STUDY PROTOCOL

PROTOCOL TITLE: A Randomized Double-Blind Controlled Trial of Creatine in Female Methamphetamine Users

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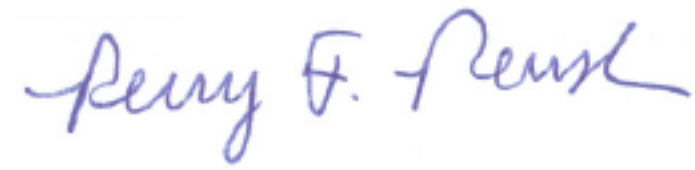
Investigator's Agreement

1. I have read this protocol and agree that the study is ethical.
2. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.



Signature of Principal Investigator

Perry F. Renshaw 09/05/2018

Name of Principal Investigator (printed or typed) Date

BACKGROUND AND SIGNIFICANCE

Methamphetamine Causes Neuronal Excitotoxicity That Involves Bioenergetic Compromise:

Methamphetamine (MA) addiction is a chronic relapsing conditions that causes devastating physical and psychiatric harm to affected individuals [1]. These include increased risk of psychosis [2], depression/anxiety [1], suicidal behavior [3], completed suicide [4], and even all-cause mortality when compared to users of cocaine, alcohol or cannabis [5]. However, since discontinuation of MA use leads to negative emotional states, abstinence from MA poses intense difficulty for dependent individuals. Given these observations, basic and clinical research studies have focused on the development of new pharmacological interventions [6], but have not led to Food and Drug Administration (FDA) approved pharmacotherapies that improve cognitive deficits and depressive symptoms during MA discontinuation [7].

Methamphetamine has deleterious effects on dopaminergic brain systems [8], and prolonged amphetamine exposure is associated with Parkinson's disease [9]. Animal studies suggest that MA use predisposes to Parkinson's via degeneration of the midbrain dopaminergic neurons that project to striatum [10]. A recent epidemiologic study found a significant correlation between the development of Parkinson's disease (165% higher risk) in MA users followed for up to 10 years [11]. This finding was replicated in a larger sample of MA users (n=40,472) versus an appendicitis group (n=207,831; hazard ratio=1.76), and even a cocaine group (n=35,335; hazard ratio=2.44) [12].

Converging evidence implicates mitochondrial dysfunction in MA toxicity [8, 13-15]. Mitochondrial pathways interact to cause MA-induced neuronal apoptosis and death [16]. MA inhibits enzyme complexes of the electron transport chain, resulting in dopaminergic neurotoxicity because electron transport chain inhibitors increase reactive species [17-19]. Inhibition of complex I activity by MA [16] also decreases ATP production. MA produces mitochondrial fragmentation in progenitor cells [20], releasing apoptogenic molecules from mitochondria [21].

Brain Phosphocreatine (PCr) Levels and Glutamate Excitotoxicity in Methamphetamine Use:

A key phosphorus (^{31}P) magnetic resonance spectroscopy (MRS) finding from our ongoing research is significantly decreased phosphocreatine (PCr) in MA users, an effect that is greater in females than males [22]. Notably, in rats creatine administration significantly increases the brain content of both creatine and PCr [23]. In human studies, the increase in brain total creatine (PCr + creatine) after oral creatine supplementation is a finding replicated by three independent groups, including ours [24-26].

The importance of assessing glutamatergic systems in MA users is attested to by the fact that more than 80% of neurons are excitatory, and that greater than 90% of synapses release glutamate [27]. Of relevance to our preliminary proton (^{1}H) MRS findings showing an association between the glutamine/glutamate ratio and lifetime MA use, it has been reported that PCr stimulates synaptic glutamate uptake thereby reducing extracellular glutamate [28], which is another potential neuroprotective mechanism of creatine. Importantly, depletion of PCr and ATP is an early event in glutamate excitotoxic neurodegeneration [29, 30]. Therefore, based on our finding of decreased PCr in MA users, it is of interest that a recent ^{1}H-MRS investigation reported that glutamate levels in frontal white matter are significantly higher in abstinent MA users versus control subjects [31], which is compatible with MA-induced neurotoxicity.

Female Methamphetamine Initiation, Addiction and Relapse are Influenced by Depression:

The prevalence of pre-morbid depressive disorders in MA users is high, with a majority reporting a significant lifetime history of depression [1, 3, 70]. For example in one study [70], MA users had a 62% rate of depression and a 23% rate of suicidality prior to MA use. After MA was initiated, the rate of depression increased to 79% [70]. Studies reporting gender differences in psychopathology have found that MA use is associated with depression in both adult [60] and

adolescent [71] females. In one study, depressive symptoms were endorsed on the Addiction Severity Index (ASI) by 68% of female MA users [3]. In another, early-onset MA use in females was significantly associated with premorbid depressive disorders, while the same was *not* true for males [72]. Female MA users with depression are less likely to be employed, more likely to use MA to manage their mood, use more grams of MA per 30-day period, use MA more times per day on more consecutive days, and are more likely to be binge users [73]. The diagnosis and treatment of depression and anxiety in MA users is complicated by the fact that withdrawal-associated dysphoria is persistent, and may be the result of *MA-induced neurotoxicity* [74]. Therefore, an ideal intervention for depression and anxiety in the setting of MA addiction would be one that targeted *both* neurotoxicity *and* negative emotional states.

Research has shown that females may respond better to treatment of MA use disorders than males [60, 75]. In fact, patient gender predicts both treatment engagement and abstinence during rehabilitation [76], a gender difference *not* found in cocaine- or alcohol-dependent research samples [77]. As a result, the recommendation has been made to take gender into account in developing treatments for MA use disorders [60, 75].

Creatine is a Novel Strategy for Cognitive Enhancement and Neuronal Repair in MA Addiction:

Our preliminary data, combined with the extant literature, suggest that creatine administration is a safe, hypothesis-driven strategy for: (a) Increasing brain PCr, NAA and GABA levels, thus providing neuroprotection and neuronal repair; (b) Reducing both depression and anxiety symptoms; and (c) Improving cognitive deficits in female MA users. Based on evolving understanding of MA neurotoxicity, a novel therapeutic strategy that has been suggested is to utilize cognitive enhancement and neuronal repair as pharmacotherapy targets in stimulant addiction [56, 57]. This stems, in part, from the fact that solely addressing the drug's addictive properties may be insufficient to address the diverse neuropathological injuries caused by MA [15]. However, in the absence of approved medications for MA use disorders, an initial step toward pursuing this innovative strategy is to assess the clinical and translational impact of a neuroprotective agent such as creatine in MA users.

Summary Significance and Relevance for This Proposal:

The lack of safe and effective pharmacological treatments for MA use disorders is a critical barrier to improved treatment outcomes. This proposal builds on the published translational findings of reduced PCr[22] and NAA [34, 124] levels in MA use disorders, and the clinical and neuroimaging findings from our preliminary study of creatine for MA-using females. At the same time, it follows the recommendation of experts – including NIDA Director Dr. Nora Volkow and the eminent substance abuse researcher Dr. George Koob – that strategies outside the brain dopamine reward system be adopted [56, 125, 126]. Achievement of these *Specific Aims* would validate the notion of neuroprotective agents as potential treatments for MA addiction [15], and in particular those which are also capable of improving mood/anxiety and cognitive symptoms. Incorporating pre- and post-treatment imaging into studies of substance misuse can facilitate identification of the neural predictors and correlates of effective MA treatment [127]. Because the effects of drug use on brain function impede patients' ability to benefit from treatment, studies of drug-related alterations in neurobiology utilizing translational study designs are warranted [127]. Thus, we propose an 8-week, randomized, placebo-controlled trial of creatine for females with MA addiction.

