Lack of Efficacy of 5 Grams Daily of Creatine in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: Creatine plays a pivotal role in brain energy homeostasis and has been tried in the treatment of neurologic, neuromuscular, and atherosclerotic disease with a paucity of side effects. Creatine monohydrate supplementation may enhance cognitive functions in healthy subjects. Several independent lines of evidence suggest the possible involvement of altered cerebral energy metabolism in schizophrenia. Creatine effects on brain energy metabolism and its possible cognitive-enhancing properties raise the possibility of developing a new therapeutic strategy in schizophrenia by focusing on treating metabolic hypoactive brain areas including frontal regions.

Method: Twelve schizophrenia patients (DSM-IV criteria) were enrolled into a treatment study with creatine or placebo, and each treatment was administered for 3 months (dosage, 3–5 grams per day) in a randomized, double-blind crossover design. Ten patients completed the study, which was conducted from November 2004 to February 2006. Rating scales included the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) scale, scales for the assessment of side effects, and a cognitive battery.

Results: Creatine treatment was not superior to placebo in improving the scores of PANSS, CGI, or the neurocognitive measures administered. Side effects of creatine treatment were few.

Conclusion: Three months of creatine administration failed to detect any efficacy in treating symptoms of schizophrenia, but further research is suggested.

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Creatine plays a pivotal role in brain energy homeostasis, being a temporal and spatial buffer for cytosolic and mitochondrial pools of the cellular energy currency adenosine triphosphate.[1,2] Creatine supplementation is widely used in enhancing athletic performance, and has been tried in the treatment of neurologic, neuromuscular, and atherosclerotic disease with a paucity of side effects.[1] We have recently completed an open study of creatine administration in depression, which demonstrated a beneficial effect in unipolar patients.[3]

Creatine, which enters the brain via a specialized sodium dependent transporter, seems to have an impact on cognitive functioning. Bartlett et al.[4] reported lower levels of hippocampal creatine-containing compounds in patients with obstructive sleep apnea, a disorder associated with intermittent hypoxia and cognitive decrements, and these lower levels were correlated with worse obstructive sleep apnea severity and poorer neurocognitive performance. Valenzuela et al.[5] investigated elderly subjects with the use of magnetic resonance spectroscopy in different brain regions before and after 5 weeks of focused memory training; improvement in a word recall test was associated with an increase of creatine and choline signals in the hippocampus.

Studies in humans show that oral administration of creatine affects brain levels of creatine. Dechent et al.[6] showed by means of quantitative localized proton magnetic resonance spectroscopy in vivo that oral creatine supplementation of 20 g per day for 4 weeks caused a significant increase of mean concentration of total creatine across brain regions. Lyoo et al.[7] used magnetic resonance spectroscopy following oral supplementation of creatine or placebo and reported that creatine administration (0.3 g per kilo of body weight per day for the first 7 days and 0.03 g per kilo per day for the next 7 days) significantly increased brain creatine and phosphocreatine levels as compared with a placebo group.

Several studies have looked at the effects on cognition of creatine administration. Watanabe et al.[8] reported that dietary supplementation of creatine (8 g per day for 5 days) reduced mental fatigue when subjects repeatedly perform a simple mathematical calculation, and Rae et al.[9] reported that creatine supplementation (5 g per day for 6

weeks) had a highly significant positive effect on both working memory (backward digit span) and Raven's Advanced Progressive Matrices in healthy volunteers.

Taken together, these studies show that low levels of creatine are associated with poorer cognitive functioning, that creatine administered orally reaches the brain, and that creatine administration can improve cognitive functioning. These findings suggest a role of creatine in influencing cognitive performance, possibly via its effects on brain energy metabolism.

Several independent lines of evidence suggest the possible involvement of altered cerebral energy metabolism in the pathophysiology of schizophrenia. Most (but not all) studies reveal decreased metabolism in the frontal cortex in schizophrenia, which was termed *hypofrontality*.[10] A direct link to phosphocreatine and adenosine triphosphate energy systems came from studies[11,12] using ^{31}P-MRS (phosphorus magnetic resonance spectroscopy) with or without chemical shift imaging, which enabled the measurement of adenosine triphosphate, phosphocreatine, and inorganic phosphate. These studies showed reduced adenosine triphosphate in the frontal lobe and in the left temporal lobe of schizophrenic patients as compared with controls.[13] Altered brain energy metabolism could be due to impairment of mitochondria, and a variety of studies reviewed by Ben-Shachar[14] suggest impaired mitochondrial energy metabolism in schizophrenia.

Creatine effects on brain energy metabolism and its possible cognitive-enhancing properties raise the possibility of developing a therapeutic strategy for treating schizophrenia by focusing on treating metabolic hypoactive brain areas including frontal regions. This study was designed to explore whether creatine monohydrate administration would have beneficial effects on cognition and/or on positive and negative symptomatology in schizophrenia.

