OPEN LABEL TRIAL OF CREATINE AS A TREATMENT OPTION FOR METHAMPHETAMINE USING FEMALES

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Methamphetamine (MA) is a powerful drug that results in short- and long-term consequences for users. Study findings suggest that female MA users have higher rates of comorbid depression and anxiety than male MA users. Further, neuroimaging studies have found that female MA users have lower levels of brain phosphocreatine (PCr) measured by magnetic resonance spectroscopy (MRS) brain compared to male MA users.

Treatment options for the comorbidity of depression and MA dependence are limited. The results of an integrative review of treatment options for comorbid MA use and depression suggest that psychological, a combination of psychological with pharmacological and pharmacological approaches are not effective. Further, gender differences with response to treatment are understudied.

Magnetic resonance spectroscopy has been used in drug abuse research to investigate brain chemistry changes with substance use. There have been nearly 50 publications over the past 10 years that describe MRS changes in substance use disorders. While MRS studies of MA dependence have been most frequently studied, information from all drug classes have demonstrated quantitative correlates of injury relevant to substance use.

The nutritional supplement creatine has been used as an adjunctive treatment for depression in female adolescents and adults. Further, creatine has been associated with increased brain PCr levels in healthy volunteers. Considering, a within subjects study was

conducted using 8 weeks of daily creatine to treat depression among female MA users.

Primary outcomes of the study included Hamilton Depression Rating Scale (HAMD) scores and brain PCr levels. Secondary outcomes included Beck Anxiety Inventory (BAI) scores and substance use. The results of the study showed a reduction in HAMD scores as early as week 2. Brain PCr levels were found to be higher at the second scan compared to the first scan ($M = 0.233$, $SD = 0.009$, $t(9) = -2.905$, $p < .01$). Also, BAI scores were reduced as early as week 1, as well as a reduction by over half in MA-positive urine drug screens by week 6 (baseline: 50% MA positive urine drug screens; week 6: 21.4%). Finally, creatine was well tolerated.

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CHAPTER 1

INTRODUCTION

The focus of this research was comorbid methamphetamine (MA) use and depression among females. The study proposed an intervention of 8 weeks of creatine treatment for females diagnosed with major depressive disorder and MA dependence. The Hamilton Depression Rating Scale (HAMD) was used to measure depression throughout the course of the study. In addition, phosphorus magnetic resonance spectroscopy (^{31}P MRS) was used to compare pre- and postcreatine treatment brain phosphocreatine (PCr) concentrations. This chapter includes a background about MA use rates, describes consequences of MA use, outlines rates of depression among MA users and discusses comorbid anxiety among MA users. Finally, it describes the statement of the problem, study purpose, specific aims and significance of the study.

Methamphetamine Use Rates

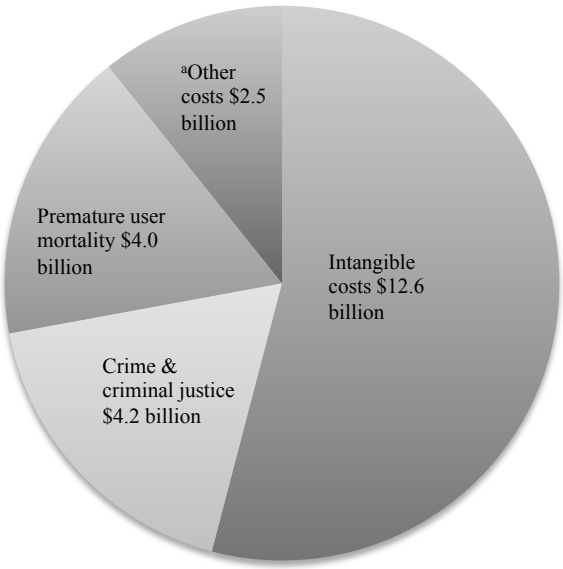
Methamphetamine is a psychostimulant drug with high abuse potential. It can be smoked, snorted, injected or ingested orally to produce a release of high levels of dopamine into the brain and a reduction of dopamine uptake. Methamphetamine use results in feelings of pleasure, increased energy, and greater alertness lasting up to 12 hours. In 2013, the National Survey on Drug Use and Health reported that 595,000

Americans aged 12 or older reported using MA in the past month (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). Over the past decade MA use rates have fluctuated with current use rates stabilizing. Even though overall use rates are steady, use rates among males and females are approaching equal proportions (Durell, Kroutil, Crits-Christoph, Barchha & Van Brunt, 2008). This use rate pattern is unlike other drugs of abuse, which typically demonstrate males using more than females (Durell et al., 2008). In some states, more females than males consider MA as their drug of choice. For example, in a 2013 report in the state of Utah, more females (27.6%) were diagnosed with MA as a primary substance of abuse than males (15.4%) upon admission to substance abuse treatment (Division of Substance Abuse and Mental Health, 2014). In comparison to other drugs of abuse, alcohol is most frequently diagnosed as a primary substance of abuse for males (40.1%) and females (27.8%), marijuana is the second most frequently diagnosed primary substance of abuse for males (18.7%) and heroin and prescription opiates combined is the third primary substance of abuse for females (20.7%) and males (16.5%; Division of Substance Abuse and Mental Health, 2014).

Consequences of Methamphetamine Use

Even though the number of MA users in America has stabilized, it remains a public health concern because its use is associated with a substantial amount of crime. In addition, its consequences, which are discussed below, lead to short- and long-term medical and psychiatric concerns (Rawson, Gonzales & Brethen, 2002). The most recent estimated economic costs to society related to MA use were obtained in 2005 and published in 2009, and these costs were estimated at $23.4 billion (Nicosia, Pacula &

Lundberg, 2009). Given the uncertainty in estimating the costs, a RAND Corporation study provides a lower bound estimate of $16.2 billion and an upper range of $48.3 billion annually (Nicosia, Pacula & Lundberg, 2009). Health threats also present major economic challenges to individuals and the overall economy (Figure 1), both in terms of increased health care costs and lost productivity (Office of National Drug Control Policy, 2010). These health threats include the risk of contracting human immunodeficiency virus (HIV), cardiovascular complications, heart disease, hypertension and stroke (Yu, Larson & Watson, 2003). Additional short- and long-term consequences of MA use include depression (McKetin, Lubman, Lee, Ross, & Slade, 2011; Thomas, Angoa Perez, Francescutti-Verbeem, Shah, & Kuhn, 2010), anxiety (Glasner-Edwards, Mooney, Marinelli-Casey, Hillhouse, Ang, & Rawson, 2010a), insomnia, paranoia (McGregor et



[a]Other costs = $1.3 billion in health care costs and child endangerment and $1.2 billion in lost productivity and drug treatment

Figure 1. Methamphetamine economic burden to society from a RAND Corporation study (data from Nicosia, Pacula & Lundberg 2009, figure by Tracy Hellem, author)

al., 2005), and structural and chemical changes to the brain (Sekine et al., 2003; Yoon et al., 2010). Depression is particularly concerning because depression and MA use are highly comorbid (Semple, Zians, Strathdee & Patterson, 2007), and this comorbidity confounds treatment outcomes and general prognosis (Glasner-Edwards et al., 2008a).

Rates of Depression Among Methamphetamine Users

The relationship between MA use and depression is likely bidirectional, with MA use contributing to changes in mood and being used as a self medicating behavior to reduce symptoms of depression (McKetin, Lubman, Lee, Ross & Slade, 2011; Semple, Zians, Strathdee, & Patterson, 2007). The prevalence of premorbid depressive disorders among patients with MA use disorders is high, with the majority of MA users reporting a significant lifetime history of depression (Darke, Kaye, McKetin & Duflou, 2008; Zweben et al., 2004). For example, in a study by Hall, Hando, Darke and Ross (1996), 301 MA users reported a 62% (n =187) rate of depression and a 23% (n = 69) rate of suicidality prior to MA use. After initiating MA, users' rate of depression increased to 79% (n = 238; Hall, Hando, Darke & Ross, 1996). Notably, female MA users report higher levels of depressive symptoms than males (Glasner-Edwards, Mooney, et al., 2008a, 2008b; Semple, Zians, Strathdee, & Patterson, 2007). Semple and colleagues (2007) noted that 60% (n = 87) of MA using women in their study met criteria for moderate to severe depression. In another study, female MA users demonstrated significantly higher depression scores, measured by the Beck Depression Inventory, than did male MA users (19.2 vs. 13.2; Dluzen, 2008), and 38.8% of females (n = 219) compared to 29.8% of males (n = 151) were diagnosed with depression in another study

(Hser, Evans & Huang, 2005). In a study of adolescent and young adult MA users, 49% (*n* = 49) were found to meet criteria for a current mood or anxiety disorder and 68% (*n* = 68) had a lifetime history of a mood or anxiety disorder, with more females (*n* = 25) reporting a lifetime history of a mood or anxiety disorder than males (*n* = 21; Lubman, Allen, Rogers, Cementon & Bonomo, 2007). It is likely that neurobiological and psychosocial mechanisms contribute to increased incidence of depressive symptoms in females (Dluzen & Li, 2008).

Comorbid Anxiety and Methamphetamine Use

In addition to depression, anxiety symptoms are often comorbid in MA users, with women reporting more generalized, phobic and obsessive compulsive anxiety symptoms than men (Zweben et al., 2004). More than one third of women with MA dependence (34.9%, *n* = 66) have a comorbid anxiety disorder and importantly, these anxiety disorders are four times more likely to be primary rather than substance induced (24%, *n* = 45 versus 6%, *n* = 11; Salo, Flower, Kielstein, Leamon, Nordahl, & Galloway, 2011).

Intervention research has shown that 3 years posttreatment, 23.4% (*n* = 123) of participants with MA dependence meet criteria for a current anxiety disorder, which is associated with increased frequency of MA use during the follow up period (Glasner-Edwards, Mooney, Marinelli-Casey, Hillhouse, Ang, & Rawson, 2010b). Longitudinal studies have also shown that anxiety disorders predict the following adverse outcomes after treatment for MA dependence: poorer adherence, increased drug or alcohol dependence, psychiatric hospitalization and more than triple the odds of one or more

lifetime suicide attempts (odds ratio = 3.1; Glasner-Edwards, Mooney, Marinelli-Casey, Hillhouse, Ang, & Rawson, 2010c).

Although the casual and temporal relationships between anxiety and MA use disorders have yet to be fully elucidated, the above findings coupled with the fact that anxiety disorders are associated with longer and more frequent MA usage, progression to dependence and injection use (Darke et al., 2008) highlight the importance of identifying and targeting anxiety symptoms, particularly among female MA users. However, as described in the following paragraphs, depression and neuroimaging findings are the primary outcomes of this dissertation, and therefore, anxiety is collected as a secondary outcome, and is not described in as much detail as the primary outcomes.

Statement of the Problem

No clear treatment model exists to suggest how the comorbidity of depression and MA use is best managed (Hellem, Lundberg, & Renshaw, 2014). In studies of antidepressants for the treatment of MA withdrawal, dependence and comorbid mood disorders, findings have suggested that antidepressants are ineffective or have unacceptable side effect profiles (Cruickshank et al., 2008; Elkashef et al., 2008; Galloway, Newmeyer, Knapp, Stalcup, & Smith, 1996; Heinzerling et al., 2010; Shoptaw et al., 2008; Shoptaw et al., 2006). Indeed, one placebo controlled trial of the selective serotonin reuptake inhibitor (SSRI) sertraline found that participants (n = 59) randomized to SSRI experienced sustained cravings and had an increased rate of relapse (Shoptaw et al., 2006). This led investigators to conclude that sertraline is contraindicated in the treatment of MA dependence (Shoptaw et al., 2006). In addition, well conducted studies

of the non-SSRI antidepressant bupropion (*n* = 36; Shoptaw et al., 2008) and mirtazapine (*n* = 30; Colfax et al., 2011) found no difference from placebo in ratings of depression. Further, research on the effects of psychological approaches such as cognitive behavioral therapy or motivational interviewing is limited and requires further exploration in larger more heterogeneous samples of MA users (Hellem, Lundberg, & Renshaw, 2014).

Neuroimaging techniques, such as ^{31}P and proton (^{1}H) MRS, are important for improving our understanding of the effects of depression and MA on the brain. In neuroimaging studies of drug abuse and mood disorders, PCr is of particular interest because it serves an important role as a high energy buffer to maintain constant adenosine triphosphate (ATP) levels through the action of creatine kinase. The enzyme creatine kinase controls the transfer of a phosphate group from PCr to adenosine diphosphate (ADP), thereby replenishing brain ATP. Given that ATP production occurs in mitochondria, it is not surprising that converging lines of evidence implicate mitochondrial dysfunction in depression (Jou, Chiu, & Liu, 2009; Rezin, Amboni, Zugno, Quevedo, & Streck, 2008; Shao et al., 2008) and MA use (Sung et al., 2013).

Magnetic resonance spectroscopy studies reveal a conflicting pattern of metabolic change in adults with depression: either higher concentrations of PCr (*n* = 17; Kato, Takahashi, Shioriri, & Inubushi, 1992; Kondo et al., 2011) or lower concentrations of PCr (*n* = 55) when compared to healthy volunteers (*n* = 49; Forester et al., 2009; Iosifescu et al., 2008; Moore, Christensen, Lafer, Fava, & Renshaw, 1997), with the latter pattern indicating that some patients with depression have brain energy stores that are not being accessed to support cerebral activity. Along those same lines, in a recent ^{31}P MRS MA study, Sung and colleagues (2013) found decreased PCr in female MA users (*n* = 23)

compared to male MA users (n = 28). Collectively, these study findings suggest the possibility of an alteration in high energy phosphate metabolism in individuals with depression and in individuals who use MA.

Creatine is an organic acid occurring naturally in vertebrates, where it takes part in energy homeostasis in tissues with fluctuating energy demands (Kondo et al., 2011). Exogenous creatine has been shown to increase brain concentrations of PCr (Kondo et al., 2011; Lyoo et al., 2003). Lyoo and colleagues (2003) administrated oral creatine at a dose of 0.3 g/kg/day for 7 days and 0.03 g/kg/day for 7 days in a sample of adult healthy volunteers (n = 10), and the results demonstrated that brain PCr concentrations increased in the treatment group compared to a placebo group. Similarly, in a study of depressed female adolescents (n = 5) who took 4 grams of adjunctive oral creatine for 8 weeks, brain PCr levels increased significantly (p = 0.02) when compared to a control group, and as PCr levels increased, a reduction in depression rating scores was noted (Kondo et al., 2011). However, there are no published reports of neuroimaging findings in depressed adults who have taken creatine.

Purpose of the Study

When taking into consideration that PCr levels are lower in female MA users and in some patients with depression, and that oral creatine may increase PCr levels and decrease depression, it is reasonable to hypothesize that oral creatine treatment will increase PCr levels and reduce depression in a sample of depressed female MA users. This hypothesis was tested by a within subjects design by giving 14 depressed MA using females oral creatine for 8 weeks and measuring PCr pre- and posttreatment with ^{31}P

MRS. Depressive symptoms were measured by the HAMD.

Specific Aims

The first specific aim of this study was to describe changes in HAMD scores over the course of the study. The hypothesis of this aim was that there would be a decrease in HAMD scores over time with creatine treatment. (Note, HAMD scores were collected three times prior to intervention, weekly during the intervention and three times post intervention).

The second specific aim of this study was to compare pre- and postcreatine treatment brain PCr levels using ^{31}P MRS. The hypothesis of this aim was, compared to baseline, PCr levels would statistically significantly higher at the posttreatment scan.

Significance

Creatine is an attractive candidate for the treatment of depression in MA users for a number of reasons. First, previous MRS studies have reported decreased brain creatine plus PCr levels in MA dependent individuals (Sung et al., 2013). Because of MA's neurotoxic effects, MA users may benefit from an increase in PCr levels. Second, depression has been associated with high levels of drug craving (Nakama, Chang, Cloak, Jiang, Alicata & Haning, 2008), which can be related to relapse, and therefore, treating depression in female MA users may improve treatment outcomes. Third, antidepressant effects have been documented in preclinical and clinical trials of creatine (Allen, D'Anci, Kanarek, & Renshaw, 2010; Kondo et al., 2011) Finally, creatine is available over the counter and offers a relatively inexpensive treatment option.

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CHAPTER 2

REVIEW OF THE LITERATURE

This inquiry is based on the assumptions that a bidirectional relationship between methamphetamine (MA) and depression may exist, MA use and depression result in changes in high energy phosphate brain metabolism, and exogenous creatine may correct or modify high energy phosphate brain metabolism in depressed female MA users. The following review of the literature is composed of four sections focused on these concepts. The first section is an overview of the history of MA and comorbid depression and MA use, the second section discusses gender differences in depression, the third section reviews magnetic resonance spectroscopy (MRS) and MRS studies of depression and MA and the fourth section presents the history and use of creatine treatment.

History of Methamphetamine: Medicinal and Illicit Use

Methamphetamine is a powerful central nervous stimulant with high potential for abuse and dependence. It is a derivative of amphetamine that was initially synthesized by a German chemist in 1887, and studied extensively for the first time in the early 1930s (Anglin, Burke, Perrochet, Stamper, & Dawud-Noursi, 2000). Because of its stimulation on the sympathetic branch of the autonomic nervous system, the first medical use of amphetamine was in 1932 as a nasal spray for the treatment of asthma (Anglin, et al.,

2000). MA was first synthesized from ephedrine by a Japanese pharmacologist in 1893 (Suwaki, Fukui, & Konuma, 1997), but it did not became widely used until World War II when Japan, Germany, and the United States distributed it to military personnel to enhance performance. The first epidemic of illicit MA use occurred in 1945 – 1957, with an estimated 5% of Japanese young adult abusers (Anglin et al., 2000).

In the United States, over the counter amphetamine tablets were available until 1951. In the 1960s, amphetamine was used as a medication to treat obesity, narcolepsy and depression, with use reaching its peak when 31 million prescriptions were written in 1967 (Hanson, Venturelli, & Fleckenstein, 2000). During the same decade, a liquid form of MA was used as a treatment for heroin addiction, and as a result, a new abuse pattern developed involving MA alone or MA and heroin combined (Anglin et al., 2000). The first illicit MA laboratories appeared in San Francisco in 1962, and by the mid-1960s, motorcycle gangs in the Bay Area seized the manufacturing and distribution of MA along the West Coast (Miller, 1997). Methamphetamine started out as a prescribed medication but within decades it became a substance of abuse associated with crime, gangs and violence.

Methamphetamine use decreased in the 1970s largely due to restrictions on legal production by the Controlled Substance Act of 1970. Subsequently, increased production of illicit MA resulted, and at the same time, typical MA users shifted from white and blue collar workers to college students, young professionals, and women (Anglin et al., 2000). In 1971, all forms of amphetamine were classified as Drug Enforcement Administration (DEA) Schedule II drugs (Miller, 1997). Despite these efforts, in the 1980s, MA use began to rise again, largely due to the production of MA in clandestine labs. Greater

involvement of Mexican drug traffickers occurred in the late 1980s after increased law enforcement efforts targeted the sales of ephedrine, an ingredient found in over the counter cold remedies and the main ingredient in MA (Anglin et al., 2000). By the early 1990s, the use of MA had spread from the West toward Southwestern and Midwestern states, and simultaneously, another surge of MA use occurred in Hawaii. In 1996, there was an annual 169% increase in MA laboratory seizures, and in response to the widespread public health concern regarding MA use and production, the Comprehensive Methamphetamine Control Act was passed (Anglin et al., 2000).

With the turn of the century, MA use rates continued to rise with an estimated 12 million Americans over the age of 12 having used MA in their lifetime (Substance Abuse and Mental Health Services Administration [SAMHSA], 2004). Over the last several years, MA rates have been declining, however, the consequences of MA use are still a major public health concern. Both acute and chronic MA abuse have serious medical and psychiatric repercussions. Short- and long-term health effects of MA abuse include stroke, (Perez, Arsura, & Strategos, 1999), cardiac arrhythmia (Haning & Goebert, 2007), depression (McKetin, et al., 2011; Thomas, Angoa Perez, Francescutti-Verbeem, Shah, & Kuhn, 2010), anxiety (Glasner-Edwards et al., 2010), insomnia, paranoia (McGregor et al., 2005), and structural and chemical changes to the brain (Sekine et al., 2003; Yoon et al., 2010).

In the sections that follow, research that underscores the comorbidity of MA use and depression, including studies that show alterations in brain energy metabolism are discussed. There is a specific focus on the increased risk and response to treatment for females with comorbid depression and MA use.

Comorbid Depression and Methamphetamine Use

Among the consequences of MA use, depression is of significant concern because MA use and depression are highly comorbid, and this comorbidity worsens the overall prognosis and treatment outcomes (Glasner-Edwards et al., 2010). The association between MA use and depression is likely bidirectional (McKetin, et al., 2011; Semple et al., 2007), with short- and long-term MA use resulting in mood changes, and MA use being a compensatory behavior to alleviate symptoms of depression (Koob et al., 2013). Further, MA is known to reduce concentrations of dopamine and serotonin, which predispose MA users to depression (Sekine et al., 2003; Thomas et al., 2010).

Unlike many other drugs of abuse, MA use rates are greater in females than males (Division of Substance Abuse and Mental Health, 2014), and the average age of onset of MA use in females is younger (19.2 years) compared with males (20.6 years; Dluzen & Liu, 2008). Furthermore, females report that their initial MA use is an attempt to lose weight or a result of coping with a negative mood, whereas males report ability to work more and improve sex as reasons for their initial use (Bretch, O'Brien, von Mayrhauser, & Anglin, 2004). As such, it is not surprising that several studies have shown that comorbid depression and MA use rates are higher in females compared to males (Glasner-Edwards, Mooney, et al., 2008a, 2008b; Semple et al., 2007). However, it is important to note that in the general population rates of depression are higher in females than males, and therefore, this comorbid depression and MA use in females may represent a type of self-medication or may be the result of existing gender differences.

Gender Differences in Depression

Gender differences in the prevalence of depression are well documented. Consistent study findings suggest that approximately twice as many females are depressed than males (Andersen, Thielen, Bech, Nygaard, & Diderichsen, 2011; Hankin et al., 1998; Piccinelli & Wilkinson, 2000; Weissman & Olfson, 1995). By the middle teenage years, females experience more than double the rate of depressive disorders found in males (Garrison et al., 1997; Wade, Cairney, & Pevalin, 2002). This approximate 2:1 gender difference in depression continues throughout the reproductive years (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). In addition to increased incidence, initial episodes of depression are longer in duration and more severe in symptomatology in females compared to males (McCauley et al., 1993). Females are more likely than males to have atypical symptoms of depression, such as hypersomnia (i.e., excessive sleep) and hyperphagia (i.e., excessive eating), to have comorbid anxiety disorders, and to attempt suicide (Gorman, 2006). Globally, depression is among the most common disorders affecting females throughout their lives, and is the leading cause of disability among women between the ages of 15 and 44 years (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Moreover, depression is associated with high-risk behavior such as illicit drug use (Marmorstein, Iacono, & Malone, 2010).

Recently the Utah Department of Health published a report on depression and antidepressant use in Utah (Gaskill, 2010). Using health insurance claims from 899,323 Utah residents, antidepressant use was examined, and over 6 million pharmacy claims from 2009 were reviewed. Of interest, they reported that 84,000 individuals were prescribed antidepressants, resulting in antidepressants being the most widely prescribed

medication in the state. When comparing antidepressant utilization by gender, researchers noted that females are prescribed antidepressants at a rate of more than twice that of males. A recent study by Mental Health America ranked Utah the most depressed state in the nation (Healthcare, 2007). Their results indicated that among adults, 10.1% experienced a depressive episode in the past year (Healthcare, 2007).

Neuroimaging as a Translational Tool

A barrier to translational psychiatry and substance use disorder research is the lack of measurable correlates of illness and recovery. Magnetic resonance spectroscopy is a useful probe of tissue chemistry and metabolites of biochemical interest that can be measured to improve our understanding of the effects of depression and MA on the brain. Proton (^{1}H) and phosphorus (^{31}P) MRS are commonly used nuclei in evaluating the central nervous system. Studies utilizing ^{1}H MRS measure cerebral concentrations of creatine, *N*-acetyl aspartate (NAA), glutamate (Glu), glutamine, (Gln), gamma-aminobutyric acid (GABA), choline (Cho) and *myo*-inositol (mI). By contrast, ^{31}P MRS studies examine concentrations of phosphocreatine (PCr), phosphomonoesters (PME), beta nucleotide triphosphate (β-NTP, largely ATP), and intracellular pH.

Magnetic Resonance Spectroscopy Studies of Depression

Phosphorus MRS findings in adults with depression (n = 56) have consistently shown a characteristic pattern of metabolic change: reduced β-NTP concentrations and higher PCr concentrations when compared to healthy volunteers (n = 35; Iosifescu et al., 2008; Moore, Christensen, Lafer, Fava, & Renshaw, 1997; Volz et al., 1998). This

pattern, which is more common in females than males (Renshaw et al., 2001), suggests that some depressed patients have increased brain energy stores that are not being accessed to support cerebral activity. This specific pattern of altered energy metabolism is associated with an increased likelihood of treatment response to both selective serotonin reuptake inhibitors (SSRI) antidepressants and thyroid hormone (Iosifescu et al., 2008). There is one published report of ^{1}H MRS in depression with a sample of adolescents (n = 5), and these findings also indicate alterations in brain energy metabolism (Steingard et al., 2000). In healthy adults (n = 10), administration of the dietary supplement creatine can induce resting brain energy metabolism changes (Lyoo et al., 2003), suggesting the possibility of using creatine treatment to modify brain high energy phosphate metabolism in patients with depression.

Magnetic Resonance Spectroscopy Studies of Methamphetamine

Several ^{1}H MRS studies have suggested neuronal loss and glial dysfunction in chronic MA users. Specifically, levels of the neuron associated amino acid NAA and levels of creatine+PCr have been reported as decreased in the basal ganglia (n = 39; Ernst, Chang, Leonido-Yee, & Speck, 2000; Sekine et al., 2003), and in the anterior cingulate cortex (n = 69; Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007) in MA users compared to healthy controls (n = 38). Alterations in Cho and mI are also involved in neural processes that have been associated with long-term MA use. Study findings suggest that Cho concentrations increase shortly after abstinence is initiated, possibly as a result of the brain attempting to repair MA induced injury (Ernst et al., 2000; Nordahl et al., 2005). *Myo*-inositol is considered a glial marker (Brand, Richter-

Landsberg, & Leibfritz, 1993), and therefore, findings of increased mI levels may reflect glial proliferation in MA users (Ernst et al., 2000; Sung et al., 2007).

There is one published report of ^{31}P MRS findings in MA dependence, and the findings suggest lower PCr concentrations in MA users compared to healthy controls. Interestingly, female MA users (n = 23) had significantly lower PCr ratios than male MA users (n = 28; Sung et al., 2013). These data are consistent with alterations in high energy phosphate metabolism in MA dependent participants, since PCr serves as a buffer to maintain constant ATP levels. Exogenous creatine treatment, which has been shown to increase PCr in 10 healthy volunteers (Lyoo et al., 2003), might provide beneficial effects directly by targeting the abnormality in the PCr-ATP buffering system caused by MA use.

Creatine Treatment

A French scientist, Michel Eugene Chevreul, first described creatine as a nitrogenous organic acid that occurs naturally in vertebrate animals in the 1830s. Acting as a substrate for hydrogen ions, creatine facilitates the production of ATP from ADP, thus increasing the amount of free energy available within cells (Kamber et al., 1999). Creatine has a role in high-energy phosphoryl group transfer during skeletal muscle contraction via the creatine kinase reaction. The enzyme creatine kinase catalyzes the reversible reaction of creatine and ATP, forming PCr and ADP (McLeish & Kenyon, 2005). The intracellular creatine/PCr ratio plays an important role in maintaining an adequate supply of energy, in the form of cellular ATP (Wallimann, Wyss, Brdiczka, Nicolay, & Eppenberger, 1992). Phosphocreatine may be viewed as a reservoir of high

energy phosphate, which supplies ATP, the primary energy source in cells, on demand. Consequently, creatine plays a significant role in energy homeostasis of cells with intermittently high energy requirements (McLeish & Kenyon, 2005).

Creatine plays a role in transferring energy from the mitochondria to the cytosol in tissues with high-energy requirements such as brain and skeletal muscle (Wyss et al., 1998). Creatine was also recently identified as a potent natural survival and neuroprotective factor for developing nigral dopaminergic neurons (Andres et al., 2005). Creatine supplementation improves the function of the creatine kinase/PCr system by increasing cellular creatine and PCr levels, improving the rate of ATP resynthesis, and maintaining cellular-energy homeostasis (Jost et al., 2002).

Clinical trials in humans provide evidence for creatine's effect on brain function. A study published by Rae et al. (2003) showed that increasing oral creatine intake resulted in a significant positive effect on both working memory and intelligence in 45 vegetarian young adults. These results were in agreement with the observations that brain creatine levels correlate positively with recognition memory (Ferrier et al., 2000), and that creatine supplementation reduces mental fatigue on a serial calculation task (Watanabe, Kato, & Kato, 2002). The latter study also showed reduced activation stimulated oxyhemoglobin delivery to the activated area following creatine supplementation (Watanabe et al., 2002). This suggests that creatine supplementation is acting to smooth fluctuations in the blood oxygen level-dependent response curve, which results from brain activation (Gjedde, Poulsen, & Ostergaard, 1999; Madsen, Cruz, Sokoloff, & Dienel, 1999), possibly by altering rates of ATP synthesis in the mitochondria through the mitochondrial creatine kinase adenine nucleotide translocase

porin complex (Wallimann et al., 1992; Walter et al., 2000).

