Citicoline, Creatine, and Omega-3 Effects in Middle Age Women

Protocol Summary

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Background and Introduction

Citicoline (CDP-choline; cytidine 5'-diphosphocholine) is a nucleotide that plays an important role in cellular metabolism. It has a number of putative mechanisms of action, including as a phospholipid precursor for neuronal membrane repair, for prevention of beta-amyloid deposition, and for promotion of neurotransmitter systems (Conant & Schauss, 2004). Citicoline has been used therapeutically for stroke, traumatic brain injury, and cognitive dysfunction in the elderly (Adibhatla & Hatcher, 2005; Conant & Schauss, 2004) and it is available as a dietary supplement in the United States and Japan.

Citicoline appears to work synergistically with omega-3 fatty acids (Carlezon et al., 2005), which must be incorporated into brain membranes in order to have antidepressant efficacy (Hirashima et al., 2004). Omega-3 is also available as a dietary supplement in the United States. It is high in EPA (eicosapentanoic), an active anti-inflammatory, and has been used by many to help stabilize mood and to support a healthy nervous system.

In separate studies, the effects of creatine have also been evaluated (Lyoo et al., 2003; Allen et al., 2010). Low doses of creatine, 4-5 grams/day appear to have marked antidepressant effects, especially in women (Lyoo and Renshaw, unpublished results; Kondo and Renshaw, unpublished results).

References and Appendices:

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Purpose and Objectives

We propose that nutritional supplements that combine citicoline, omega-3 fatty acids, and creatine are likely to have marked benefits, especially for female consumers. We aim to determine the functional effects of citicoline, creatine and omega-3 fatty acids in combination when administered for a duration of four weeks (28 days) at a daily dosage to non-psychiatric adult female subjects. The doses of 500 mg of citicoline, 5 grams of creatine, and 2 grams of omega-3 fatty acids have been selected from previous investigations and have demonstrated minimal side effects.

Study Population

Age of Participants: 40-60

Sample Size:
At Utah: 20
All Centers:

Inclusion Criteria:
- Healthy female subjects, age 40-60 years
- No significant medical condition
- No history of co-morbid psychiatric disorder, current Axis I or II diagnosis or previous pharmacotherapeutic trial

Exclusion Criteria:
- Head injury w/ LOC > 5 minutes
- Use of any psychotropic medication
- History of a fish allergy
- History of a medical condition that decreases coagulability
- Use of anticoagulant medication

Design

Secondary/Archival Data Analysis
Survey/Questionnaire Research
Interviews and Focus Groups
Prospective Clinical Research

Study Procedures

Recruitment/Participant Identification Process:
Healthy, adult females will be recruited from the surrounding community through posting of flyers and word of mouth. All rules for posting flyers will be followed at every institution we canvass. Potential subjects will initially be screened over the phone by the study coordinator within a week of potential subjects calling the study voicemail number listed on the flyers. The PI will review every phone screen to ensure that potential participants meet the most basic inclusion criteria for this study.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained in-person at the Brain Institute's clinical location at the University Neuropsychiatric Institute.

Description of the consent process(es), including the timing of consent:

Once the subject is deemed eligible for the study, consent will be obtained from the subject before any study-specific procedures are complete. During the consent process, participants will be able to take as long as they need to ask questions, read and sign the consent form.

Procedures:

The study is designed for a one-month completion. Potential subjects will be screened in a 10-20 minute phone interview to determine eligibility. The first visit will involve subjects reviewing and signing the consent form prior to engaging in any study procedures. All procedures listed are for research purposes only.

Subjects will provide a urine sample for drug screening and a blood sample for serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). A visual acuity test will be given as well as weight and height measurements. The physical assessments will take approximately 30 minutes to complete. Neuropsychological and clinical rating scales will be administered as well, taking approximately 1 hour and 30 minutes. Each of the two visits should take approximately 2 hours to complete. The subjects will then be given their complete supply of citicoline, creatine and omega-3 tablets and instructed to take a combined daily dose over the next 28 days. They will be asked to return after 14 days for additional neuropsychological testing and clinical measures that will take approximately 1 hour. After 28 days, subjects will return for a repeat of measures for a second 2-hour evaluation session.