Specific Aims for this proposal are: 1. <u>To define the extent of restoration in bioenergetic dysfunction and neuronal viability following creatine supplementation in female MA users</u>. We hypothesize that creatine will be superior to placebo in the degree of improvement in PCr and NAA levels, measured with ^{31}P-MRS and ^{1}H-MRS. Changes to the glutamine/glutamate ratio and GABA will be assessed in an exploratory manner. ***2.*** <u>To assess creatine's antidepressant/anxiolytic effect in female MA users</u>. We hypothesize that creatine will be

superior to placebo in reducing Hamilton Depression Rating Scale (HAMD) and Beck Anxiety Inventory [97] scores.**3**.To Measure the Degree of Cognitive Improvement Associated with Creatine in Female MA Users. We hypothesize that creatine will be associated with greater improvement in cognitive function tests, compared with placebo. In addition to these Specific Aims, we will examine urine drug testing results in an exploratory manner, to determine whether creatine vs. placebo is associated with a greater number of MA-free tests

In addition to these ***Specific Aims***, we will monitor subjects' MA use, as improvements in brain bioenergetics, mood/anxiety and may decrease MA usage. Therefore, we will record urine drug testing results, to determine whether creatine vs. placebo is associated with a greater number of MA-free tests during the 8 weeks of randomized treatment.

PARTICIPANT SELECTION CRITERIA

123 women will be randomly assigned in a 1:1 ratio to either creatine or placebo for eight weeks. Table 1 outlines eligibility criteria.

TABLE 1 INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA:

- Female gender, ages 18-55 inclusive
- Current primary diagnosis of MA dependence or abuse, with MA preferred drug of abuse (Lifetime MA use > 20 grams)
- Current diagnosis of Major Depressive Disorder (MDD)
- Current HAMD score ≥ 10
- Clinical Global Impressions–Severity (CGI-S) depression score ≥ 4
- If taking a psychotropic medication for depressed mood, regimen must be stable for ≥ 4 weeks prior to randomization

EXCLUSION CRITERIA:

- Persons unable to provide adequate informed consent
- Persons who are at clinically significant suicidal or homicidal risk
- Primary substance-related diagnosis *other* than MA dependence or abuse
- Comorbid substance dependence diagnosis, other than nicotine (substance abuse diagnoses are not excluded)
- Positive pregnancy test, due to the unknown effects of MRI scanning on the unborn fetus
- Positive test for antibody to the Human Immunodeficiency Virus (HIV)
- History of renal disease
- Clinically significant medical or neurological illness identified by history, physical exam and laboratory testing
- Known or suspected intellectual disability, or developmental disorder, e.g. autism
- History of hypersensitivity reaction to creatine

WITHDRAWAL / EARLY TERMINATION CRITERIA:

- Withdrawal of informed consent
- Suicide attempt
- Psychiatric hospitalization
- Onset of bipolar disorder or psychotic disorder
- Positive pregnancy test
- Incarceration
- Inability to comply with study protocol

- Treatment with electroconvulsive therapy (ECT)
- Increase in HAMD score > 25% from baseline
- Serious adverse event

- **HEALTHY CONTROL SUBJECTS:**

- Female gender, ages 18-55 inclusive
- No current or past DSM-5 diagnosis, as determined by clinical and structured interviews
- No first-degree relatives with known or suspected DSM-5 diagnosis

DESIGN

The proposed study will use a randomized, double-blind, placebo-controlled design. 123 participants will be randomly assigned in a 1:1 ratio to placebo or 5 grams of daily creatine treatment for eight weeks. We also plan to recruit 24 age-matched females (18-55).

STUDY PROCEDURES

All procedures performed by study personnel are research-related. None of the study activities will be considered standard of care. There will be no cost to study subjects for their participation. Participants will be compensated for their time and travel. Table 2A and 2B outlines the schedule of study procedures for treated participants and healthy controls.

Consent will be obtained before any study procedures are initiated. Potential participants will be informed of the study and offered a consent form to review. They will be encouraged to discuss study participation with their relatives. If a potential participant expresses interest in study participation, the informed consent process will be conducted. After the informed consent process, individuals will be offered time to consider study participation and to ask questions. Subjects and parents/guardians will have the opportunity to discuss the study with a study team member in a setting free of coercion. The language of the informed consent form is written at a level easily understood by the subject and any questions asked by the subject will be answered honestly and free of bias. A specific meeting time will be set up between a study team member and the participant where the entire informed consent document will be carefully explained in its entirety. The length of the meeting will be designed so there is the necessary amount of time for all questions to be answered.

Randomization of participants to the two treatment conditions will take place according to a randomization list generated prior to the start of recruitment. 47 (50%) will be randomized to placebo. The study will be conducted as a double-blind trial, with neither participants nor research staff aware of participant assignment. Except in cases of medical emergency, the double-blind will not be "broken" until recruitment is closed and the final participant has completed 8 weeks of treatment with investigational drug. There is no "washout period" for any participant in this study, and participants randomized to placebo will continue treatment with a psychotropic medication throughout their time in the study.

At the screening visit, an ECG will be conducted in order to examine the heart and ensure participant safety; an adult cardiologist will also evaluate all individuals during the screening phase. If during the MRI/MRS scans we unexpectedly discover something that warrants further inspection, we will refer the participant to her primary care provider for follow-up, along with the MRI/MRS report that shows the findings. Any costs related to following up on unexpected findings will be the responsibility of her and/or her insurance provider. In conjunction with the brain scans performed pre- and post-treatment, a brief battery of cognitive tests will be administered, to evaluate change associated with creatine or placebo. Trained psychometricians administer tests on the day of scanning. Scoring is done blind to subjects' group status, clinical ratings and imaging results. The cognitive testing battery instruments were

chosen because they are sensitive to frontal lobe integrity: the Wisconsin Card Sorting Task (WCST)[129], the Stroop Color-Word Test[130, 131], and the Wechsler Memory Scale (WMS-IV)[132].Furthermore, the WCST[133], Stroop Test[134] and WMS-IV [90]each have been associated with performance deficits in MA users.