Creatine is currently being investigated as a treatment for neuromuscular and neurodegenerative diseases. As a treatment for muscular dystrophy, creatine has been shown to significantly improve muscle strength and daily activities in (n = 36; Walter et al., 2000). In a study of Huntington's disease, supplementation with creatine demonstrated increased brain and serum creatine concentrations, which returned to baseline after a washout period (n = 64; Hersch et al., 2006), suggesting that oral creatine may increase brain creatine availability and activity. Because of strong evidence that mitochondrial impairment plays a role in the pathogenesis of Parkinson's disease (Andres et al., 2005), creatine has been explored as a treatment option. Study findings suggest that creatine supplementation may delay increases in the Unifed Parkinson's disease Scale by as much as 50% in 67 medication naïve adults with Parkinson's disease (Investigators, 2006). Collectively, these study findings suggest the potential neuroprotecive effects of creatine treatment.

Creatine's Potential Antidepressant Effects

Data from preclinical animal studies suggest that creatine has sex dependent antidepressant properties. The Prosolt Forced Swim Test (FST) is the most widely employed experimental animal model of depression. Fed to rats, diets enriched with 4% creatine for 6 weeks confer a longer period until immobility in female rats compared with rats fed 0% creatine. In male rats, however, creatine has the opposite effect (Allen, D'Anci, Kanarek, & Renshaw, 2010). Moreover, supplementation with 4% creatine in female rats was of greater benefit for reducing depression like behavior than 10mg/kg of

fluoxetine (Allen, D'Anci, Kanarek, & Renshaw, 2012). The gender specific nature of these findings may be due to the fact that estrogen receptors are quite common in mitochondria (Gorman, 2006). Estrogen has potent effects on mitochondria, particularly at times of mitochondrial stress (Simpkins, Yang, Sarkar, & Pearce, 2008).

In an 8 week open label study of 4 grams of creatine augmentation in female adolescents (n = 5) who failed to respond to an SSRI, Childhood Depression Rating Scores (CDRS) were reduced by 56% (Kondo et al., 2011), and further, the researchers noted that brain PCr concentrations increased when compared to a control group (n = 10; Kondo et al., 2011). In a placebo controlled trial of creatine augmentation in female adults, the creatine augmented group (n = 25) showed statistically significant improvements in depression rating scores from baseline compared with the placebo group (n = 27; Lyoo et al., 2012). In both published depression studies, creatine was well tolerated with few adverse events reported. The exact intracellular mechanism underlying how adjunctive creatine bolsters antidepressant efficacy of SSRI therapy remains unknown, but its engagement in brain energy metabolism is one possible explanation.

To date, no studies have examined the effect of creatine supplementation in female MA users. Given the gender specific effects of creatine in animal models (Allen et al., 2010) clinical trials in males should be deferred until efficacy and safety have been shown.

Safety Profile and Toxicity of Creatine

Retrospective and prospective studies in humans have found no evidence for long-term or short-term significant side effects from creatine supplementation taken at

recommended doses (Mihic, MacDonald, McKenzie, & Tarnopolsky, 2000; Poortmans et al., 1997; Poortmans & Francaux, 1999, 2000). Most controlled studies of creatine report an absence of side effects or report no differences in the incidence of side effects between creatine and placebo (Shao & Hathcock, 2006). Mihic and colleagues (2000) have demonstrated that creatine loading increases fat free mass, but does not affect blood pressure or plasma creatinine in adult males and females.

Reports in the popular media of links between creatine use and muscle strains, muscle cramps, heat intolerance, and other side effects are not supported by the medical literature (Shao & Hathcock, 2006). Studies conducted in athletes and military personnel indicate a substantial safety level of both short- and long-term creatine supplementation in healthy adults (Bennett et al., 2001; Greenwood, Kreider, Greenwood, & Byars, 2003; Greenwood, Kreider, Melton, et al., 2003; Kreider et al., 2003; Poortmans & Francaux, 1999; Robinson, Sewell, Casey, Steenge, & Greenhaff, 2000). Concerns about high dose creatine's association with renal toxicity are based exclusively on two published case reports, and in one of the cases, the patient had a documented preexisting kidney condition (Koshy, Griswold, & Schneeberger, 1999; Pritchard & Kalra, 1998). Literature reviews and expert consensus panels have concluded there is no evidence supporting an association between creatine and renal disease (Farquhar & Zambraski, 2002; Poortmans et al., 1997; Terjung et al., 2000; Yoshizumi & Tsourounis, 2004).

Concern has been raised regarding creatine's potential for adverse effects on the kidneys and renal system, in part because creatine supplementation can increase urinary creatine and creatinine excretion (Harris, Saderlund & Hultman, 1992). In response to these concerns, Poortmans and Francaux conducted studies of the effect of creatine

supplementation on renal function, showing that short-term supplementation did not alter glomerular filtration rate in 5 male athletes (Poortmans et al., 1997), and that chronic supplementation of up to 5 years' duration did not impair renal function in 9 healthy athletes (Poortmans & Francaux, 1999). In a letter published in *The Lancet*, Poortmans and Francaux (1998) reported that laboratory results show that oral creatine supplementation has no adverse effects on the renal responses of 20 healthy individuals.

Schilling and colleagues (2001) conducted a retrospective study of participants (n = 26) who had been taking oral creatine from 0.8 to 4 years, at an average dose of 9.7 grams per day. Data were collected on 65 health related variables. These included a complete blood count, 27 serum chemistries, and anthropometric data including vital signs and % body fat. On all 65 variables, group means fell within the normal clinical range. The authors concluded that long-term creatine supplementation does not result in adverse health effects (Schilling et al., 2001).

Evidence to date suggests that even aging, debilitated, medically fragile patients are able to tolerate creatine supplementation. Bender and colleagues studied elderly patients with Parkinson's disease who had received either placebo or 4 grams/day of creatine for 2 years. They found no differences between the creatine (n = 40) and placebo (n = 20) groups in laboratory markers of renal dysfunction (Bender, Samtleben, Elstner & Klopstock, 2008). Interestingly, the participants who received creatine performed better on the depression subscale of the Unified Parkinson Disease Rating Scale (Bender et al., 2006).

Summary

In summary, the prevalence of depression is more common in females than males, and individuals with an underlying mental illness may use substances to alleviate negative emotions. Females in particular have higher rates of MA use compared with males, which is unlike other drugs of abuse. Research studies suggest that females tend to use MA as a mechanism for losing weight or to cope with depression.

Magnetic resonance spectroscopy abnormalities in MA dependent participants are suggestive of neuronal loss, glial dysfunction, and reduced levels of PCr. The nutritional supplement creatine is under investigation as a treatment for Parkinson's disease, Huntington's disease, muscular dystrophy, and major depressive disorder (MDD). Magnetic resonance spectroscopy studies of creatine treatment demonstrate an increase in brain PCr, suggesting that creatine may improve high energy phosphate metabolism. In addition, creatine treatment has been shown to have sex dependent antidepressant properties in animals. Finally, in depression studies of females, creatine treatment has demonstrated a decrease in depressive symptoms.

The proposed study will fill a gap by describing the results of creatine treatment in female adults with comorbid depression and MA use. Previous research has shown that adjunctive creatine treatment may reduce depression in adult and adolescent females with MDD, but there are not any published reports of creatine as a treatment option for comorbid depression and MA use. Understanding if a novel over the counter treatment option with few side effects is efficacious would be an important step in MA research.

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CHAPTER 3

FRAMEWORK, METHODOLOGY, ANALYSIS AND DATA, AND SAFETY MONITORING PLAN

In this section, an overview of the framework for this study, including definitions of and relations among key concepts, study design, data collection methods, statistical analysis plan and data and safety monitoring plan is provided.

Theoretical Framework

The hypotheses and aims of this study are based on both theorized and measured physiological responses to MA use and the self-medication hypothesis of drug use. Methamphetamine is known to reduce concentrations of dopamine and serotonin, which may result in depressive symptoms (Sekine et al., 2003; Thomas et al., 2010). Increasing evidence from human and animal studies indicate a relationship between dopamine and serotonin transmission in the central nervous system and depression. In preclinical animal studies of MA administration, a 65% reduction of vesicular dopamine uptake was observed 1 hour after MA treatment (Brown, Hanson, & Fleckenstein, 2000). In human positron emission tomography MA studies, findings demonstrate significant decreases in dopamine transport density in abstinent MA users compared to healthy controls (McCann et al., 1998; Volkow et al., 2001). In addition, research has shown that MA use results in

a decrease in serotonin transporter density (Sekine et al., 2006) and serotonin transporter activity (Fleckenstein, Gibb, & Hanson, 2000). This reduction in uptake and transportation is interpreted as resulting in lower concentrations of dopamine and serotonin (Fleckenstein et al., 2000). In agreement with the evidence that there is an association between decreased dopamine and serotonin levels and depression, these findings suggest that a reduction in dopamine uptake and transport density may be linked to the depressive symptoms experienced by MA users.

A key MRS finding has noted a decrease in PCr levels in MA users, an effect that was more prominent in females (Sung et al., 2013). Neuronal energy demands are met through a shift in the creatine kinase reaction equilibrium (PCr^{2+} + ADP <===> Cr + ATP^{2+}), which is designed to maintain a constant ATP concentration (Andres, Ducray, Schlattner, Wallimann & Widmer, 2008). The report of PCr being lower in MA users (*n* = 51) relative to healthy controls (*n* = 23; Sung et al., 2013) provides some evidence that MA use compromises brain energy metabolism.

The self-medication hypothesis of drug use posits that individuals use substances as compensatory behavior to alleviate symptoms of an underlying mental illness (Khantzian, 1985). Further, it explains that the substance an individual comes to rely on is not a random choice (Khantzian, 1985). Considering the common symptoms of depression: anhedonia, sleep disturbances, weight loss or gain, and fatigue, it is not unreasonable to think that a depressed individual would use MA to alleviate symptoms. However, there is a paucity of literature discussing the self-medication hypothesis in MA users. There are published reports discussing reasons for initiating MA use, and to get more energy (*n* = 44) or stay awake (*n* = 34), escape (*n* = 24) and lose weight (*n* = 19)

were frequent responses (Bretch et al., 2004; Semple et al., 2007).

In summary, the relationship between MA use and depression appears to be bidirectional. As explained above, MA use causes disturbances in dopamine, serotonin, and brain energy metabolism predisposing an individual to depression. Moreover, individuals with depression, specifically those who experience low energy, sleep disturbances, weight gain and fatigue, may gravitate towards MA to alleviate depressive symptoms. However, there is a gap in the literature addressing the self-medication hypothesis in MA users, but it is not unreasonable to surmise that individuals with depression use MA to relieve their symptoms, and in turn, MA use causes further depression.

Methodology

This study involved a within subjects design to describe the relationships between creatine treatment and depression and creatine treatment and brain PCr levels. Longitudinal prospective depression data were collected from 14 females with depression who use MA. Neuroimaging data were collected pre- and postcreatine treatment from 10 of the females. Statistical analyses included a linear mixed effects repeated measures model and a paired t-test and Wilcoxon Signed Ranks test.

Study Design

A within subjects design of creatine monohydrate treatment of 14 depressed female MA users (the power analysis calculation is descried in the Statistical Analysis section of this chapter) was proposed. This was a pilot study to collect preliminary data

for a grant submission that proposed a randomized control trial (RCT) of creatine and placebo in depressed female MA users. All participants in this pilot study were treated with 5 grams of daily creatine for 8 weeks. The recommended creatine dose, 5 grams daily for 8 weeks, was based on doses that are most commonly used in clinical research trials and safety and efficacy consideration (Kondo et al., 2011; Lyoo et al., 2012). A dose of 5 grams daily was well tolerated in the only RCT of creatine as a treatment option for depression in adult females. Lyoo and colleagues (2012) reported no differences between the placebo and creatine groups with respect to adverse events, and there was a statistically significant decrease in HAMD scores in the creatine group. A dose of 5 grams was also well tolerated in the current study and adverse events are reported in Chapter 6. The following example doses have been used orally in adults (age $\geq$ 18):

- For older adults (age = 71 years): 0.3 grams/kilogram for 5 days, followed by 0.07 grams/kilogram for 79 days (Chilibeck, Chrusch, Chad, Shawn, Davison & Burke, 2005)
- Cholesterol reduction: 20-25 grams per day for 5 days followed by 5-10 grams daily (Earnest, Alamada & Mitchell, 1996)
- Chronic obstructive pulmonary disorder: 5.7 grams 3 times per day for 2 weeks, followed by 5.7 grams per day (Fuld et al., 2005), and 0.3 grams/kilogram per day for 7 days followed by 0.07 grams/kilogram daily for 7 weeks (Faager, Skold, Rundgren, Tollback & Jakobsson, 2006)
- Congestive heart failure: 20 grams for 5 days (Andrews, Greenhaff, Curtis, Perry & Cowley, 1998)
- Depression: 3-5 grams daily for 4 to 8 weeks (Kondo et al., 2011; Lyoo et al.,

2012; Roitman, Green, Osher, Kami & Levine, 2007)

- Muscular dystrophy: 10 grams daily for 8 weeks (Walter et al., 2000)

Variables

For specific aim one, *to describe changes in HAMD scores over the course of 8 weeks of creatine treatment in depressed female MA users,* there is not an independent variable and depression is the dependent variable. For specific aim two, *to compare pre- and postcreatine treatment in depressed MA users measured by* ^{31}*P MRS,* there is not an independent variable and the dependent variable is PCr levels.

Participant Selection Criteria

Using purposive sampling, 14 depressed female MA users were recruited for this open label trial of oral creatine. Table 1 and the following text describe study eligibility criteria. Females were considered for participation if they were between the ages of *18 – 64 years*, and met the operational definition of depression as a *HAMD of 15 or greater and DSM-IV criteria of major depressive disorder (MDD)* identified by the Structured Clinical Interview for DSM-IV Disorders (SCID-I/P) with psychotic screen (First, Spitzer, Gibbon, & Williams, 2007). An age range of 18 – 64 was chosen based on data published by the Utah Division of Substance Abuse and Mental Health (2014) regarding primary substance of choice by age. These data show that second to alcohol, MA was the preferred drug of abuse for adults between 35 and 64 years old. Further, MA was the third most preferred drug of abuse for adults between the ages of 25 and 34 years and the fourth preferred drug of abuse for adults less than 25 years of age (Division of Substance

Table 1

Study eligibility and early termination criteria

Inclusion Criteria	Exclusion Criteria	Early Termination Criteria
• Female gender, ages 18-64 years inclusive • Diagnosis of methamphetamine dependence or abuse within the past 12 months identified by the Structured Clinical Interview for DSM-IV Disorders with psychotic features (SCIP-I/P) • Methamphetamine preferred drug of choice • Current diagnosis of major depressive disorder identified by the SCIP-I/P • Current Hamilton Depression Rating Scale score $\geq$ 15	• Diagnosis of bipolar disorder or psychosis identified by the SCIP-I/P • History of or current diagnosis of renal disease, such as chronic renal failure, acute renal failure or end stage renal disease • Diabetes type I or II • Colitis or diverticulitis • Seizure disorder • Current suicide risk identified by the Columbia Severity Suicide Rating Scale • Current treatment with an antipsychotic, mood stabilizer or antidepressant • Positive HIV test identified by lab testing • Elevated liver enzymes identified by lab testing • Positive pregnancy test • Contraindication to magnetic resonance scan	• Intolerable or clinically significant side effects to creatine • Hospitalization for suicide ideation • Positive pregnancy test • Incarceration • Initiation of an antipsychotic, mood stabilizer or antidepressant

Abuse and Mental Health, 2014). In a study of posttreatment status of MA users who entered outpatient treatment, 62.7% (*n* = 71), compared with 62.9% (*n* = 72) at baseline, of the sample reported continued depression despite MA discontinuation 12 months after treatment initiation (Rawson et al., 2002), and therefore, females who met SCID-I/P diagnostic criteria for *MA dependence or abuse within the last 12 months* were considered for participation.

With respect to exclusion criteria, individuals who met criteria for *bipolar disorder or psychotic features* on the SCID-I/P were not invited to participate. Individuals were not considered for study participation if they had *renal disease* because to date it cannot definitively be stated if short- or long-term creatine usage is harmful to the kidneys. Females were also excluded if they were *diabetic* because one report suggests that creatine might influence insulin production, although studies of creatine administration on insulin production in humans have not yet been conducted (Benzi, 2004). Since GI discomfort has been reported in some individuals taking creatine (Smith & Dahm, 2000), females with *GI diseases, such as colitis (e.g., infectious colitis, ulcerative colitis, Crohn's disease, and ischemic colitis) or diverticulitis*, were excluded.

Females with a diagnosed *seizure disorder* were also be excluded, because in one report, the authors suggest that creatine might be implicated in possibly related seizure activity, although it is important to mention that the reported seizure activity was associated with hypoglycemia, secondary to a cardiovascular accident or cardiac arrest (Haller, Meier & Olson, 2005). Moreover, the seizure events were reported through the Food and Drug Administration's MedWatch System, but they did not undergo a formal review (Haller, Meier & Olson, 2005). *Current suicide risk* identified by administration

of the C-SSRS excluded a female's participation. Females *treated with an antidepressant, antipsychotic or mood stabilizing medication* were also excluded. The purpose of this study was to evaluate creatine administration as a stand alone treatment rather than an augmentation treatment. Finally, a *positive HIV test or elevated liver enzymes*, which were determined by a blood draw at the screening visit, excluded individuals as well as a *contraindication to magnetic resonance scan*, such as ferromagnetic items in the body that could not be removed.

Study withdrawal criteria included early termination if a participant experienced intolerable or clinically significant side effects to creatine, hospitalization for suicide ideation, positive pregnancy test, incarceration, and/or initiation of an antidepressant, antipsychotic or mood stabilizer. In addition, the principal investigator (PI) retained the right to withdraw participants from the study without their permission, in the event they were unwilling or unable to maintain adherence to the research protocol. Screening, enrollment and early termination data are presented in Chapter 6.

Definitions

Definitions used in describing the status of participants in the trial were as follows: "screened" participants were those who signed an informed consent form and provided any demographic or baseline assessments whether or not they met the eligibility criteria. "Enrolled" participants were those who meet eligibility criteria, completed the baseline ^{31}P MRS scan and were dispensed study medication at visit 1. "Completed" participants were those who completed the duration of the study through the follow up visits. "Partial completed" participants were those who completed 8 weeks of study drug

administration.

The study was divided into three phases: screening (or baseline), treatment and follow up phases (Table 2).

Recruitment and Informed Consent

Participants were recruited from Assessment and Referral Services (ARS). The following information about ARS and Interim Group Services is summarized from information posted on http://medicine.utah.edu/ars. Assessment and Referral Services is a freestanding clinic within the Department of Psychiatry at the University of Utah. It occupies 6000 square feet in downtown Salt Lake City close to public transportation and approximately 3 miles from the University of Utah. It consists of 20 full time staff and approximately 30 part-time staff. Salt Lake Behavioral Health Services contracts with ARS to provide two different functions. One is to provide assessments and referrals for individuals in Salt Lake County who have been arrested for driving under the influence; or who are seeking substance abuse services voluntarily or due to other court mandates. The second is to provide Interim Group Services (IGS), which are free groups for individuals awaiting Salt Lake County funded substance abuse treatment services.

There are two primary purposes of IGS. The first is to serve as the first step for adults who are residents of Salt Lake County and do not have the monetary benefit to pay

Table 2. Study phases

	Baseline phase			Treatment phase								Follow up phase		
Week #	-1	0	1	2	3	4	5	6	7	8	9	10	11	12

for substance abuse treatment. In almost all cases, those individuals are referred to IGS to begin the process of admission to treatment. The second purpose of IGS is to offer individuals a safe and supportive environment while they wait for treatment availability, which may be up to a 3 month wait.

At their first IGS meeting, individuals are provided with information regarding the scheduling of their clinical assessment. Assessments include a clinical interview, the American Society of Addiction Medicine Placement Criteria, and information from the Bureau of Criminal Identification if the individual has a pending legal issue. Individuals are then referred to the appropriate treatment agency based on issues such as their clinical needs, need for county funding, level of care indicated, and the compatibility between the agency's location and hours of operation with the individual's residence and employment situation.

During the assessment, ARS staff screened individuals for study participation. If an individual was female, between the ages of 18 – 64, reported depression and MA as a primary drug of choice, the screener provided the potential participant with the PI's phone number. Subsequently, females who called were asked preliminary screening questions by phone, and if they passed the phone screening, a formal informed consent process with the PI was scheduled to occur in a private office at ARS.

Consent for study participation was obtained prior to the conduct of any study procedures, including the initial assessment to determine whether the participant met study inclusion criteria. The participants completed an assessment of understanding of the consent process after the consent process was completed to document their understanding of the nature of the study. The informed consent process was open ended, and females

were given the opportunity to ask questions and take the consent form home to review it before signing it.

During the informed consent process, the study purpose, study procedures, risks and benefits of participation, contact information and statement about research related injuries were discussed. In addition, an explanation of reasons that the PI would withdraw participants from the study, the compensation schedule and use of protected health information (PHI) were also discussed.

Study fliers with the PI's contact information were also hung around ARS, and interested females called for additional information. If a female passed the preliminary phone screening, she was invited to attend an informed consent process visit.

Facilities

A private office at ARS was used for conducting screening and subsequent study visits. The office is stocked with clinical equipment, such as a blood pressure machine and a scale to measure weight, and blood drawing supplies. In addition, urine pregnancy and drugs of abuse tests were stored in the private office. Neuroimaging took place in the MRI suite at the University of Neuropsychiatric Institute (UNI) on a Siemens MAGNETOM Verio 3.0 Tesla 70cm bore MRI scanner.

Data Collection and Management

Study data were recorded on Case Report Forms (CRFs). Completed CRFs were filed in participant binders and stored in a locked office with access limited to research personnel. De-identified data from CRFs were entered into SPSS® version 20 for

Macintosh computer. Forms that had missing or inconsistent data were recorded in the database; however, a "missing data" code (-99) was entered in place of each piece of missing or inconsistent data.

Measures

The following instruments and their purpose with respect to the current study are listed as follows:

- Structured Clinical Interview for DSM-IV Disorders (SCID-I/P) with psychotic screen was used to determine study eligibility (e.g., determine if MDD and MA dependence/abuse within the last 12 months is present or absent)
- Hamilton Depression Rating Scale (HAMD) was used to evaluate change in the severity of depression over the course of the study
- Beck Anxiety Inventory (BAI) was used to evaluate change in the severity of anxiety over the course of the study because anxiety and MA dependence and anxiety and depression are often comorbid
- Columbia Suicide Severity Rating Scale (C-SSRS) was used to determine eligibility criteria and as a safety tool to assess suicidality over the course of the study
- Drug History Questionnaire (DHQ) was used to collect baseline drug use history to describe the sample
- Urine drug testing was used to measure the presence (or absence) of substances of abuse (e.g., MA, opiates, THC, cocaine and benzodiazepines)

  In the following paragraphs, psychometric properties of each of these

measurements are discussed. Internal consistency, test retest reliability and interrater reliability and content, construct, and criterion related validity from published reports are outlined. However, it is worth pointing out that traditional psychometric approaches are questioned as being appropriate for scales like the HAMD and BAI considering they were developed based on clinical classifications rather than an underlying construct (Fayers & Hand, 2002). Regardless, since traditional psychometric properties are more commonly understood and reported, they are included for the HAMD and BAI in the following paragraphs, and a more detailed discussion regarding reliability and validity of these scales is included in Chapter 6. Further, reliability estimates from the current study are also discussed in Chapter 6.

In addition to the above mentioned measurements, self-report drug use over the past 48 hours data for methamphetamine, cocaine, THC, opiates and benzodiazepines will be collected. Self-report drug use data will include use (yes or no), and if yes, quantity. Consistent with the self medication hypothesis (Khantzian, 1985), if mood symptoms improve, drug use may be reduced, and use will be monitored by self-report use as well as urine drug testing (discussed below). Demographic data, including age, race, ethnicity, marital status, income level, history of antidepressant treatment, and years of education were also collected to describe the sample, as well as an inquiry regarding treatment program attendance. Finally, adverse effects were monitored using a checklist of medication adverse effects.

Structured clinical interview for DSM-IV disorders. The SCID-I/P is a semi-structured clinician administered interview used to determine Axis I disorders (First, Spitzer, Gibbon, & Williams, 1997). Considering that the SCID-I/P is based on DSM-IV

diagnostic criteria, reliability for categorical constructs is reported in terms of Kappa, which is a statistic that corrects for chance agreement (Viera & Garrett, 2005). Relevant to the sample recruited in this study, Kappa values ranging from .64 to .90 (Lobbestael, Leurgans, & Arntz, 2011; Segal, Kabacoff, Hersen, Van Hasselt, & Ryan, 1995; Skre, Onstad, Torgersen, & Kringlen, 1991; Williams, et al., 1992; Zanarini & Frakenburg, 2001; Zanarini, et al., 2000) have been reported for the MDD section of the SCID-I/P and .76 – 1.0 (Lobbestael, Leurgans, & Arntz, 2011; Skre, Onstad, Torgersen, & Kringlen, 1991; Williams, et al., 1992; Zanarini, et al., 2000) for the substance dependence/abuse section. Also relevant to the sample of interest, interrater reliability for raters was found to be Kappa = 0.81 for the depression module and Kappa = 0.78 for the substance use disorder module of the SCID-I/P were reported for a sample of 922 females (Bromberger et al., 2005).

Validity of the SCID-I/P can be evaluated in terms of how well it reflects the DSM-IV diagnostic criteria, although, this can be complex because the SCID-I/P is typically used as the "gold standard" to which other measures are compared to (First et al., 1997). Extensive pilot and field testing suggest acceptable content validity of the SCID-I/P in mixed age samples (First et al., 1997). A summary of the criterion related validity studies indicate there is a high level of correspondence between SCID-I/P determined diagnoses and other variables including clinical symptoms of disorders (First et al., 1997). Relevant to the sample that was recruited, there is good evidence for concurrent validity in a sample of substance abusers (n = 83 inpatient and n = 17 day treatment participants) with a current diagnosis of major depression on the SCID and the Addiction Severity Index (ASI) psychological severity score (M = 0.62, SD = 0.14, $p <$

.001; Kranzler, Kadden, Babor, Tennen, & Rounsaville, 1996). In addition, in the same sample, excellent discriminate validity for current alcohol and drug abuse/dependence SCID diagnoses and the ASI alcohol score have been established ($M = 0.60$, $SD = 0.22$, $p < 0.001$; Kranzler et al., 1996).

Hamilton Depression Rating Scale. The HAMD is a semistructured clinician administered depression rating scale and is the most widely used rating scale for depression (Bagby, Ryder, Schuller & Marshall, 2004; Hamilton, 1960). The original HAMD consisted of 17-items, and later it was revised to a 21-item scale with four additional items (diurnal variation, paranoid ideation, obsessive/compulsive symptoms, and depersonalization/derealization) that are not summated in the total score (Iannuzzo, Jaeger, Goldberg, Kafantaris & Sublette, 2006). The 17-item HAMD consists of 17 items that are rated on a 3 or 5 point scale that represent the level of severity for that symptom (i.e., item) over the prior 7 days. An item score of 0 indicates absence of symptoms for that item, whereas an item score of 1-5 suggests mild to severe symptoms for that item. The total range is from 0 to 50, with scores of 0 to 3 suggesting "normal" or "no illness;" those between 4 and 7 indicating "borderline ill;" scores between 8 and 15 representing "mildly ill;" scores between 16 and 26 signifying "moderately ill" and capture diagnostic criteria for major depressive disorder; scores greater than or equal to 27 are considered to be in the range of "markedly" or "severely ill" (Furukawa, Akechi, Azuma, Okuyama, & Higuchi, 2007).

Internal consistency of the HAMD has been reported with Cronbach's alpha ranging from 0.46 – 0.92 (Bagby et al., 2004). Cronbach's alpha of 0.46 was reported from a study evaluating depression severity in a sample of 100 elderly participants with

physical illness, and the author concluded that the HAMD is an unreliable tool for measuring depression in their population of interest (Hammond, 1998). Test retest reliability is satisfactory at the item level with Pearson's r $\geq$ 0.70 in all of the published studies (Bagby, et al., 2004). Finally, reports of interrater reliability have shown acceptable agreement among raters, with Kappa values of 0.81 – 1.00 (Iannuzzo et al., 2006). The use of a structured interview guide has been shown to increase interrater reliability from a Pearson's r as low as 0.39 without the structured interview guide to a Pearson's r of 0.78 with the structured interview guide (Bagby, et al., 2004).

Validity of the HAMD has been extensively evaluated, and findings suggest that it is a highly valid instrument for defining and measuring depression in adult patients with mental illness (Bagby, et al., 2004). However, there are no reports on the HAMD being valid in a sample of MA users. There are questions on the HAMD related to sleep and appetite and responses to these questions could be influenced by amount and frequency of MA use. For example, an MA using individual may report insomnia because she recently used MA for several days in a row. As such, questions on the HAMD related to sleep would be scored based on her insomnia related to MA use and not necessarily based on her mood (i.e., depression).

In the area of content validity, concern with regard to the HAMD adequately capturing the current operationalized definition of depression has been raised (Bagby et al., 2004). The HAMD items are based on the DSM criteria for depression, and the DSM has been revised three times since the inception of the HAMD. However, the core items of depression on the DSM remain unchanged, and similarly, the core items of the HAMD have remained the same for 40 years (Bagby et al., 2004).

Fourteen separate instruments have been used to evaluate convergent validity, and several of the studies reported intercorrelations ≥ .70. To measure discriminant validity, investigators have attempted to detect depression in patients with medical conditions rather than psychiatric disorders. Their findings suggest that positive predictive power was low and variable even though sensitivity, specificity, and negative predictive power were large and consistent (Bagby et al., 2004). Also, studies have been conducted comparing predictive validity of the HAMD with other scales measuring depression, such as the Beck Depression Inventory (BDI) and Zung Self-Rating Depression Scale, and the HAMD was found to be more sensitive to change than other scales (Bagby et al., 2004).

