., Eldreth, D. A., London, E. D., Kiehl, K. A., Mouratidis, M., Contoreggi, C., . . . Kimes, F. R. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *NeuroImage, 19*(3), 1085-1094.

Borkowska, A. & Rybakowski, J. K. (2001). Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. *Bipolar Disorders, 3*(2), 88-94.

Brown, E. S. (2005). Bipolar disorder and substance abuse. *Psychiatric Clinics of North America, 28,* 415-425.

Brown, E. S., Sunderajan, P., Hu, L. T., Sowell, S. M., & Carmody, T.J. (in press). A randomized, double-blind, placebo-controlled, trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. *Neuropsychopharmacology.*

Brown, E. S., Suppes, T., Adinoff, B., & Thomas, N. R. (2001). Drug abuse and bipolar disorder: Comorbidity or misdiagnosis? *Journal of Affective Disorders, 65,* 105-115.

Carey, K. B., & Carey, M. P. (1990). Enhancing the treatment attendance of mentally ill chemical abusers. *Journal of Behavior Therapy and Experimental Psychiatry, 21*(3), 205-209.

Carpenter, K. M., Schreiber, E., Church, S., & McDowell, D. (2006). Drug Stroop performance: Relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addictive Behaviors, 31,* 174-181.

Carroll, K. M., Rounsaville, B. J., Gordon, L.T., Nich, C., Jatlow, P., Bisighini, R. M., & Gawin, F. H. (1994). Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Archives of General Psychiatry, 53,*177-187.

Claasen, D., Fakhoury, W. K., Ford, R., & Priebe, S. (2007). Money for medication: Financial incentives to improve medication adherence in assertive outreach. *Psychiatric Bulletin, 31,* 4-7.

Clark, L., & Goodwin, G. (2008). Attentional and executive functioning in bipolar disorder. In J. F. Goldberg and K. E. Burdick. (Eds.), *Cognitive dysfunction in bipolar disorder: A guide for clinicians* (pp. 23-47). Washington, DC: American Psychiatric Publishing.

Clark, L., Iverson, S. D., & Goodwin, G. M. (2002). Sustained attention deficit in bipolar disorder. *The British Journal of Psychiatry, 180,* 313-319.

Colom, F., Vieta, E., Martínez-Arán, A., Reinares, M., Benabarre, A., & Gastó, C. (2000). Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *Journal of Clinical Psychiatry, 61*, 549-555.

Colom, F., Vieta, E., Martínez-Arán, A., Reinares, M., Goikolea, J. M., Benabarre, A., . . . Corominas, J. (2003). A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of General Psychiatry, 60*, 402-407.

Colom, F., Vieta, E., Tacchi, M. J., Sánchez-Moreno, J., & Scott, J. (2005). Identifying and improving non-adherence in bipolar disorders. *Bipolar Disorder, 7*(5), 24-31.

Deckersbach, T., Nierenberg, A. A., Kessler, R., Lund, H. G., Ametrano, R. M., Sachs, G., . . . Dougherty, D. (2010). Cognitive rehabilitation for bipolar disorder: An open trial for employed patients with residual depressive symptoms. *CNS Neuroscience & Therapeutics, 16*, 298-307.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation.

Dell'Osso, L., Pini, S., Cassano, G. B., Mastrocinque, C., Seckinger, R. A., Saettoni, M., . . . Amador, X. F. (2002). Insight into illness in patients with mania, mixed mania, bipolar depression and major depression with psychotic features. *Bipolar Disorders, 4*(5), 315-22.

DiMatteo, M. R. (2004). Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Medical Care, 42*, 200-209.

Di Sclafani, V., Tolou-Shams, M., Price, L. J., & Fein, G. (2002). Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug and Alcohol Dependence*, *66*, 161-171.

Donohoe, G., Owens, N., O'Donnell, C., Burke, T., Moore, L., Tobin, A., & O'Callagan, E. (2001). Predictors of compliance with neuroleptic medication among inpatients with schizophrenia: A discriminate function analysis. *European Psychiatry,16*(5), 293-298.

Elgamal, S., Sokolowska, M., & MacQueen, G. (2008). Memory deficits associated with bipolar disorder. In J. F. Goldberg and K. E. Burdick. (Eds.), *Cognitive dysfunction in bipolar disorder: A guide for clinicians* (pp. 49-67). Washington, DC: American Psychiatric Publishing.

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The Timeline followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. *Journal of Consulting and Clinical Psychology, 68*(1), 134-144.