TABLE 2A Schedule of Procedures for Methamphetamine-dependent Females												
	Screening	**Treatment Phase**									**Follow Up Phase**	
Study Week →	**-2 to 0[a]**	**1***	**2***	**3***	**4***	**5***	**6***	**7***	**8***	**9**	**10**	**11**
Informed Consent, Demographics	X											
Medical History & Physical Exam, ECG	X											
Hematology & Chemistries	X									X		
Phlebotomy for Creatinine Levels	X				X					X		
HIV	X											
Pregnancy Test and vital signs	X	X	X	X	X	X	X	X	X	X	X	X
PRISM Diagnostic Interview	X											
ASI	X									X		
Randomization to Creatine or Placebo	X											
Treatment with Creatine or Placebo		X	X	X	X	X	X	X	X			
Urine Drug Screen / Other Drug Use	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Food Frequency Questionnaire	X									X		
Cognitive Tests: WCST, STROOP and WMS-IV (with WASI vocabulary)***	X									X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Treatment Program Attendance	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Scales: HAMD**, BAI**, CGI-S**, C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X

^{31}P-MRS and ^{1}H-MRS****	X									X		

***During the 8 Treatment Weeks, MA Subjects Have 2 Study Visits Per Week (separated by ≥ 48 hours)**

****Procedure will be collected at one of the twice weekly visits**

*****MA subjects with difficulty scheduling the cognitive testing appointment may be allowed to omit these measures and continue in the study as to not delay treatment and in order to facilitate timely enrollment, which is critical for this population.**

******If an individual is screened and determined to be a good fit for study participation but also has a contraindication to MRI scanning, the principal investigator may allow them into the study, however, they will not be scanned for their safety.**

CGI-S = Clinical Global Impressions-Severity Depression Score; C-SSRS = Columbia-Suicide Severity Rating Scale; HAMD = Hamilton Rating Scale for Depression; BAI = Beck Anxiety Inventory; PRISM = Psychiatric Research Interview for Substance and Mental Disorders; STROOP = Stroop Color Word Test; WCST = Wisconsin Card Sorting Test; WMS-IV = Wechsler Memory Scale; WASI = Wechsler Abbreviated Scale of Intelligence; ASI = Addiction Severity Index.

[a]Screening may happen over the course of 2-3 visits.

TABLE 2B Schedule of Procedures for Healthy Controls

	Screening									**Final Visit**
Study Week →	**-1 to 0[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed Consent, Demographics	X									
Medical History & Physical Exam, ECG	X									
Hematology & Chemistries	X									
Phlebotomy for Creatinine Levels	X									
HIV	X									
Pregnancy Test	X									X
PRISM Diagnostic Interview	X									
Food Frequency Questionnaire	X									X
Urine Drug Screen / Other Drug Use	X									X
Concomitant Medications	X									X
Vital Signs	X									X
Cognitive Tests: WCST, STROOP and WMS-IV (with WASI vocabulary)	X									X
Treatment Program Attendance	X									X
Clinical Scales: HAMD**, BAI**, CGI-S**, C-SSRS	X									X

^{31}P-MRS and ^{1}H-MRS	X									X

CGI-S = Clinical Global Impressions-Severity Depression Score; C-SSRS = Columbia-Suicide Severity Rating Scale; HAMD = Hamilton Rating Scale for Depression; BAI = Beck Anxiety Inventory; PRISM = Psychiatric Research Interview for Substance and Mental Disorders; STROOP = Stroop ColorWord Test; WCST = Wisconsin Card Sorting Test; WMS-IV = Wechsler Memory Scale; WASI = Wechsler Abbreviated Scale of Intelligence.
[a]Screening may happen over the course of 2-3 visits.

RISKS AND BENEFITS TO STUDY PARTICIPANTS

- During the intake and assessment interview, participants may become emotionally upset when asked about their psychiatric history including suicide attempts, or physical and sexual abuse.
- There is a 50% chance that the participant will be assigned to placebo, in which they will not receive creatine.
- Participants may experience discomfort or swelling when blood is drawn for laboratory tests. Rarely, infection can result from blood draws.
- It is possible that the participant's illness could worsen during the study. This could be related or unrelated to the study. Individuals with Major Depressive Disorder are at risk for depression, suicidal ideation, and suicide attempts as part of their illness. If the participant's illness worsens to the point that the study doctor considers them a danger to themselves or others, they will be hospitalized. If the participant is hospitalized they will be withdrawn from the study. In the event of hospitalization, the participant or the participant's insurance company will be responsible for the associated costs.
- It is possible that treatment with creatine will not be effective for the participant's depression, and that study participation will therefore delay the start of effective treatment.
- The researchers will take precautions to safeguard the participant's confidentiality, but it is possible that a breach of confidentiality could occur. A Certificate of Confidentiality has been obtained for this study.
- The participants may experience gastrointestinal discomfort as a result of taking study medication. We recommend taking the study medication with food to reduce possible stomach discomfort.
- 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 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:
    - 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 [6] implants.
    - Ocular [118] 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 your child has 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 the participants have any such devices, or has had a surgery where metal devices were placed in their body, they cannot take part in the study unless cleared for MRI scanning by the surgeon who implanted the medical device(s) or unless the principal investigator allows the individual to take part in the study without being scanned.

- Serious risks 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 FDA has approved the 3T scanner for routine clinical studies in children. The FDA has decided that MRI machines of 8T or less do not pose a risk. 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 brain scans do not cause pain. Apart from the scanner noise, the participant 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 the participant leaves the scanner.
- The participant may feel cramped inside the scanner. There is a mirror placed inside the scanner so that your child can see his or her face, and look out into the scanning room. The technologist will be able to hear the participant at all times.
- Very rarely, someone having an MRI scan feels a tingling in his or her back. This is due to the magnetic field changing quickly during the scan.
- The precautions taken will avoid all the known risks related to MRI scans. The participant can stop the scan at any time.

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

- Participants will receive a thorough medical and psychiatric evaluation, and will be followed more closely than in routine clinical care.

Other than direct benefits to the participants, there are possible indirect benefits:

- Results from the study will help doctors understand the way creatine affects MA users with depression, and thus, this could help us improve treatment options.
- The brain scans may improve our understanding of the biology of depression in female MA users. However, that would not directly benefit the participants.
- The participants will receive a copy of the clinical MRI of their brain, if they wish. A copy of the MRI scan report will also go to the research team.

DATA SAFETY MONITORING PLAN

The study team will perform monitoring of the study records on a continuous basis. Co-investigator, Young-Hoon Sung, will oversee data accuracy and completeness.

a. Adverse Events/Serious Adverse Events to the IRB, FDA and NIDA

i. Reporting to the University of Utah Institutional Review Board. Adverse events (AEs) and Serious Adverse Events (SAE) that are unexpected and unrelated will be reported to the University of Utah Institutional Review Board (IRB) with the annual request for study continuation. For AEs/SAEs that are unexpected, related to study participation and place participants at risk will be reported via the IRB's electronic reporting system as soon as possible after the PI learns of the event, but in all cases within 10 working days.

ii. Reporting to the Food and Drug Administration. The PI shall notify the Food and Drug Administration (FDA) in a written investigational new drug [118] safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. In each written IND safety report, the investigators shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If the FDA determines that additional data are needed, the agency may require further data to be submitted.
   a. The study team will send an annual report 60 days within the “study may proceed” date.

iii. Reporting to the National Institute on Drug Abuse. The PI will notify the grant program officer by email of SAEs as soon as possible and in no event later than 15 calendar days. Other AEs will be summarized in the annual progress report.

b. Reporting IRB Actions to NIDA. The grant program officer will be made aware of IRB actions via email correspondence from the PI.

c. *Reporting Protocol Changes.* Changes to the protocol will be submitted to the IRB and FDA for approval before the changes are implemented. Once the IRB and FDA have issued approval of protocol changes, the PI will submit a summary of the protocol changes and the protocol to the grant program officer. The NIDA program officer must agree upon proposed protocol changes before they can be implemented.

d. *Reporting Protocol Violations/Deviations to the IRB and FDA*

i. Reporting to the University of Utah Institutional Review Board. If a protocol violation/deviation meets one or more of the following criteria, the PI will submit the violation/deviation via ERICA within 10 working days from the time the investigator learns of the event.
   - Intended to eliminate apparent immediate hazard to a research participant; or
   - Harmful (caused possible harm to participants or others, or places them at increased risk of harm – including physical, psychological, economic, or social harm, such as breach of confidentiality); or
   - Possible serious or continued noncompliance (such as a deviation that has happened previously and is now being repeated).

ii. Reporting to the Food and Drug Administration. Protocol violations/deviations will be summarized in the annual IND report.