Beck Anxiety Inventory. The Beck Anxiety Inventory (BAI) is a 21-item self-report instrument for assessing the severity of anxiety (Beck, Brown, Epstein, & Steer, 1988). Each item offers four response choices scored from 0 to 3, with a higher score representing a more severe experience of the symptom. Adequate internal consistency has been reported in samples of nonpsychiatric patients, inpatient psychiatric patients and outpatient psychiatric patients with Cronbach's alpha ranging from 0.83 to 0.95 (De Ayala, Vonderharr-Carlson & Kim, 2005). Test-retest reliability is satisfactory with a mean reliability estimate of 0.66 and time intervals between administrations ranging from 7 to 112 days with an average of 32 days (De Ayala et al., 2005). Relevant to how the BAI was administered for this study, a 1 week test retest estimate of 0.75 has been reported (Beck et al., 1988). Since the BAI is a self-report tool, there are no reports of interrater reliability.

Validity of the BAI has been evaluated and results indicate that it is a valid tool for measuring the construct of anxiety. With regard to content validity, the BAI addresses

the majority of DSM symptoms of generalized anxiety in addition to 11 out of 13 of the DSM symptoms of panic disorders (Beck et al., 1988). Findings from studies of construct validity indicate acceptable convergent and discriminate validity. For convergent validity, correlations in the range of 0.47 to 0.71 between the BAI and the Cognition Checklist Anxiety Subscale, the State Trait Inventory, the Anxiety Subscale of the Symptom Checklist-90-Revised, and the Hamilton Rating Scale for Anxiety and anxiety diaries have been reported (De Ayala et al., 2005). Studies of discriminant validity have shown that the BAI is highly correlated with the Beck Depression Inventory (r = .61; Steer, Ranieri, Beck, & Clark, 1997) but factor analysis results indicate that the Beck Depression Inventory items load on different factors than BAI items (Beck et al., 1988).

Methamphetamine contributes to a large release of norepinephrine in the central nervous system, and these levels have been noted to be elevated for several months after discontinuing MA use (Rothman et al., 2001). Heightened anxiety in both active MA users and abstinent individuals may be due to changes in the noradrenergic system (Rothman et al., 2001). Consequently, anxiety data are being collected as a possible confounding variable.

Columbia Suicide Severity Rating Scale. The C-SSRS is a semistructured clinician administered scale to assess for suicidality (Posner et al., 2011). There are two forms of the C-SSRS: a baseline scale and a past week scale. The baseline scale is used to establish lifetime and current suicide attempts or ideation, and the past week scale evaluates sucidality over a period of 7 days (Posner et al., 2011). Reports of internal consistency in studies of adults with depression and/or other psychiatric concerns have shown acceptable internal reliability with a Cronbach's alpha = 0.73 for baseline and past

week (Posner et al., 2011). In a study of adolescents with a history of a recent suicide attempt, internal consistency of the C-SSRS was noted to be high, Cronbach's alpha = 0.937 for the initial visit and 0.946 for the past week visit (Posner et al., 2011).

Three separate studies of adults or adolescents with psychiatric diagnoses – a treatment study of adolescent suicide attempters (n = 124), a medication efficacy trial with depressed adolescents (n = 312) and a study of adults presenting to an emergency department for psychiatric reasons (n = 237) – evaluated convergent and divergent validity. Pearson's r was calculated from comparing components on the C-SSRS with other instruments measuring similar constructs. These results indicate strong convergent validity, with the C-SSRS baseline moderately correlated with the Scale for Suicide Ideation (r = 0.52), and the C-SSRS past week scale moderately correlated with the suicide item on the Montgomery Asberg Depression Rating Scale (MADRS; r = 0.69; Posner, et al., 2011). The past week C-SSRS was compared with depression items on the MADRS and BDI, and the C-SSRS demonstrated strong divergent validity when items on the MADRS and BDI did not overlap with items on the C-SSRS except with the suicide items (Posner et al., 2011). Finally, an assessment of predictive validity, using the Columbia Suicide History Form and the suicide evaluation board classifications, demonstrated that baseline C-SSRS ratings significantly predicted suicide attempts (Posner et al., 2011).

Drug History Questionnaire. The DHQ is a single page form that includes nine different classes of drugs: alcohol, cannabis, hallucinogens, depressants, inhalants, narcotics, stimulants, tranquilizers, and other drugs (Sobell, Kwan & Sobell, 1995). The following self-report information is collected for each individual drug class: 1) was the

drug ever used, and if so 2) number of years used; 3) was the drug prescribed; 4) last year the drug was used; and 5) frequency of past use during a typical month. Self-report data collection is often the only viable approach to assessing drug history, and participants' responses may be influenced by their ability to recall information or their willingness, or lack thereof, to share information (Napper, Fisher, Johnson & Wood, 2011). There are relatively few published studies that have addressed the psychometric properties of self-report measures of drug use. The only published report of psychometric properties of the DHQ evaluated test retest reliability (Sobell et al., 1995). The results of the study indicate that drug abusers currently in a treatment setting can reliably (Pearson's r values ranged from 0.53 – 0.89) report drug use information (Sobell et al., 1995). The DHQ is being collected to evaluate drug use characteristics.

Urine drug testing. Urine drug testing is regarded as the gold standard for drug testing because urinary assay allows for the evaluation of presence or absence of certain drugs with acceptable specificity, sensitivity, low cost, and noninvasive administration (Manchikanti et al., 2010). In this study, FDA cleared, Clinical Laboratory Improvement Amendment (CLIA) waived five panel (opiates, benzodiazepines, cocaine, THC and methamphetamine) drug screening test manufactured by Drug Test Success will be used. The five panel test was compared with other commercially available rapid drug tests using approximately 300 specimens, and accuracy results showed > 97% agreement ("One Step Drug Test: Marijuana, Cocaine, Opiates, Amphetamine, Methamphetamine and Benzodiazepines," n.d.). Specificity and sensitivity tests indicate that the five panel test is highly specific at detecting positive tests at 5 minutes after the card was dipped in urine, and very sensitive at $\pm$ 25 % cutoff range for the respective urine metabolites

("One Step Drug Test: Marijuana, Cocaine, Opiates, Methamphetamine and Benzodiazepines," n.d.). The use of drugs of abuse may influence an individual's mood, and therefore, urine drug testing occurred at each study visit.

Study Procedures

To determine if an individual was eligible for study participation, a screening visit was conducted. At the screening visit, the SCID-I/P was administered to determine a diagnosis of MDD or other Axis I disorders and MA dependence or abuse within the past 12 months. The HAMD, BAI, C-SSRS and DHQ were also administered. Finally, a urine sample for a pregnancy and drugs of abuse panel was collected, as well as vital signs and recording of concomitant medications and self-report drug use. Following the screening visit, participants were scheduled for the baseline ^{31}P-MRS procedure. At the baseline ^{31}P-MRS visit, the HAMD, BAI and C-SSRS were administered, as well as collection of urine for pregnancy and drugs of abuse testing, vital sign monitoring, recording of concomitant medication and self-report drug use.

At the first study visit the HAMD, BAI and C-SSRS were administered, as well as collection of urine for pregnancy and drugs of abuse testing, vital sign monitoring and recording of concomitant medication, self-report drug use and study medication dispensing. Participants were then to be seen twice weekly for a total of 8 weeks (see Table 3 for a list of procedures by week). After 56 days ($\pm$ 3 days) of creatine treatment, participants were scheduled for their end of treatment ^{31}P MRS scan. Finally, participants were seen for three follow up visits, 7 days ($\pm$ 3 days), 14 days ($\pm$ 3 days) and 21 days ($\pm$ 3 days) after their last dose of creatine.

Table 3. List of study procedures by week

	Baseline phase			Treatment phase								Follow up phase		
Week #	-1	0	1	2*	3*	4*	5*	6*	7*	8*	9	10	11	12
Informed Consent	x													
Demographics	x													
Medical History & Physical Exam	x													
Phlebotomy for Serum Labs (CBC & CMP)	x										x			
Phlebotomy for HIV Screening	x													
Urine Sample for Pregnancy & Drug of Abuse Testing	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IGS and Other Treatment Program Attendance	x	x	x	x	x	x	x	x	x	x	x	x	x	x
**Dispense Study Medication			x	x	x	x	x	x	x	x				
DHQ & SCID-I/P	x													
***HAMD & BAI	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C-SSRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs, Con Meds, Self-report Drug Use	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Monitoring				x	x	x	x	x	x	x	x	x	x	x
^{31}P MRS Scan		x									x			

CBC = complete blood count; CMP = comprehensive metabolic panel; IGS = Interim Group Service; DHQ = Drug History Questionnaire; SCID-I/P = Structured Clinical Interview for DSM-IV Disorders with psychotic screen; HAMD = Hamilton Depression Rating Scale; BAI = Beck Anxiety Inventory; C-SSRS = Columbia Suicide Severity Rating Scale; ^{31}P MRS = phosphorus magnetic resonance spectroscopy

*During the 8 weeks of treatment, participants will be seen twice weekly (visits separated by at least 48 hours)

**Study medication will be dispensed at the first study visit of the week

***HAMD & BAI will be collected at one of the twice weekly study visits

Magnetic Resonance Spectroscopy

All participants were scanned using a 3 Tesla clinical whole-body MRI system (Siemens Medical Solutions, Erlangen, Germany) located at the University of Utah Neuropsychiatric Institute (UNI). Scanning consisted of a phosphorus spectra (^{31}P-MRS) scan with anatomic images. The magnetic resonance (MR) system is equipped with multinuclear capability, with 8 kHW wideband RF amplifiers, and the necessary hardware and software for conducting multinuclear experiments. Anatomic MRI scans screen participants for gross structural abnormalities, and acquire high resolution images for the use of gray and white matter segmentation and coregistration with spectra data. Participants were placed supine on the scanner table and were given a set of foam earplugs to attenuate sound. After localizer imaging, anatomical MRI was obtained using a three-dimensional chemical Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence. The parameters for the structural MRI were as follows; T1 weighted image: TR=2000 ms, TE=3.37 ms, TI=1100 ms, average number=1, flip angle=8°, FOV=256 mm, matrix 256x192x144, bandwidth=300 Hz/pixel, slice thickness 1.0 mm and no gap. To screen for structural abnormalities, a board-certified Radiologist at the University of Utah reviewed all images.

Compensation

Participants were compensated up to a total of $290 in the form of gift cards to a variety of local businesses including, but not limited to, restaurants, grocery stores, bookstores, and coffee shops, as long as the locations did not sell alcohol or cigarettes. Compensation was given using the schedule below.

1. $25 - Screening
2. $25 - Baseline neuroimaging
3. $25 - Visit 1 (initiation of study drug)
4. $10 - First weekly visits for weeks 2-8 (total = $70)
5. $5 - Second weekly visits for weeks 2-8 (total = $35)
6. $25 - Week 9 (end-of-treatment neuroimaging)
7. $25 - Week 10
8. $10 - Week 11
9. $50 - Week 12

Study Drug

Administration

Five grams of creatine was dispensed on Day 0. Participants were instructed to take creatine with food, and to stir creatine into a noncarbonated drink such as water, juice, coffee, or tea. Participants were directed to take creatine daily for 8 weeks. At each study visit, study medication adherence was assessed. Participants were asked to maintain empty bottles of creatine and return them at weekly visits. Participants were informed to store creatine at room temperature. The half life of creatine is between 72 and 96 hours, and therefore, up to four doses of creatine could be missed before the participant was withdrawn from the study for noncompliance.

Storage and Accountability

The study drug was stored at room temperature in a locked room with access limited to authorized individuals. An inventory that includes a signed account of study drug received, dispensed to and returned by each participant was maintained. At the conclusion of the study, final drug supply (used and unused) inventory and reconciliation was conducted. A copy of the final inventory is filed in the regulatory binder.

Data Analysis

Power Analysis

Based on prior clinical experience regarding treatment completion among female MA users, for this pilot study, a sample size of 10 was initially proposed. Considering a 40% attrition rate, 14 participants were proposed to achieve a sample size of 10. To determine the minimum effect that would likely be detected with a sample size of 10, a nondirectional power analysis was performed with alpha = 0.05. Effect for the power analysis was specified as average baseline (over three measures) HAMD scores compared with average HAMD scores during active treatment (over eight measures). A gradual onset of effect during active treatment is assumed, starting with an effect of 0 and ending with an effect of 0.5, resulting in an average effect during treatment of 0.25. The effect to be tested was treated as a linear combination of the separate measures (y*), and a pattern of correlation of 0.5 was used. This generated a standard deviation (SD) for y* that will be different from the within-occasion SD for Y itself. Then the effect magnitude specified was divided by the SD(y*) to generate an “effective” or de facto effect size, which resulted in an effect size of 1.09 with a power of 0.87.

Statistical Analyses

To address the primary hypothesis that there would be a decrease in HAMD scores over time with creatine treatment, change from baseline over time was analyzed using linear mixed effect model repeated measures (MMRM) with maximum likelihood estimation. Likelihood based mixed effect models provide an overall framework to analyze longitudinal data that include data that are missing at random (MAR) by estimating the individual slope to summarize each participant's response (Mallinckrodt et al., 2003). Hamilton Depression Rating Scale scores from the baseline period were averaged and compared with the mean HAMD scores from the treatment period.

To address the secondary hypothesis that compared to baseline, PCr levels would be higher at the posttreatment scan, a paired t-test and Wilcoxon Ranked Signs test was performed.

Study Personnel

The investigative team comprised of the PI, a PhD candidate from the College of Nursing, clinical research coordinators and research faculty from the Diagnostic Neuroimaging group of the Department of Psychiatry. The PI had primary responsibility for screening participants for study eligibility, data collection and analysis and manuscript preparation. The PI trained the three clinical research coordinators on all aspects of the study and data collection, including administration of the HAMD and BAI, to assist when the PI was unavailable. Dr. Kelly Posner, creator of the C-SSRS, by way of an instructional DVD, provided C-SSRS training. The research faculty were responsible for the MRS methods, acquisition and analysis.

Human Subjects and Data and Safety Monitoring Plan

Description of Protocol and Participants

The purpose of this feasibility study was to evaluate changes in depression rating scores and brain PCr levels in female MA users who took creatine for 8 weeks. The sample consisted of 14 females between the ages of 18 and 64 of age who signed the consent form and took the first dose of creatine (see Table 1 study eligibility criteria). The sample was primarily recruited from ARS, the substance abuse evaluation clinic that is part of the University of Utah's Department of Psychiatry. The investigative team comprised of faculty and staff from the Department of Psychiatry and College of Nursing. The PI was a PhD candidate in the College of Nursing.

Study participants were asked to attend an informed consent process and screening visit, precreatine MRS visit, twice weekly treatment period visits for 8 weeks, a postcreatine treatment MRS visit and three follow up visits. The HAMD was collected once per week, whereas urine sample for drug screen testing, self-report substance use and the C-SSRS were collected twice weekly. Finally, 5 grams of daily creatine was dispensed weekly for 8 weeks.

Investigational New Drug

This study was conducted under IND application 114316, which was issued to Dr. Perry Renshaw by the Division of Psychiatry of the FDA in January 2012. In December 2013, the current study was submitted as a subprotocol of the IND, and after the 30 day FDA review period and the University of Utah Institutional Review Board (IRB)

approval was issued, the study was started. Regulations under Section 21, Part 312 of the Code of Federal Regulations (CFR; Food and Drug Administration, 2014) were followed for this IND study

Risks to Study Participants

Methamphetamine using females with depression were proposed for this study. Pregnant females and nursing mothers were excluded from participation since the effects of MRS and creatine exposure on a fetus or developing child are unknown. Pregnancy testing was administered at every visit, and if a female became pregnant during the course of the study, she would have been withdrawn and referred to obstetrics and gynecology care.

The following are risks that could have resulted from study participation. During the screening visit, participants could have become emotionally upset when asked about their psychiatric history including suicide attempts, or physical and sexual abuse. It was also possible for participants to experience discomfort or swelling when blood was drawn for laboratory tests. Rarely, infection can result from blood draws, and if an infection had occurred, the participant would have been referred for appropriate care. Further, intravenous drug users could have experienced a trigger to use drugs during the blood draw. Counseling about the trigger would have been offered at the time of blood draw as necessary. It is possible that a participant's illness could have worsened during the study. If the participant's illness worsened to the point that they were a danger to herself or others, she would have been referred for appropriate care. If the participant were hospitalized for worsening illness, she would have been withdrawn from the study.

As a requirement by the Division of Psychiatry of the FDA, the C-SSRS was collected at every visit, and if a female had endorsed current serious suicide risk, she would have been referred by a phone call from the PI to psychiatric care with her primary psychiatrist. In the case of no primary psychiatrist or the inability to contact the primary psychiatrist, the female would have been referred to emergency care at UNI.

Magnetic resonance imaging/magnetic resonance spectroscopy scans do not use ionizing radiation. Instead, magnetic fields and radio waves are used to take pictures. There are no known risks related to MRI scans other than the risk of injury when metallic objects are brought into the scanning room by mistake. Serious injury can occur during an MRI scan to persons who have a cardiac pacemaker, metal clips on blood vessels (also called stents), artificial heart valves, artificial limbs, brain stimulator devices, implanted drug pumps, cochlear implants, ocular implants or known metal fragments in eyes, exposure to shrapnel or metal fillings, other metallic surgical parts, orthodontic braces, body jewelry or piercings that cannot be removed for the scan, and certain transdermal patches. Participants were screened for these items before they were cleared for the MRI/MRS scans. Participants could have experienced claustrophobia, dizziness, headaches, or a metallic taste in the mouth while inside the scanner. These symptoms are temporary, and would have stopped when the participant left the scanner.

Other than to comply with FDA regulations, information obtained about participants in the course of the study did not leave the University of Utah in any form that would identify participants. Confidentiality was assured by locking all consent forms and case report forms in locked cabinets located in a locked office. Participants were assigned a code (i.e., participant ID) for all documentation and data analysis files.

Benefits to Study Participation

There were no guaranteed benefits to participation in this research. However, potential benefits to participants included a comprehensive psychiatric and medication evaluation, treatment and close monitoring by study personnel at no cost and a copy of their magnetic resonance imaging (MRI) scan. If a participant seemed to truly benefit from the study medication and wished to continue it after the study ended, the PI would make an effort to provide information about creatine that is available as a nutritional supplement in the United States.

Data Safety and Monitoring

Clinical data were collected using standardized paper CRFs and were only identified with the study's ID of the participants. The codes that link the name of the participant and the study ID were kept confidential by the investigative team on a password protected, encrypted, electronic file. Collected CRFs were securely transported to the PI's data entry center. The PI was responsible for entering the data into SPSS® version 20 for Macintosh computer. The PI monitored data on a continuous basis and the PI's dissertation committee chair, Gwen Latendresse, and committee member, Perry Renshaw, provided oversight.

Reporting Mechanisms

Adverse events (AEs), which are discussed in detail in Chapter 6, were reported to the University of Utah Institutional Review Board (IRB) and FDA in the annual request for study continuation report. There were no Serious Adverse Events (SAEs)

reported in this study.

Funding and Conflict of Interest

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CHAPTER 4

A REVIEW OF TREATMENT OPTIONS FOR COMORBID METHAMPHETAMINE USE DISORDERS AND DEPRESSION[1]

Abstract

Comorbid methamphetamine (MA) use and depression interferes with treatment outcomes. Female MA users are known to have higher rates of depression than male MA users, although this is also true for the general population. There are limited treatment options for the management of depression among MA users. In this integrative review, data on treatment strategies for comorbid depression and MA use disorders is summarized. English-language articles were identified from PsychINFO, CINAHL, PubMed, and Medline as well as from reference lists of key articles. Search terms included *methamphetamine, depression,* and *treatment.* Research articles describing psychological (n = 3), pharmacological (n = 6), nutritional supplement (n = 1), and psychological combined with pharmacological (n = 3) approaches for the treatment of MA use or withdrawal and/or depression are included in this review. Psychological and combination psychological with pharmacological approaches have not been shown to be

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effective in treating these comorbid conditions. Antidepressants have been determined to be ineffective and/or to introduce side effects. Gender differences with response to treatment were examined in only one of the published studies. There is a large gap in knowledge regarding treatment of comorbid MA use disorders and depression. Considering that female MA users experience higher rates of depression than male MA users, a focus on gender specific treatment approaches is warranted.

Introduction

Methamphetamine, a derivative of amphetamine, is a potent stimulant that affects the brain and central nervous system. Methamphetamine use results in increased dopamine release in the brain, as well as reduction of dopamine uptake, causing feelings of pleasure, increased energy, and greater alertness, and as a result, MA has high abuse potential. Methamphetamine use rates have fluctuated over the past decade in the United States with more stable rates over the past 4 years. In 2013, the National Survey on Drug Use and Health reported that 595,000 Americans 12 years or older reported using MA in the past month (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). In comparison, in 2005 and 2006, past month MA initiates reached 2.4 million in Americans older than 12 years of age (SAMHSA, 2012). Even though rates of MA use have declined nationally, the consequences of MA abuse are still a public health concern. Both acute and chronic MA abuse have serious medical, psychiatric and dental repercussions. Short- and long-term health effects of MA abuse include stroke, (Perez et al., 1999), cardiac arrhythmia (Haning & Goebert, 2007), depression (McKetin, Lubman, Lee, Ross, & Slade, 2011; Thomas et al., 2010), anxiety (Glasner-Edwards et

al., 2010), insomnia, paranoia (McGregor et al., 2005), and structural and chemical changes to the brain (Sekine et al., 2003; Yoon et al., 2010). Depression, in particular, is a public health concern because cost-of-illness research has indicated that depression is associated with considerable economic burden, with the majority of the burden deriving from lost work productivity (Wang, Simon, & Kessler, 2003). Along those same lines, depression also impacts our healthcare system as nearly 70% of patients seen in a primary care setting present with symptoms consistent with depression (Robinson, Geske, Prest, & Barnacle, 2005), but accurate depression diagnoses are often delayed by comorbid medical conditions (Katon, 2004). Finally, with respect to MA dependency and comorbid depression, research shows that this dual diagnosis worsens the overall prognosis and confounds treatment outcomes (Glasner-Edwards et al., 2010).

Comorbid Methamphetamine Use and Depression

It is not uncommon for depression and substance use to occur simultaneously (McKetin et al., 2011; Thomas et al., 2010). The association between the two conditions is likely bidirectional, with short- and long-term substance use resulting in mood changes, and substance use being a compensatory behavior to alleviate symptoms of depression (Koob et al., 2013). Methamphetamine has unique effects as its chronic use is known to reduce brain concentrations of dopamine and serotonin, which predisposes MA users to depression (Sekine et al., 2003; Thomas et al., 2010). Moreover, MA directly influences brain monoamine regulation resulting in a state that includes several of the features of major depression, including mood, sleep and appetite disturbances (London et al., 2004). However, symptoms of depression are not exclusive to MA use. Studies of other

substances of abuse, such as cocaine, heroin, alcohol, and nicotine, have documented increased rates of depression that exceed general population estimates. Similarly, a pattern of elevated comorbid substance use disorders and depression generally involves more females than males. For example, in a study of adults seeking treatment for cocaine abuse, 34.8% (n = 32) of females versus 28.6% (n = 59) of males, also met criteria for lifetime major depression (McCance-Katz, Carroll, & Rouansaville, 1999). Findings from large survey studies are similar for both opioid use disorders and major depression as well as alcohol dependence and major depression. Rates have been documented as 63.5% (n = 141) of females compared to 45.7% (n = 162) of males (Grella, Karno, Warda, Niv, & Moore, 2009), and 48.5% (n = 102) of females compared to 24.3% (n = 86) of males, respectively, meeting criteria for comorbid depression and an opioid use disorder or alcohol dependence (Kessler, Crum, Warner, Nelson, Schulenberg, & Anthony, 1997). The prevalence of daily nicotine use and comorbid depression, on the other hand, appears to be higher in males (36.8%; n = 326) compared to females (33.6%; n = 674; Husky, Mazure, Paliwal, & McKee, 2008).

Several studies have shown that depression rates are higher in MA using females compared to males (Glasner-Edwards, Mooney, et al., 2008a, 2008b; Semple et al., 2007). With that said, it is unclear if this is a result of an existing gender difference, a type of self-medication, or a consequence of MA use, however, the prevalence of pre-morbid depressive disorders in MA users has been documented to be high, with a majority reporting a significant lifetime history of depression (Drake, Kaye, McKetin, & Duflou, 2008; Hall, Andrus, Oostveen, Althaus, & VonVoigtlander, 1996; Zweben et al., 2004). For example, in one study, MA users had a 62% (n = 187) rate of depression and a

23% (*n* = 69) rate of suicidality prior to initiating MA use, and after MA use was initiated, depression rates increased by nearly 20% (Hall et al., 1996). Further, using the Beck Depression Inventory (BDI) Semple and colleagues (2007) noted that 60% (*n* = 88) of MA using females in their study met criteria for moderate to severe depression, and these females were three times more likely to have used MA "to cope with mood" compared to females with lower levels of depressive symptoms. Moreover, in a longitudinal study of MA dependent adults participating in the Methamphetamine Treatment Project, 70% (*n* = 368) of the females who met criteria for major depressive disorder at study initiation still met criteria for depression at a 3 year follow up visit (Glasner-Edwards, Mooney, et al., 2008a). In contrast, in one study of MA dependent adults, rates of depression were noted as higher in males (31%; *n* = 32) than females (28%; *n* = 7), but as the authors noted, the instrument used, the Psychiatric Diagnostic Screening Questionnaire, does not indeed detect DSM criteria, but rather, serves as a screening tool (Polcin, Buscemi, Nayak, Korcha, & Galloway, 2012). Nonetheless, the majority of these findings highlight that females in general are more likely than males to have depression, and with substance use disorders, gender differences are underscored in ways that suggest greater rates of comorbid depression in females relative to males.

Diagnosing and Treatment of Depression Among Methamphetamine Users

The diagnosis and treatment of depression among MA users is problematic because intoxication and withdrawal symptoms mirror symptoms of depression. There are at least three distinct syndromes to consider when assessing MA users: 1) expected

effects from MA use and symptoms of withdrawal when MA use is discontinued; 2) depressive symptoms that develop during periods of active MA use; and 3) a depressive disorder that is independent from MA use. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) offers guidelines for discerning independent depressive disorders and substance induced disorders. According to the DSM-5, if depressive symptoms develop before substance use was initiated or if symptoms occur and persist for 4 weeks or longer after substance use is terminated, criteria are met for an independent depressive disorder (American Psychiatric Association [APA], 2013). Also, based on DSM-5 criteria, depressive symptoms that manifest during a period of substance use that is insufficient to attain intoxication or withdrawal effects would be a diagnosis of an independent depressive disorder (APA, 2013). Conversely, criteria for substance induced depression are met when depressive symptoms occur during or soon after intoxication or withdrawal from a substance that is capable of producing the symptoms (APA, 2013). Yet, there are no published studies that have addressed the reliability of DSM-5 criteria for differentiating between substance intoxication and withdrawal symptoms versus an independent depressive disorder.

There is some evidence, though, of acceptable reliability (kappa = 0.75) for a current independent diagnosis of depression among substance users as well as reliability (kappa = 0.66) for current substance induced depression in a study evaluating the Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV (PRISM; Hasin, Samet, Nunes, Meydan, Matseoane, & Waxman, 2006), although these measures of reliability are limited to one report and it is not well documented if the PRISM is widely used. It is also noteworthy that time constraints in a clinical setting may

not permit for rigorous patient interviewing to separate substance induced symptoms from more enduring symptoms. In the face of these challenges with distinguishing between an independent depressive disorder and a substance induced depressive disorder, the significance of these differential diagnoses is centered on treatment planning and improving outcomes.

Despite the evidence regarding depression rates in MA users, little is known about treatment options for depression among MA users. Treatment approaches for MA dependence have been recently reviewed (Ciketic, Hayatbakhsh, Doran, Naiman, & McKetin, 2012; Lee & Rawson, 2008), but the issue of managing comorbid conditions has not been examined closely. Therefore, the purpose of this paper is to summarize published reports on treating depression in MA users with a particular focus on treatment response differences by gender. Evaluating treatment response by gender is important since rates of MA use among males and females approach nearly equal proportions (Durell, Kroutil, Crits-Christoph, Barchha, & Van Brunt, 2008). This use rate pattern is unlike that observed with many other drugs of abuse, which typically demonstrate men using more than females (Durell et al., 2008). Given the paucity of information with regard to treating comorbid MA use disorders and depression, this chapter will help provide a review of treatment approaches and their outcomes.

Methods

Following Whittemore and Knafl's (2005) guidelines, an integrative review was conducted with a specific focus on treatment approaches for depression in MA use disorders. Methods were used to identify relevant literature included searching electronic

databases and searching the reference lists of key papers. The electronic databases searched included: PsychINFO, CINAHL, PubMed, and Medline. The key search terms included in the search were "methamphetamine," "depression," and "treatment." Next, data were evaluated for inclusion. Articles were selected for their relevance to the research focus. Publications reporting findings from preclinical or animal studies were excluded. Finally, the data were extracted from primary sources and organized by treatment approach.

Results

There is very little documentation available regarding the treatment of comorbid MA use and depression. The peer reviewed publications selected for this integrative review included empirical research reports that described findings from randomized controlled trials and nonrandomized trials. Publications emerged beginning in the early to mid-1990s. The search yielded three articles reporting psychological approaches for managing comorbid depression and MA dependence. There were six articles found reporting findings from studies evaluating pharmacological approaches to treating MA dependence or withdrawal, and even though the primary outcome of these studies was not to treat comorbid depression and MA dependence, they were included in this review because depression was a secondary outcome measure. There was one article reporting the results of a nutritional supplement trial of comorbid unipolar or bipolar depression and MA dependence identified in the search. Finally, three articles were found reporting findings from a study investigating the combination of a pharmacological and psychological approach for the treatment of MA dependence.