Each participant will be given a supplement log at the end of visit 1. They will be asked to complete the log during the 28 days to indicate that the daily dose of supplements were taken according to instructions. The study coordinator will check the log on the second and third visits as well as count the remaining supplement pills. If participants do not comply with the daily supplement schedule, then the PI will determine if the participant should be withdrawn from the study.

Clinical Assessment

The Mini International Neuropsychiatric Interview (M.I.N.I.) will be administered to each subject. The M.I.N.I. is a diagnostic interview designed to assess basic functioning and symptoms for lifetime psychiatric disorders. Subjects meeting diagnostic criteria for any psychiatric disorder, past or current Axis I or II, will not be included in the study. The Positive and Negative Affect Scale (PANAS) will be given to each subject as a self-evaluation scale in which subjects will rate their current feelings and emotions. Mood and life style questionnaires will also be given to each subject. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered at each visit. Finally, the Monitoring of Side Effects Scale (MOSES) will be given to study participants during the second and third visit to assess for any treatment side effects. If a subject becomes upset or uncomfortable during any part of the clinical assessment, they will be offered a chance to

take a break as well as other resources/referrals to help. They will also be reminded about how their confidentiality and privacy are protected as well as the voluntary nature of the study. The clinical assessment portion of the study should take approximately 30 minutes.

Neuropsychological Testing

In addition to the clinical rating scales to be completed, the proposed investigation also includes a battery of neuropsychological tests designed primarily to evaluate general intellectual capacity, executive/attentional functions, and memory processing. A trained psychometrician will administer these measures. All test scoring will be completed blind to subjects' treatment group status and clinical ratings. The neuropsychological tests were chosen because they are standard, well-known measures that can be administered and scored reliably. Given the importance of accurately obtaining IQ estimates from subjects, we will administer four subtests from the WAIS III. These neurocognitive measures are well known to the principal investigator, and previous studies have demonstrated reliable performance (Maher, Manschreck, Woods, Yurgelun-Todd, & Tsuang, 1995; Pope & Yurgelun-Todd, 1996; Yurgelun-Todd & Kinney, 1993). The measures include the following: Wechsler Adult Intelligence Scale (WAIS-IV): WAIS-IV Vocabulary Subtest, WAIS-IV Information Subtest, WAIS-IV Digit Span Subtests, WAIS-IV Block Design Subtest; WAIS-IV Coding Subtest; WAIS-IV Symbol Search Subtest; California Verbal Learning Test (CVLT)/ California Verbal Learning Test (CVLT-C); Rey-Osterreith Complex Figure Test (ROCFT); Continuous Performance Test (CPT); Stroop Color-Word Test; Trail Making Test; The Wisconsin Card Sort Test (WCST).

WAIS-IV Vocabulary Subtest: This subtest of the Wechsler Adult Intelligence Scale-Revised measures the subject's verbal ability and has been shown to be highly correlated with measures of general intellectual ability.

WAIS-IV Information Subtest: This subtest assesses the general knowledge of persons who grew up in the United States. The items are arranged in order of difficulty, from the simplest to the most difficult, which few adults could answer. It measures verbal skills, breadth of knowledge, and remote memory. It reflects formal education and a motivation for academic achievement. Among brain injured populations, information tends to be one of the least affected measures and can therefore serve as an estimate of premorbid ability.

WAIS-IV Digit Span Subtest: This subtest primarily measures the efficiency of attention. A subject repeats a string of digits presented by the experimenter. In the first part the subject repeats the digits forward; on the second part the subject repeats the numbers in reverse sequence. Failure on one of the two trials of this may be due to distraction, non-cooperation, inattentiveness or lack of concentration. Repetition backwards uses "working memory" and involves mental double-tracking in that both the recall of the number sequence and the reversing operations must proceed simultaneously.

WAIS-IV Block Design Subtest: This test of visuoconstructional ability is recognized as a test of visuospatial planning and function. It has been shown to be correlated with measures of general intellectual ability. In this test, the subject is presented with identical red and white blocks and asked to construct 8 designs presented to him on a stimulus card. The blocks are made up of distinguishable faces, 2 red sides, 2 white sides,

and 2 red & white sides split diagonally. Concrete minded persons have particular difficulty constructing the designs with diagonal patterns.