Trial Stopping Rules

In our open-label study of 5 grams of daily creatine for 8-weeks, there were no unanticipated problems or SAEs reported. Considering this is a feasibility study of double-blind, placebo-controlled creatine at the same dose as our open-label study, and the open-label creatine was well tolerated with a low side effect profile, we have not adopted rules for stopping the study. We have, however, developed criteria for early termination of participants and the criteria are listed below:

- Suicide attempt
- Psychiatric hospitalization

- Onset of bipolar disorder or psychotic disorder
- Positive pregnancy test
- Incarceration
- Inability to comply with the study protocol

IMAGING METHODS AND DATA ANALYSIS

1. Neuroimaging Protocol

i. Magnetic Resonance Imaging (Siemens Trio 3T MRI system)

MRI scans will be conducted twice: at the baseline visit, and following 8 weeks of treatment with study drug. The 3.0 Tesla Siemens whole-body clinical scanner (Siemens Medical Solutions, Erlangen, Germany) located within the University Neuropsychiatric Institute (UNI) will be used to acquire this data. Participants will first undergo a routine anatomic MRI protocol, which includes MRI images acquired in the axial and coronal planes. Specifically, the anatomic scan protocol consists of a T1 weighted structural scan (MPRAGE), and double-echo T2 weighted scan, and a Fluid Attenuated Inversion Recovery scan (FLAIR). The purposes of the MR anatomic screening session include screening subjects for gross structural abnormalities and acquiring images for use in brain cortical thickness measurements. Anatomic MRI examinations will be performed with a quadrature radio-frequency coil. After localization, anatomical imaging will be obtained using a T1-weighted, sagittal oriented 3D-Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR/TE/TI 2100/3.97/1100 ms, matrix 256x256, FOV 256x256 mm, flip angle 12 degree, slice thickness 1.5 mm, slab 192 mm, bandwidth 190 Hz/pixel). Axial proton-density and T2 weighted images will be acquired to screen for brain structural abnormalities using 2D Double echo T2 weighted turbo spin echo (TSE) sequence (TR 7110 ms, TE 28/84 ms, FOV 240x210, slice thickness 3 mm, flip 150°, bandwidth 179 Hz/pixel). FLAIR sequence (TR/TE/TI 8000/90/2500 ms, slice thickness 5 mm, FOV 240x168, voxel size 0.8x0.6x5.0 mm, bandwidth 200 Hz/pixel, turbo factor 13) will be used to detect juxtacortical-cortical lesions. All anatomic MRI images will be read by a board-certified Radiologist to screen for structural abnormalities.

ii. Measurement of *In-Vivo* Brain Chemistry Using Phosphorus-31 Magnetic Resonance Spectroscopy (^{31}P-MRS)

a. Phosphorus MRS

Phosphorus spectroscopy data will be acquired on the same Siemens 3T system. We aim to keep the duration of each MRSI examination at or under 25 minutes. A 3D-MRSI sequence with elliptically weighted phase-encoding will be used to collect ^{31}P-MRSI data to minimize T2 signal decay. Acquisition parameters will be: data matrix size 16x16x8; TR 2000 ms; tip-angle 90 degree for hard RF pulse; Rx bandwidth ±1 kHz; complex-points 1024; readout duration 256 ms; pre-acquisition delay 0.3ms; FOV 240x240 mm^2; 16 NEX.

iii. Spectral Analysis of ^{31}P-MRS Data

Spectroscopy will be analyzed using Liner Combination of Model Spectra (LCModel) [135], which analyzes an *in vivo* spectrum as a linear combination of model in vitro spectra from individual metabolite solutions. This model is fully automatic and user independent. A nearly model-free constrained regularization method is used for convolution and baseline. For quantification, absolute metabolite concentrations (institutional units) will be estimated using the unsuppressed water signal as an internal concentration reference. Also, total creatine levels will be used as a denominator for calculating the relative concentration for the comparison with previous reports. The standard Siemens libraries of model metabolite spectra provided with LCModel will be used in the basis set. The metabolites from the basis set will include alanine, aspartate, creatine, gamma-amino butyric acid, glucose, glutamine, glutamate, glycerophosphocholine, glutathione, myo-inositol, scyllo-inositol, lactate, N-acetylaspartate, N-

acetylaspartylglutamate, phosphocholine, phosphocreatine, phosphoethanolomine, scyllo-inositol, and taurine. For the reliability of detection, the Cramer-Rao lower bounds (CRLB) will be determined: the acceptable upper limit of estimated standard deviations will be set at 20% [136].

Post processing of ^{31}P-MRS data will be conducted using jMRUI software (jMRUI v. 4.0, European Community) with the AMARES algorithm (Advanced Method for Accurate, Robust and Efficient Spectral fitting of MRS data with use of prior knowledge). Before fitting the FID (Free-induction-decay) data, a Hamming filter will be applied to reduce signal contamination from neighboring voxels, with apodization of 10 Hz line broadening. Fourier transformation, frequency shifts correction, and zero-order/first order phase correction as well as baseline correction will be applied. The structural image-processing tool FSL (FMRIB Software Library, Release 4.1, The University of Oxford) will be used to account for gray matter, white matter, and cerebrospinal fluid (CSF), in order to correct the partial volume effects on metabolite concentrations. The MRS grid will be positioned over the images in an identical fashion between baseline and treatment scans for each participant. The peak area for each ^{31}P-MRS metabolite will be calculated as a percentage of the total phosphorus signal.

Overall Analytic Strategy: The analyses proposed are generalized estimating equations (GEE) regression modeling, which will be used for our longitudinal data analyses with group comparison across treatment visits for the variables of metabolite levels, depression/anxiety symptoms, and cognitive tests. GEE allows robust estimations of standard errors and permits adjustment for time-varying covariates. We assume that measurements made closer in time are more correlated than those made farther apart. Thus, first-order autoregressive structure is assumed. For our repeated measurement data, GEE fits a population-averaged model with working correlation structure to statistically evaluate the time effect of creatine supplementation. We will control for age, other drug abuse, anxiety scores, and tissue partial volume effects in each GEE model. Sidak multiple comparison procedure will be employed to adjust for family wise error (FWE) rate. The Sidak tests make conservative controls of FWE, giving slightly smaller adjusted p-values than the Bonferroni correction.