Psychological Approaches

All of the studies evaluating psychological approaches to treating comorbid depression and MA use investigated cognitive behavioral therapy (CBT) as an intervention (see Table 4). During the last 3 decades, CBT has been considered one of the most effective types of therapy for treatment of alcohol and drug dependencies (Anton et al., 2005; DeRubeis & Crits-Christoph, 1998; Mattick & Heather, 1993), but little evidence exists regarding the use of CBT for treating comorbid depression and MA use. In fact, Peck and colleagues (2005) compared 16 weeks of CBT, contingency management (CM), CBT plus CM, and gay specific CBT, and noted a 75% decrease in MA use across all groups randomized to the four difference conditions, but no statistically significant changes in depression were detected. In another study, participants assigned to CBT reported nearly 50% less amphetamine use over 6 months, but CBT had only a short-term effect on depression rating scores (Baker et al., 2004). Baker and colleagues (2004) did not separate the findings by type of amphetamine so changes specific to MA use are unknown. Collectively, these findings suggest that CBT is useful for reducing MA use but not for the treatment of comorbid MA use and depression.

Stepped-care, which is a health care model that supports starting with a less intensive approach to treatment and transitioning to more intensive therapy if indicated (Murphy, Lynch, Oslin, McKay, & TenHave, 2007), has also been evaluated for treatment of alcohol and drug use disorders. As with CBT, there are limited reports of stepped-care being effective for comorbid depression and MA use. In a feasibility study, a stepped-care approach was shown to be effective in reducing depressive symptoms (Kay-Lambkin, Baker, McKetin, & Lee, 2010), however, these findings warrant further

Table 4

Psychological approaches for the treatment of comorbid depression and methamphetamine use

Author	Sample	Study design	Intervention	Depression as primary or secondary	Tool for measuring depression	Length of time in study	Results
Baker et al., 2004	214 amphetamine users (62.6% male)	Randomized controlled trial	MI CBT	Secondary	Beck Depression Inventory II	Not specified, but participants randomized to 2 or 4 sessions of CBT + self-help booklet or self-help booklet alone	There was a statistically significant improvement in depression rating scores between pre- and post-treatment ($F_{1,148}$=48.61, p<0.001) and between pretreatment and 6-month follow up ($F_{1,146}$=51.77, p<0.001), and no differences in scores between posttreatment and 6 months
Kay-Lambkin, Baker, McKetin, & Lee, 2010	18 current MA users (56% male)	Non randomized trial	One-session integrated brief integration (BI) Fixed integrated CBT/MI Stepped care intervention	Primary	Beck Depression Inventory II	20 weeks	Participants receiving stepped care intervention reported a 53% decrease in depression rating scores compared to a 48% decrease in the control group
Peck, Reback, Yang, Rotheram-Fuller, & Shoptaw, 2005	162 gay and bisexual male MA users	Non randomized trial	CBT CM CBT + CM Gay specific CBT	Primary	Beck Depression Inventory	16 weeks	No statistically significant differences in depression were noted

MI = motivational interviewing; CBT = cognitive behavioral therapy; MA = methamphetamine; BI = brief integration; CM = contingency management

exploration and replication in a larger sample of MA users. Two of the studies evaluating psychological approaches to the treatment of MA included participants of both genders (Baker et al., 2004; Kay-Lambkin et al., 2010), whereas one of the studies included male homosexual participants only (Peck et al., 2005). Of the two studies that included both males and females, treatment response results were not separated by gender. However, even though there was a gender bias favoring the enrollment of males, 62.6% (n = 134; Baker et al., 2004) and 56% (n = 11; Kay-Lambkin et al., 2010), more females (83.3%; n = 178) were likely to complete treatment compared to males (60.5%; N = 129; Baker et al., 2004).

Pharmacological Approaches

There is one published study on the use of an antidepressant for the management of MA withdrawal, four published studies on the utilization of antidepressants in treating MA dependence, one published study evaluating a stimulant for the treatment of MA dependence, and one published study on the utility of a nutritional supplement in treating comorbid depression and MA use (see Table 5). In the studies evaluating the use of antidepressants, the authors also compared differences in depressive symptoms between the groups randomized to an antidepressant or placebo. The findings consistently demonstrated no significant changes in depressive symptoms (Cruickshank et al., 2008; Elkashef et al., 2008; Galloway, Newmeyer, Knapp, Stalcup, & Smith, 1994; Galloway, Newmeyer, Knapp, Stalcup, & Smith, 1996; Shoptaw et al., 2008).

Brown and Gabrielson (2012) reported findings from a randomized controlled trial of the nutritional supplement citicoline or placebo for bipolar or unipolar depression

Table 5

Pharmacological approaches for the treatment of comorbid depression and methamphetamine withdrawal or dependence

Author	Sample	Study design	Intervention	Depression as primary or secondary	Tool for measuring depression	Length of time in study	Results
*Cruickshank et al., 2008	31 amphetamine or MA dependent adults (63% male)	RCT	Mirtazapine or placebo	Secondary	Depression-Anxiety-Stress Scale	2 weeks	No significant changes in depression in either condition
**Galloway et al., 1994	151 cocaine dependent adults 32 MA dependent adults (71% male)	Double blind, randomized trial	Imipramine 10, 50, 100 or 150mg	Secondary	Beck Depression Inventory	26 weeks	No significant intergroup differences in depressive symptoms were observed
**Galloway et al., 1996	32 MA dependent adults (91% male)	Double blind, randomized trial	Imipramine 10 or 150mg	Secondary	Beck Depression Inventory	26 weeks	No significant intergroup differences in depressive symptoms were observed
** Elkashef et al., 2008	151 MA dependent adults (67% male)	RCT	Bupropion or placebo	Secondary	Hamilton Depression Rating Scale	12 weeks	No statistically significant changes in depression in either condition
** Shoptaw et al., 2008	73 MA dependent adults (64% male)	RCT	Bupropion or placebo	Primary	Beck Depression Inventory	12 weeks	No statistically significant changes in depression in either condition
** McGaugh et al., 2009	8 MA dependent adults (39% male)	Non randomized feasibility trial	Modafinil	Primary	Hamilton Depression Rating Scale	6 weeks	Statistically significant decrease in depression ratings (t=-2.50, df=29, p=0.03)
**Brown & Gabrielson, 2012	48 MA dependent adults with unipolar or bipolar depression (54% male)	RCT	Citicoline or placebo	Primary	Inventory of Depressive Symptomatology-Clinician Version	12 weeks	Citicoline group experienced a 33% improvement in depression rating scores compared to a 13% improvement in the placebo group

MA = methamphetamine; RCT = randomized controlled trial
*Study of MA withdrawal
**Study of MA dependence

among MA dependent adults. Their study results demonstrated a 33% improvement in depression rating scores measured by the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) in the citicoline group, whereas the placebo group demonstrated a 13% improvement in IDS-C scores (Brown & Gabrielson, 2012). It is worth noting that citicoline (generic name for CDP-choline when used as a supplement) is a complementary and alternative medicine approach for the treatment of depression. In the United States, citicoline, which is a natural occurring compound, is sold as a nutritional supplement over the counter (Adibhatla & Hatcher, 2005). Apart from the mood finding, self-report MA use and urine drug screen findings indicated no significant differences in MA use from study entry to study completion (Brown & Gabrielson, 2012). Finally, there were no significant differences noted with regard to frequency and amount of MA use for the duration of the study between groups (Brown & Gabrielson, 2012). These findings suggest that citicoline is not effective in the treatment management of comorbid MA dependence and depression, although the study needs to be replicated in a larger sample focused solely on either unipolar or bipolar depressed participants.

In an open label study evaluating a nonamphetamine stimulant, modafinil, for the treatment of MA dependence, the authors reported a statistically significant decrease in Hamilton Depression Rating Scale (HAMD) scores from beginning of the study to completion (McGaugh et al., 2009). However, there was no change in the number of positive urine drug screens during the course of the 6 week trial (McGaugh et al., 2009). These findings should be interpreted with caution considering the sample size at study initiation was eight and only four participants remained at study completion. Furthermore, the choice of a parametric statistical method may not have been appropriate

based on the small sample size.

Only one of the published findings of pharmacological approaches to treating either MA dependence or depression among MA users separated results by gender (Elkashef et al., 2008). All of the studies enrolled more males than females with the exception of the open label modafinil study, which enrolled four females and three males (McGaugh et al., 2009).

Pharmacological and Psychological Approaches

There are three published studies regarding the combination of pharmacological and psychological approaches to the treatment of MA dependence (see Table 6). The majority of the studies suggest that pharmacological and psychological studies are not effective for treatment of MA dependence (Heinzerling et al., 2010; Shoptaw et al., 2006) and/or the participants experienced undesirable side effects (Shoptaw et al., 2006). Indeed, in the placebo controlled trial of the selective serotonin reuptake inhibitor (SSRI) sertraline, the researchers found that participants randomized to the SSRI experienced sustained craving and had an increased rate of relapse (Shoptaw et al., 2006). On the other hand, in a sample of HIV positive MA abusing males, in a single blind study of modafinil combined with CBT, medication responders experienced a decrease in depressive symptoms over 12 weeks, with medication response being defined as a greater than 50% reduction in the number of days of self-report MA use (McElhiney, Rabkin, Rabkin, & Nunes, 2009). Since 55% of the males were on antiretroviral therapy (McElhiney et al., 2009), it is possible that there was an interaction between the antiretroviral medication and modafinil resulting in changes in mood. Nonetheless, the

Table 6

Psychological plus pharmacological approaches for the treatment of methamphetamine dependence

Author	Sample	Study design	Intervention	Depression as primary or secondary	Tool for measuring depression	Length of time in study	Results
Shoptaw et al., 2006	229 MA abusing or dependent adults (61% male)	RCT	Sertraline or placebo + CM Sertraline or placebo only	Secondary	Beck Depression Inventory	12 weeks	No significant differences for sertraline, contingency management or their interaction in depression ratings
McElhiney, Rabkin, Rabkin, & Vunes, 2009	13 MA abusing or dependent HIV+ males	Single blind, non randomized feasibility trial	Modafinil + CBT	Secondary	Beck Depression Inventory	16 weeks	Methamphetamine craving and depression ratings decreased in medication responders (defined as > 50% reduction in reported days used per week at end of study compared with beginning of study).
Heinzerling et al., 2010	71 MA dependent adults (70% male)	RCT	Modafinil or placebo + CBT and CM	Secondary	Beck Depression Inventory II	12 weeks	No significant differences noted in reducing depression, MA craving or retention between the two groups

MA = methamphetamine; RCT = randomized controlled trial; CM = contingency management; CBT = cognitive behavioral therapy

results of this study are not generalizable when taking into account the small homogenous sample (n = 10 completers).

Of the three studies evaluating the combination of pharmacological and psychological interventions for the treatment of MA dependence, one of them included only males (McElhiney et al., 2009). The other two studies did not separate the findings by gender, and both studies enrolled more males than females (Heinzerling et al., 2010; Shoptaw et al., 2006).

Discussion

This review explored treatment approaches for the management of comorbid depression and MA use. The results yielded a total of 13 publications. Studies evaluating psychological approaches, such as cognitive behavioral therapy, are limited, and results suggest that psychological interventions may be useful in treating MA dependence but not depression among MA users. In studies of antidepressants for treatment of MA withdrawal, dependence and comorbid mood disorders, findings have suggested that antidepressants are ineffective.

However, results from a randomized control trial of the nutritional supplement citicoline demonstrate that citicoline may be effective in reducing depressive symptoms in a sample of unipolar and bipolar depressed MA using adults, but not effective in reducing MA dependence. Citicoline is an endogenous intermediate in the biosynthetic pathways of structural membrane phospholipids. Of relevance, citicoline increases brain dopamine and norepinephrine levels, presumably by increasing the activity of tyrosine hydroxylase (Secades and Lorenzo, 2006). Considering that chronic MA use results in

disturbances in the dopaminergic systems, perhaps citicoline administration helps correct these disturbances, and in turn, mood is improved.

In a small open label study of a nonamphetamine stimulant, modafinil, for the treatment of MA dependence, depressive symptoms improved over the course of the study, but concerns of a small sample size (n = 4 completers) needs to be examined when evaluating these results. Moreover, in a small (n = 10 completers) study of modafinil combined with CBT in HIV positive males, depressive symptoms improved and self-report MA use was reduced over the 12 week treatment period. Modafinil has stimulant-like effects, which may explain lower depression rating scores while taking it (Price & Taylor, 2005). Finally, studies investigating a nonamphetamine stimulant or antidepressant in addition to psychological approaches in treating MA dependence have demonstrated to be ineffective, have undesirable side effect profiles, or enrolled a small homogenous sample, which limits generalizability of the study results. Only one of the published reports separated treatment response results by gender. Overall, there were a higher percentage of males enrolled in each study, which is not too surprising considering that several of the studies enrolled HIV positive males only.

The main finding from this review, that treatment options are scarce for comorbid depression and MA use disorders, was anticipated given that there is little evidence based research guiding the management of comorbid mood and substance use disorders. Findings from RCT of pharmacotherapy for a comorbid substance use disorder, with alcohol being the primary substance evaluated, and bipolar disorder consistently reveal that there are no changes in either depressive or manic symptoms (Brown, et al., 2009; Salloum, Cornelius, Daley, Kirisci, Himmelhoch, & Thase, 2005; Stedman, Pettinati,

Brown, Kotz, Calabrese, & Raines, 2010; Tolliver, Desantis, Brown, Prisciandaro, & Brady, 2012) or reductions in alcohol use (Brown, et al., 2009; Stedman, et al., 2010; Tolliver, et al., 2012).

Results, however, are inconsistent from RCT studies of pharmacotherapy management of comorbid substance use disorders, with opiates, alcohol or cocaine largely investigated, and unipolar depression. Studies demonstrate either a reduction in cocaine or alcohol use but no changes in depressive symptoms (Ciraulo, et al., 2005; Hernandez-Avila, Modesto-Lowe, Feinn, & Kranzler, 2004; Pettinati, et al., 2010), reduced alcohol use and depressive symptoms (Moak, Anton, Latham, Voronin, Waid, & Durazo-Arvizu, 2003), or no changes in opiate, alcohol, or cocaine use and/or depressive symptoms (Carpenter, Brooks, Vosburg, & Nunes, 2004; Petrakis, Carroll, Nich, Gordon, Kosten, & Rounsaville, 1998; Pettinati, Volpicelli, Luck, Kranzler, Rukstalis, & Cnaan, 2001; Schmitz, Averill, Stotts, Moeller, Rhoades, & Grabowski, 2001). Moreover, experimental and nonexperimental studies evaluating psychological approaches for the treatment of comorbid mood disorders and substance use disorders show varying results, but overall demonstrate that MI combined with CBT may result in short-term reduced substance use and improvements in mental status (Cleary, Hunt, Matheson, & Walter, 2008).

One of the goals of this review was to investigate if treatment response differs by gender. However, reporting results by gender was not common, and more males compared to females were enrolled in most of the studies. Because rates of substance use overall generally favors males, (Durell et al., 2008), this finding was expected. Nonetheless, barriers to seeking substance abuse treatment and treatment retention that

are specific to females are worth considering. For instance, substance abusing females worry about losing custody of their children if they seek services for substance related issues (Brady & Ashley, 2005). Further, limited access to and lack of financial support for childcare services in addition to responsibilities as a mother are frequently reported as obstacles to females seeking substance abuse treatment (Brady & Ashley, 2005; van Olphen & Freudenberg, 2004). Lastly, reports suggest that females experience greater social stigma and guilt than males do, which may serve as an additional impediment to females seeking substance abuse treatment (Booth & McLaughlin, 2000; Brady & Ashley, 2005).

Studies of comorbid depression and substance use disorders are faced with particular challenges. Notably, attrition rates are remarkably high (Gelkopf, Weizman, Melamed, Adelson, & Bleich, 2006; Sayre, Schmitz, Stotts, Averill, Rhoades, & Grabowski, 2002), and teasing apart symptoms of depression as a primary diagnosis from substance withdrawal symptoms can be difficult. Along those same lines, measuring the severity of depression in substance abusing and dependent populations is not easy. The oscillation between intoxication with and withdrawal from substances may artificially drive depression rating scores up or down. Even though depression is common with abuse or dependence in all classes of substances, the distinct pharmacological effects of MA are unique. During periods of intoxication, by way of increased synaptic dopamine concentrations, MA may exert mood elevating effects, however, once MA use is stopped, the “crash” or “come down” results in symptoms of depression.

Recommendations

The findings of this review demonstrate the limitations of treatment options for the management of comorbid depression and MA use disorders. Even though investigations of modafinil should be interpreted cautiously due to small, heterogeneous samples sizes, clinicians might consider prescribing it for patients with depression and MA use disorders. Also, detailed psychiatric and substance use histories should be collected for making a distinction between a primary diagnosis of depression versus substance induced depression.

Until there is a broader evidence based foundation for the treatment of comorbid depression and MA use disorders, attention should be focused on designing and conducting high quality clinical trials. Future studies should include larger sample sizes in addition to standardized outcome measures. Also, standardized treatment and follow up periods would be advantageous for understanding treatment effects. Lastly, as clinicians and clinical investigators investigate new strategies for treating comorbid depression and MA use disorders, more gender specific attention is warranted.

Conclusions

No clear treatment model exists to suggest how to optimally manage comorbid depression and MA use disorders. Several studies have shown that female MA users experience depression at rates higher than males MA users, although this is also true in the general population. Investigating treatment options for MA users that have greater efficacy and/or safer side effect profiles is an important next step. Also, standardizing measurement and reporting for future studies in this area (e.g., using the same depression

rating scale and reporting outcomes by gender) would be useful for interpreting results and understanding additional gaps in our knowledge of comorbid MA use and depression. High quality studies of comorbid depression and MA use disorders are required for building a more expansive foundation of evidence based practice to guide clinical and research recommendations.

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CHAPTER 5

THE UTILITY OF MRS FOR UNDERSTANDING SUBSTANCE USE DISORDERS[1]

Abstract

Magnetic resonance spectroscopy (MRS), a noninvasive and nonionizing imaging technique, is being widely used in substance abuse research. It provides useful information with regard to brain metabolism, neuronal health, neurotransmission and cellular membrane integrity and the effects substances have on these processes. Both proton (^{1}H) and phosphorus (^{31}P) MRS have been applied to evaluate substance induced injury within the brain, recovery from substance use disorders as well treatment response to medication. A search of the literature published during the past decade resulted in nearly 50 publications that utilized MRS to investigate brain chemistry changes associated with substance use disorders. While methamphetamine (MA) use disorders received the most attention in the last 10 years, information from all drug classes demonstrated quantitative correlates of injury relevant to substance use. The most consistent finding noted was decreased content of *N*-acetylaspartate (NAA), a marker of neuronal vitality. The relationship between brain chemistry changes with substance use

[1] This chapter was coauthored with Xianfeng Shi, Gwen Latendresse and Perry F. Renshaw and was submitted to the Journal of American Psychiatric Nurses Association on October 15, 2014.

and the impact on cognition was understudied over the past 10 years. The few studies that have been published in this area suggest a negative correlation between changes in neurochemistry and measures of attention, but continued work needs to be conducted to gain a better understanding of the effects of substances on cognition. The concern of small sample sizes in addition to low statistical power needs to be considered when evaluating reports of MRS substance abuse studies. At the same time, the potential impact of continued MRS application in the field of substance abuse is profound when considering its ability to investigate treatment response and potentially predict relapse.

Introduction

Magnetic resonance spectroscopy is gaining popularity in substance abuse research as a tool for identifying brain biomarkers and monitoring response to treatment. This noninvasive imaging technique does not use ionizing radiation making it low-risk for research on a number of populations including children. Magnetic resonance spectroscopy provides in vivo data on the concentration of neurometabolites, which can be used to track diseases and assist in developing novel treatments targeted at bioenergetics. The utility of MRS in substance use disorders is providing important insights into the cerebral consequences and etiology of drug abuse in addition to observing changes over time during abstinence.

Magnetic Resonance Spectroscopy Technique

Similar to magnetic resonance imaging (MRI), the fundamentals of MRS are based on nuclear magnetic resonance (Castillo, Kwock, & Mukherji, 1996). Chemists

have applied in vitro spectroscopy as a technique for evaluating compounds in a solution since around the 1950s, but the application of MRS to study humans is relatively new. The Food and Drug Administration (FDA) approved the use of MRS as a clinical tool in 1995 (Gujar, Maheshwari, Bjorkman-Burtscher, & Sundgren, 2005), and while data can be collected from human tissue in nearly any part of the body, the brain has been most frequently studied. Most published studies of human brain biochemistry report findings using two MRS-visible nuclei: ^{1}H and ^{31}P; however, other methods include carbon-13 (^{13}C) and fluorine (^{19}F; Lyoo & Renshaw, 2002).

Proton MRS has the advantage over other MR active nuclei of utilizing the same hardware that is used for routine clinical MRI, and consequently, it is readily accessible and the associated costs are relatively low (Barker & Lin, 2006). Due to the high sensitivity of the proton nucleus, and its ubiquitous presence in a range of compounds found in human tissue, information from ^{1}H MRS is relatively straightforward to obtain and interpret. An advantage to ^{31}P MRS is the extensive information it provides with regard to bioenergetics, cellular membrane precursors and break down products (Reddy & Keshavan, 2003). On the other hand, technical aspects of ^{31}P MRS, such as low spatial resolution and signal-to-noise ratios (SNR), limit its clinical applicability (Barker & Lin, 2006), but ^{31}P MRS is gaining popularity in research. Along those same lines, the main advantage of utilizing ^{13}C MRS is the rich information it offers about glial-neuronal interactions (Mason & Krystal, 2006), but because it requires particular hardware, ^{13}C-labeled substrate infusions, and specialized expertise, it is not commonly used clinically or in research (Barker & Lin, 2006).

Finally, advantages to using ^{19}F MRS is that it offers the ability to detect

fluorinated medications in the brain (Mason & Krystal, 2006) and its sensitivity to motion is less than other MRS techniques (Strauss, Unis, Cowan, Dawson, & Dager, 2002). However, as with ^{13}C MRS, it requires specialized hardware and expertise, and its applicability is limited to research focused on studies of drug distribution and/or pharmacokinetics.

There are different field strengths for human brain MRS, ranging from 0.5 Tesla (T) to 7 T (Barker & Lin, 2006). Higher field strengths have the advantage of increased SNR, enhanced signal detection and better spatial resolution (Lyoo & Renshaw, 2002). In substance abuse research, field strengths of 1.5 – 4 T are commonly used.

A superconducting magnet creates a strong magnetic field and serves as the common factor in both MRI and MRS. The set up for MRS studies is similar to MRI with the exception of extra steps required for data acquisition and analysis. Shimming, the first step in acquiring clinical data from MRS, is a process used to achieve homogeneity of the magnetic field (Gujar et al., 2005). As the concentration of water far exceeds the concentration of neurometabolites by a factor of more than 10,000, a second important step in spectroscopy is suppression of the water signal. Other MRS considerations include application of specific acquisition methods such as single-voxel (SV) versus chemical shifting imaging (CSI) and repetition and echo time parameters; however, it is beyond the scope of this paper to discuss details with regard to these methods (see de Graaf, 2007). Importantly, planning and performing MRS research differs from MRI research. Further, it requires knowledge of biophysics and an understanding of which acquisition methods to use to answer a research question.

Measurable Compounds

In MR imaging, the signal, primarily from hydrogen atoms of water, is displayed as images. In MRS imaging, the signal derives from much less concentrated compounds, and results are represented as a collection of peaks referred to as a resonance within a spectrum (Gujar et al., 2005). Measured in parts per million (ppm), the peaks are distributed along the *x*-axis, and the intensity of the peaks is represented on an arbitrary scale along the *y*-axis (see Figure 2). In brain MRS, the most commonly observed resonance peaks are NAA, creatine (Cr), choline (Cho), and *myo*-inositol (mI). Peaks that are also detected, but not as commonly, include gamma-aminobutyric acid (GABA), glutamate (Glu) and glutamine (Gln). The spectrum of resonances provides information about the function of neuronal structure, phospholipid metabolism and cellular membrane integrity (see Table 7).

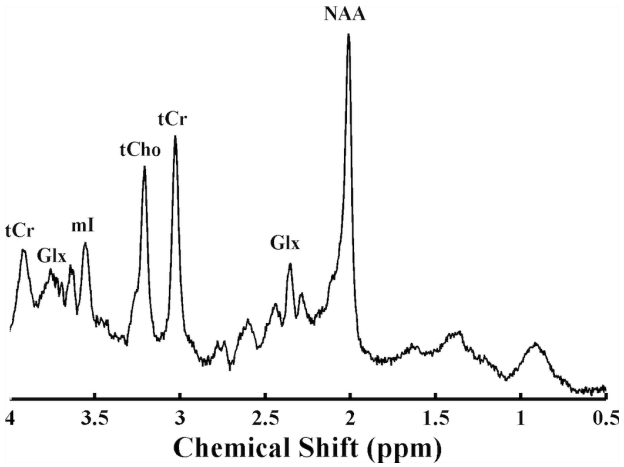

Figure 2. Proton magnetic resonance spectrum from human anterior cingulate cortex using a short TE (30s). Metabolites are labeled total creatine (tCr), glutamine + glutamate (Glx), *myo*-inositol (mI), total choline (tCho), *N*-acetylaspartate (NAA). Figure from Xianfeng Shi.

Table 7. Metabolites displayed in a resonance of spectrum

Metabolite	Spectrum location (ppm)	Role	Physiologic Significance
N-acetylaspartate (NAA)	2.02	Marker of neuronal integrity	Lower concentrations are considered a sign of neuronal loss or damage
Creatine (Cr) and phosphocreatine (PCr)	3.03 & 3.94	Brain energy metabolism	Decreased Cr seen in liver disease and decreased PCr seen in depression
Choline (Cho)	3.20	Cell membrane turnover	Higher levels of Cho with demyelination and tumors
Myo-inositol (mI)	3.56	Glial marker	Increased mI seen in Alzheimer's disease, diabetes mellitus and multiple sclerosis & decreased mI in chronic hepatic & hypoxic encephalopathies, stroke, Graves' disease & lymphoma
Glutamate (Glu) and glutamine (Gln)	2.40	Brain metabolism	Increased Glu with brain injury and in encephalopathy/hyperammonemias
Gamma-Aminobutyric acid (GABA)	3.03	Neuronal control	Decreased GABA may be associated with neuronal dysfunction

N-acetylaspartate

N-acetylaspartate is observed at 2.02 ppm in the spectrum and is the most prominent signal in the water suppressed proton spectrum. The precise physiological role of NAA is not known, but one of its functions relates to neuronal and axonal integrity while another role involves mitochondrial bioenergetics (Gujar et al., 2005). Lower concentrations of NAA have been interpreted as a sign of neuronal loss or damage in neurological (Achtnichts et al., 2013; Verma et al., 2013), sleep (Yadav et al., 2014) and psychiatric disorders (Kraguljac et al., 2012; Maltezos et al., 2014).

Creatine

The creatine resonance is a composite peak consisting of both Cr and phosphocreatine (PCr), and is observed at 3.03 and at 3.94 ppm. Creatine and PCr are believed to be sensitive to changes in brain energy metabolism. Similar to NAA, alterations in brain Cr concentrations are considered to reflect mitochondrial dysfunction (Sung et al., 2013) as well as changes in cerebral energy metabolism (Iosifescu et al., 2008). The energy buffering system in the brain is made up of PCr and adenosine triphosphate (ATP), and a phosphate group is transferred from PCr to adenosine diphosphate (ADP) by the enzyme creatine kinase, thereby replenishing ATP. Given that there are changes in neuronal energy requirements, mitochondrial dysfunction causes reductions in the formation of PCr transferred by mitochondrial creatine kinase (Sung et al., 2013). Lower concentrations of Cr have been seen in liver disease (Barker & Lin, 2006), and reduced levels of PCr have been noted in depression (Forester et al., 2009; Iosifescu et al., 2008; Kondo et al., 2011; Moore, Christensen, Lafer, Fava, & Renshaw,

1997).

Choline

The Cho containing compounds glycerophosphocholine and phosphocholine contribute to the Cho peak observed at 3.20 ppm. Concentrations of glycerphosphocholine and phosphocholine vary depending on brain region with higher levels found in myelin (Licata & Renshaw, 2010). Choline containing compounds play an important role in the synthesis and degradation of cellular membranes and are considered sensitive to changes in membrane turnover (Gujar et al., 2005). Therefore, an increase in Cho levels, as seen in neurodegenerative disorders (Bustillo, 2013) and with demyelination and tumors (Gujar et al., 2005) may reflect an increase in cellular production (Castillo et al., 1996; Gujar et al., 2005).

Myo-inositol

The mI peak occurs at 3.56 ppm. The exact role of mI within the brain is not clear, but it is considered to be a glial marker with its function relating to osmoregulation. For example, it maintains osmotic balance through regulation of plasma membrane mI transport (Haris, Cai, Singh, Hariharan, & Reddy, 2011). Elevated mI content has been seen in Alzheimer's disease, diabetes mellitus and multiple sclerosis, whereas decreased mI has been observed in chronic hepatic and hypoxic encephalopathies, stroke, Graves' disease and lymphoma (Haris et al., 2011).

Glutamate and Glutamine

Both Glu and Gln resonate closely together as peaks located between 2.10 and 2.50 ppm. The peak seen at 2.40 ppm is typically referred to as a combined Glu and Gln resonance and is referred to as Glx (Licata & Renshaw, 2010). These metabolites make up the glutamate glutamine cycle, which plays a central role in brain metabolism. Injury to the brain may result in impaired transportation of Glu and as a result, increased values may be detected (Shutter, Tong, & Holshouser, 2004).

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid, or GABA, is detected as a peak at 3.03 ppm. As the primary inhibitory neurotransmitter in the central nervous system, GABA plays an important role in neuronal control. Decreased brain GABA concentrations may suggest neuronal dysfunction (Long et al., 2013). Glutamate, Gln and GABA are notorious for being difficult to measure, and despite developments to improve obtaining data from these metabolites, they are not as commonly reported as other neurometabolites.