Fals-Stewart, W., Shanahan, T., & Brown, L. (1995). Treating alcoholism and substance abuse: A neuropsychiatric perspective. *Psychotherapy in Private Practice, 14*, 1-21.

Fein, G., Klein, L., & Finn, P. (2004). Impairment on a simulated gambling task in long-term alcoholics. *Alcohol Clinical and Experimental Research*, *24*, 1487–1491.

Feinman, J A., & Dunner, D. L. (1996).The effect of alcohol and substance abuse on the course of bipolar affective disorder. *Journal of Affective Disorders, 37*, 43-49.

Fenton, W. S., Blyler, C. R., & Heinssen, R. K. (1997). Determinants of medication compliance in schizophrenia: Empirical and clinical findings. *Schizophrenia Bulletin, 23*(4), 637-651.

Ferrier, I. N., Stanton, B. R., Kelly, T. P., & Scott, J. (1999). Neuropsychological function in euthymic patients with bipolar disorder. *The British Journal of Psychiatry, 175*, 246-251.

Fillmore, M. T., & Rush, C. R. (2002). Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence, 66*, 265-273.

First, M. The official website for the Structured Clinical Interview for DSM Disorders (SCID). Retrieved from http://www.scid4.org

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (User's Guide and Interview) Clinician Version. New York, Biometrics Research Department, New York Psychiatric Institute.

Forester, B. P., Streeter, C. C., Berlow, Y. A., Tian, H., Wardrop, M., Finn, C. T., . . . Moore, C. M. (2009). Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: A lithium-7 magnetic resonance spectroscopy study. *American Journal of Geriatric Psychiatry, 17*(1), 13-23.

Gaudiano, B. A., Weinstock, L. M., & Miller, I. W. (2008). Improving treatment adherence in bipolar disorder: A review of current psychosocial treatment efficacy and recommendations for future treatment development. *Behavior Modification, 32*(3), 267-301.

Goldberg, J. F. & Burdick, K. E. (Eds.). (2008). *Cognitive dysfunction in bipolar disorder: A guide for clinicians*. Washington, DC: American Psychiatric Publishing.

Goldberg, J. F., Garno, J. L., Leon, A. C., Kocsis, J. H., & Portera, L. (1999). A history of substance abuse complicates remission from acute mania in bipolar disorder. *Journal of Clinical Psychiatry, 60*, 733-740.

Golden, C. J. (1975b). The measurement of creativity by the Stroop color and word test. *Journal of Personality Assessment, 39*, 502-506.

Golden, C. J., & Freshwater, S. M. (2002). *The Stroop color and word test: A manual for clinical and experimental uses*. Wood Dale, IL: Stoelting Co.

Goldman, M. (1995). Recovery of cognitive function in alcoholics: The relationship to treatment. *Alcohol Health and Research World, 19,* 148-154.

Gonzalez-Pinto, A., Mosquera, F., Alonso, M., Lopez, P., Ramirez, F., Vieta, E., & Baldessarini, R. J. (2006). Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disorders, 8*(5), 618-624.

Grace, J., & Malloy, P.F. (2001). *Frontal Systems Behavioral Scale (FrSBe): Professional manual*. Lutz, FL: Psychological Assessment Resources.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., . . . Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 61,* 807-816.

Green, M. F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*(9), 3-8.

Giuffrida, A. & Torgerson, D. J. (1997). Should we pay the patient? Review of financial incentives to enhance patient compliance. *BMJ, 315*(7110), 703-707.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56-62.

Herbeck, D. M., Fitek, D. J., Svitikis, D. S., Montoya, I. D., Marcus, S. C., & West, J. C. (2005). Treatment compliance in patients with comorbid psychiatric and substance use disorders. *American Journal on Addictions, 14*(3), 195-207.

Hinkin, C. H., Castello, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., . . . & Stefaniak, M. (2002). Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. *Neurology, 59,* 1944-1950.

Hirschfeld, R. M. A., Lewis, L., & Vornik, L. A. (2003). Perceptions and impact of bipolar disorder: How far have we really come? Results of the national depressive and manic-depressive association 2000 study of individuals with bipolar disorder. *Journal of Clinical Psychiatry, 64,* 161-174.

Holmes, M. K., Erickson, K., Luckenbaugh, D. A., Drevets, W. C., Bain, E. E., Cannon, D. M., . . . Zarate, C. K. (2008). A comparison of cognitive functioning in medicated and unmedicated subjects with bipolar depression. *Bipolar Disorders, 10*(7), 806-815.

Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006).Executive function, working memory, and medication adherence among older adults. *Journal of Gerontology, 61B*(2), 102-107.

Jamison, K. R. (2000). Suicide and bipolar disorder. *Journal of Clinical Psychiatry, 61*(9), 47-51.

Jamrozinski, K. (2010). Do euthymic bipolar patients have normal cognitive functioning? *Current Opinion in Psychiatry, 23*, 255-260.

Jensen, A. R. (1965). Scoring the Stroop test. *Acta Psychologia, 24*, 398-408.

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology, 146*, 373-390.

Johnson, B. A., Roache, J. D., Javors, M. A., DiClemente, C. C., Cloninger, C. R., Prihoda, T. J., . . . Hensler, J. (2000). Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. *Journal of the American Medical Association, 284*(8), 963-971.

Jovanovski, D., Erb, S., & Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: A quantitative review of the evidence. *Journal of Clinical and Experimental Neuropsychology, 27*, 189-204.

Julius, R. J., Novitsky, M. A., & Dubin, W. R. (2009). Medication adherence: A review of the literature and implications for clinical practice. *Journal of Psychiatric Practice, 15*(1), 34-44.

Keck, P. E., Jr., McElroy, S. L., Strakowski, S. M., West, S. A., Sax, K. W., Hawkins, J. M., . . . Haggard, P. (1998). 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *American Journal of Psychiatry, 155*, 646-652.

Keefe, R. S., Bilder, R. M., Davis. S. M., Harvey, P. D., Palmer, B. W., Gold, J. M. . . . Lieberman, J. A. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry, 64*(6), 633-647.

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Edlund, M. J., Frank, R. G., & Leaf, P. J. (1996). The epidemiology of co-occurring addictive and mental disorders: Implications

for prevention and service utilization. *American Journal of Orthopsychiatry*, *66*(1), 17-31.

Kupfer, D. J., Frank, E., Grochocinski, V. J., Cluss, P. A., Houck, P. R., & Stapf, D. A. (2002). Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *Journal of Clinical Psychiatry, 63*(2), 120-125.

Levy, B., & Weiss, R. D. (2009). Cognitive functioning in bipolar and co-occurring substance use disorders: A missing piece of the puzzle. *Harvard Review of Psychiatry, 17*(3), 226-230.

Lew, K.H., Chang, E.Y., Rajagopalan, K., & Knoth, R. L. (2006).The effect of medication adherence on health care utilization in bipolar disorder. *Managed Care Interface, 19*(9), 41-46.

Lingam, R., & Scott, J. (2002).Treatment non-adherence in affective disorders. *Acta Psychiatrica Scandinavia*, *105*, 164-172.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology Psychotherapy, 18*(1), 75-79.

Maalouf, F. T., Klein, C., Clark, L., Sahakian, B. J., LaBarbara, E. J., Versace, A., . . . Phillips, M. L. (2010). Impaired sustained attention and executive dysfunction: Bipolar disorder versus depression-specific markers of affective disorder. *Neuropsychologia*, *48*, 1862-1868.

Mackin, R. S., & Areán, P. A. (2007). Cognitive and psychiatric predictors of medical treatment adherence among older adults in primary care clinics. *International Journal of Geriatric Psychiatry, 22*, 55-60.

Martínez-Arán, A., Vieta, A., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J. . . . Salamero, M. (2004). Cognitive function across manic or hypomania, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry, 161*, 262-270.

McCaul, M. E., Svikis, D. S., & Moore, R. D. (2001). Predictors of outpatient treatment retention: patient versus substance use characteristics. *Drug and Alcohol Dependence, 62*, 9-17.

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., . . . Argeriou, M. (1992). The fifth edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment, 9*, 199-213.

Mertens, J. R., & Weisner, C. M. (2000). Predictors of substance abuse treatment retention among women and men in an HMO. *Alcoholism: Clinical and Experimental Research, 24*(10), 1525-1533.

Miklowitz, D. J., & Johnson, S. L. (2006).The psychopathology and treatment of bipolar disorder. *Annual Review of Clinical Psychology, 2*, 199-235.

Mittenberg, W., & Motta, S. (1993). Effects of chronic cocaine abuse on memory and learning. *Archives of Clinical Neuropsychology, 8*(6), 477-483.

Moeller, F. G., Dougherty, D. M., Barratt, E. S., Schmitz, J. M., Swann, A. C., & Grabowski, J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment, 21*, 193-198.