Overall Power and Sample Size Calculations: For this pilot study, considering a 20% attrition rate, 95 participants will be recruited to achieve a sample size of 75. To determine the minimum effect that would likely be detected with a sample size of 75, a power analysis was performed. Effect for the power analysis was specified as average baseline (over two measures) HAM-D scores compared with average HAM-D 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 [105] 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 Analysis for Specific Aim 3: Cognitive testing data with a repeated measures design will evaluate the cognitive improvement after 8 weeks of creatine supplementation, specifically in executive and working memory deficits, found in MA users. The relative improvements on WCST, Stroop and WMS-IV scores associated with creatine versus placebo will be tested conservatively with the assumption of independence among comparisons. Independent variables include a time variable of "visit" (baseline and 8 weeks of treatment), creatine” (placebo or creatine group), and an interaction term, "creatine × visit", where a significant interaction will indicate significant differences between treatments. The depression effect will be

tested by stratifying depressed and non-depressed MA users. Power and Sample Size Calculations: Previous reports, meta-analysis, and our preliminary data suggest that the cognitive deficits of MA users have medium-to-large (0.5 to 0.8) effect size, especially in the episodic memory, compared to healthy subjects.Thus, the proposed sample size (n=76) will have enough power (> 80%) based on Cohen's guidelines with adjusted Sidak p-values of 0.0169. [137, 138]

ADMINISTRATIVE RESPONSIBILITIES

Resources:

The facilities at the University of Utah that are available for the proposed research include the following: the Brain Institute, Assessment and Referral Services and UNI. The Brain Institute currently occupies 5,900 square feet of office and laboratory space in a building in the University of Utah Research Park adjacent to the Health Sciences campus. It also occupies clinical space in UNI, the site of the Brain Institute's PRISMA 3T MRI research scanner. Assessment and Referral Services [4] is a freestanding clinic within the Department of Psychiatry. It occupies 6000 square feet in downtown Salt Lake City close to public transportation and approximately three 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 three 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 third is to provide Interim Group Services (IGS), which are free groups for individuals awaiting Salt Lake County funded substance abuse treatment services.

Recruitment of Participants:

Primarily, participants will be recruited from ARS. Staff at ARS will refer women who identify methamphetamine as their primary drug of choice to the study staff. In addition, women will be recruited from the Clinical Assessment Center (CAC) at UNI. Staff at CAC will contact members of the study team to inform them if a MA-using woman interested in participating. The study team member will then follow-up with the interested woman to arrange a screening assessment.

Study information flyers will also be hung at ARS, 12-step recovery program meeting locations, Fellowship Hall, other drug-use referral locations, and public transportation such as buses and trax. Additionally, participants will be recruited by radio advertisements on select radio stations in the Salt Lake City area.

Study details will also be available on utahbrain.org.

CONTROL OF INVESTIGATIONAL DRUG

The University of Utah Research Pharmacy will prepare and dispense the creatine/placebo. They will dispense the study medication in a blinded fashion to a study team member, and it will be stored at room temperature in a locked office that is accessible only to research personnel. The study will be conducted in compliance with all applicable FDA regulations for IND studies.

The blind will be broken following the culmination of the study or at the request of a medical professional dealing with a medical emergency in a case in which it would help a study participant. The Research Pharmacy will be contacted in order to break the blind.

DATA COLLECTION, MANAGEMENT AND PROTECTED HEALTH INFORMATION

The study team will create case report forms (CRFs) for data collection. The consent, permission and assent forms, CRFs, laboratory results, radiology reports, MRI registration forms, and other necessary documents will be filed in each study participant's binder. Study participant binders will contain protected health information such as name, date of birth, age, address, and phone number. Binders will be stored in locked cabinets located in locked offices. Only essential study team members will have access to participant binders.

Using a password-protected computer with access limited to study personnel, the research team will maintain a computerized screening and enrollment log. Participant screening, eligibility status, and consent for participation status will be recorded in this log. Before the performance of any study procedures, potential participants (and where applicable their parent(s) or guardians(s)), verbal and written informed consent will be obtained. When a participant is screened for study eligibility, they will be assigned a screening ID number. The individual will maintain the screening ID until they have completed the first scanning visit. If a subject is determined to be ineligible during screening, the reason for the screen failure will be recorded on the computerized screening and enrollment log. Once a subject has completed screening enrolled for study participation, they will be assigned a subject ID number, which will be used to identify all of the data collected from them during the study.

Data from CRFs will be entered into SPSS. No personal identifiers from study participants will be entered into SPSS. Forms that have missing or inconsistent data will be recorded in the database; however a "missing data" code will be entered in place of each piece of missing or inconsistent data. Two study team members -- the individual who enters the data, and a second individual monitoring data entry -- will check each CRF form entered into SPSS for accuracy and completeness.

RECORD RETENTION

In keeping with 21CFR312.57, study records will be maintained for at least two years after the drug is approved by the FDA or after shipment and delivery of the drug for investigational use has ceased and the FDA has been notified.

BIBLIOGRAPHY

1. Darke, S., et al., *Major physical and psychological harms of methamphetamine use.* Drug and alcohol review, 2008. 27(3): p. 253-62.
2. Sato, M., *A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis.* Ann N Y Acad Sci, 1992. 654: p. 160-70.
3. Zweben, J.E., et al., *Psychiatric symptoms in methamphetamine users.* The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 2004. 13(2): p. 181-90.
4. Marshall, B.D. and D. Werb, *Health outcomes associated with methamphetamine use among young people: a systematic review.* Addiction, 2010. 105(6): p. 991-1002.
5. Callaghan, R.C., et al., *All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study.* Drug and alcohol dependence, 2012.
6. Elkashef, A., et al., *The NIDA Methamphetamine Clinical Trials Group: a strategy to increase clinical trials research capacity.* Addiction, 2007. 102 Suppl 1: p. 107-13.
7. Xi, Z.X. and E.L. Gardner, *Hypothesis-driven medication discovery for the treatment of psychostimulant addiction.* Current drug abuse reviews, 2008. 1(3): p. 303-27.
8. Davidson, C., et al., *Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment.* Brain research. Brain research reviews, 2001. 36(1): p. 1-22.
9. Garwood, E.R., et al., *Amphetamine exposure is elevated in Parkinson's disease.* Neurotoxicology, 2006. 27(6): p. 1003-6.
10. Guilarte, T.R., *Is methamphetamine abuse a risk factor in parkinsonism?* Neurotoxicology, 2001. 22(6): p. 725-31.
11. Callaghan, R.C., et al., *Incidence of Parkinson's disease among hospital patients with methamphetamine-use disorders.* Mov Disord, 2010. 25(14): p. 2333-9.
12. Callaghan, R.C., et al., *Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs.* Drug Alcohol Depend, 2012. 120(1-3): p. 35-40.
13. Virmani, A., F. Gaetani, and Z. Binienda, *Effects of metabolic modifiers such as carnitines, coenzyme Q10, and PUFAs against different forms of neurotoxic insults: metabolic inhibitors, MPTP, and methamphetamine.* Annals of the New York Academy of Sciences, 2005. 1053: p. 183-91.
14. Tata, D.A. and B.K. Yamamoto, *Interactions between methamphetamine and environmental stress: role of oxidative stress, glutamate and mitochondrial dysfunction.* Addiction, 2007. 102 Suppl 1: p. 49-60.
15. Krasnova, I.N. and J.L. Cadet, *Methamphetamine toxicity and messengers of death.* Brain research reviews, 2009. 60(2): p. 379-407.
16. Gluck, M.R., et al., *Parallel increases in lipid and protein oxidative markers in several mouse brain regions after methamphetamine treatment.* Journal of neurochemistry, 2001. 79(1): p. 152-60.
17. Jenkins, J.A., et al., *The influence of gender and the estrous cycle on learned helplessness in the rat.* Biol Psychol, 2001. 58(2): p. 147-58.
18. Bisagno, V., R. Bowman, and V. Luine, *Functional aspects of estrogen neuroprotection.* Endocrine, 2003. 21(1): p. 33-41.
19. Argov, Z., et al., *Bioenergetic heterogeneity of human mitochondrial myopathies: phosphorus magnetic resonance spectroscopy study.* Neurology, 1987. 37(2): p. 257-62.