A Decade of MRS Studies in Substance Use Disorders

Alcohol

Seven ^{1}H MRS studies have been conducted over the past decade to evaluate the effects of alcohol use on brain chemistry. With the exception of two studies (Hermann et al., 2011; Yeo et al., 2013), all of the studies employed scanners with a field strength of 1.5 T (Bartsch et al., 2007; Ende et al., 2005; Gazdzinski, Durazzo, Weiner, & Meyerhoff, 2008; Meyerhoff et al., 2004; Miese et al., 2006). Magnetic resonance

spectroscopy studies of alcohol use over the past decade appear to be largely consistent with reports of an association between long-term alcohol use and neuronal injury in a variety of brain regions (Gazdzinski et al., 2008; Meyerhoff et al., 2004; Yeo et al., 2013). For instance, Meyerhoff and colleagues (2004) noted that levels of frontal white matter (WM) NAA were lower in heavy drinkers when compared to light drinkers. Moreover, the damage caused by alcohol use appears to persist after 1 week of abstinence (Gazdzinski et al., 2008), but there is evidence of at least partial recovery after 2 to 3 months of abstinence (Bartsch et al., 2007; Ende et al., 2005). For example, Ende et al. (2005) found increased concentrations of Cho in the superior frontal gyrus, cerebellar vermis and dentate nucleus compared to baseline Cho measurements in alcoholic dependent individuals who were abstinent for 12 weeks.

Along side neuronal injury, changes in glutamatergic neurotransmission have also been reported with higher concentrations of Glu noted in treatment seeking alcohol users during acute alcohol withdrawal but not in healthy comparison participants (Hermann et al., 2011). Lastly, differences in mI levels were also noted in alcohol users versus comparison participants with reports of lower mI with alcohol use (Gazdzinski et al., 2008). Taken together, these findings highlight the neurotoxicity of chronic alcohol consumption with the potential for sustained short-term effects but the possibility of recovery with abstinence over time.

While changes in neurochemistry with alcohol use have been well documented over the past 10 years, less is known about how these alterations influence cognition. One study employed neuropsychological testing to understand the association between brain chemistry and attention and concentration in alcohol users (Bartsch et al., 2007). The

authors reported an increase in frontomesial NAA with 6-7 weeks of abstinence accompanied by improvements in attention, but no correlation between cognitive function and cerebral Cho levels, or between long-term memory, nonverbal and verbal cognitive abilities and NAA or Cho (Bartsch et al., 2007). These findings suggest that the relationship between brain chemistry and cognition may be region specific and perhaps provide evidence of repair to neuronal viability with abstinence. More work in this area, though, would be able to provide a better understanding of these relationships.

Methamphetamine

It is not surprising that there are more MRS studies of MA (n = 9) use published in the last 10 years than any other substance of abuse in light of the public health concerns surrounding MA use (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). The majority of published studies have utilized ^{1}H MRS at 1.5 T (Ernst & Chang, 2008; Nordahl et al., 2005; Salo, Buonocore, et al., 2011; Salo, Nordahl, et al., 2011; Salo et al., 2007) or 3 T (Cloak, Alicata, Chang, Andrews-Shigaki, & Ernst, 2011; Howells et al., 2014; Y. H. Sung et al., 2007) while one study reported findings from a ^{13}C MRS study using a 1.5 T field strength scanner (Sailasuta, Abulseoud, Harris, & Ross, 2010) and another study used ^{31}P MRS imaging at 3 T (Sung et al., 2013).

Results from ^{1}H MRS studies have noted that MA use is associated with lower levels of NAA in the frontal lobe (n = 30) and anterior cingulate cortex (ACC; n = 70) but not in the occipital cortex (n = 36; Howells et al., 2014; Nordahl et al., 2005; Salo et al., 2007; Sung et al., 2007). Further, concentrations of Glu in frontal white matter have been reported to be significantly higher in female MA users (n = 5) abstinent for at least 7

days compared with healthy controls (*n* = 6; Sailasuta, Abulseoud, Hernandez, Haghani, & Ross, 2010), which is consistent with MA induced neurotoxicity.

Further, a ^{31}P MRS study noted that PCr levels in MA users (*n* = 51) were significantly decreased when compared to values observed in healthy controls (*n* = 23), and this effect was greater in females (*n* = 23) than males (*n* = 28; Sung et al., 2013). Lastly, longitudinal studies of 5 months of abstinence in MA users provide evidence for normalization of brain chemistry with reports of frontal GM Glx decreasing after 1 month of abstinence as well as a negative correlation between abstinence and Glx concentrations 5 months later (Ernst & Chang, 2008). Moreover, ACC Cho concentrations were noted to be elevated with short-term abstinence (*n* = 25; Nordahl et al., 2005; Salo et al., 2011), suggesting that the rate of cell membrane turnover is high in the early stages of brain recovery from MA use. The findings from these studies join evidence implicating serious consequences of MA use, and since there are no pharmacological therapies approved by the FDA for the treatment of MA abuse or dependence, these findings draw attention to the need to develop treatment options aimed at brain bioenergetics.

The association between changes in brain chemistry in MA users and its effect on cognition is also under studied. Since 2004, one study used a neuropsychological test, the Spatial Stroop Attention Test (Stroop, 1935), to evaluate the relationship between ^{1}H MRS findings and selective attention. Findings from this study indicate that ACC NAA/Cr values negatively correlated with measures of attentional control in MA users (*n* = 36) while healthy volunteers (*n* = 16) did not exhibit a correlation between attentional control and ACC NAA/Cr ratios (Salo et al., 2007). Given the implications of the ACC's role in attention, it is not surprising to observe neuronal injury combined with decreased

attention in MA users.

3,4-methylenedioxymethamphetamine

The main neurometabolites of interest in ^{1}H MRS studies of MDMA, or 3,4-methylenedioxymethamphetamine (commonly known as "Ecstasy") have been NAA and mI concentrations. Findings from these studies (n = 7) over the last decade have not demonstrated a consistent pattern of MDMA effects on the brain (Daumann et al., 2004; de Win, Jager, Booij, Reneman, Schilt, Lavini, Olabarriaga, den Heeten, et al., 2008; de Win, Jager, Booij, Reneman, Schilt, Lavini, Olabarriaga, Ramsey, et al., 2008; de Win et al., 2007), even when employing higher field strengths at 3 or 4 T (Cowan et al., 2007; Cowan, Joers, & Dietrich, 2009).

Only one study reported significant differences in neurometabolites in MDMA users relative to healthy volunteers, and in this study, the authors noted elevated basal ganglia mI with MDMA use (n = 31) but not in a non-MDMA using comparison group (n = 33; Liu et al., 2011). It is not clear why reports over the past 10 years have produced conflicting results that were reported in prior decades, which do suggest that MDMA has possible neurotoxic effects (Chang, Ernst, Grob, & Poland, 1999). One possibility for this discrepancy is the challenges associated with studying pure MDMA users. The majority of MDMA users are polysubstance users with concurrent marijuana use reported more frequently than other drugs of abuse (Singer, Linares, Ntiri, Henry, & Minnes, 2004), and it has been suggested that marijuana may provide neuroprotective effects (Costa, 2007). Another consideration is the potential that ^{1}H MRS is not sensitive enough to detect changes in brain chemistry related to MDMA use. None of the published studies over the

last decade utilized neuropsychological testing as a method to understand the relationship between brain chemistry and cognition in MDMA users.

Cocaine

Magnetic resonance spectroscopy studies of cocaine are limited to ^{1}H MRS since 2004. Of the five published reports, two of them evaluated changes in specific neurometabolites following pharmacological treatment, and the findings suggest that cocaine induced injury may normalize with pharmacotherapies targeting brain bioenergetics (Schmaal, Veltman, Nederveen, van den Brink, & Goudriaan, 2012; Streeter et al., 2005). For instance, Schmaal and colleagues (2012) administered a potential glutamatergic drug, *N*-acetylcysteine (NAC) 1 hour prior to a ^{1}H MRS scan, and they documented a significant increase in dorsal anterior cingulate cortex (dACC) Glu after a single oral dose (n = 10). Support for the need to target the glutamatergic system in cocaine users is found in a cross sectional ^{1}H MRS study that demonstrated lower levels of Glu in chronic crack cocaine users (n = 14) when compared to noncrack cocaine using controls (n = 14; Yang et al., 2009).

Adding to the evidence that cocaine induces injury to the brain, GABA concentrations in the left prefrontal lobe have been found to be significantly lower in cocaine users with and without a history of comorbid alcohol use (n = 23), but not in a healthy comparison group (n = 20; Ke et al., 2004). On the whole, results from these ^{1}H MRS studies of cocaine users demonstrate the need for further development of treatments focused on repairing glutamatergic injury and disruptions of GABA pathways.

Consistent with other drugs of abuse and MRS studies, there is limited published

information regarding brain chemistry alterations from cocaine use and the influence of these changes on cognition. Indeed, in the last 10 years, there are no reports of studies employing concurrent neuropsychological testing and MRS methods in cocaine users.

Opiates

Over the past decade, comparatively fewer studies have employed MRS methods to investigate opiate induced changes in neurometabolites. The few studies (*n* = 3) that have been conducted have primarily been focused on opiate maintenance therapy in opiate users by conducting ^{1}H (Hermann et al., 2012) and ^{31}P (Silveri et al., 2004) MRS. Results from the ^{1}H MRS study using a 3 T field strength suggest an imbalance of the glutamate system with higher levels of ACC Glx noted in older opiate users (number of older opiate users not provided) relative to nonopiate users (*n* = 20), as well as increased Cho concentrations in left frontal WM observed across all age groups of opiate users (*n* = 17) compared to controls (Hermann et al., 2012). Alterations in brain bioenergetics were indicated in the 1.5 T ^{31}P MRS study of methadone maintenance therapy initiation in heroin users with reduced levels of PCr found in the orbitofrontal and occipital cortices with heroin use (*n* = 43) but not in a healthy comparison group (*n* = 15; Silveri et al., 2004). Because of the limited number of MRS studies in opiate use, it is difficult to definitively assess the impact of opiate use on the brain; however, the few published reports provide some evidence that there are differences in neurochemistry in opiate users starting opiate maintenance therapy in comparison to nonopiate users. Finally, none of these studies evaluated the effects of changes in neurochemistry related to opiate use on cognition.

Marijuana

The effects of marijuana use on brain chemistry have been well studied over the past decade. Eight reports have been published and the findings suggest that marijuana use results in altered brain metabolites. Nearly all of the published studies described higher field strength ^{1}H MRS studies at 3 T (Muetzel et al., 2013; Prescot, Locatelli, Renshaw, & Yurgelun-Todd, 2011; Prescot, Renshaw, & Yurgelun-Todd, 2013; Sung, Carey, et al., 2013) or 4 T (Chang, Cloak, Yakupov, & Ernst, 2006; Mashhoon, Jensen, Sneider, Yurgelun-Todd, & Silveri, 2013; Silveri, Jensen, Rosso, Sneider, & Yurgelun-Todd, 2011). Disturbances of ACC glutamatergic neurotransmission, suggested by reduced Glu levels, appear to be a consistent finding in marijuana users (n = 30; Prescot et al., 2011; Prescot et al., 2013) in addition to evidence of alterations in neuronal integrity (e.g., lower NAA concentrations) in recreational and chronic marijuana users (n = 43; Hermann et al., 2007; Prescot et al., 2011; Prescot et al., 2013) and comorbid marijuana and methamphetamine users (n = 8; Sung et al., 2013).

Moreover, decreased concentrations of NAA and Glu in the basal ganglia were seen in regular marijuana users (N = 45: Chang et al., 2006). Changes in the thalamus have also been noted with increased mI (n = 13; Mashhoon et al., 2013) and increased mI/Cr (n = 15; Silveri et al., 2011) documented in chronic marijuana users with respect to healthy volunteers. A less consistent finding involves reports of possible changes in Cr. For example, Prescot and colleagues (2011) found decreased ACC Cr in marijuana users (n = 17) compared to healthy controls (n = 17), whereas Chang et al. (2006) demonstrated increased thalamic Cr in marijuana users (n = 45) relative to nonmarijuana users (n = 30).

Even though alterations in brain metabolism and neuronal integrity are

consistently reported in ^{1}H MRS studies of marijuana, the clinical implications of these findings are not as well known. In the single study that examined the association between neurochemistry and cognition in marijuana users, the authors reported a positive correlation between basal ganglia mI and simple reaction time in nonmarijuana users (*n* = 30) and poorer performance on the simple reaction time and psychomotor tests for both nonmarijuana users (*n* = 30) and marijuana users with lower basal ganglia mI (*n* = 45; Chang et al., 2006). Interestingly, with the exception of memory testing, marijuana users outperformed the comparison group in all cognitive domains, but these results were not compared with neurometabolites (Chang et al., 2006). Because both of the groups demonstrated substandard performance on some cognitive testing and the marijuana users overall performed better than the nonmarijuana users, the impact of marijuana use on brain chemistry is inconclusive.

Nicotine

Magnetic resonance spectroscopy studies of nicotine use over the last 10 years have mostly targeted the ACC utilizing field strength of at least 3 T. The main neurometabolites of interest have been GABA, Glu and Glx, and although there are inconsistencies noted in the findings, they generally suggest that nicotine use results in brain chemistry changes. To illustrate, when compared to former nicotine users (*n* = 9) and nicotine naïve adults (*n* = 16), there were no differences in ACC or left hippocampus Glu concentrations in chronic nicotine users (*n* = 16; Gallinat & Schubert, 2007), whereas, in nicotine using females who relapsed during nicotine replacement therapy (*n* = 5), dACC Glu/Cr levels were found to be reduced relative to a nicotine abstinent group (*n*

= 4; Mashhoon et al., 2011).

It is possible that Glu serves as a biomarker for relapse considering changes in Glu were not found in treatment naïve nicotine users yet were identified in females seeking treatment. As an alternative, perhaps gender influences Glu since reduced concentrations were noted in a female specific group only. Along the same lines of the Glu finding, alterations in cortical GABA concentrations were also noted in nicotine using females (n = 6) versus nicotine using males (n = 10; Epperson et al., 2005), suggesting that GABA levels may also vary by gender.

Magnetic resonance spectroscopy studies of nicotine have also evaluated changes in NAA and Cho, and these findings indicate the possibility of nicotine use resulting in neurotoxicity as evidenced by reduced NAA levels in the left hippocampus among nicotine users (n = 13) compared to nonnicotine users (n = 13), as well as higher ACC Cho concentrations with increased lifetime nicotine exposure (Gallinat et al., 2007). The association between Cho and lifetime nicotine use suggests that nicotine use may cause changes in cell density or accelerate the rate of cortical membrane turnover (Gallinat et al., 2007). Because nicotine is widely used across the world and commonly used by most other substance users, furthering our understanding of its effects on the brain is important for educational and treatment approach purposes. Findings from these studies suggest that gender specific treatment approaches targeted on glutamatergic system and focusing on neuronal repair may be important.

Translating the clinical implications related to MRS and nicotine use is difficult given the paucity of research on the effects of changes in brain chemistry on cognitive function. However, the findings from the single published report suggest a negative

correlation between dACC GABA/Cr concentrations and attentional bias toward smoking cues in 15 smokers, which the authors interpreted as the dACC having an important function in overall cognitive control (Janes et al., 2013).

A Synthesis of Research Efforts During the Last Decade

Using MRS imaging, there has been considerable progress over the last decade in understanding how substances of abuse impact brain chemistry. Proton MRS was ubiquitous among the reports, whereas ^{31}P and ^{13}C MRS studies were less common. There were not any studies that evaluated changes in every peak of the spectrum, but rather, studies largely appeared to focus on specific visible metabolites that were known for being altered by the drug of interest. Additionally, field strength also plays a role in determining which neurometabolites are measurable, as field strengths of at least 3 T are recommended for evaluating Glu, Gln and GABA (Di Costanzo et al., 2003).

The MRS studies of drug abuse disorders over the last 10 years demonstrate an inconsistent overlap in brain chemistry changes across drug classes, thus suggesting that changes in neurometabolites may be substance of abuse specific rather than a universal impact from drug use. The most consistent findings were lower NAA levels associated with alcohol, MA, marijuana and nicotine use and reduced mI content in alcohol, MDMA and marijuana users, indicating that use of these substances may result in decreased neuronal health. Moreover, the report of increased Cho values with abstinence was consistent among alcohol and MA users, therefore suggesting that the rate of cellular membrane production may increase with brain recovery.

Fewer consistent findings were noted from studies of Glu, Glx and GABA

concentrations. Increased Glu levels and decreased Glx concentrations were documented in abstinent alcohol users and MA users, whereas crack cocaine, marijuana and nicotine users were found to have decreased Glu concentrations and cocaine and nicotine use were associated with lower GABA levels. The increase in Glu together with the decrease in Glx in abstinent drug users raises the possibility of persistent neurotoxicity, while decreases in Glu and GABA concentrations may reflect alterations in neurotransmission. Finally, reports of Cr were limited to studies in marijuana, which demonstrated an inconsistent pattern of changes in Cr, and one possible explanation for this inconsistency is the variation in brain regions examined. However, reports from ^{31}P MRS studies consistently indicate reductions in PCr content, suggesting brain energy metabolism alterations in drug users.

What Are The Gaps?

The majority of the studies used ^{1}H MRS methodology to attempt to understand changes in brain chemistry among drug users. However, there is a gap in knowledge with respect to how substances of abuse impact brain metabolic energy. Brain energy metabolism can be quantified using ^{31}P MRS imaging, and the major peaks identified in the ^{31}P spectra include PCr, inorganic phosphate (P_i), phosphomonoesters (PMEs), phosphodiester (PDE), the α-, β- and γ-nucleotide triphosphates (NTPs) and diphosphates (NDPs). Only two of the 45 published articles over the last decade applied ^{31}P MRS imaging, and while the findings from these studies suggest that substance use compromises high energy phosphate metabolism, the small number of publications and small sample sizes limit generalizability.

There is limited information regarding how changes in neurochemistry relate to cognitive function. Four of the studies published since 2004 conducted neuropsychological testing in conjunction with MRS scanning. Since NAA has been identified as a marker of neuronal integrity, it is not surprising that there is a relationship between improvements in attention with increasing NAA levels in abstinent alcohol users. On the other hand, the finding from Chang et al. (2006) which demonstrated higher performance in marijuana users was not expected considering several neurometabolites, including NAA, were noted to be lower in marijuana users. The inconsistencies and lack of information with respect to the relationship between brain chemistry and cognition underscore the need for more attention in this area.

Studies of MRS and substance abuse are notorious for small sample sizes. The largest sample size noted in the review of articles from the last decade involved 231 treatment-seeking and nontreatment seeking alcohol users (Yeo et al., 2013). This is a remarkably large sample size compared to the majority of other studies, which on average included approximately 30 participants. Concerns regarding external validity and low statistical power is raised with a small sample size. In fact, in a review of neuroimaging meta-analyses, the median statistical power of 461 individual studies was 8% (Button et al., 2013). If low statistical power is typical in neuroimaging research, the likelihood of statistically significant findings reflecting a true effect is jeopardized (Button et al., 2013).

Where We Are Headed?

Information gleaned from MRS studies of substance users has provided useful insight on the neurobiological effects of substance use and abstinence. Because MRS scans reveal concentrations of target chemicals in brain regions, its utility is becoming more widespread in examining pharmacological treatment approaches. With respect to MRS substance abuse studies, two of the 47 studies published since 2004 focused on investigating neurometabolite changes with the treatment of medications focused on repairing glutamateric and GABA pathway disruptions caused by cocaine use (Schmaal et al., 2012; Streeter et al., 2005).

If future pharmacological development studies adapt the approach of including MRS, our understanding of how medications work in the brain of drug users may allow for more targeted treatment modalities. In addition to pharmaceutical development, MRS may be used in the specialty of substance abuse for diagnostic purposes. Overall, in psychiatry research, the diagnostic potential of MRS remains unfulfilled, but the recent advances in MRS offers the possibility of identifying brain biomarkers for disease. For instance, in Parkinson's disease, reduced cingulate NAA/Cr ratios have been noted in individuals with Parkinson's disease, and thus, identified as a clinical biomarker of disease progression (Sharma et al., 2013).

Finally, future uses of MRS also include evaluating treatment response, and a study by Kondo et al. (2011) demonstrates an application of this approach. Phosphorus MRS was conducted before and after depressed adolescents were treated with an investigational medication, creatine, which was hypothesized to increase brain PCr content. The researchers noted a significant increase in PCr concentrations at the end of

treatment scan in parallel with a decrease in reported depressive symptoms (Kondo et al., 2011). The results from this study offer the opportunity for drug addiction researchers to consider study designs that take the neurobiology of addiction coupled with targeted treatment approaches into consideration.

Conclusions

Proton and ^{31}P MRS has provided a window into the brain and the effects substances have on neurometabolites. In the last decade, the consistent finding of reduced NAA concentrations across several classes of substances of abuse may offer a biomarker of substance abuse. As seen in treatment studies of cocaine use disorders, MRS is also a useful tool for gaining insight into treatment response. The potential impact of developing treatments intended to repair neuronal and brain pathways is profound in substance abuse research as there are limited approved treatment options for substance use disorders. Even though there are limitations of MRS in substance abuse research, such as small sample size and low statistical power, this methodology could continue as a pivotal role for improving treatment outcomes, but further improvements in design and analysis are recommended.

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CHAPTER 6

WITHIN SUBJECTS STUDY OF CREATINE IN DEPRESSED FEMALES WHO USE METHAMPHETAMINE[1]

Abstract

Depression among methamphetamine (MA) users is more prevalent in females than males, but gender specific treatment options for this comorbidity have not been described. Reduced brain phosphocreatine (PCr) levels have been shown to be lower in female MA users compared to males, and, of relevance, studies have demonstrated an association between treatment resistant depression and reduced brain PCr concentrations. The nutritional supplement creatine monohydrate has been shown to reduce symptoms of depression in female adolescents and adults taking selective serotonin reuptake inhibitors as well as to increase brain PCr in healthy volunteers. Therefore, a study of creatine monohydrate for the treatment of depression in female MA users was proposed.

Fourteen females with major depressive disorder (MDD) and comorbid MA dependence were enrolled in an 8 week open label trial of 5 grams of daily creatine

[1] This chapter was coauthored with Young-Hoon Sung, Xianfeng Shi, Marjorie Pett, Gwen Latendresse, Rebekah Huber, Jubel Morgan, Danielle Kuykendall, Kelly J. Lundberg, and Perry F. Renshaw

monohydrate and of these 14, 11 females completed the study. Depression was measured using the 17-item Hamilton Depression Rating Scale (HAMD) and PCr levels were measured using phosphorus (^{31}P) magnetic resonance spectroscopy (MRS) pre- and postcreatine treatment. Secondary outcome measures included anxiety symptoms, measured with the Beck Anxiety Inventory (BAI), and MA use, monitored by twice weekly urine drug screens and self-report MA use. The results of a linear mixed effects repeated measures model analysis showed reduced HAMD scores as early as week 2 when compared to baseline. This improvement was maintained through study completion. Brain PCr concentrations were shown to be higher at the ^{31}P MRS scan compared to the baseline scan; $M_{\text{baseline}} = 0.223$ ($SD = 0.013$) versus $M_{\text{post treatment}} = 0.233$ ($SD = 0.009$), $t(9) = 2.905$, $p < .01$, suggesting that creatine might increase PCr levels. Moreover, average BAI scores were reduced as early as week 1 and remained lower through study completion. Finally, a reduction in MA positive urine drug screens by greater than 50% was observed by week 6 (baseline: 50% MA positive urine drug screens; week 6: 21.4%).

Creatine was well tolerated, and adverse events that were reported, such as cold and flu symptoms (n =10), indigestion (n = 1), flank pain (n = 1), polydipsia (n = 1), headache (n = 3), swelling in hands (n = 4), diarrhea (n = 4), stomach discomfort (n = 3), numbness and tingling in hands (n = 1), muscle cramps (n = 2), blurry vision (n = 1), lightheaded (n = 1) and nausea (n = 1) were not related to study participation. The current study suggests that creatine treatment may be a promising therapeutic approach for comorbid depression and anxiety in MA dependence in females.

Introduction

Depression and MA use disorders are highly comorbid. In a number of studies, rates of depression among MA users are consistently documented as greater than 35% (Dyer & Cruickshank, 2005; Kay-Lambkin, Baker, Lee, Jenner, & Lewin, 2011; McKetin, Lubman, Lee, Ross, & Slade, 2011; Sutcliffe et al., 2009). In contrast, according to a survey conducted by the Centers for Disease Control and Prevention (CDC), general population rates for current depression are 9.0%, including 3.4% for major depressive disorder (Centers for Disease Control and Prevention, 2010). Among MA users and the general population, females are more likely than males to have depression, but the gender differences in MA use disorders are substantially higher. For example, findings from the CDC survey suggested that 4.0% of females compared to 2.7% of males met criteria for current depression (Centers for Disease Control and Prevention, 2010), whereas rates as high as 70% in females compared to 30% in males have been documented in MA users (Glasner-Edwards et al., 2008).

There are no clear pharmacological treatment modalities for comorbid depression and MA use disorders (Hellem, Lundberg, & Renshaw, 2014). In fact, there is limited available data on medication treatment options for MA dependence and/or withdrawal. For example, investigations of antidepressants as a treatment option for MA dependence (Colfax et al., 2011; Elkashef et al., 2008; Galloway, Newmeyer, Knapp, Stalcup, & Smith, 1996; Heinzerling et al., 2010; Shoptaw et al., 2008; Shoptaw et al., 2006) or withdrawal (Cruickshank et al., 2008) have reported that antidepressants are not an effective treatment option. Notably, in a randomized controlled trial, MA dependent adults (n = 120) assigned to 100 milligrams of the selective serotonin reuptake inhibitor

(SSRI) sertraline daily for 12 weeks had no change in self-report MA use and had more MA positive urine drug screens compared to the placebo group (n = 109; Shoptaw et al., 2006).

Neuroimaging findings from studies on both depression and MA use disorder are associated with changes in brain energy metabolism (Forester et al., 2009; Iosifescu et al., 2008; Kondo et al., 2011; Sung, Yurgelun-Todd, et al., 2013). Phosphorus MRS is the only method available to measure in vivo brain chemistry changes. Because of its role in adenosine (ATP) production, PCr is one of the main neurometabolites of interest in psychiatry neuroimaging research, and it has been found to be decreased in depressive (Forester et al., 2009; Iosifescu et al., 2008; Moore, Christensen, Lafer, Fava, & Renshaw, 1997) and MA use disorders (Sung et al., 2013). Interestingly, this effect was shown to be greater in female MA users (n = 32) than male MA users (n = 28; Sung et al., 2013), and, like depression rates among MA users, these findings highlight the differences between male and female MA users. Clinically, lower concentrations of brain PCr have been associated with poorer treatment outcomes (Iosifescu et al., 2008; Renshaw, Parow, Hirashima, Ke, Moore, Frederick, et al., 2001), and thus, novel treatment approaches aimed at moderating this brain energy deficiency, particularly in females, are warranted.

Due to its critical role in bioenergetic metabolism, creatine monohydrate has shown promise in treating a number of disorders. For example, creatine has been reported to be neuroprotective in neurodegenerative disorders such as Parkinson's and Huntington's disease (Adhihetty & Beal, 2008), improve neurological symptoms in rats with traumatic brain and spinal cord injury (Hausmann, Fouad, Wallimann, & Schwab,

2002; Rabchevsky, Sullivan, Fugaccia, & Scheff, 2003; Sullivan, Geiger, Mattson, & Scheff, 2000) and have gender specific antidepressant effects in rats (Allen et al., 2010; 2012). For example, when male and female rats were administered creatine, the female rats' performance improved on the forced swim test, a tool to measure depression in rats, whereas the male rats' performance declined (Allen et al., 2010). Along those same lines of creatine's gender dependent antidepressant effects, adjunctive oral creatine use has been associated with reduced depressive symptoms in female adolescents (Kondo et al., 2011) and adults (Lyoo et al., 2012) taking an SSRI. Also of relevance, creatine administration has been shown to increase brain PCr concentrations (Dechent, Pouwels, Wilken, Hanefeld, & Frahm, 1999; Lyoo et al., 2003).

On the basis of these preliminary findings, this pilot study was focused on female MA users diagnosed with comorbid depression in an open label study of stand alone creatine treatment for comorbid depression and MA use disorders. In this clinical trial, it was hypothesized that there would be a decrease in depressive symptoms as well as an increase in brain PCr levels with 8 weeks of creatine treatment. Because co-occurring anxiety is highly prevalent among depressed substance users (Grant et al., 2004; Lubman, Allen, Rogers, Cementon, & Bonomo, 2007) and among depressed individuals in the general population (Hirschfeld, 2001), anxiety data were collected as a secondary outcome measure.

Methods

Recruitment and Consent

A total of 21 females were screened for study participation and 14 females completed the baseline assessments and were enrolled in this open label study of creatine (see Figure 3). Of these 14 females, 11 completed the study. Females were informed of the study by recruitment flyers and staff referrals from a clinic that provides substance abuse assessment and referrals for adults with substance abuse and/or mental health issues. The inclusion criteria for study entry were: 1) female gender, ages 18 – 64 years inclusive, 2) diagnosis of major depressive disorder (MDD) with a current major depressive episode as determined by the Structured Clinical Interview for DSM-IV Disorders (SCID-I/P; First et al., 2007), 3) a score of greater than or equal to 15 on the 17-item HAMD (Hamilton, 1960), 4) identification of MA as primary drug of choice and 5) a SCID-I/P diagnosis of MA dependence or abuse within the last 12 months. The exclusion criteria included: 1) a SCID-I/P diagnosis of bipolar disorder, 2) known or suspected diagnosis of schizophrenia or schizoaffective disorder, 3) a diagnosis of renal disease, type I or II diabetes mellitus, colitis, diverticulitis or seizure disorder, 4) human immunodeficiency virus (HIV) seropositive status or elevated liver enzymes by lab determination, 5) current treatment with an antidepressant, mood stabilizer or antipsychotic medication, 6) current serious suicide risk identified by the Columbia Suicide Severity Rating Scale (C-SSRS), 7) positive urine pregnancy test and 8) contraindication to magnetic resonance scan. Gift card compensation to locations with alcohol and cigarette sale restrictions was offered to participants after each completed visit. If each visit was attended, participants were compensated a total of $290.