Narasimhan, M., Pae, C., Masand, N., & Masand, P. (2007). Partial compliance with antipsychotics and its impact on patient outcomes. *International Journal of Psychiatry in Clinical Practice, 11*(2), 102-111.

Nomamiukor, N., & Brown, E. S. (2009). Attrition factors in clinical trials of comorbid bipolar and substance-related disorders. *Journal of Affective Disorders, 112*, 284-288.

Office of Applied Studies. (2004). *Results from the 2003 National Survey on Drug Use and Health: National findings* (DHHS Publication No. SMA 04-3964, NSDUH Series H-25). Rockville, MD: Substance Abuse and Mental Health Services Administration.

O'Malley, S., Adamse, M., Heaton, R. K., & Gawin, F. H. (1992). Neuropsychological impairment in chronic cocaine abusers. *American Journal of Drug and Alcohol Abuse, 18*, 131-144.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *The New England Journal of Medicine, 353,* 487-497.

Osuji, I. J., & Cullum, C. M. (2005).Cognition in bipolar disorder. *Psychiatric Clinics of North America, 28,* 427-441.

Pace-Schott, E. F., Morgan, P. T., Malison, R. T., Hart, C. L., Edgar, C., Walker, M., & Stickgold, R. (2008). Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. *The American Journal of Drug and Alcohol Abuse, 34*(1), 109-121.

Pallant, Julie. (2001). *SPSS survival manual: A step by step guide to data analysis using SPSS for Windows (versions 10 and 11)*. New York, NY: Open University Press.

Patel, M. X., & David, A. S. (2005). Medication adherence: Predictive factors and enhancement strategies. *Psychiatry Medical Progress*, 64-68.

Porrino, L. J., & Lyons, D. (2000). Orbitofrontal and medial prefrontal cortex and psychostimulant abuse: Studies in animal models. *Cerebral Cortex, 10*, 326-333.

Porrino, L. J., Smith, H. R., Nader, M. A., & Beveridge, T. J. R. (2007). The effects of cocaine: A shifting target over the course of addiction. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(8), 1593-1600.

Powell, D. H., Kaplan, E. F., Whitla, D., Catlin, R., & Funkenstein, H. H. (1993). MicroCog: Assessment of cognitive functioning version 2.1. San Antonio, TX: The Psychological Corporation.

Prisciandaro, J. J., Rembold, J., Brown, D. G., Brady, K. T., & Tolliver, B. K. (2011). Predictors of clinical trial dropout in individuals with co-occurring bipolar disorder and alcohol dependence. *Drug and Alcohol Dependence, 118*, 493-496.

Prouteau, A., Verdoux, H., Briand, C., Lesage, A., Lalonde, P., Nicole, L., . . .Stip, E. (2005). Cognitive predictors of psychosocial functioning outcome in schizophrenia: a follow-up study of subjects participating in a rehabilitation program. *Schizophrenia Research, 77*, 343-353.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. *The Journal of the American Medical Association, 264*, 2511–2518.

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation*. Tucson, AZ: Neuropsychology Press.

Robbins, T. W., Ersche, K. D., & Everitt, B. J. (2008). Drug addiction and the memory systems of the brain. *New York Academy of Science, 1141*, 1-21.

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders, 93*, 105-115.

Robinson, D. G., Woerner, M. G., Alvir, J. M., Bilder, R. M., Hinrichsen, G. A., & Lieberman, J. A. (2002). Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophrenia Research, 57*(2-3), 209-219.

Roiser, J. P., Cannon, D. M., Gandhi, S. K., Tavares, J. T., Erickson, K., Wood, S.,. . . Drevets, W. C. (2009). Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. *Bipolar Disorder, 11*(2), 178-189.

Rush, A. J., Trivedi, M. H., Ibrahim, H. I., Carmody, T. J., Arnow, B., Klein, D. N., . . . Keller, M. B. (2003).The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self-Report (QIDS-SR): Psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*, 573-583.

Sajatovic, M., Bauer, M. S., Kilbourne, A. M., Vertrees, J. E., & Williford, W. (2006). Self-reported medication treatment adherence among veterans with bipolar disorder. *Psychiatric Services*, 57, 56-62.

Sajatovic, M., Ignacio, R. V., West, J. A., Cassidy, K. A., Safavi, R., Kilbourne, A. M., & Blow, F. C. (2009). Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinical. *Comprehensive Psychiatry, 50*, 100-107.