20. Tian, C., L.C. Murrin, and J.C. Zheng, *Mitochondrial fragmentation is involved in methamphetamine-induced cell death in rat hippocampal neural progenitor cells.* PloS one, 2009. 4(5): p. e5546.
21. Jayanthi, S., et al., *Methamphetamine induces neuronal apoptosis via cross-talks between endoplasmic reticulum and mitochondria-dependent death cascades.* FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 2004. 18(2): p. 238-51.
22. Sung, Y.H., et al., *Decreased frontal lobe phosphocreatine levels in methamphetamine users.* Drug Alcohol Depend, 2013. 129(1-2): p. 102-9.
23. Royes, L.F., et al., *Effectiveness of creatine monohydrate on seizures and oxidative damage induced by methylmalonate.* Pharmacology, biochemistry, and behavior, 2006. 83(1): p. 136-44.
24. Dechent, P., et al., *Increase of total creatine in human brain after oral supplementation of creatine-monohydrate.* The American journal of physiology, 1999. 277(3 Pt 2): p. R698-704.
25. Lyoo, I.K., et al., *Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate.* Psychiatry research, 2003. 123(2): p. 87-100.
26. Pan, J.W. and K. Takahashi, *Cerebral energetic effects of creatine supplementation in humans.* American journal of physiology. Regulatory, integrative and comparative physiology, 2007. 292(4): p. R1745-50.
27. Raichle, M.E. and D.A. Gusnard, *Appraising the brain's energy budget.* Proceedings of the National Academy of Sciences of the United States of America, 2002. 99(16): p. 10237-9.
28. Xu, C.J., et al., *Phosphocreatine-dependent glutamate uptake by synaptic vesicles. A comparison with atp-dependent glutamate uptake.* The Journal of biological chemistry, 1996. 271(23): p. 13435-40.
29. Beal, M.F., *Mitochondrial dysfunction in neurodegenerative diseases.* Biochim Biophys Acta, 1998. 1366(1-2): p. 211-23.
30. Tsuji, K., et al., *Transient increase of cyclic AMP induced by glutamate in cultured neurons from rat spinal cord.* J Neurochem, 1995. 65(4): p. 1816-22.
31. Sailasuta, N., et al., *Metabolic Abnormalities in Abstinent Methamphetamine Dependent Subjects.* Substance abuse :] research and treatment, 2010. 2010(4): p. 9-20.
32. Chang, L., et al., *Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities.* The American journal of psychiatry, 2005. 162(2): p. 361-9.
33. Ernst, T., et al., *Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study.* Neurology, 2000. 54(6): p. 1344-9.
34. Nordahl, T.E., et al., *Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependent subjects: a preliminary proton MRS study. Magnetic resonance spectroscopy.* Psychiatry research, 2002. 116(1-2): p. 43-52.
35. Sekine, Y., et al., *Metabolite alterations in basal ganglia associated with methamphetamine-related psychiatric symptoms. A proton MRS study.* Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 2002. 27(3): p. 453-61.
36. Smith, L.M., et al., *Brain proton magnetic resonance spectroscopy in children exposed to methamphetamine in utero.* Neurology, 2001. 57(2): p. 255-60.
37. Sung, Y.H., et al., *Relationship between N-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: a proton magnetic resonance spectroscopy study.* Drug and alcohol dependence, 2007. 88(1): p. 28-35.
38. Taylor, M.J., et al., *Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy.* Journal of neurovirology, 2007. 13(2): p. 150-9.

39. Patel, T.B. and J.B. Clark, *Synthesis of N-acetyl-L-aspartate by rat brain mitochondria and its involvement in mitochondrial/cytosolic carbon transport.* The Biochemical journal, 1979. 184(3): p. 539-46.
40. Clark, J.B., *N-acetyl aspartate: a marker for neuronal loss or mitochondrial dysfunction.* Developmental neuroscience, 1998. 20(4-5): p. 271-6.
41. Bates, T.E., et al., *Inhibition of N-acetylaspartate production: implications for 1H MRS studies in vivo.* Neuroreport, 1996. 7(8): p. 1397-400.
42. Addolorato, G., et al., *Novel therapeutic strategies for alcohol and drug addiction: focus on GABA, ion channels and transcranial magnetic stimulation.* Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 2012. 37(1): p. 163-77.
43. Nishiyama, T., et al., *Haplotype association between GABAA receptor gamma2 subunit gene (GABRG2) and methamphetamine use disorder.* Pharmacogenomics J, 2005. 5(2): p. 89-95.
44. Lin, S.K., et al., *Gender-specific contribution of the GABA(A) subunit genes on 5q33 in methamphetamine use disorder.* Pharmacogenomics J, 2003. 3(6): p. 349-55.
45. Gerasimov, M.R., et al., *Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine.* Synapse, 1999. 34(1): p. 11-9.
46. Willuhn, I., et al., *Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse.* Current topics in behavioral neurosciences, 2010. 3: p. 29-71.
47. Ranaldi, R. and K. Poeggel, *Baclofen decreases methamphetamine self-administration in rats.* Neuroreport, 2002. 13(9): p. 1107-10.
48. Li, S.M., et al., *GABA(B) receptor agonist baclofen attenuates the development and expression of d-methamphetamine-induced place preference in rats.* Life Sci, 2001. 70(3): p. 349-56.
49. DeMarco, A., et al., *Racemic gamma vinyl-GABA (R,S-GVG) blocks methamphetamine-triggered reinstatement of conditioned place preference.* Synapse, 2009. 63(2): p. 87-94.
50. Voigt, R.M., et al., *Administration of GABA(B) receptor positive allosteric modulators inhibit the expression of previously established methamphetamine-induced conditioned place preference.* Behavioural brain research, 2011. 216(1): p. 419-23.
51. Voigt, R.M., A.A. Herrold, and T.C. Napier, *Baclofen facilitates the extinction of methamphetamine-induced conditioned place preference in rats.* Behav Neurosci, 2011. 125(2): p. 261-7.
52. Agmo, A., et al., *GABAergic drugs inhibit amphetamine-induced distractibility in the rat.* Pharmacology, biochemistry, and behavior, 1997. 58(1): p. 119-26.
53. Mizoguchi, H. and K. Yamada, *Pharmacologic Treatment with GABA(B) Receptor Agonist of Methamphetamine-Induced Cognitive Impairment in Mice.* Current neuropharmacology, 2011. 9(1): p. 109-12.
54. Arai, S., et al., *GABAB receptor agonist baclofen improves methamphetamine-induced cognitive deficit in mice.* European journal of pharmacology, 2009. 602(1): p. 101-4.
55. Vocci, F.J., *Cognitive remediation in the treatment of stimulant abuse disorders: a research agenda.* Experimental and clinical psychopharmacology, 2008. 16(6): p. 484-97.
56. Sofuoglu, M., *Cognitive enhancement as a pharmacotherapy target for stimulant addiction.* Addiction, 2010. 105(1): p. 38-48.
57. Loftis, J.M. and M. Huckans, *Cognitive enhancement in combination with 'brain repair' may be optimal for the treatment of stimulant addiction.* Addiction, 2011. 106(5): p. 1021-2.
58. Cohen, J.B., et al., *Women with methamphetamine dependence: research on etiology and treatment.* Journal of psychoactive drugs, 2007. Suppl 4: p. 347-51.