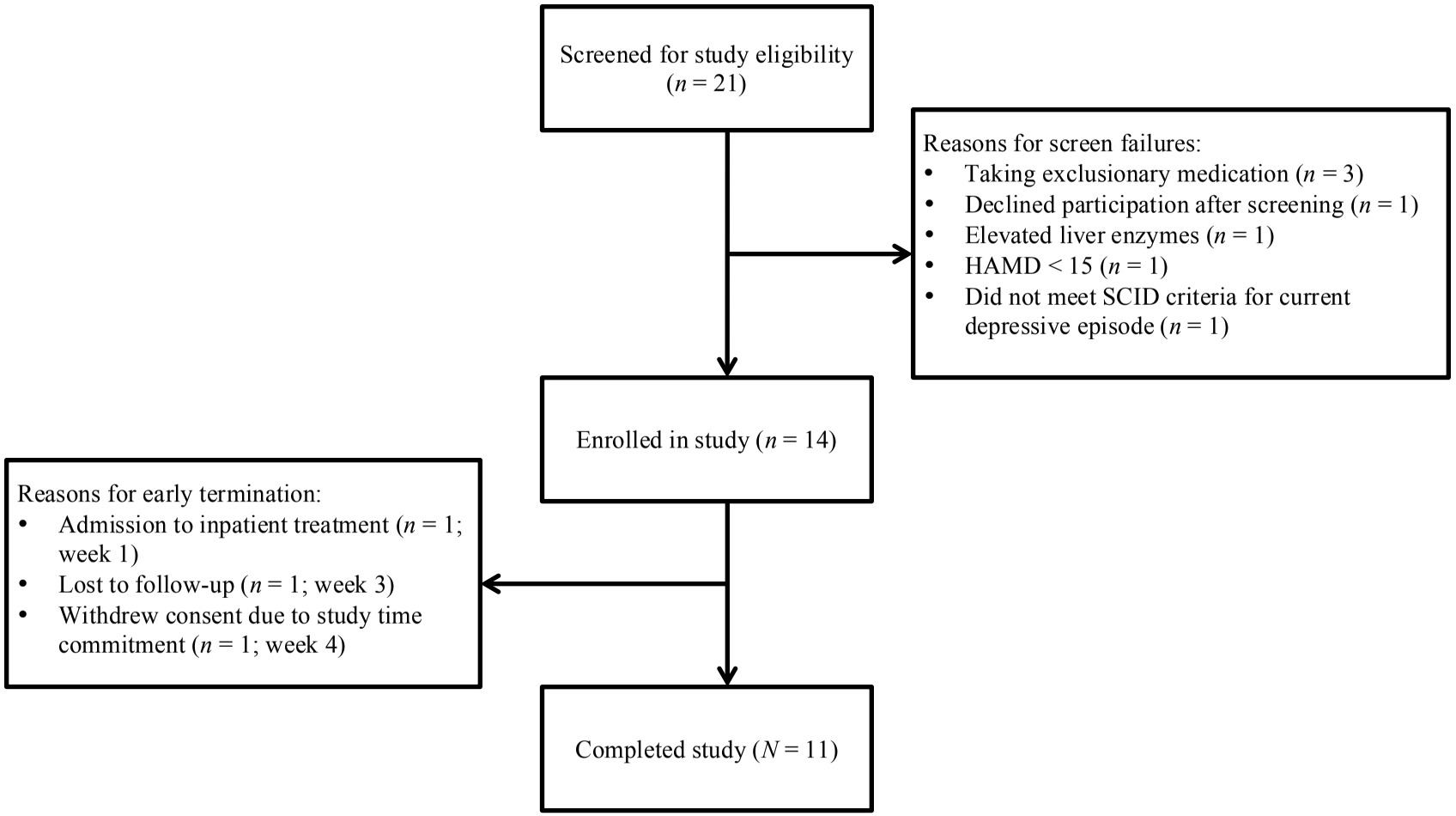


Figure 3. Screening, enrollment and study completion data

Prior to obtaining written informed consent, the study was fully explained to potential participations. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Utah Institutional Review Board. The study was conducted under investigational new drug Investigational New Drug (IND) number 114,316.

Study Design and Procedures

In this within subjects design, each enrolled participant was treated with fixed dose Creapure® brand of creatine (Alzchem, LLC, Trostberg, Germany) 5 grams by mouth daily for 8 weeks. Prior to and following the 8 week treatment phase, baseline and follow up phases were conducted, each of which were comprised of three visits. To determine study eligibility, the same researcher administered the SCID-I/P for each participant after consent was obtained. During the baseline phase, a complete blood count, comprehensive metabolic panel, including liver enzymes to assess for active liver disease, and HIV testing were obtained. Laboratory studies, with the exception of HIV testing, were repeated at the conclusion of treatment, to prospectively identify abnormalities associated with creatine administration. At each study visit, vital signs and concomitant medications were collected in addition to self-report drug use (e.g., cigarettes, alcohol, cocaine, MA, THC, heroin and nonprescribed prescription opiates) over the past 48 hours and adverse events were monitored twice weekly using a medication adverse effect checklist during the 8 week intervention period. Participants completed the medication adverse effect checklist, and the principal investigator (PI) reviewed each adverse effect to determine expectedness and relationship to study

participation.

Attendance in outpatient treatment and/or 12 step programs (e.g., Narcotics or Alcoholics Anonymous) was also assessed at each study visit. A member of the investigative team completed the C-SSRS at every study visit as well as weekly HAMD and BAI assessments. Since four researchers administered the HAMD on different participants throughout the study, an interrater reliability analysis using the Kappa statistic was performed to determine consistency among raters. The intraclass correlation coefficient for the HAMD raters was determined to be 0.98. Urine samples were collected twice weekly for testing of MA, opiates, benzodiazepines, THC and cocaine in addition to pregnancy testing. Finally, creatine adherence was assessed weekly as well as collection of used and unused creatine bottles. If participants missed more than three daily doses of creatine, they were withdrawn from the study for protocol noncompliance. Similarly, if participants missed more than three consecutive study visits, they were withdrawn from the study for protocol noncompliance.

Phosphorus MRS scans were acquired using a Siemens 3 T MRI scanner (Siemens AG, Munich, Germany) that is approved for clinical use. Two dimensional-chemical shift imaging (2D-CSI) free induction decay pulse sequence was used with TR / TE = 3000 / 2.3 ms, number of average = 36, field of view = 20 cm × 20 cm, acquisition matrix 8 × 8, size of vector = 1024, voxel dimension=2.5 cm × 2.5 cm, flip angle = 90°, slice thickness = 2.5 cm, and bandwidth = 2.5 kHz. Advanced Method for Accurate, Robust and Efficient Spectral (AMARES; Vanhamme, van den Boogaart, & Van Huffel, 1997) fitting routine within jMRUI software package (Naressi, et al, 2001) was used for quantitation of ^{31}P metabolites of the frontal lobe. Phosphocreatine integral values were

expressed relative to the total phosphorus signal (Blumberg, et al, 1999).

Outcome Measures

The primary outcome measure was the weekly change in HAMD scores from baseline. The secondary outcome measures were the weekly changes in BAI scores from baseline, postcreatine treatment changes in brain PCr values in addition to percent of weekly positive MA urine drug screens. Treatment response for the HAMD (Furukawa et al., 2007) and BAI (Leyer, Ruberg, & Woodruff-Borden, 2006) was defined a priori as a decrease of 50% or more from baseline. (Note: a discussion of HAMD and BAI reliability and validity can be found in Chapter 3). Because classical methods of reliability measurement are often not tenable with a longitudinal design (DeShon, Ployhart, & Sacco, 1998), within occasion reliability, using a linear mixed effects model with maximum likelihood, for the HAMD and BAI were calculated, and these results indicated an estimated reliability (Donaldson, 2008; Singer & Willet, 2003) of 0.52 for both scales. The HAMD reliability of 0.52 is similar with the only other published report (Laenen, Alonoso, Molenberghs, Vangeneugden, & Mallinckrodt, 2009) of within occasion reliability using a linear mixed effects model, and possible explanations for this low reliability are discussed in the Discussion section. There are no published reports of within occasion reliability using a linear mixed effects model for the BAI.

Statistical Analysis

Based on prior clinical experience regarding treatment completion among female MA users, for this pilot study, a sample size of 10 was initially proposed. A power

analysis was performed to determine the minimum effect that would be detected with 10 completed participants. The HAMD scores from the first three visits were averaged and considered "baseline," and the effect for the power analysis compared the average treatment HAMD scores with the baseline HAMD score. Assuming a gradual onset of effect during the treatment phase, an initial effect of 0 was used with an ending effect of 0.5, resulting in an average treatment effect of 0.25. A linear combination of the separate measures (y*) was used to test the effect in addition to a 0.5 pattern correlation. Thus, a standard deviation (SD) for y* was generated and divided by the SD(y*) to calculate a de facto effect size, which resulted in a value of 1.09 for the effect size with a power of 0.87.

Descriptive statistics are reported for baseline demographic variables, retention and missed medication doses. Analyses for the primary outcome measure and change in BAI scores outcome were performed using a linear mixed effects model repeated measures analysis, which is capable of handling missing data and time varying covariates (Mallinckrodt et al., 2003). Time was included as a fixed factor and subject was treated as a random factor. Age was used a covariate. Sidak correction, a method to compensate for multiple comparisons, (West, Welch, & Gałecki, 2006) was used to control for Type I error. A paired t-test and Wilcoxon Signed Ranks test was conducted to evaluate changes in brain PCr levels. An alpha value of less than 0.05 was considered significant for one tailed tests. The data were analyzed with IBM SPSS Statistics for Mac Version 20.

Results

Participants

Of the 21 females screened for participation, 14 (M = 37.4, SD = 9.9 years of age) were enrolled in the study (see Figure 3). All of the participants met SCID-I/P criteria for MDD as a primary disorder. The average baseline HAMD score was 17.5 (SD = 2.7; see Tables 8 and 9), which suggests moderate illness with respect to severity of depression (Furukawa et al., 2007). All participants met SCID-I/P criteria for lifetime MA dependence and 57% of the sample met criteria for current MA dependence. Current comorbid substance use disorders included alcohol (7.1%), cannabis (7.1%) and opioid (28.6%), and current comorbid psychiatric disorders included social phobia (7.1%) and posttraumatic stress disorder (7.1%). On average, the participants used an estimated lifetime amount of 5,662.9 (SD = 9,671.0) grams of MA with a mean of 18.9 (SD = 9.4) years of total use. Concomitant medications reported at baseline included: Enalapril (n = 1), vitamins (n = 1), Estridiol (n = 1), Proventil (n = 1), Aciphex (n = 1), Neurontin (for nerve pain) (n = 1), Methadone (n = 1) and Ambien (n = 1).

Primary Outcome

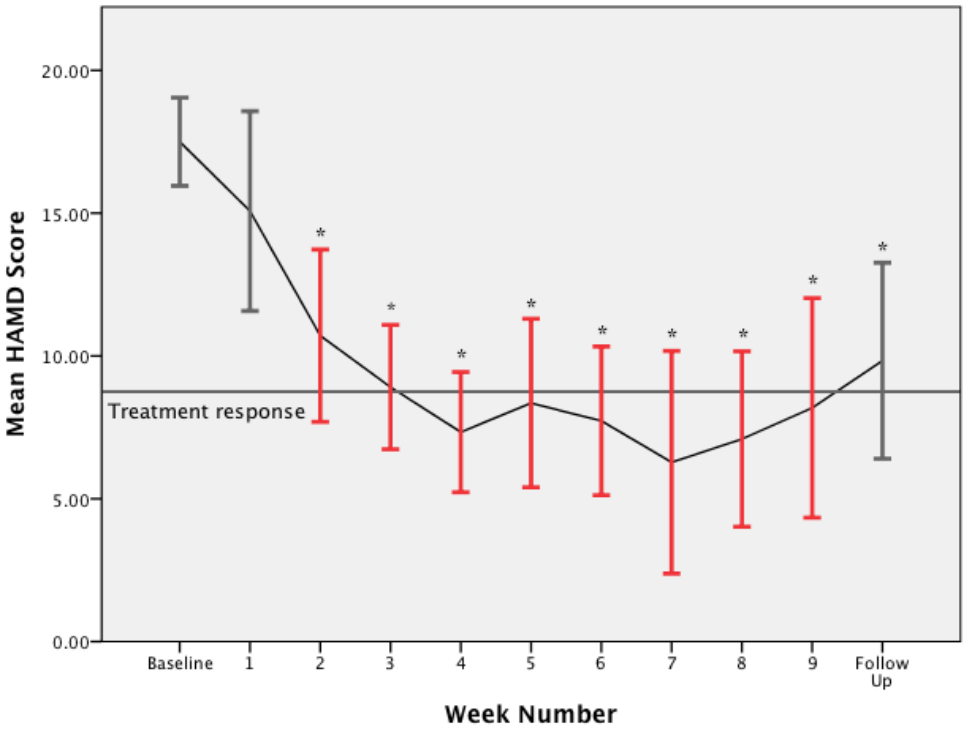
With respect to linear mixed model assumptions, visual inspection did not reveal any obvious deviations from linearity of the residual plot, homoscedasticity or normality of residuals. Significant improvements in depressive symptoms were found as early as week 2 (M = 10.04, SD = 1.19 days on creatine) and maintained through the follow up period (see Figure 4). There was not a significant age by time interaction, and thus, age

Table 8. Baseline demographic characteristics (frequencies)

Characteristic	n	%
Race		
Caucasian	13	92.9
American Indian	1	7.1
Ethnicity		
Not Hispanic or Latino	14	100
Marital status		
Married	2	14.3
Divorced	4	28.6
Never married	8	57.1
Education level		
Did not graduate high school	5	35.7
Graduated high school or GED	3	21.4
Part college	4	28.6
Graduated 2 year college	2	14.3
Employment status		
Employed full-time	2	14.3
Employed part-time	1	7.1
Unemployed	8	57.1
Student	1	7.1
Homemaker	2	14.3
Antidepressant treatment history	9	64
DSM-IV diagnoses		
Major Depressive Disorder (MDD)	14	100
Alcohol use disorder, current	1	7.1
Stimulant use disorder, current	8	57.1
Cannabis use disorder, current	1	7.1
Opioid use disorder, current	4	28.6
Social phobia, current	1	7.1
PTSD, current	1	7.1
Substance induced anxiety, current	4	28.6
Active in treatment program	9	64

Table 9. Baseline demographic characteristics (descriptive statistics)

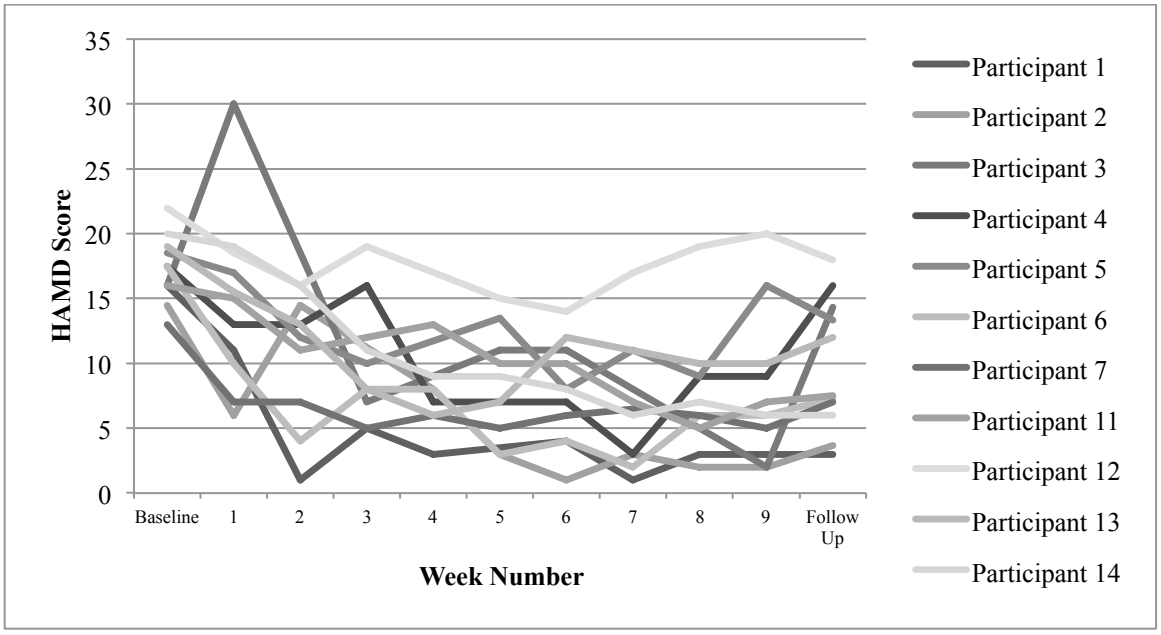
Characteristic	Mean	SD	Range
Age in years	37.4	9.9	24 – 52
Estimated lifetime use of methamphetamine in grams	5,662.9	9,671.0	10.5 – 37,280.0
Abstinence from methamphetamine in days	52.9	94.6	0 – 363
Total years of methamphetamine use	18.9	9.4	4 – 35
Hamilton Depression Rating Scale score	17.5	2.7	13 – 22
Beck Anxiety Inventory score	19.6	11.1	5 – 39



HAMD = Hamilton Depression Rating Scale
* Change in HAMD score statistically significant from baseline ($p < .05$).
Error bars represent 95% confidence interval
Red error bars indicate the treatment period

Figure 4. Change in mean Hamilton Depression Rating Scale scores

was removed from the model. By visual inspection of individual HAMD scores (see Figure 5), it appears that scores improved relatively consistently with the exception of 2 participants. One of these two outliers had a drastic increase in her HAMD score (30) at week 1, followed by a drastic decrease to a score of 13 at the next visit she attended (week 3). The other outlier's HAMD score did not drop below 14, whereas all other participants scored below 14 by week 4. Differences in baseline characteristics, which are discussed in the Discussion section, might explain these outliers. Finally, change scores are presented in Table 10.



HAMD = Hamilton Depression Rating Scale
Treatment period = weeks 2 – 9
Treatment response = score of 8.75 or below

Figure 5. Change in individual Hamilton Depression Rating Scale scores

Table 10

Percent change in Hamilton Depression Rating Scale and Beck Anxiety Inventory scores

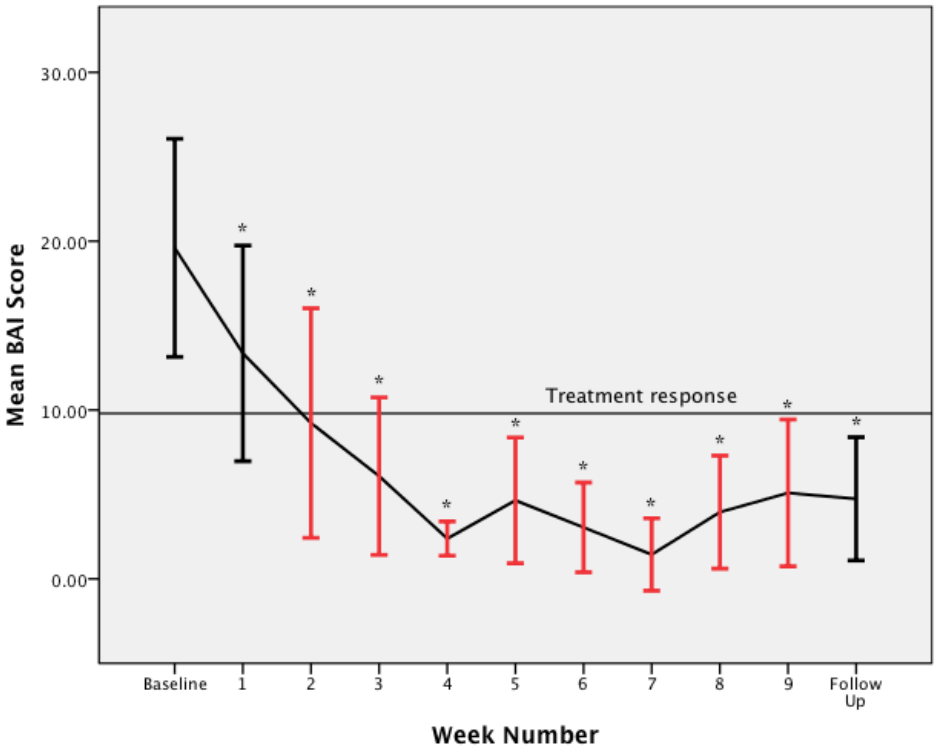
		HAMD score		Percent change in score			BAI score		Percent change in score		
Time	N	Mean	SD	Mean	SD	*p* value	Mean	SD	Mean	SD	*p* value
Baseline	14	17.50	2.67	--	--	--	19.57	11.21	--	--	--
Week 1	14	15.07	6.06	-14.41	33.75	< .01	13.36	11.06	-39.58	36.44	< .01
Week 2	12	10.71	4.75	-39.18	25.09	< .01	9.23	11.25	-60.73	33.11	< .01
Week 3	11	9.81	4.45	-48.31	18.09	< .01	6.08	7.34	-69.02	25.53	< .01
Week 4	9	7.33	2.74	-54.87	17.01	< .01	2.39	1.32	-78.20	18.35	< .01
Week 5	10	8.35	4.12	-52.83	20.09	< .01	4.65	5.21	-79.60	22.02	< .01
Week 6	11	7.73	3.88	-56.06	19.80	< .01	3.05	3.72	-82.35	22.00	< .01
Week 7	9	6.28	5.07	-65.39	22.92	< .01	1.44	2.79	-94.75	9.07	< .01
Week 8	11	7.36	4.59	-60.47	19.80	< .01	3.95	4.98	-78.82	24.04	< .01
Week 9	11	7.82	5.72	-55.04	26.18	< .01	4.82	6.63	-77.10	25.88	< .01
Follow up	11	9.83	5.11	-43.87	26.17	< .01	4.74	5.43	-75.89	24.46	< .01

HAMD = Hamilton Depression Rating Scale; BAI = Beck Anxiety Inventory

Secondary Outcomes

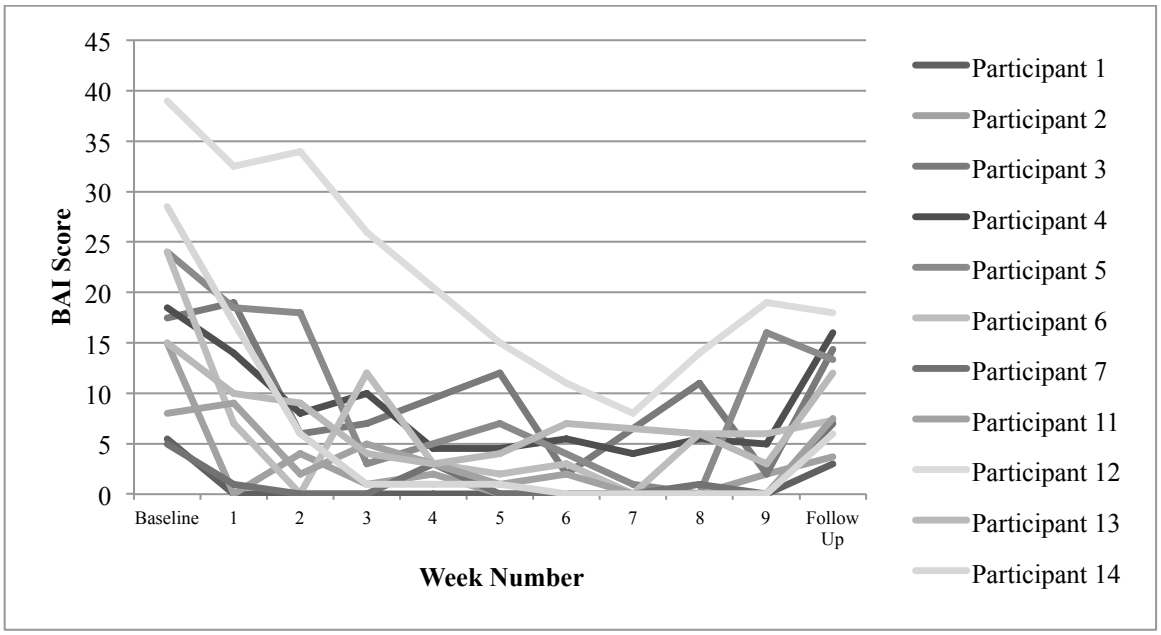
Anxiety. With respect to linear mixed model assumptions, visual inspection did not reveal any obvious deviations from linearity of the residual plot, homoscedasticity or normality of residuals. Significant improvements in anxiety symptoms were found as early as week 1 (M = 4.70, SD = 1.57 days on creatine) and maintained through the follow up period (see Figure 6. There was not a significant age by time interaction, and thus, age was removed from the model. By visual inspection of individual BAI scores (see Figure 7), it appears that scores improved relatively consistently with the exception of 1 participant. This 1 outlier had a higher baseline BAI score (39.0 compared to a range of 5.0 - 28.5), and her score increased at week 2 after a small decrease at week 1, whereas the remaining participants' scores decreased at week 1 and continued to decrease. Differences in baseline characteristics, which are discussed in the Discussion section, might explain this outlier. Finally, percentage change scores are presented in Table 10.

Phosphocreatine. One of the enrolled participants was unable to complete the MRS scan, and therefore, there were a total of 10 scan completers. A paired t-test was used to evaluate pre- and postcreatine PCr values, and the results of the test indicated that after 8 weeks of creatine treatment, mean PCr values were significantly higher than baseline measures; $M_{\text{baseline}} = 0.223$ ($SD = 0.013$) versus $M_{\text{post treatment}} = 0.233$ ($SD = 0.009$), $t(9) = 2.905$, $p < .01$, 95% CI [0.002, 0.019]. The standardized effect size, d, was 0.92. Because of the small sample size and nonnormal distribution of the dependent variable (i.e., PCr), a Wilcoxon Signed Ranks test was also performed. The results of this test were similar to the results from the paired t-test: median PCr values increased from the baseline scan; $Md_{\text{baseline}} = 0.226$ versus $Md_{\text{post treatment}} = 0.236$ ($Z = 2.293$, $p = .01$).



BAI = Beck Anxiety Inventory
* Change in BAI score statistically significant from baseline ($p < .05$).
Error bars represent 95% confidence interval
Red error bars indicate the treatment period

Figure 6. Change in mean Beck Anxiety Inventory scores

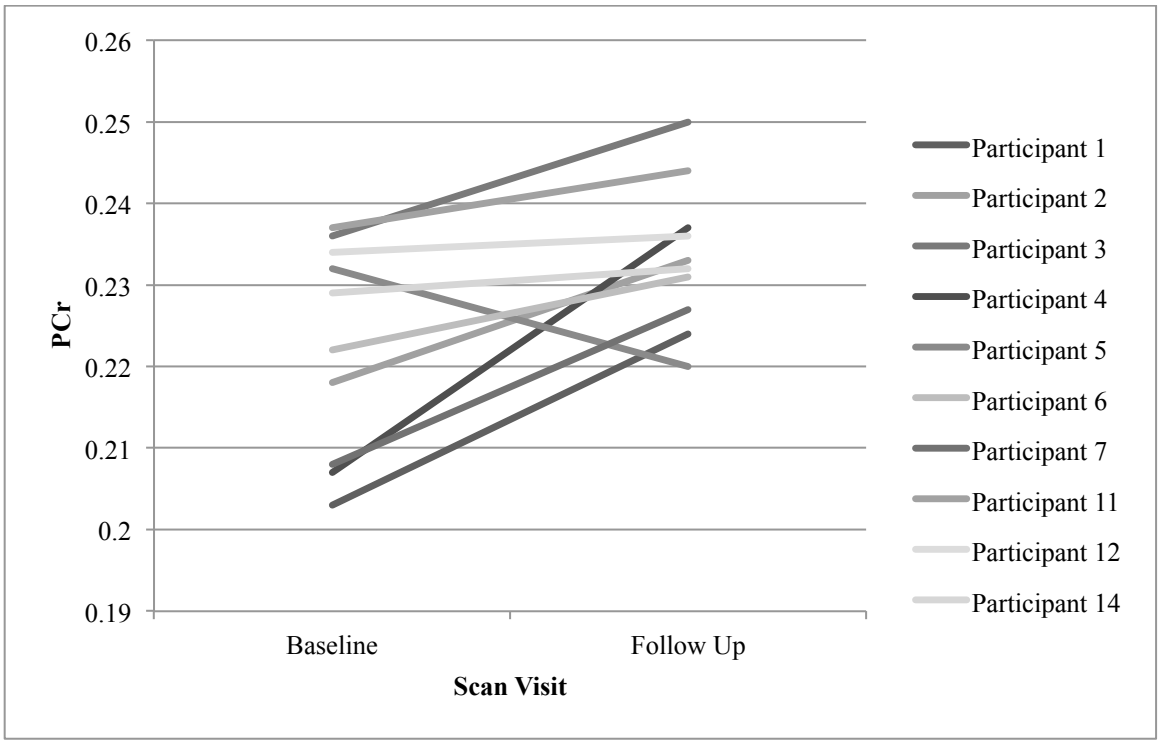


BAI = Beck Anxiety Inventory
Treatment period = weeks 2 – 9
Treatment response = 9.8

Figure 7. Change in individual Beck Anxiety Inventory scores

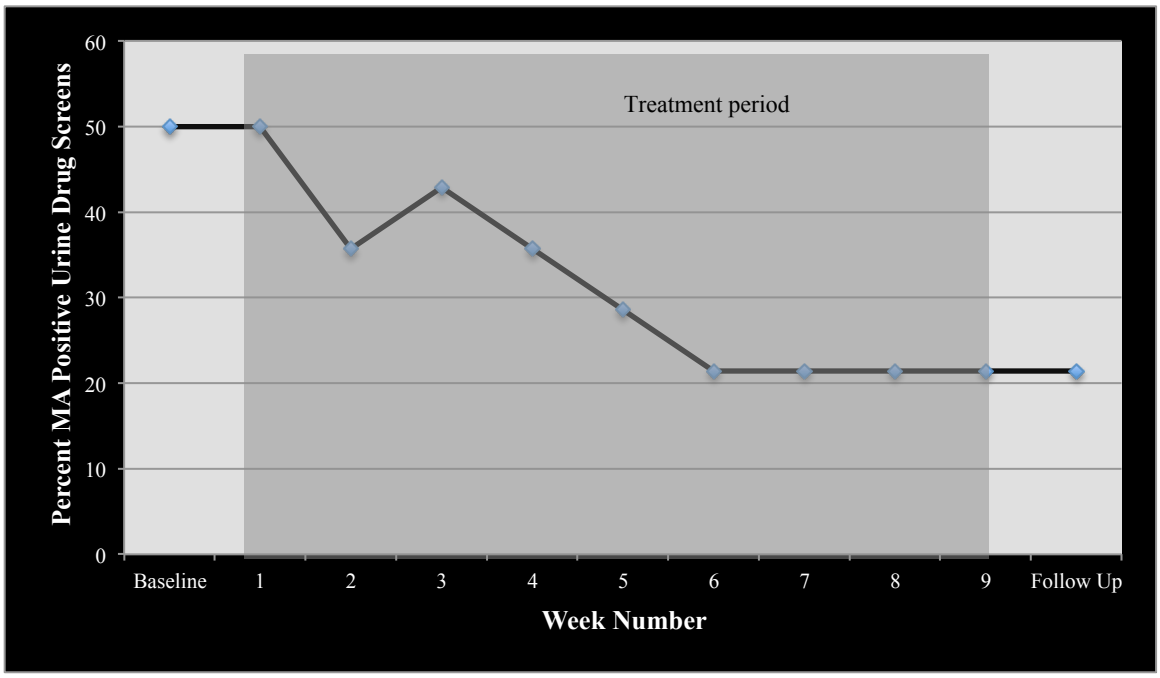
The results of both the paired t-test and Wilcoxon Signed Ranks suggest that creatine treatment may increase brain PCr levels. A visual inspection of the individual PCr levels at the baseline to posttreatment scans demonstrate that all but 1 participant's PCr appeared to consistently increase by the second scan. The outlier's PCr decreased by the posttreatment scan (0.22 compared to 0.23 at baseline; see Figure 8), and noncompliance with taking creatine daily may explain why her values did not increase.