Sajatovic, M., Valenstein, M., Blow, F. C., Ganoczy, D., & Ignacio, R. V. (2006). Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disorder, 8*, 232-241.

Schmidt, M. (1996). *Rey Auditory Verbal Learning Test: A Handbook*. Los Angeles: Western Psychological Services.

Schutte, P. C. (2007). *Assessing the effects of momentary priming on memory retention during an interference task*. Computer Science, Vol. (pg 1-56). Master of Science. Richmond, Virginia: Virginia Commonwealth University.

Siqueland, L., Crits-Christoph, P., Frank, A., Daley, D., Weiss, R., Chittams, J., . . . Luborsky, L. (1998). Predictors of dropout from psychosocial treatment of cocaine dependence. *Drug and Alcohol Dependence, 52*, 1-13.

Siqueland, L., Crits-Christoph, P., Gallop, R., Barber, J., Griffin, M. L., Thase, M. E., . . . Gladis, M. (2002). Retention in psychosocial treatment of cocaine dependence: Predictors and impact on outcome. The *American Journal of Addictions, 11*, 24-40.

Skre, I., Onstad, S., Torgersen, S., & Kringlen, E. (1991). High interrater reliability for the Structured Clinical Interview for DSM-III-R Axis I (SCID-I). *Acta Psychiatrica Scandanavica, 84*(2),167-173.

Sobell, L. C., & Sobell, M. B. (1996). *Timeline Followback user's guide: A calendar method for assessing alcohol and drug use*. Toronto, Ontario, Canada: Addiction Research Foundation.

Sonne, S. C., Brady, K. T., & Morton, W. A. (1994). Substance abuse and bipolar affective disorder. *Journal of Nervous and Mental Disease, 182,* 349-352.

Spreen, O. S. E. (1998). *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed.). New York: Oxford University Press.

Stilley, C. S., Sereika, S., Muldoon, M. F., Ryan, C. M., & Dunbar-Jacob, J. (2004). Psychological and cognitive functioning: Predictors of adherence with cholesterol lowering treatment. *Annals of Behavioral Medicine, 27*(2), 117-124.

Stotts, A. L., Mooney, M. E., Sayre, S. L., Novy, M., Schmitz, M. & Grabowski, J. (2007). Illusory predictors: Generalizability of findings in cocaine treatment retention research. *Addiction Behaviors, 32*(12), 2819-2836.

Strakowski, S. M., & DelBello, M. P. (2000).The co-occurrence of substance use and bipolar disorders. *Clinical Psychology Review, 20*(2), 191-206.

Strakowski, S. M., DelBello, M. P., Fleck, D. E., &Arndt, S. (2000). The impact of substance abuse on the course of bipolar disorder. *Biological Psychiatry, 48,* 477-485.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York: Oxford University Press.

Streeter, C. C., Terhune, D. B., Whitfield, T. H., Gruber, S., Sarid-Segal, O., Silveri, M. M., . . . & Yurgelun-Todd, S. A. (2008). Performance on the Stroop predicts treatment compliance in cocaine dependent individuals. *Neuropsychopharmacology, 33,* 827-836.

Suppes, T., Leverich, G. S., Keck, P. E., Jr., Nolen,W. A., Denicoff, K. D., Altshuler, L. L., . . . Post, R.M. (2001). The Stanley Foundation Bipolar Treatment Outcome Network II: Demographics and illness characteristics of the first 261 patients. *Journal of Affective Disorders, 67,* 45-49.

Svarstad, B. L., Shireman, T. I., & Sweeney, J. K. (2001). Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatric Services, 52*, 805-811.

Swann, A. C., Dougherty, D. M., Pazzaglia, P. J., Pham, M., & Moeller, F. G. (2004). Impulsivity: A link between bipolar disorder and substance abuse. *Bipolar Disorders, 6*, 204-212.

Thase, M. E., Fava, M., Halbreich, U., Kocsis, J. H., Koran, L., Davidson, J., . . . Harrison, W. (1996). A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Archives of General Psychiatry, 53*, 777-784.

Tiffany, S.T., Singleton, E., Haertzen, C. A., & Hennington, J. E. (1993). The development of a cocaine craving questionnaire. *Drug and Alcohol Dependence, 34*(1), 19-28.

Torrent, C., Martínez-Arán, A., Daban, C., Sánchez-Moreno, J., Comes, M., Goikolea, J. M., . . . & Vieta, E. (2006). Cognitive impairment in bipolar II disorder. *The British Journal of Psychiatry, 189*, 254-259.