METHOD

The study, which was conducted from November 2004 to February 2006, was approved by the Helsinki Committee (institutional review board) of Ben Gurion University. Twelve schizophrenic patients (DSM-IV criteria), ranging from 27 to 54 years old, with more than 2 years of illness in a stable condition (no gross changes in clinical presentation in the last 6 months as judged by the patient's psychiatrist) were recruited after giving informed consent. Patients had to present negative and cognitive symptoms (as judged by the patient's psychiatrist) along with 3 or more items of the Positive and Negative Syndrome Scale (PANSS)[15]-Negative subscale scored at 4 points or above, and all items of the PANSS-Positive subscale scored at less than 4 points.

Patients with alcohol or drug abuse in the 6 months prior to entry into the study or with any clinically significant unstable medical condition or laboratory abnormality were excluded.

Six patients were started on treatment with creatine monohydrate (capsules provided by Solgar Ltd.) for 3 months (3 g daily in the first month and then 5 g daily for another 2 months, following Kieburtz[16] and Rae et al.[9]) and afterwards were continued for 3 months on placebo. The other 6 patients were administered placebo for 3 months followed by creatine monohydrate for 3 months in the same dosages and procedure. Treatment order was randomly assigned and both patients and researchers were blind to treatment condition. Patients' neuroleptic treatment was not affected by study participation. Mood stabilizers, benzodiazepines, and anticholinergic medications were allowed with doses documented throughout the study. After completing 2 months of treatment, 1 female patient from the creatine-first group was withdrawn at her request due to moderate nausea. One male patient, also from the creatine-first group, was withdrawn from the study after 4 months due to poor compliance. Ten patients completed the entire study.

The Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions scale (CGI),[17] Abnormal Involuntary Movement Scale (AIMS),[18] and adverse effect/side effects assessment were administered at baseline and thereafter monthly by a researcher blind to treatment condition (placebo/creatine). Neuropsychological tests were administered by the same blind researcher, at baseline and after 3 and 6 months, in the following standardized sequence: Digit Span (from the Wechsler Memory Scale-Revised[19]); Rey Auditory Verbal Learning Test (RAVLT)[20]; Wisconsin Card Sorting Test–64-item version (WCST-64)[21]; and the Complex Figure Drawing, either the Rey[22] (baseline and 6-month assessment) or the equivalent Taylor Complex Figure[23] (after 3 months). From this battery, 7 outcome measures were calculated: Digit Span Total, RAVLT-Recall, RAVLT-Recognition, Wisconsin Card Sort-Categories Completed, Wisconsin Card Sort-Perseverative Errors, Complex Figure-Copy Phase, and Complex Figure-Immediate Recall.

RESULTS

Twelve patients diagnosed with schizophrenia were enrolled into the study: 7 outpatients and 5 inpatients; 7 men and 5 women. Mean ± SD age was 42.8 ± 8 years; age at illness onset, 27.9 ± 12 years; illness duration, 14.9 ± 7 years; and years of education, 9.9 ± 2. Number of hospitalizations ranged from 0 through 10, and treatment dose in chlorpromazine equivalent (mg/day) was 500 ± 204. One man of the creatine-first treated group had diabetes mellitus type II, and 1 woman of the placebo-first treated group had asthma. The mean ± SD PANSS score at baseline was 66 ± 14.

Table 1. Treatment Effect of Creatine Versus Placebo Supplementation in Patients With Schizophrenia (X ± SEM, N = 10)

Measure	Baseline	Change	Treatment Effect (df = 1,8)
Clinical scales			
PANSS total			F = 0.24; p = .6
Creatine	64.7 ± 5.1	2.2 ± 1.8	
Placebo	64.3 ± 4.5	0.6 ± 1.5	
PANSS-Positive			F = 0.1; p = .8
Creatine	11.6 ± 1.4	0.4 ± 0.8	
Placebo	11.8 ± 1.1	–0.9 ± 1.2	
PANSS-Negative			F = 0.4; p = .6
Creatine	20.7 ± 2.0	1.5 ± 0.8	
Placebo	20.1 ± 1.6	0.8 ± 0.6	
PANSS-General Psychopathology			F = 1.8; p = .2
Creatine	33.3 ± 2.1	2.0 ± 0.9	
Placebo	32.4 ± 2.3	–0.4 ± 1.1	
CGI-Severity of Illness			F = 0.96; p = .4
Creatine	4.4 ± 0.3	0.4 ± 0.2	
Placebo	4.3 ± 0.3	0.0 ± 0.2	
Neuropsychological measures			
Digit span total			F = 0.04; p = .8
Creatine	11.4 ± 1.6	0.1 ± 0.6	
Placebo	10.9 ± 1.7	0.3 ± 0.6	
RAVLT-Recall			F = 1.14; p = .3
Creatine	55.5 ± 4.9	0.6 ± 2.7	
Placebo	55.7 ± 6.3	4.2 ± 2.4	
RAVLT-Recognition			F = 0.72; p = .4
Creatine	5.6 ± 2.1	–0.7 ± 1.3	
Placebo	5.2 ± 2.2	1.2 ± 2.0	
WCST-64–categories completed			F = 0.29; p = .6
Creatine	0.7 ± 0.3	–0.1 ± 0.2	
Placebo	1.0 ± 0.4	–0.2 ± 0.1	
WCST-64–perseverative errors[a]			F = 0.42; p = .5
Creatine	25.1 ± 5.0	–4.6 ± 2.9	
Placebo	25.7 ± 4.7	–1.4 ± 3.3	
Complex figure–copy phase			F = 1.36; p = .3
Creatine	20.8 ± 2.1	–2.8 ± 1.7	
Placebo	19.0 ± 3.2	1.5 ± 2.2	
Complex figure–immediate recall phase			F = 1.21; p = .3
Creatine	8.6 ± 2.1	0.6 ± 1.3	
Placebo	8.4 ± 2.7	2.1 ± 0.5	