Methamphetamine use. At baseline, 50% of the urine drug screens were positive for MA. By week 6, the percentage of urine drug screens positive for MA was reduced by more than half (21.4%). The percentage of urine drug screens positive for MA remained at 21.4% from week 6 through the follow up period (see Figure 9). Self-report MA use



PCr = phosphocreatine

Figure 8. Individual brain phosphocreatine levels pre- and postcreatine treatment



MA = methamphetamine

Figure 9. Percentages of positive methamphetamine urine drug screens from baseline through follow up

also reduced throughout the course of the study. At baseline, a mean of 0.26 (*SD* = 0.02) grams of daily MA was reported, and by the end of 8 weeks of creatine treatment a mean of 0.13 (*SD* = 0.03) grams of daily MA was reported.

Retention and Missed Visits

A total of 11 participants (78.6%) completed the study from baseline through follow up. Three participants dropped out of the study: 1 participant was admitted to inpatient substance abuse treatment during the first week of creatine treatment, another participant was considered lost to follow up after missing three consecutive study visits during weeks 3 and 4 of creatine treatment and the third drop out was due to the participant withdrawing consent after 4 weeks of creatine treatment because of the study

time commitment (see Figure 3). On average, there were a total of two missed visits per participant.

Medication Adherence, Safety and Tolerability

Medication adherence was monitored by counting returned used and unused vials of creatine. Participants took on average 83.3% of dispensed study medication. A paired t-test was used to evaluate pre- and postserum creatinine values as an indicator of medication adherence. The results of the test suggested that the 11 participants who completed the 8 weeks of creatine administration increased their mean serum creatinine values from pretreatment ($M = 0.76$, $SD = 0.09$) to posttreatment ($M = 0.89$, $SD = 0.14$), $t(10) = 4.11$, $p = .002$, 95% CI [0.060, 0.202]).

Creatine appeared to be well tolerated, and none of the participants withdrew due to adverse effects from creatine. Using the medication adverse effect checklist, participants reported a total of 32 adverse effects during the treatment phase of the study (see Table 11). The investigator reviewed each adverse effect, and because there is inconsistent published data regarding adverse effects of creatine, none of the events were considered related to study participation. All of the reported adverse effects were mild in severity and resolved without intervention. Adverse events included: cold and flu symptoms (n =10), indigestion (n = 1), flank pain (n = 1), polydipsia (n = 1), headache (n = 3), swelling in hands (n = 4), diarrhea (n = 4), stomach discomfort (n = 3), numbness and tingling in hands (n = 1), muscle cramps (n = 2), blurry vision (n = 1), lightheaded (n = 1) and nausea (n = 1). There were no abnormalities detected on laboratory assessments that were drawn at end of treatment.

Table 11

Adverse events during the treatment phase by week

Adverse Event name	Week 1 *n* (%)**	Week 2 *n* (%)**	Week 3 *n* (%)**	Week 4 *n* (%)**	Week 5 *n* (%)**	Week 6 *n* (%)**	Week 7 *n* (%)**	Week 8 *n* (%)**	Week 9 *n* (%)**	Total *n (%)***
Cold or flu symptoms	2 (14.3)	4 (30.7)	--	--	3 (27.2)	1 (9.1)	--	--	--	10 (71.4)
Indigestion	1 (7.1)	--	--	--	--	--	--	--	--	1 (7.1)
Flank pain	1 (7.1)	--	--	--	--	--	--	--	--	1 (7.1)
Polydipsia	1 (7.1)	--	--	--	--	--	--	--	--	1 (7.1)
Headache	1 (7.1)	--	1 (8.3)	--	--	--	--	--	1 (9.1)	3 (21.4)
Swelling in hands	1 (7.1)	1 (7.1)	--	--	--	1 (9.1)	1 (9.1)	--	--	4 (28.6)
Diarrhea	--	1 (7.1)	1 (8.3)	2 (18.2)	--	--	--	--	--	4 (28.6)
Stomach discomfort	--	1 (7.1)	--	1 (9.1)	--	--	--	--	1 (9.1)	3 (21.4)
Numbness & tingling in hands	--	1 (7.1)	--	--	--	--	--	--	--	1 (7.1)
Muscle cramps	--	--	1 (8.3)	1 (9.1)	--	--	--	--	--	2 (14.3)
Blurry vision	--	--	1 (8.3)	--	--	--	--	--	--	1 (7.1)
Lightheaded	--	--	--	--	--	1 (9.1--	--	--	1 (9.1)	1 (7.1)
Nausea	--	--	--	--	--	--	--	--	--	11 (78.6)§
Total	7 (50.0)	8 (62.4)	4 (33.3)	3 (27.3)	3 (27.3)	3 (27.3)	1 (9.1)	0	3 (27.3)	

* % calculated by participants active in study by week
**% calculated by total number enrolled
§ Total number of participants who experienced an adverse event

Discussion

The current study is the first open label trial of 5 grams of daily creatine for the treatment of depression in female MA users. This study demonstrated improvements in depressive symptoms, measured by the HAMD, as early as the second week of creatine treatment and maintained through study completion. Further, anxiety symptoms, measured by the BAI, were reduced as early as the first week of study participation and also maintained throughout the study. Urine drug screens positive for MA were reduced from 50% to 21.4% by the sixth week of creatine treatment and were maintained until the end of the study, and 8 weeks of creatine treatment was associated with a mean increase in brain PCr concentrations. Finally, creatine was well tolerated with few reported adverse effects. In summary, this study shows positive effects from creatine treatment on depression, anxiety, MA use and brain bioenergetics in female MA users with comorbid depression.

The finding related to reduced HAMD scores is consistent with other studies of creatine in depressed females. In fact, both Lyoo and colleagues (2012) and Kondo et al. (2011) noted decreased HAMD and CDRS scores, respectively, with 8 weeks of creatine augmentation. The exact antidepressant mechanism of creatine is not clear, but one possible explanation involves its role in cellular energy metabolism. As a guanidine compound, the liver, kidney or pancreas endogenously produces creatine, and exogenously it is found in products containing meat (Adhihetty & Beal, 2008). Cellular entry of creatine into the brain, heart and skeletal muscle is reliant on the sodium chloride dependent creatine transporter (Adhihetty & Beal, 2008; Brown et al., 2014), and it exists as both intracellular free creatine and PCr, which is referred to as the total creatine pool

(Adhihetty & Beal, 2008).

Several lines of evidence suggest mitochondrial dysfunction in the pathophysiology of depression (Jou, Chiu, & Liu, 2009; Rezin, Amboni, Zugno, Quevedo, & Streck, 2008; Streck et al., 2014) and with MA neurotoxicity (Sung, Yurgelun-Todd, et al., 2013; Yamamoto, Moszczynska, & Gudelsky, 2010). As a key regulator of energy production, one of the consequences of mitochondrial dysfunction is reduced ATP production (Streck et al., 2014). The role of the creatine-PCr system is to provide an intracellular buffer against ATP depletion. Creatine treatment may increase brain intracellular PCr, and this might explain why reduced depressive symptoms are associated with oral creatine treatment. Further, this may also explain our finding of increased brain PCr levels, which is consistent with other creatine neuroimaging studies. Kondo and colleagues (2011) reported a significant increase in PCr values in participants treated with 8 weeks of daily creatine compared to untreated controls and Lyoo et al. (2003) showed an increase in brain PCr concentrations in participants treated with daily creatine for 2 weeks compared to a placebo group.

There were 2 outliers with respect to change in HAMD scores. As descried in the results section, one of these two outliers had a drastic increase in her HAMD score at week 1 (score of 16 at baseline and score of 30 at week 1) followed by a drastic decrease to a score of 13 at the next visit she attended (week 3). This particular participant's SCID-I/P diagnoses were similar to the other participants with diagnoses of recurrent major depressive disorder and current stimulant use disorder. Her estimated total amount of lifetime MA use, however, was higher (37,280 grams) than the other participants (range 10.5 – 13,440). It is possible that the increased amount of total lifetime MA use

played a role in the severity and fluctuation of symptoms.

The other outlier's HAMD score did not drop below 14, whereas all other participants scored below 14 by week 4. In addition to SCID-I/P diagnoses of recurrent major depressive disorder and current stimulant use disorder, she also met criteria for a current opioid use disorder and current substance induced anxiety disorder. In fact, she was taking methadone and started a methadone taper during the fourth week of study participation. Tapering from methadone may explain why her HAMD score never dropped below 14, as it is possible that she was experiencing symptoms from the taper that resulted in symptoms of depression. However, since variables that relate to changes in methadone doses were not collected in the present study, this is merely a speculation.

The BAI score outlier was the female tapering from methadone. She presented with high anxiety symptoms at baseline (score = 39) after a small decrease at week 1 (score = 16); her symptoms increased at week 2 (score = 34), whereas the remaining participants' scores (range of scores = 0 – 18) continued to decrease at week 2. She was prescribed methadone for chronic pain, and it is possible that pain symptoms and the anticipation of the upcoming methadone taper, which started during the fourth week of study participation, explain why her anxiety scores were higher in the beginning of the study than the other participants' scores. Her BAI scores steadily decreased from week 2 to week 7 (score = 8), and then increased each week from week 7 through study completion (final score = 18). However, as mentioned above, since variables that relate to changes in methadone doses were not collected in the present study, this is merely a speculation.

In this study, a decrease in the number of positive urine drugs for MA and self-

report amount of daily MA use throughout the course of the study was observed. By week 6, the percentage of positive MA urine drugs screens was less than almost half of the positive drugs screen for MA that were observed at baseline, and by the end of the treatment period, the amount of self-reported MA use was reduced by half. In agreement with the self-medication hypothesis of drug use, which suggests that individuals use substances in an effort to cope with mood symptoms (Khantzian, 1985), it is possible that as the severity of depressive and anxiety symptoms were reduced, MA use was also reduced.

However, it is worth pointing out that the 3 participants who dropped out of the study were actively using MA, whereas nearly half (45.5%) of the study completers maintained abstinence from MA from study entry through study completion. Nonetheless, this is the first monotherapy study that reports a decrease in the number of positive MA urine drug screens. There have been studies that have investigated a medication versus placebo in conjunction with usual care in an outpatient psychiatric clinic setting (e.g., cognitive behavioral therapy, counseling or contingency management). For example, Shoptaw et al. (2009) evaluated bupropion compared to placebo for MA dependence in an outpatient treatment clinic where participants also received CBT and CM. While the percent of positive MA urine drug screens decreased over the course of the 12 week medication period, the difference in percent of positive MA urine drug screens between the placebo and bupropion groups was not significant (Shoptaw et al., 2008). Therefore, it is possible that CBT or CM had an effect on MA use or CBT or CM coupled with study participation had an effect on MA use. Regardless, the results from this study suggest that creatine, without standard of care treatment, might be

effective at reducing MA use.

The reliability estimate, using a linear mixed effects model with maximum likelihood (Donaldson, 2008; Singer & Willet, 2003) for the HAMD and BAI reported in this study is not commonly reported, but it is a more appropriate reliability measure for longitudinal data (DeShon, Ployhart, & Sacco, 2010; Donaldson, 2008; Laenen et al., 2009) Laenen and colleagues (2009) calculated a reliability estimate of the HAMD from two clinical trials evaluating the efficacy of two antidepressants using a linear mixed-effects model analysis. The results from their study are similar to the results from the current study with average reliability estimates around 0.50 and 0.60 (Laenen et al., 2009). The Laenen et al. study and the present study analyzed reliability from a homogenous sample, which, because reliability is a population dependent concept (Laenen et al., 2009), may explain lower reliability estimates than what we are used to seeing with classical reliability measurements. Further, as Laenen and colleagues pointed out, the Pearson correlation coefficient is commonly reported, which does not take into account patients evolving with time, and an overestimation of reliability is calculated.

There are not any published studies of within occasion reliability of the BAI to compare the reliability estimate from the present study with. The same rationale explained for the low reliability estimate of the HAMD, however, also applies to the low reliability estimate of the BAI in the present study.

It is noteworthy that psychometric studies require much larger sample sizes than the sample of this study. With that said, the reliability estimate of 0.52 for both the HAMD and BAI was not surprising because the present study did not have an adequate number of participants to calculate reliability measures. Cronbach's alpha is the most

ubiquitous reported reliability estimate as a measure of internal consistency, but it is not mathematically possible to calculate Cronbach's alpha for the present study considering the small sample size. Both the HAMD (Hamilton, 1960) and BAI (Beck et al., 1988) evolved from clinical classifications, and Feinstein (1987) refers to research scales based on clinical symptoms of disease as clinimetric (as opposed to psychometric).

The difference between psychometric and clinimetric scales are that the former are based on variables that are selected according to their relationship to an underlying construct, whereas clinimetric scale items are deliberately chosen according to how the variables relate to symptoms (Fayers and Hand, 2002). Despite the popularity of using traditional psychometric approaches to evaluating scale reliability, Fayers and Hand (2002) question the appropriateness of using these traditional approaches with clinimetric scales.

Nonetheless, considering the sample of depressed MA users included in the present study, concern of reliability and validity in the traditional psychometric sense should not go unnoticed. Because the effects of MA use and/or withdrawal from MA mimic symptoms of depression and anxiety, further psychometric studies that consider clinimetric ideas (Fayers and Hand, 2002) with adequate sample sizes should be considered.

This study has limitations that merit consideration. First, the lack of a placebo group makes it difficult to know if creatine, as opposed to the Hawthorne effect (McCarney, Warner, Iliffe, van Haselen, Griffin, & Fisher, 2007), played a role in reducing depressive and anxiety symptoms and MA use. Three of the participants were homeless and may have benefited from the individual attention from the research team as

well as the gift card compensation. Future studies with a placebo group and/or a control group that does not receive creatine but is assessed over time are warranted.

Another limitation to consider is that this study recruited a small sample, but it is note worthy that the a priori power analysis resulted in a power of 0.87 and effect size of 1.09 for a sample of 10 completers for the primary outcome measure, and our total sample size included 11 participants for the primary outcome. In addition, as the first study of creatine in depressed female MA users, the feasibility of recruiting and retaining participants needed to be established. An attrition rate of 21.4% is lower than most other treatment trials of MA dependence, as rates are commonly reported as 45% - 67% (Brown & Gabrielson, 2012; Cruickshank et al., 2008; Elkashef et al., 2008; McGaugh et al., 2009; Shoptaw et al., 2008).

Finally, this study was limited to females with comorbid depression and MA dependence because of preclinical studies that suggest creatine has antidepressant effects in female but not male rodents (Allen et al., 2010). Consequently, gender effects of creatine were not evaluated in this study; and therefore, future studies with male MA users included are necessary. Finally, HAMD criteria of 15 and above was used even though a score of greater than 15 suggests moderate illness (Furukawa et al., 2007). A score of 15 or greater was selected to capture females with dysthymia in addition to moderate to severe depression since dysthymia is also associated with poor treatment outcomes (Katon et al., 2002); however, none of the enrolled participants' baseline HAMD scores were less than 16.

Clinical Implications

The present study suggests that creatine provides a promising therapeutic approach for comorbid depression and MA dependence in females with regard to its tolerability, safety profile and easy attainability. Depression is a mediator and moderator of MA use, and comorbid depression among MA users confounding treatment outcomes and worsening overall prognosis is well documented. If creatine can help address the symptoms of depression among MA users, it would improve treatment outcomes and reduce the risk of relapse.

Conclusions

The present study showed that creatine as a stand alone treatment may be beneficial for treating depressive and anxiety symptoms, MA dependence and increasing brain PCr concentrations in females. Creatine was well tolerated with minimal adverse events and is an inexpensive, easily attainable product. Replication of the current study in a larger sample with depressed male and female MA users is required. Importantly, though, given that there are not any FDA approved treatments for either MA dependence or comorbid depression and MA use disorders, interventions with the potential to reduce mood symptoms, improve brain bioenergetics and reduce MA use are urgently required.

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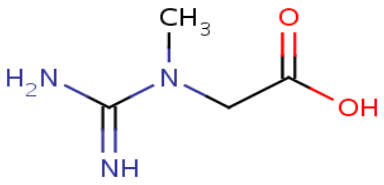
APPENDIX A

REGULATORY MATERIALS

This appendix contains regulatory materials such as the Investigational New Drug (IND) application and safe to proceed letter from the Food and Drug Administration (FDA); Institutional Review Board (IRB) approved informed consent form and IRB approval letters.

Introductory Statement

Drug information:
AlzChem will provide creatine monohydrate to the Brain Institute at the University of Utah for drug abuse research. (Please refer to AlzChem's Drug Master File (DMF) 16538). The active ingredient, creatine monohydrate (a-methyl guandino-acetic acid), is considered a dietary supplement according to the Dietary Supplement Health Education Act that was passed in 1994 by the Food and Drug Administration (FDA) Act. The following is the formula of creatine monohydrate:



The formulation of the dosage that will be used is 4-10 grams per day and the product will be administered orally. We propose to investigate creatine monohydrate's potential role in drug abuse research over the course of the next 5-7 years.

Previous Human Experience with Creatine:
A French scientist Michel Eugene Chevreul first described creatine as a nitrogenous organic acid that occurs naturally in vertebrate animals in the 1830s. The capacity for creatine biosynthesis via the creatine-kinase-phosphocreatine energy buffering system was established early in the evolutionary history of life on Earth [1]. Acting as a substrate for hydrogen ions, creatine facilitates the production of adenosine triphosphate (ATP) from adenosine diphosphate (ADP), thus increasing the amount of free energy available within cells [2].

Creatine is under investigation as a treatment for neuromuscular and neurodegenerative diseases. Walter et al. [3] administered creatine to treat Muscular Dystrophy in a double-blind placebo-controlled trial. The study enrolled 32 participants and 5 grams/day of creatine was administered [3]. The researchers noted a significant improvement in muscle strength and daily activities in the creatine group and there were no reported side effects from creatine use [3].

Creatine supplementation has also been used for the treatment of Huntington's Disease (HD). Study findings suggest that phosphocreatine (PCr) and inorganic phosphate are reduced in resting muscles of HD patients [4]. Creatine supplementation in animal models of HD has been shown to improve motor performance, extend survival, attenuate the loss in body and brain weight, reduce neuron atrophy, and lower the number of Huntington-positive aggregates [5-7]. Moreover, creatine supplementation has been shown to be neuroprotective and reduce lesion volume in mitochondrial toxin models of HD [8]. Hersch and colleagues [9] conducted a double-blind placebo-controlled trial testing the safety and tolerability of creatine adminstration in a HD population. In addition, they evaluated brain and serum biomarkers of creatine availability and activity [9]. Subjects were instructed to take 8 grams of creatine daily for 16 weeks, which was well tolerated and safe [9]. The researchers noted increased brain

and serum creatine concentrations in the creatine-treated group, which returned to baseline after a washout period [9].

There is strong evidence that mitochondrial impairment plays a role in the pathogensis of Parkinson's disease (PD) [10], and due to this bioenergetic impairment, creatine has been explored as a treatment option. Matthews et al. [8] noted that oral creatine supplementation resulted in protection against an electron transport chain of mitochondria called 3-nitropropionic acid, 1-methyl-4-phenyl-2,3,6-tetrahydropyridine (MPTP) induced dopamine depletion in mice. In a randomized double-blind clinical trial of creatine in early PD patients, researchers reported that creatine delayed increases in the Unifed Parkinson's Disease Scale by as much as 50% [11]. Creatine is currently under investigation in a phase III trial examining 1,720 patients with early stage PD (http://clinicaltrials.gov/ct2/show/NCT00449865?term=NET-PD&rank=1).

Creatine supplementation has been studied as a treatment intervention for schizophrenia. Kapstan and colleagues [12] enrolled 12 patients in a placebo-controlled study of creatine supplementation. Creatine was administered at a dose of 3-5 grams/day for three months, and found to be safe. Adverse effects were limited to nausea reported by one female subject, and vomiting in one male subject [12].

Amital et al. (2006) treated ten Post-Traumatic Stress Disorder (PTSD) patients with with creatine in an open-label study [13]. Participants were treated with creatine monohydrate 3 grams/day for one week, then 5 grams/day for an additional three weeks. Notably, average Hamilton Depression Rating Scale [14] (HAM-D) score was reduced from 24.1 $\pm$ 5 at study entry to 20.4 $\pm$ 6 after one month of creatine treatment (p=0.006) [13]. Total scores on the HAM-D, Hamilton Anxiety Rating Scale [15] and Clinician Administered PTSD Scale [16] showed greater improvement for patients with co-morbid major depressive disorder (N=6) compared with scores for patients without psychiatric co-morbidity [13].

Also, relevant to consideration of creatine as a treatment for mental disorders is the work of Rae and colleagues, who showed that creatine supplementation improves both working memory and intelligence testing scores in adults [17]. Forty-five adults were treated with 5 grams/day for six weeks in a double-blind, placebo-controlled design. Creatine supplementation had a significant positive effect (p=0.0001) on subjects' working memory (backward Digit Span Recall) and intelligence test scores (Raven's Advanced Progressive Matrices).

Kondo and colleagues [19] conducted a study under IND 104,586 examining the possible role creatine could play in treating female adolescents with major depressive disorder (MDD). Five female adolescents who had been taking fluoxetine (Prozac®) for over eight weeks and still met diagnostic criteria for MDD were treated with 4 grams of creatine daily for eight weeks. Mean depression rating scores measured by the Children Depression Rating Scale decreased by 56% and no serious adverse events occurred [19].

Sakellaris and colleagues [20] facilitated an open label pilot study to examine creatine acting as a neuroprotectant for children and adolescents with traumatic brain injury (TBI). 39 subjects were enrolled in the study and were given 0.4g/kg oral creatine for six months. They noted that creatine decreased the duration of posttraumatic amnesia, intubation, and intensive care unit stay. Significant improvement was recorded in the categories of headache ($p < 0.001$), dizziness ($p = 0.005$) and fatigue ($p < 0.001$). No side effects were seen due to creatine administration [20].

There have not been any reports of creatine being withdrawn from the market for any reason to date.

General Investigational Plan:

Rationale for the drug or research plan:

Methamphetamine (MA) is a derivative of an amphetamine and is a powerful stimulant that affects the brain and central nervous system. Even though rates of MA use are declining nationally [21], the consequences of MA dependence are still a public health concern. MA dependence is a highly refractory condition, which results in serious impairment of social and occupational functioning [22]. Long-term MA use may result in persistent psychiatric symptoms including drug-induced psychosis [23]. Additionally, MA users often report previous suicide attempts and violent behavior changes [24].

MA use is of great concern in the state of Utah because it's the primary drug of threat in the state, and accounts for 15.6% of substance abuse treatment admissions [25, found at http://www.dsamh.utah.gov/]. Of those in treatment, nearly 75% are women and mothers [25]. The Utah Division of Substance Abuse and Mental Health indicates that MA peaked in Utah in 2006, and regardless of use rates, MA remains more widely abused than heroin, cocaine, or prescription drugs (Health, 2010). In addition, Utah state data indicates that within Salt Lake County, MA is the primary drug of choice among females between the ages of 18 and 24 [25].

Consistent study findings suggest that approximately twice as many females are depressed as men [26-29]. By the middle teenage years, females experience more than double the rate of depressive disorders found in males [30, 31]. This approximate 2:1 gender difference in depression continues throughout the reproductive years [32]. In addition to increased incidence, initial episodes of depression are longer in duration and more severe in symptomatology in females compared to males [33]. Females are more likely than males to have atypical symptoms of depression, such as hypersomnia and hyperphagia, to have co-morbid anxiety disorders, and to attempt suicide [34]. Globally, depression is among the most common disorders affecting females throughout their lives, and is the leading cause of disability among women between the ages of 15 and 44 years [35]. Moreover, depression is associated with high-risk behavior such as illicit drug use [36].

Recently the Utah Department of Health published a report on depression and antidepressant use in Utah [37]. Using health insurance claims from 899,323 Utah residents, antidepressant use was examined, and over six million pharmacy claims from 2009 were reviewed. Of interest, they reported that 84,000 individuals were prescribed antidepressants, resulting in antidepressants being the most widely prescribed medication in the state. When comparing antidepressant utilization by gender, researchers noted that females are prescribed antidepressants at a rate of more than twice that of males. A recent study by Mental Health America ranked Utah the most depressed state in the nation [38]. Their results indicated that among adults, 10.1% experienced a depressive episode in the past year [38].

Kalechstein and colleagues [39] examined the association between psychiatric symptoms and MA dependence in a sample of 1,580 substance-using individuals. They assessed demographics, history of substance dependence and psychiatric symptomatology. 170 participants self-reported MA dependency, and of these 170, 29.4% reported needing psychiatric services, 49.4% reported a previous suicide attempt, and 57.1% reported presence of depressive symptoms in the past year [39]. Moreover, the researchers noted a prevalence of depression in females as being two to three times greater than depression in males [39]. Researchers from the Methamphetamine Treatment Project noted that 68% of all women reported a history of feeling depressed at some point in their lifetime, whereas 50% of all men reported a history of feeling depressed at some point in their lifetime [24]. Likewise, 28% of MA dependent women reported a suicide attempt during their lifetime, compared to only 13% of men [24].

There is no clear treatment model recommending how depression and MA use cormorbidity is best managed. Stepped-care is a model of healthcare delivery that facilitates the integration of evidence-based treatments into clinical practice, and it has been recommended in the alcohol and drug field [40]. Kay-Lambkin et al. [40] explored the effectiveness of stepped-care in a sample of depressed MA users, and their findings indicate improvement in depression. However, they noted their pilot study is the first to examine the efficacy of stepped-care in depressed MA users, and stepped-care is not commonly utilized as a treatment option for this population [40].

The causal nature of the association between depression and MA use continues to be debated in the literature. Some authors argue that MA use results in biological and psychological changes that increase an individuals risk for depression [41]. Others have proposed that substance use in general is a compensatory behavior to alleviate symptoms of an underlying mental illness, which is referred to as the self-medication hypothesis [42].

Data from preclinical animal studies suggest that creatine has sex-dependent antidepressant properties. The Prosolt Forced Swim Test (FST) is the most widely employed experimental animal model of depression. Fed to rates, diets enriched with 4% creatine for six weeks confer a longer latency to immobility in female rats compared with rats fed 0% creatine. In male rats, however, creatine has the opposite effect [43]. Moreover, supplementation with 4% creatine in female rats was of greater benefit for reducing depression-like behavior than 10mg/kg of fluoxetine (Allen, 20110, unpublished findings). The gender-specific nature of these findings may be due to the fact that estrogen receptors are quite common on mitochondria [44]. Estrogen has potent effects on mitochondria, particularly in times of mitochondrial stress [45]. Estrogen has cell-specific effects on a variety of physiologic endpoints, including regulation of mitochondrial biogenesis and activity [46].

In an eight-week open label study of creatine augmentation in female adolescents who failed to respond to an SSRI, Children Depression Rating Scores (CDRS) were reduced by 44% [19]. Moreover, the researchers noted that brain PCr concentrations increased with eight-weeks of creatine use when compared to a comparison group [19]. To date, no studies have examined the effect of creatine supplementation in female MA users. Given the gender-specific effects of creatine in animal models [43], clinical trials in males should be deferred until efficacy and safety has been shown.