Torres, I. J., DeFreitas, C. M., & Yatham, L. N. (2008). Cognition and functional outcome in bipolar disorder. In J. F. Goldberg and K. E. Burdick. (Eds.), *Cognitive dysfunction in bipolar disorder: A guide for clinicians* (pp. 217-234). Washington, DC: American Psychiatric Publishing.

Trivedi, M. H., Rush, A. J., Ibrahim, H. M., Carmody, T. J., Biggs, M. M., Suppes, T., . . . Kashner, T. M. (2004). The inventory of depressive symptomatology, clinician rating (IDS-C), and self-report (IDS-SR), and the quick inventory of depressive symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. *Psychological Medicine, 34*, 73-82.

Turner, T. H., LaRowe, S., Horner, M. D., Herron, J., & Malcolm, R. (2009). Measures of cognitive functioning as predictors of treatment outcome for cocaine dependence. *Journal of Substance Abuse Treatment, 37*(4), 328-334.

Uchiyama, C. L., D'Elia, L. F., Dellinger, A. M., Becker, J. T., Selnes, O. A., Wesch, J. E., . . . Miller, E. N. (1995). Alternate forms of the Auditory-Verbal Learning Test: Issues

of test comparability, longitudinal reliability, and moderating demographic variables. *Archives of Clinical Neuropsychology, 10*(2), 133-145.

Van Gorp, W. G., Altshuler, L., Theberge, D. C., Wilkins, J., & Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. *Archives of General Psychiatry, 55*, 41-46.

Verdejo-García, A., Bechara, A., Recknor, E. C., & Pérez-García, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: An examination of the behavioral, cognitive, and emotional correlates of addiction. *Journal of the International Neuropsychological Society, 12*, 405-415.

Verdejo-García, A., & Pérez-García, M. (2007). Profile of executive deficits in cocaine and heroin polysubstance users: Common and differential effects on separate executive functions. *Psychopharmacology, 190*, 517-530.

Weiss, R. D., Greenfield, S. F., Najavits, L. M., Soto, J. A., Wyner, D., Tohen, M., & Griffin, M. L. (1998). Medication compliance among patients with bipolar disorder and substance use disorder. *Journal of Clinical Psychiatry, 59*(4), 172-174.

Williams, C. C., & Collins, A. (2002). Factors associated with insight among outpatients with serious mental illness. *Psychiatric Services, 53*(1), 96-98.

Williams, J.B.W, Gibbon, M., First, M. B, Spitzer, R. L, Davis, M., Borus, J., . . .Wittchen, H. (1992). The structured clinical interview for DSM-III-R (SCID) II: Multi-site test-retest reliability. *Archives of General Psychiatry, 49*, 630-636

Winokur, G., Turvey, C., Akiskal, H., Coryell, W., Solomon, D., Leon, A., . . . Keller, M. (1998). Alcoholism and drug abuse in three groups - bipolar I, unipolars, and their acquaintances. *Journal of Affective Disorders, 50*, 81-89.

Wolfe, J., Granholm, E., Butters, N., Saunders, E., & Janowsky, D. (1987). Verbal memory deficits associated with major affective disorders: A comparison of unipolar and bipolar patients. *Journal of Affective Disorders, 13*, 83-92.

World Health Organization. (2003). *Adherence to long-term therapies: Evidence for action.* Geneva, Switzerland: Author.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry, 133*, 429-435.

Yun, L. W. H., Maravi, M., Kobayashi, J. S., Barton, P. L., & Davidson, A. J. (2005). Antidepressant treatment improves adherence to antiretroviral therapy among depressed HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes, 38,* 432-438.

Zanarini, M.C., Skodol, A.E., Bender, D., Dolan, R., Sanislow, C., Schaefer, E., . . .Gunderson, J.G. (2000). The collaborative longitudinal personality disorders study: Reliability of axis I and II diagnoses. *Journal of Personality Disorders, 14(4), 291-299.*

Zanis, D. A., McLellan, A. T., & Corse, S. (1997). Is the addiction severity index a reliable and valid assessment instrument among clients with severe and persistent mental illness and substance abuse disorders. *Community Mental Health Journal, 33*(3), 213-227.

Zarate, C. A., Tohen, M., Land, M., & Cavanagh, S. (2000). Functional impairment and cognition in bipolar disorder. *Psychiatric Quarterly, 71*(4), 309-329.