WAIS-IV Coding Subtest: This subtest assesses visual-motor coordination, motor and mental speed.

WAIS-IV Block Symbol Search Subtest: A series of paired groups, each pair consisting of a target group and a search group. The examinee indicates, by marking the appropriate box, whether either target symbol appears in the search group.

California Verbal Learning Test (CVLT): This verbal learning test assesses the subject's immediate and delayed recall, as well as suggesting the strategy utilized for retrieval of newly-learned information. Subjects are asked to remember a 16-item word list, which is presented on five trials. After each trial, the subject is asked to recall all of the words that they can remember. A second list is then presented to provide an interference condition. The subject is then asked to recall the first word list. After a temporal delay, the subject is again asked to recall the first word list. Test results provide scores for assessing verbal learning, strength of memory following interfering tasks, proactive interference, accuracy of recognition memory and storage versus retrieval of newly learned information.

Continuous Performance Test (CPT): This classic test of sustained attention has been adapted to a computerized version that can be administered to study subjects in 14 minutes. A subject is required to attend vigilantly to a series of visual stimuli and to indicate when target stimuli appear, disregarding distracter stimuli in which the target stimuli are embedded. This task generates measures of reaction time, omission errors, and commission errors, as well as an index of overall performance. Poor performance on the CPT has been associated with a number of psychiatric disorders. Scores include reaction time, omission errors, and commission errors, as well as an index of overall performance.

Rey-Osterreith Complex Figure Test: This complex figure test is an assessment of visuo-organizational ability, visual attention, and visual memory. The subject is asked to copy a complex figure, which is then evaluated for strategy, constructional accuracy, and detail reproduction. After removing the stimulus and the copy, the subject is asked to reproduce what he can recall from the figure. Approximately 30 minutes later, he is asked again to reproduce the figure. The complex design can be scored in both recall conditions on the basis of the number of elements, which have been correctly recalled. The difference between immediate and delayed performance scores is a measure of temporary decay for visuospatial memory.

Stroop Color-Word Test: This test measures the ability to inhibit inappropriate responses and resist interference. This test procedure includes three sections (color naming, word reading and interference) and is designed to establish competing response tendencies within the study subject and to assess the ability to suppress the interfering stimuli. Dependent measures include both reaction time to complete each condition, as well as total errors of omission and commission per condition. Difficulty with inhibition is reflected by an increase in errors and/or time in the interference section relative to the color naming or word reading sections.

Trail Making Test: This test is designed to measure visual conceptual and visuomotor tracking, as well as maintenance of cognitive set. The subject must first draw lines to

connect consecutively numbered circles on one work sheet (Part A) and then connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between the two sequences (Part B). Trails B is the more sensitive of the two tests -- particularly to frontal-lobe dysfunction -- as scores on this section are indicative of the subject's ability to shift sets and process concurrent stimuli.

The Wisconsin Card Sort Test: The Wisconsin Card Sort Test (WCST): This test assess a person's ability to form abstract concepts, utilize feedback, and to shift and maintain set, and has been used extensively in the evaluation of patients with frontal lobe damage, as it has been shown to be sensitive to frontal dysfunction. The test consists of 4 stimulus cards, varying in color, geometric form, and number. Without a time limit, the subject has to match each of the cards in the deck to a key card. No explanation is given to the subject as to the criterion being used in making a match. For each attempt, the subject is told if the trial is a correct or incorrect match. After each sequence of ten correct responses, the tester changes the match criterion without giving warning to the subject. Total number of categories correct, perseverative and other error types are dependent variables.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

This study is designed to explore whether oral supplementation of citicoline, creatine, and omega-3 fatty acids in combination for one month will result in cognitive improvements that correlate with brain activation and metabolism changes in 20 healthy adult females, ages 40-60. Data will be expressed as mean ± standard deviation, except where noted. Variables will be compared using ANOVAs with a=.05. All statistics will be computed using SPSS version 11.0 for the Macintosh. We will also examine the association between neuropsychological measures of attention, cognitive inhibition and memory as well as clinical measures for mood.