The indication(s) to be studied:

We propose to investigate creatine monohydrate's potential role in drug abuse research. As an initial step in testing the antidepressant and neuroprotective effects of creatine supplementation, we propose an open-label clinical trial of creatine administration in female MA users.

The general approach to be followed in evaluating the drug:

The general approach includes creatine supplementation in a methamphetamine using population.

Kinds of clinical trials to be conducted in the first year:

As an initial step, we propose an open-label clinical trial of creatine administration in female MA users. Female MA users will be recruited for study participation, and once eligibility is determined, study participants will undergo baseline neuroimaging (magnetic resonance spectroscopy (MRS)) and then begin creatine supplementation at 5 grams per day for 8 weeks. Study participants will undergo a second MRS scan after completing 8 weeks of creatine supplementation. Depression will be measured using two reliable scales: Hamilton Depression Rating Scale (HAM-D) and Montegomery-

Asberg Depression Rating Scale (MADRS). Adverse event monitoring will occur at each study visit. Upon completion of the open-label trial, we will propose a randomized control trial design involving placebo and creatine in depressed female MA users.

The estimated number of patients to be given the drug in those studies:

We will request approval to recruit 20 participants in the open-label trial and up to 100 participants in the double-blind placebo controlled trial.

Any risks of particular severity or seriousness anticipated on the basis of the toxicology data in animals or prior studies in humans with the drug or related drugs:

There are not any concerns of severity of seriousness anticipated. Creatine supplementation has been studied in animals and humans and adverse events are limited to mild gastrointestinal discomfort.

Investigator's Brochure:

There is not an investigator's brochure for creatine monohydrate.

Protocol:

Please see the protocol attached to the 1572.

Chemistry, Manufacturing, and Control Information:

Please refer to AlzChem's DMF 16538 for information regarding chemistry, manufacturing and control information. Note a placebo is not proposed for the initial study. If a placebo-controlled trial is proposed later, information regarding the placebo will be provided.

Labeling:

See attached drug label.

Environmental analysis requirements:

Please refer to AlzChem's DMF 16538.

Pharmacology and Toxicology Information:

Please refer to AlzChem;s DMF 16538.

Previous Human Experience with the Investigational Drug:

See section **ii. *Previous Human Experience with Creatine***

Additional Information:

Drug dependence and abuse potential: N/A
Radioactive drugs: N/A
Pediatric studies: N/A
Other information: N/A

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114316

STUDY MAY PROCEED

Perry F. Renshaw, M.D., Ph.D., M.B.A
The Brain Institute
The University of Utah
383 Colorow Drive
Salt Lake City, UT 84108

Dear Dr. Renshaw:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for creatine.

We have completed our 30-day, safety review of your application and have concluded that you may proceed with your proposed clinical investigation for Improvements in depression scores in female methamphetamine users.

In addition, we have the following Clinical comment for your consideration:

- We understand that you will propose a randomized, double-blind, placebo control trial involving creatine treatment in depressed female MA users after you have completed this open-label trial. Please submit the detailed protocol of the randomized double-blind, placebo control trial design to FDA for review

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];

- Reporting any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
02/08/2012

Consent and Authorization Document

BACKGROUND

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether or not to volunteer to take part in this research study.

Dr. Perry Renshaw is the physician who helps oversee this study. He is a Psychiatrist at the University of Utah School of Medicine in the Department of Psychiatry.

The purpose of the study is to see if the investigational medication creatine helps reduce symptoms of depression in female methamphetamine (MA) users. Another purpose of the study is to see if the use of creatine results in changes in brain chemistry.

You are being asked to participate in this study because you have used methamphetamine within the past twelve months, methamphetamine is your preferred drug of choice, and you have depression. If you decide you would like to take part in the study, you will first undergo a screening visit to see if you qualify for the study. If the screening requirements are met you can enroll in the study if you choose.

The study drug creatine is found naturally throughout your body. Creatine has a role in transferring energy during skeletal muscle contraction and maintaining energy balance in cells with intermittently high energy requirements. In humans, brain and muscle are two such tissue types. Previous creatine studies suggest that its neuroprotective benefits would be useful for protecting the brain from damage associated with drug use. There is also evidence of creatine providing treatment similar to anti-depressants. The current study will provide more information on how effective creatine is in reducing depression in methamphetamine users. Other studies using creatine have shown it to be effective in treating patients suffering from Muscular Dystrophy, depression, Parkinson's disease, Huntington's disease, and brain trauma. Creatine has been studied extensively at doses ranging from 4 g daily to 25 g daily with a very safe side effect profile. This study will require the use of 5 g daily of creatine.

This study will use rating scales and questionnaires to understand your mood. In addition, the study will use Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) brain scans to see if the structure and/or chemicals in the brain change when you are treated with creatine.

STUDY PROCEDURES

This research study is called an open label trial. This means that everyone will receive creatine. In other words, there is no placebo involved.

There will be 21 visits in the study over 12-14 weeks. You will be asked to schedule 3 weekly visits for the first 3 weeks, and then twice weekly for the 8 weeks while you are taking creatine, and then 3 additional visits approximately 7 days apart after you finish taking creatine. Your twice-weekly visits must be at least 48-72 hours apart. You will be asked to take part in the following procedures during your study visits:

- **Vitals:** Your vitals will be checked at each visit. Vitals include your blood pressure, pulse, and your weight.
- **Medical History and Physical:** This is similar to what your doctor does at your yearly checkup. The study team will ask you questions about your medical history and a study clinician will give you a complete physical exam.
- **Blood Draw (venipuncture):** We will draw about 2 tablespoons of your blood at two study visits. We will run tests on your blood to check for systemic medical illnesses. We will do an HIV test. If you are found to be HIV positive, you will be referred to the Utah AIDS foundation for a full evaluation and treatment referral. We will run the following tests on your blood:
    - Complete blood count (CBC)
    - Comprehensive metabolic panel (CMP)
    - HIV test
- *Additional tests may be ordered if we believe they are necessary. This means that you may have up to 4 blood draws total.
- **Urine Sample:** We will ask you to provide a urine sample at each visit. We will run the following tests on your urine:
    - Pregnancy test. Participants who are pregnant will not be enrolled in the study, due to the unknown effects of creatine and MRI scans on a developing fetus. Participants will be informed if their pregnancy test is positive.
    - Drug screen for marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
- **Structured Clinical Interview for DSM-IV Disorders:** We will administer this interview at the screening visit.
- **Drug History Questionnaire (DHQ):** During your initial screening we will ask you questions about your drug and alcohol history.

7. **Drug intake Diary:** We will ask you a series of questions about your current drug and alcohol use at each visit.
8. **Hamilton Depression Rating Scale:** We will administer a depression rating scale once a week.
9. **Columbia-Suicide Severity Rating Scale:** We will administer a suicide rating scale at each visit.
10. **Beck Anxiety Scale:** We will administer an anxiety rating scale once a week.

11. **Concomitant Mediations:** Concomitant medications are any medications other than the study drug that you may be taking. We will ask you if you started taking any new medications at each visit.
12. **Side Effects Monitoring:** After you start the study drug you will be asked questions regarding any possible side effects you may experience at each visit.
13. **MRI Brain Scan:** You will have two MRI/MRS (magnetic resonance imaging and magnetic resonance spectroscopy) brain scans. Total time in the MRI machine could last up to 120 minutes for each MRI/MRS visit. These scans take pictures of the structure and chemical make up of your brain. They do not cause pain and do not use radiation. The MRI scanner looks like a large cylinder with a tube in the middle. You will be asked to lie down on your back on a foam-padded table, and put your head into a special holder. The table slides inside the "hole" of the scanner. Soft foam rubber sponges may be placed on both sides and under your head for comfort. The foam will also help keep your head still. You will hear different sounds while the pictures are taken. These sounds can be loud. The sounds change depending on the type of picture that is being taken. Some examples are scans that sound like: a hammer hitting a piece of wood, an electric saw, loud beeping or clicking, or buzzing noises. These sounds may be repeated several times. We will provide you with a copy of your MRI/MRS scan and you can also request a copy of the scan interpretation.

- **Study Medication:** Study medication will be given to you after you have completed the first brain scan. You will be asked to bring back your unused study medication at each visit. You will be asked to mix the creatine in at least 4 ounces of water or juice, and then you will drink it.

Visit Schedule:

Screening Visit:

During the screening you be evaluated to see if you meet study inclusion criteria.

1. We will collect your demographic information.
2. Vital signs.
3. A trained individual will administer the Structured Clinical Interview for DSM-IV Disorders (SCID), the Hamilton-Depression Rating Scale (HAM-D), and the Beck Anxiety Inventory (BAI).
4. We will administer the Columbia-Suicide Severity Rating Scale (C-SSRS).
5. We will obtain a urine sample for a pregnancy test and a drug of abuse test. We will test for drugs such as marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
6. We will write down all the medications you are taking, including vitamins and over-the-counter remedies.
7. We will ask you if you have any medical conditions.
8. We will collect a detailed drug use history using the Drug History Questionnaire.

9. You will be asked to describe your recent drug use (past 2 days) including caffeine, nicotine, alcohol, and illegal street drugs.
10. Medical history and physical exam (the physical exam may take place at the first brain scan visit or visit one).
11. *Phlebotomy for comprehensive metabolic panel (electrolytes and liver function tests), complete blood count, HIV.

*Additional tests may be ordered if we believe they are necessary for determining study eligibility

If you do not qualify for the study because of the following disqualifications, you will not be able to enter the study:

- Pregnancy
- Major medical illness
- Bipolar disorder, schizophrenia, or schizoaffective disorder
- Positive HIV test
- Taking medications for depression

First Brain Scan Visit:

1. Vital signs.
2. Physical exam (if it did not occur at the first visit).
3. We will administer the HAM-D, C-SSRS and BAI.
4. We will obtain a urine sample for a pregnancy test and a drug of abuse test. We will test for drugs such as marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
5. We will write down all the medications you are taking, including vitamins and over-the-counter remedies.
6. You will be asked to describe your recent drug use (past 2 days) including caffeine, nicotine, alcohol, and illegal street drugs.
7. Brain scan.

Visits 3-16 (occur twice weekly for 8 weeks):

1. Vital signs.
2. Physical exam (if it did not occur at the first two visits).
3. We will administer the C-SSRS
4. We will administer the HAM-D and BAI at one of the twice weekly visits.
5. We will obtain a urine sample for a pregnancy test and a drug of abuse test. We will test for drugs such as marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
6. We will write down all the medications you are taking, including vitamins and over-the-counter remedies.
7. You will be asked to describe your recent drug use (past 2 days) including caffeine, nicotine, alcohol, and illegal street drugs.

8. We will assess for possible side effects of creatine.
9. We will dispense the study medication.
10. You will return unused and used bottles of creatine.

Visit 17/18 (Second Brain Scan Visit):

1. Vital signs.
2. We will administer the HAM-D, C-SSRS and BAI.
3. We will obtain a urine sample for a pregnancy test and a drug of abuse test. We will test for drugs such as marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
4. We will write down all the medications you are taking, including vitamins and over-the-counter remedies.
5. You will be asked to describe your recent drug use (past 2 days) including caffeine, nicotine, alcohol, and illegal street drugs.
6. *Phlebotomy for comprehensive metabolic panel (electrolytes and liver function tests) and complete blood count.
7. We will assess for possible side effects of creatine.
8. You will return unused and used bottles of creatine.
9. Brain scan.

*Additional follow-up tests may be ordered if we believe they are necessary

Follow-up (weeks 10, 11, 12):

1. Vital signs.
2. We will administer the HAM-D, C-SSRS, and BAI.
3. We will obtain a urine sample for a pregnancy test and a drug of abuse test. We will test for drugs such as marijuana, cocaine, benzodiazepines, methamphetamine, and opiates.
4. We will write down all the medications you are taking, including vitamins and over-the-counter remedies.
5. You will be asked to describe your recent drug use (past 2 days) including caffeine, nicotine, alcohol, and illegal street drugs.
6. We will assess for possible side effects of creatine.

RISKS

During your screening visit, you may become emotionally upset when asked about your psychiatric history including suicide attempts, or physical and sexual abuse.

You may experience discomfort or swelling when blood is drawn for laboratory tests. Rarely, infection can result from blood draws.

It is possible that treatment with creatine will not be effective in treating your depression.

The researchers will take precautions to safeguard your confidentiality, but it is possible that a breach of confidentiality could occur.

Creatine has been studied extensively since the 1980's and previous studies have shown it to be a very safe drug. Creatine overall has a safe side effect profile. You may experience mild GI discomfort from taking creatine. We will be monitoring you closely for potential side effects.

MRI/MRS scans do not use ionizing radiation like x-rays or CT scans. Instead, magnetic fields and radio waves are used to take the pictures. There are no known risks related to MRI/MRS scans – other than the risk of injury when metallic objects are brought into the scanning room by mistake. Serious injury can occur during an MRI/MRS scan to persons who have:

- Cardiac (heart) pacemakers.
- Metal clips on blood vessels (also called stents).
- Artificial heart valves.
- Artificial arms, hands, legs, etc.
- Brain stimulator devices.
- Implanted drug pumps.
- Cochlear (ear) implants.
- Ocular (eye) implants or known metal fragments in eyes.
- Exposure to shrapnel or metal fillings
- Other metallic surgical parts.
- Orthodontic braces on the teeth.
- Body jewelry or piercings that cannot be removed for the scan.
- Certain tattoos with metallic ink (please tell us if you have a tattoo)
- Certain transdermal (skin) patches such as NicoDerm (nicotine for tobacco dependence), Transderm Scop (scopolamine for motion sickness), or Ortho Evra (birth control)

If you have any such devices, or have had a surgery where metal devices were placed in your body, you cannot take part in the study unless cleared for MRI/MRS scanning by the surgeon who implanted the medical device(s).

Serious risks also exist if ferromagnetic objects (things that stick to magnets) are brought into the scanning area. These items can become dangerous flying objects, and are not allowed near the MRI scanner.

The Food and Drug Administration (FDA) has approved the 3.0T scanner for routine clinical studies in adults. Although the scans we are using in this study have no known risks, there could be ill effects that are delayed, such that they have not yet been

recognized by the FDA. The MRI/MRS scans do not cause pain. Apart from the scanner noise, you will not know the scan is taking place.

Inside the scanner, some people experience claustrophobia (fear of being in small spaces), dizziness, headaches, or a metallic taste in the mouth. Some people experience double vision or see flashing lights. These symptoms are temporary, and will stop when you leave the scanner.

You may feel cramped inside the scanner. There is a mirror placed inside the scanner so that you can see your face, and look out into the scanning room. The technologist will be able to hear you at all times, and will be able to talk to you during the scan.

Very rarely, someone having an MRI/MRS scan feels a tingling sensation in his or her back. This is due to the magnetic field changing quickly during the scan. If you feel a tingling during the scan, you should let us know right away so that the scan can be changed.

The sounds made by the scanner can be annoying, but the noise is not harmful to your hearing. You will be given earplugs or headphones to muffle the noise.

The precautions taken will avoid all the known risks related to MRI/MRS scans. You can stop the scan at any time.

Many people with positive or indeterminate HIV test results will experience stress, anxiety, or depression. You may feel sad, depressed, angry or anxious if you learn you are infected with HIV. Some persons with negative tests may continue or increase unsafe behaviors, which would increase the risk of HIV infection. Some persons are afraid that their test results will get into the wrong hands, and that discrimination might result. Although people who are infected with HIV may not feel sick and often live for many years, they are sometimes treated unfairly, badly, or in extreme cases, with violence by others who learn they have HIV or AIDS. For these reasons, you should consider your social supports (such as family and friends) and your insurance needs before you are tested. Among the possible legal consequences in Utah is that a diagnosis of AIDS disease must be reported to the State Health Department. It is possible that your HIV information can be released to health providers caring for you or your exposed child; to health officials when required by law; to insurers to permit payment; to persons involved in foster care or adoption; to official correctional, probation and parole staff; to emergency or health care staff who are accidentally exposed to your blood; or by special court order.

REPRODUCTIVE RISKS

The effect of creatine on the fetus is unknown. Pregnant women cannot take part in this study, nor should women who plan to become pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. You will also be tested for pregnancy at each visit by urine sample.
If you become pregnant while taking part in the study, you must immediately tell your research doctor. Because the effects of creatine on the fetus are unknown, you will be withdrawn from the study. Options will be discussed with you and you will be referred for prenatal care.

UNFORESEEABLE RISKS
In addition to the risks listed above, you may experience a previously unknown risk or side effect.

BENEFITS
We cannot promise any benefits to you from being in the study. However, there are some possible benefits if you participate in this study:

- You will receive a thorough medical and psychiatric evaluation including basic laboratory blood tests.
- We hope that you will benefit if you take oral creatine, but this cannot be guaranteed.
- Other than direct benefits to you, there are possible indirect benefits:
    - Results from the study will help doctors understand how and if creatine helps female methamphetamine users with depression.

The MRI part of the study may improve our understanding of the biology of methamphetamine use. However, this understanding will not directly benefit you.

ALTERNATIVE PROCEDURES
You may choose not to participate in this study.

HIV TESTING
As part of the study you will be tested for HIV also called Human Immunodeficiency Virus. The HIV testing is required as part of the study. If the HIV test is positive, the study doctor will inform you immediately of the result by contacting you through the phone number you provide. We will refer you to the Utah AIDS foundation to meet with their case management workers for counseling and treatment referral. A positive HIV test result would make you ineligible to participate in the study due to effect it may have on the brain.

We are required by Utah state law to report the results of a positive HIV test to the Utah Department of Health. Information required includes your name, age, sex, address, phone number and date of positive test.

You will be offered counseling before undergoing HIV testing.

PERSON TO CONTACT
If you have questions, complaints or concerns about this study, you can contact Tracy Hellem at (801) 386-4773 or Danielle Kuykendall at (801) 450-2196 during any hours of the day or night. If you think you may have been injured from being in this study, please call Tracy Hellem.

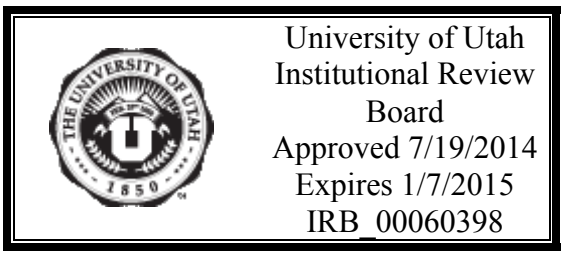
Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY
If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION



It is up to you to decide whether or not to take part in this study. If you decide to take part you are still free to withdraw at any time and without giving a reason. Refusal to participate or the decision to withdraw from this study will involve no penalty or loss of benefits to which you are otherwise entitled. If you don't take part, you can still receive all standard care that is available to you. This will not affect the relationship you have with your doctor or other staff, nor decrease the standard of care that you receive as a patient.

RIGHT OF INVESTIGATOR TO WITHDRAW

The investigator can withdraw you from the study without your approval. Possible reasons for withdrawal include: a positive pregnancy test, inability to comply with the study protocol or comply with attending the study visits (if you miss more than three visits, you will be withdrawn from the study), or worsening of your condition that requires hospitalization for safety. Other reasons for withdrawal include suicidal intent, incarceration, intolerable psychotic or mood symptoms, or adverse effects or toxicity from study drug.

COSTS AND COMPENSATION TO PARTICIPANTS

The study visits, study medication, laboratory tests, and brain scans will be provided to you at no cost. You will be compensated for your time and the amount of compensation is outlined below. Payment will be received in the dollar amounts listed below in the form of gift cards to a variety of local businesses including, but not limited to: restaurants, grocery stores, bookstores, and coffee shops. You can choose to receive gift cards at each visit or save them to receive larger amounts at one time.

10. $25 - Screening
11. $25 - Baseline neuroimaging
12. $25 - Visit 1 (initiation of study drug)
13. $10 - First weekly visits for weeks 2-8 (total = $70)
14. $5 - Second weekly visits for weeks 2-8 (total = $35)
15. $25 - Week 9 (end-of-treatment neuroimaging)
16. $25 - Week 10
17. $10 - Week 11
18. $50 - Week 12

NEW INFORMATION

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about creatine over the course of this study, the study team will tell you about it and discuss with you whether or not you want to continue in the study.

NUMBER OF PARTICIPANTS

We expect to enroll a total of 30 women in this study.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like your name, address, date of birth and telephone number
- Social Security Number – we will ask you for the last 4 digits of your Social Security Number for MRI registration purposes
- Related medical information about you like your medical history, allergies, current and past medications or therapies, drug use history, and information from physical examinations, such as blood pressure reading, heart rate, and lab results and results from the brain scans
- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- We are required by Utah state law to report the results of a positive HIV test to the Utah Department of Health. Information required includes your name, age, sex, address and date of positive test.

- To help us protect your privacy, we have obtained a Certificate of Confidentiality from the FDA. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

  The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of

federally funded projects or for information that must be disclosed in order to meet the requirements of the FDA.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: child abuse or intent to hurt self or others. The Certificate of Confidentiality also does not prevent the researchers from disclosing positive HIV tests to the Utah State Health Department as required by law.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
    - Members of the research team and University of Utah Health Sciences Center
    - The University of Utah Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights;
    - Alzchem, the company that makes the creatine that is being used in this study; and
    - The Food and Drug Administration

- If we share your information with groups outside of University of Utah Health Sciences Center, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

- As previously mentioned, we are required by Utah state law to report the results of a positive HIV test to the Utah Department of Health. Information required includes your name, age, sex, address, phone number and date of positive test.

- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Health Sciences Center

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

CONSENT
I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH

75 South 2000 East Salt Lake City, UT 84112 | 801.581.3655 | IRB@utah.edu

IRB_00060398

PI: Tracy Hellem

Title: Creatine as a Treatment Option for Depression in Methamphetamine Using Females

This Continuing Review Application has been reviewed and approved by a University of Utah IRB convened board. The convened board approved your study on 1/8/2014. The approval is effective as of 1/10/2014. Federal regulations and University of Utah IRB policy require this research protocol to be re-reviewed and re-approved prior to the expiration date, as determined by the convened board.

Your study will expire on 1/7/2015 11:59 PM**.**
Any changes to this study must be submitted to the IRB prior to initiation via an amendment form.

APPROVED DOCUMENTS

VA Consent Forms
Consent_V1.02_Dec2013 [clean].doc
VA Authorization Document Dec 2013 clean.docx

Other Documents
VA Certification of IC.pdf

Click CR_00014857 to view the application and access the approved documents.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH

75 South 2000 East Salt Lake City, UT 84112 | 801.581.3655 | IRB@utah.edu

IRB: IRB_00060398

PI: Tracy Hellem

Title: Creatine as a Treatment Option for Depression in Methamphetamine Using Females

This New Study Application has been reviewed and approved by a University of Utah IRB convened board. The convened board approved your study as a Greater Than Minimal risk study on 1/30/2013. The approval is effective as of 2/6/2013. Federal regulations and University of Utah IRB policy require this research protocol to be re-reviewed and re-approved prior to the expiration date, as determined by the convened board.

Your study will expire on 1/29/2014.
Any changes to this study must be submitted to the IRB prior to initiation via an amendment form.

APPROVED DOCUMENTS

VA Consent Forms
VA_Authorization_Document_Dec2012 clean.doc
VA_Consent_V1.00_Jan2013 [CLEAN].doc

Surveys, etc.
SCID.pdf
HAM-D 17.pdf
Beck Anxiety Inventory.pdf
Columbia Suicide Severity Rating Scale [Baseline Version].pdf
Columbia Suicide Severity Rating Scale [Since Last Clinic Visit Version].pdf
DrugHistoryQuest.pdf

Investigational Brochure
EFSA_Creatine.pdf

Literature Cited/References
Bibliography.pdf

Recruitment Materials, Advertisements, etc.
Recruitment_Flyer_v1.00.pdf

Other Documents
Certificate of Confidentiality.pdf
IND_114316_Study_May_Proceed.pdf
Creatine_VA_InformationSecurityForResearch.doc
Creatine_CofA.pdf
Creatine_1572 Dec2012.pdf

Click IRB_00060398 to view the application and access the approved documents.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

APPENDIX B

INSTRUMENTS

This appendix includes the instruments, such as the Hamilton Depression Rating Scale (HAMD), Beck Anxiety Inventory (BAI), Drug Health Questionnaire (DHQ), Columbia Suicide Severity Rating Scale (C-SSRS) and Structured Clinical Interview for DSM-IV Disorders (SCID) that were used for data collection in this study.

Patient Name:_____ **Date**:_____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

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

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

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

4. **Insomnia - Early**
   0 No difficulty falling asleep
   1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
   2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
   0 No difficulty
   1 Patient complains of being restless and disturbed during the night
   2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
   0 No difficulty
   1 Waking in early hours of the morning but goes back to sleep
   2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
   0 No difficulty
   1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
   4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
   (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   0 Normal speech and thought
   1 Slight retardation at interview
   2 Obvious retardation at interview
   3 Interview difficult
   4 Complete stupor

9. **Agitation**
   0 None
   1 "Playing with" hand, hair, etc.
   2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
    0 No difficulty
    1 Subjective tension and irritability
    2 Worrying about minor matters
    3 Apprehensive attitude apparent in face or speech
    4 Fears expressed without questioning

11. **Anxiety - Somatic**
    0 Absent
    1 Mild
    2 Moderate
    3 Severe
    4 Incapacitating
    Physiological concomitants of anxiety such as: Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching
    Cardiovascular – palpitations, headaches
    Respiratory - hyperventilation, sighing
    Urinary frequency
    Sweating

12. **Somatic Symptoms - Gastrointestinal**
    0 None
    1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
    2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
    0 None
    1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
    2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
    0 Absent
    1 Mild
    2 Severe
    0 Not ascertained
    Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
    0 Not present
    1 Self-absorption (bodily)
    2 Preoccupation with health
    3 Frequent complaints, requests for help, etc.
    4 Hypochondriacal delusions

16. **Loss of Weight**
    A. When Rating by History:
    0 No weight loss
    1 Probable weight loss associated with present illness
    2 Definite (according to patient) weight loss

    B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
    0 Less than 1 lb. weight loss in week
    1 Greater than 1 lb. weight loss in week
    2 Greater than 2 lb. weight loss in week

17. **Insight**
    0 Acknowledges being depressed and ill
    1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    2 Denies being ill at all

Total Score:_____

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring - Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____ .

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in either your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little "anxiety" could indicate that you are detached from yourself, others, or your environment.

A grand sum between **22 – 35** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time but you want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a counselor if the feelings persist.

PSYCHOACTIVE DRUG HISTORY QUESTIONNAIRE

DRUG CATEGORY Note: First Use Card Sort With Client To Determine Which Drugs Ever Used	[a] Ever Used 1 = No 2 = Yes	[b] Total Years Used	Injection Drug Use 1 =No 2 = Yes NA=not applicable	Year Last Used 19 __	[c] Frequency of Use in Past 6 Months
ALCOHOL			NA		
CANNABIS: Marijuana, hashish, hash oil			NA		
STIMULANTS: Cocaine, crack					
STIMULANTS: Methamphetamine — speed, ice, crank					
AMPHETAMINES/OTHER STIMULANTS: Ritalin, Benzedrine, Dexedrine			NA		
BENZODIAZEPINES/ TRANQUILIZERS: Valium, Librium, Halcion, Xanax, Diazepam, "Roofies"			NA		
SEDATIVES/HYPNOTICS/BARBITURATES: Amytal, Seconal, Dalmane, Quaalude, Phenobarbital			NA		
HEROIN					
STREET OR ILLICIT METHADONE			NA		
OTHER OPIOIDS: Tylenol #2 & #3, 282'S, 292'S, Percodan, Percocet, Opium, Morphine, Demerol, Dilaudid			NA		
HALLUCINOGENS: LSD, PCP, STP, MDA, DAT, mescaline, peyote, mushrooms, ecstasy (MDMA), nitrous oxide			NA		
INHALANTS: Glue, gasoline, aerosols, paint thinner, poppers, rush, locker room			NA		
OTHER: (specify)_____ _____					

[a] If "EVER USED" is NO (1) for any given line, the remainder of the line should be left blank.

[b] Code 87 = Infrequent Use (≤ 2 x/year)

Code 88 = Brief Experimental Use (< 3 months lifetime use)

[c] Frequency Codes:

0 = no use
1 = < 1x/mo.
2 = 1x/mo.
3 = 2 to 3x/mo.
4 = 1x/wk.
5 = 2 to 3x/wk
6 = 4 to 6x/wk.
7 = daily

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Frequency of Ideation:*** _____ If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation:*** _____ If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** ***Frequency of Ideation:*** _____ If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation:*** _____ If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation:*** _____ If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION		
Ideation Type *Type # (1-5)* *Description of Ideation* *Most Common Ideation:* _____ _____ *Most Severe Ideation:* _____ _____	**Since Last Visit**	
The following features should be rated with respect to both most common and most severe types of ideation experienced since last visit. Only rate most common if most severe and most common are different.	Most Common	Most Severe
Frequency ***How many times have you had these thoughts?*** 1. Less than once a week 2. Once a week 3. 2-5 times in week 4. Daily or almost daily 5. Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** 1. Fleeting - few seconds or minutes 2. Less than 1 hour/some of the time 3. 1-4 hours/a lot of time 4. 4-8 hours/most of day 5. More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** 1. Easily able to control thoughts 2. Can control thoughts with little difficulty 3. Can control thoughts with some difficulty 4. Can control thoughts with a lot of difficulty 5. Unable to control thoughts 0. Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** 1. Deterrents definitely stopped you from attempting suicide 2. Deterrents probably stopped you 3. Uncertain that deterrents stopped you 4. Deterrents most likely did not stop you 5. Deterrents definitely did not stop you 0. Does not apply; wish to die only	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** 1. Completely to get attention, revenge or a reaction from others. 2. Mostly to get attention, revenge or a reaction from others. 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Worst/Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Due to the length of the SCID, the SCID is not provided, but it can be found at the following link: http://www.scid4.org/revisions/download_pdf.html