59. Brecht, M.L., et al., *Methamphetamine use behaviors and gender differences.* Addictive behaviors, 2004. 29(1): p. 89-106.
60. Dluzen, D.E. and B. Liu, *Gender differences in methamphetamine use and responses: a review.* Gender medicine, 2008. 5(1): p. 24-35.
61. Lubman, D.I., et al., *The impact of co-occurring mood and anxiety disorders among substance-abusing youth.* J Affect Disord, 2007. 103(1-3): p. 105-12.
62. Glasner-Edwards, S., et al., *Risk factors for suicide attempts in methamphetamine-dependent patients.* The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 2008. 17(1): p. 24-7.
63. Kuo, C.J., et al., *Causes of death of patients with methamphetamine dependence: a record-linkage study.* Drug and alcohol review, 2011. 30(6): p. 621-8.
64. van, d.P.E.A., et al., *Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women.* Journal of clinical and experimental neuropsychology, 2009. 31(6): p. 706-19.
65. Milesi-Halle, A., et al., *Sex differences in (+)-amphetamine- and (+)-methamphetamine-induced behavioral response in male and female Sprague-Dawley rats.* Pharmacology, biochemistry, and behavior, 2007. 86(1): p. 140-9.
66. Reichel, C.M., et al., *Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats.* Psychopharmacology, 2012.
67. Holtz, N.A., et al., *Reinstatement of methamphetamine seeking in male and female rats treated with modafinil and allopregnanolone.* Drug and alcohol dependence, 2012. 120(1-3): p. 233-7.
68. Allen, P.J., et al., *Chronic creatine supplementation alters depression-like behavior in rodents in a sex-dependent manner.* Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 2010. 35(2): p. 534-46.
69. Lyoo, I.K., et al., *A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder.* Am J Psychiatry, 2012. 169(9): p. 937-45.
70. Hall, E.D., et al., *Neuroprotective effects of the dopamine D2/D3 agonist pramipexole against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons.* Brain Res, 1996. 742(1-2): p. 80-8.
71. Yen, C.F. and M.Y. Chong, *Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study.* Comprehensive psychiatry, 2006. 47(3): p. 215-20.
72. Yen, C.F. and Y.C. Su, *The associations of early-onset methamphetamine use with psychiatric morbidity among Taiwanese adolescents.* Substance use & misuse, 2006. 41(1): p. 35-44.
73. Semple, S.J., et al., *Psychosocial and behavioral correlates of depressed mood among female methamphetamine users.* Journal of psychoactive drugs, 2007. Suppl 4: p. 353-66.
74. Dyer, K.R. and C.C. Cruickshank, *Depression and other psychological health problems among methamphetamine dependent patients in treatment: Implications for assessment and treatment outcome.* Australian Psychologist, 2005. 40(2): p. 96-108.
75. Hser, Y.I., E. Evans, and Y.C. Huang, *Treatment outcomes among women and men methamphetamine abusers in California.* Journal of substance abuse treatment, 2005. 28(1): p. 77-85.
76. Hillhouse, M.P., et al., *Predicting in-treatment performance and post-treatment outcomes in methamphetamine users.* Addiction, 2007. 102 Suppl 1: p. 84-95.

77. Walton, M.A., et al., *Individual and social/environmental predictors of alcohol and drug use 2 years following substance abuse treatment.* Addictive behaviors, 2003. 28(4): p. 627-42.
78. Salo, R., et al., *Psychiatric comorbidity in methamphetamine dependence.* Psychiatry research, 2011. 186(2-3): p. 356-61.
79. Conway, K.P., et al., *Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions.* The Journal of clinical psychiatry, 2006. 67(2): p. 247-57.
80. Glasner-Edwards, S., et al., *Psychopathology in methamphetamine-dependent adults 3 years after treatment.* Drug and alcohol review, 2010. 29(1): p. 12-20.
81. Glasner-Edwards, S., et al., *Anxiety disorders among methamphetamine dependent adults: association with post-treatment functioning.* The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 2010. 19(5): p. 385-90.
82. Kelly, T.M., D.C. Daley, and A.B. Douaihy, *Treatment of substance abusing patients with comorbid psychiatric disorders.* Addictive behaviors, 2012. 37(1): p. 11-24.
83. Zorick, T., et al., *Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine.* Drug and alcohol dependence, 2011. 118(2-3): p. 500-3.
84. Shoptaw, S., et al., *Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence.* Drug and alcohol dependence, 2006. 85(1): p. 12-8.
85. Won, M., et al., *Manic-switch induced by fluvoxamine in abstinent pure methamphetamine abusers.* Journal of psychiatry & neuroscience : JPN, 2003. 28(2): p. 134-5.
86. Shoptaw, S., et al., *Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence.* Drug and alcohol dependence, 2008. 96(3): p. 222-32.
87. Colfax, G.N., et al., *Mirtazapine to reduce methamphetamine use: a randomized controlled trial.* Archives of general psychiatry, 2011. 68(11): p. 1168-75.
88. Salo, R., et al., *Attentional control and brain metabolite levels in methamphetamine abusers.* Biol Psychiatry, 2007. 61(11): p. 1272-80.
89. Salo, R., et al., *Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals.* Psychiatry Res, 2002. 111(1): p. 65-74.
90. McCann, U.D., et al., *Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users.* Synapse, 2008. 62(2): p. 91-100.
91. Aharonovich, E., E. Nunes, and D. Hasin, *Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment.* Drug Alcohol Depend, 2003. 71(2): p. 207-11.
92. Rae, C., et al., *Oral creatine monohydrate supplementation improves brain performance: a double-blind, placebo-controlled, cross-over trial.* Proc Biol Sci, 2003. 270(1529): p. 2147-50.
93. Watanabe, A., N. Kato, and T. Kato, *Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation.* Neurosci Res, 2002. 42(4): p. 279-85.
94. Werb, D., et al., *Methamphetamine use and malnutrition among street-involved youth.* Harm Reduct J, 2010. 7: p. 5.
95. Forrester, J.E., K.L. Tucker, and S.L. Gorbach, *The effect of drug abuse on body mass index in Hispanics with and without HIV infection.* Public Health Nutr, 2005. 8(1): p. 61-8.
96. Quach, L.A., et al., *Drug use and other risk factors related to lower body mass index among HIV-infected individuals.* Drug Alcohol Depend, 2008. 95(1-2): p. 30-6.
97. Frank, G.K., et al., *Neuroimaging studies in eating disorders.* CNS Spectr, 2004. 9(7): p. 539-48.