[a]In this measure only, higher scores reflect poorer functioning.
Abbreviations: CGI = Clinical Global Impressions, PANSS = Positive and Negative Syndrome Scale, RAVLT = Rey Auditory Verbal Learning Test, WCST-64 = Wisconsin Card Sorting Test–64-item version.

Analyses of variance of improvement scores for total PANSS and its subscales, CGI-Severity of Illness scale, AIMS, and the neuropsychological measures were performed. A 2-period crossover design was used. Treatment effect (analyzed as a within-subject comparison), treatment order effect (analyzed as between-subject comparison), and treatment order interactions were calculated. Table 1 presents baseline and change scores for the clinical and neuropsychological measures for the study completers (N = 10) during each phase of the 2-period crossover design. No significant effects of treatment (creatine vs. placebo), order (creatine first or placebo first), or treatment-order interactions were found.

Using analyses of variance of improvement scores for total PANSS and its subscales, CGI-Severity of Illness, AIMS, and the neuropsychological measures for the first 3 months only (as if the study utilized a parallel group design) for all the study subjects (N = 12), no significant effects of treatment were found for any of the clinical scales or neuropsychological measures. (Last observations carried forward were used for the 1 subject who withdrew after completing only 2 months of the study).

Creatine administration was found to be safe, with few side effects, principally nausea in 1 female patient and nausea and vomiting in 1 male patient.

DISCUSSION

This study failed to detect an effect of creatine treatment on either cognitive function or positive or negative symptomatology in patients with schizophrenia. This negative finding raises several interesting points.

There is evidence from in vitro and animal experiments that oral creatine supplementation might prevent or slow down neurodegeneration in another brain disease: Huntington's disease. However, an initial placebo-controlled clinical trial in patients with Huntington's disease in which creatine was administered in a dose similar to ours (5 g daily) for 1 year showed negative results.[24] Later studies using higher doses of creatine in patients with Huntington's disease showed that creatine treatment led both to reduced glutamate[25] and to reduced serum 8-hydroxy-2'-deoxyguanosine levels—the latter suggesting oxidative injury to DNA.[26] Several authors have thus suggested that the lack of a therapeutic effect of creatine in Huntington's disease was possibly due to treatment periods being too short and daily doses being too low to have an impact on clinical endpoints.[25] This may suggest that perhaps longer trials and/or higher doses of creatine are also needed in schizophrenia.

Rae et al.[9] reported that creatine supplementation in healthy volunteers had a significant positive effect on both working memory and Raven's Advanced Progressive Matrices, whereas in patients with schizophrenia we did not find any beneficial effects of creatine on any of the cognitive tests administered. Such a difference between healthy subjects and patients may be due to decreased capacity of schizophrenic patients to synthesize the high energy phosphate molecule creatine phosphate needed for the synthesis of the cytosolic and mitochondrial pools of the cellular energy currency adenosine triphosphate. A previous finding of low levels of brain isozyme creatine kinase in the brain of patients with schizophrenia[27] suggests a decreased capacity for synthe-

sizing creatine phosphate in schizophrenia. Creatine phosphate administration has been shown in animals to effect high-energy phosphates in ischemic myocardium,[28] and perhaps a future stable form of creatine phosphate would be a more effective agent for the treatment of cognitive impairments in patients with schizophrenia.

The main assumption of this study was that strategies enhancing brain energy metabolism might activate key hypometabolic brain areas and thus have beneficial effects in schizophrenia. The current study, although not providing support for the hypothesis that creatine monohydrate may be effective in schizophrenia, does not necessarily refute such a hypothesis. This study has several significant limitations: the study sample is small, creatine was administered for 3 months only, and the patient group consisted only of chronically ill subjects and did not include patients with relatively short periods of illness. Also, recent research in Huntington's disease[26] and in Parkinson's disease[29] suggests that longer periods and/or higher doses of creatine administration may be effective.

Creatine is believed to globally enhance brain energy metabolism. This study failed to detect an effect in schizophrenia of 3 to 5 grams of creatine per day administered over a 3-month period, but does not rule out the possibility that larger studies over longer periods and/or using higher doses of creatine might show efficacy. In this context, it is important to note that the creatine was well tolerated and induced few side effects. In addition, whereas administration of creatine is a global strategy, the use of specific agents targeting brain energy metabolism in certain brain areas might also be usefully explored.

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