98. Roser, W., et al., *Metabolic changes in the brain of patients with anorexia and bulimia nervosa as detected by proton magnetic resonance spectroscopy.* Int J Eat Disord, 1999. 26(2): p. 119-36.
99. Castro-Fornieles, J., et al., *Adolescent anorexia nervosa: cross-sectional and follow-up frontal gray matter disturbances detected with proton magnetic resonance spectroscopy.* J Psychiatr Res, 2007. 41(11): p. 952-8.
100. Ludwig, D.S., et al., *Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults.* JAMA, 1999. 282(16): p. 1539-46.
101. Balsom, P.D., K. Soderlund, and B. Ekblom, *Creatine in humans with special reference to creatine supplementation.* Sports Med, 1994. 18(4): p. 268-80.
102. Casey, A. and P.L. Greenhaff, *Does dietary creatine supplementation play a role in skeletal muscle metabolism and performance?* Am J Clin Nutr, 2000. 72(2 Suppl): p. 607S-17S.
103. Stead, L.M., et al., *Is it time to reevaluate methyl balance in humans?* Am J Clin Nutr, 2006. 83(1): p. 5-10.
104. Guerrero-Ontiveros, M.L. and T. Wallimann, *Creatine supplementation in health and disease. Effects of chronic creatine ingestion in vivo: down-regulation of the expression of creatine transporter isoforms in skeletal muscle.* Molecular and cellular biochemistry, 1998. 184(1-2): p. 427-37.
105. Dringen, R., et al., *Metabolism of glycine in primary astroglial cells: synthesis of creatine, serine, and glutathione.* Journal of neurochemistry, 1998. 70(2): p. 835-40.
106. Wyss, M. and R. Kaddurah-Daouk, *Creatine and creatinine metabolism.* Physiological reviews, 2000. 80(3): p. 1107-213.
107. Rawson, E.S. and J.S. Volek, *Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance.* J Strength Cond Res, 2003. 17(4): p. 822-31.
108. Dalbo, V.J., et al., *Putting to rest the myth of creatine supplementation leading to muscle cramps and dehydration.* Br J Sports Med, 2008. 42(7): p. 567-73.
109. Robinson, T.M., et al., *Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function.* British journal of sports medicine, 2000. 34(4): p. 284-8.
110. Kim, H.J., et al., *Studies on the safety of creatine supplementation.* Amino acids, 2011. 40(5): p. 1409-18.
111. Shao, A. and J.N. Hathcock, *Risk assessment for creatine monohydrate.* Regulatory toxicology and pharmacology : RTP, 2006. 45(3): p. 242-51.
112. Rodriguez, N.R., M.N.M. Di, and S. Langley, *American College of Sports Medicine position stand. Nutrition and athletic performance.* Medicine and science in sports and exercise, 2009. 41(3): p. 709-31.
113. Beal, M.F., *Neuroprotective effects of creatine.* Amino acids, 2011. 40(5): p. 1305-13.
114. Klein, A.M. and R.J. Ferrante, *The neuroprotective role of creatine.* Subcell Biochem, 2007. 46: p. 205-43.
115. Burrows, K.B., G. Gudelsky, and B.K. Yamamoto, *Rapid and transient inhibition of mitochondrial function following methamphetamine or 3,4-methylenedioxymethamphetamine administration.* European journal of pharmacology, 2000. 398(1): p. 11-8.
116. Cadet, J.L., S. Jayanthi, and X. Deng, *Methamphetamine-induced neuronal apoptosis involves the activation of multiple death pathways. Review.* Neurotox Res, 2005. 8(3-4): p. 199-206.
117. Deng, X., et al., *Methamphetamine induces apoptosis in an immortalized rat striatal cell line by activating the mitochondrial cell death pathway.* Neuropharmacology, 2002. 42(6): p. 837-45.

118. Prass, K., et al., *Improved reperfusion and neuroprotection by creatine in a mouse model of stroke.* J Cereb Blood Flow Metab, 2007. 27(3): p. 452-9.
119. Mirecki, A., et al., *Brain antioxidant systems in human methamphetamine users.* J Neurochem, 2004. 89(6): p. 1396-408.
120. Sestili, P., et al., *Creatine supplementation affords cytoprotection in oxidatively injured cultured mammalian cells via direct antioxidant activity.* Free Radic Biol Med, 2006. 40(5): p. 837-49.
121. Brustovetsky, N., et al., *Calcium-induced cytochrome c release from CNS mitochondria is associated with the permeability transition and rupture of the outer membrane.* J Neurochem, 2002. 80(2): p. 207-18.
122. Sullivan, P.G., et al., *Dietary supplement creatine protects against traumatic brain injury.* Ann Neurol, 2000. 48(5): p. 723-9.
123. Dolder, M., et al., *Inhibition of the mitochondrial permeability transition by creatine kinase substrates. Requirement for microcompartmentation.* J Biol Chem, 2003. 278(20): p. 17760-6.
124. Nordahl, T.E., et al., *Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study.* Archives of general psychiatry, 2005. 62(4): p. 444-52.
125. Volkow, N.D., et al., *Addiction: beyond dopamine reward circuitry.* Proceedings of the National Academy of Sciences of the United States of America, 2011. 108(37): p. 15037-42.
126. Koob, G.F., L.G. Kenneth, and B.J. Mason, *Development of pharmacotherapies for drug addiction: a Rosetta stone approach.* Nature reviews. Drug discovery, 2009. 8(6): p. 500-15.
127. Potenza, M.N., et al., *Neuroscience of behavioral and pharmacological treatments for addictions.* Neuron, 2011. 69(4): p. 695-712.
128. Furukawa, T.A., et al., *Evidence-based guidelines for interpretation of the Hamilton Rating Scale for Depression.* Journal of clinical psychopharmacology, 2007. 27(5): p. 531-4.
129. Heaton RK, C.G., Talley JL, Kay GG, Curtiss G, *Wisconsin Card Sorting Test Manual - Revised and Expanded*, F.P.A.R. Lutz, Editor. 1993.
130. JR, S., *Studies of interaction in serial verbal reactions.* Journal of Experimental Psychology, 1935. 18: p. 643-662.
131. Jensen, A.R. and W.D. Rohwer, Jr., *The Stroop color-word test: a review.* Acta Psychol (Amst), 1966. 25(1): p. 36-93.
132. D, W., *Wechsler Memory Scale: Administrative and Technical Manuals*, T.P. Corporation, Editor. 2009: San Antonio, TX.
133. Hosak, L., et al., *Comparison of Wisconsin Card Sorting Test results between Czech subjects dependent on methamphetamine versus healthy volunteers.* Psychiatr Danub, 2012. 24(2): p. 188-93.
134. Simon, S.L., et al., *The effect of relapse on cognition in abstinent methamphetamine abusers.* J Subst Abuse Treat, 2004. 27(1): p. 59-66.
135. Provencher, S.W., *Estimation of metabolite concentrations from localized in vivo proton NMR spectra.* Magn Reson Med, 1993. 30(6): p. 672-9.
136. Provencher, S.W., *Automatic quantitation of localized in vivo 1H spectra with LCModel.* NMR Biomed, 2001. 14(4): p. 260-4.
137. Cohen, J., *A power primer.* Psychol Bull, 1992. 112(1): p. 155-9.
138. J, C., *Statistical power analysis for the behavioral sciences*. 2nd ed. 1988, Hillsdale, NJ: Erlbarum: Lawrence Erlbaum Associates.